

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Eptinezumab (VYEPTI[®])

Lundbeck GmbH

Modul 4A – Anhang 4-G

Migräneprophylaxe

**Subgruppenanalysen der Studie
DELIVER**

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Abkürzungsverzeichnis

Abkürzung	Bedeutung
AESI	<i>Adverse Event(s) of Special Interest</i> (UE von besonderem Interesse)
AMNOG	Arzneimittelmarktneuordnungsgesetz
Basln	<i>Baseline</i>
CFB	<i>Change from Baseline</i> (Veränderung gegenüber dem Baselinewert)
CI	<i>Confidence Interval</i> (Konfidenzintervall)
CL	<i>Confidence Level</i>
CM	Chronische Migräne
CMH	Cochrane Mantel Haenzel
EM	Episodische Migräne
FPT	<i>Failed Previous Therapies</i>
HIT-6	<i>Headache Impact Test 6</i>
MBS	<i>Most Bothersome Symptom</i>
MD	<i>Mean difference</i> (Mittelwertdifferenz)
MMRM	<i>Mixed effect Model Repeat Measurement</i>
MOH	<i>Migraine Overuse Headache</i> (Medikamentenübergebrauchskopfschmerz)
MSQ	<i>Migraine Specific Quality of Life Questionnaire</i>
OR	<i>Odds Ratio</i>
PBO	<i>Placebo</i>
PGIC	<i>Patient Global Impression of Change</i>
PT	<i>Preferred Terms</i> nach MedDRA
RCT	<i>Randomized Controlled Trial</i> (Randomisierte kontrollierte Studie)
RD	Risikodifferenz
RR	Relatives Risiko
SE	<i>Standard Error</i> (Standardfehler)
SMD	<i>Standardized mean difference</i> (standardisierte Mittelwertdifferenz)
SMQ	<i>Standardized MedDRA Query</i>
SOC	<i>System Organ Class</i> (Systemorganklasse)
SUE	Schwerwiegendes UE
UE	Unerwünschtes Ereignis
VAS	<i>Visual Analogue Scale</i>

4 Subgruppenanalysen der Studie DELIVER

4.1 Vorwort

Die Studienergebnisse sollen hinsichtlich potenzieller Effektmodifikatoren untersucht werden. Zu diesem Zweck wurden Subgruppenanalysen durchgeführt, die in diesem Anhang 4G dargestellt sind. Dies entspricht den Vorgaben in der Dossiervorlage, nach der Subgruppenanalysen, bei denen der Interaktionsterm nicht statistisch signifikant ist, in einem separaten Anhang des vorliegenden Modul 4 dargestellt werden können (auch als unveränderte Ausgabe des Statistikprogramms). Der vorliegende Anhang enthält alle Subgruppenanalysen, Analysen mit positivem Interaktions-p-Wert sind zusätzlich in Abschnitt 4.3.1 in Modul 4 dargestellt.

Bei der Durchführung und Darstellung der Subgruppenanalysen werden gemäß Dossiervorlage die folgenden Kriterien berücksichtigt:

- Subgruppenanalysen wurden nur für die Merkmale (z.B. Alter) durchgeführt, bei denen die resultierenden Subgruppen jeweils mindestens 10 Patienten umfassen. Nach diesem Kriterium entfällt für die Studie DELIVER eine Subgruppenanalyse nach „Region“ (< 10 Patienten wurden in den USA rekrutiert).
- Subgruppenanalysen wurden für binäre Ereignisse je Merkmal nur dann durchgeführt, wenn in einer der Subgruppen mindestens 10 Ereignisse aufgetreten sind. Nach diesem Kriterium entfallen Subgruppenanalysen für unerwünschte Ereignisse, die zum Behandlungsabbruch führten und schwerwiegende unerwünschte Ereignisse.
- Subgruppenanalysen zu UE nach SOC und PT wurden nur durchgeführt, wenn das jeweilige Ergebnis für die Gesamtpopulation statistisch signifikant war. Zu a priori definierten Ereignissen (z.B. AESI, SMQs) sowie den UE-Gesamttraten (UE, schwere UE, SUE und Abbrüche wegen UE) wurden Subgruppenanalysen unabhängig vom Vorliegen statistischer Signifikanz in der Gesamtpopulation dargestellt, sofern ausreichend Ereignisse für eine valide Analyse aufgetreten sind.

Da die Analysen der UE nach SOC und PT keine signifikanten Unterschiede zwischen Eptinezumab und Placebo (BSC) ergeben haben, wurden für diese einzelnen Ereignisse keine Subgruppenanalysen durchgeführt.

- Die dargestellten Analysen waren weitestgehend nicht vorab geplant und wurden zu allen relevanten Endpunkten entsprechend posthoc durchgeführt.
- Für die Nutzenbewertung wurde Teilpopulation der Studie DELIVER herangezogen (AMNOG Population b), so dass die vollständigen Subgruppenanalysen für diese Teilpopulation und nicht für die Gesamtpopulation der Studie durchgeführt wurden.

4.2 Ergebnisse der Subgruppenanalysen nach Endpunkt

4.2.1 Gesamtmortalität

Keine Subgruppenanalyse durchgeführt

4.2.2 Migränetage/Monat

4.2.2.1 Veränderung gegenüber dem Baseline-Wert

Tabelle 4G-1: Migränetage/Monat, CFB, Interaktions-p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg p-value	EPTI 300 mg p-value
Interaction test: Age Group	0.5738	0.0917
Interaction test: EM/CM	0.4368	0.5462
Interaction test: MOH	0.9484	0.0841
Interaction test: Number of FPT	0.7850	0.1315
Interaction test: Sex	0.5383	0.3016

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-2: Migränetage/Monat, CFB, Interaktions-p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg p-value	EPTI 300 mg p-value
Interaction test: Age Group	0.4179	0.1267
Interaction test: EM/CM	0.1570	0.4400
Interaction test: MOH	0.9709	0.3944
Interaction test: Number of FPT	0.4754	0.2634

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Sex	0.7612	0.6103

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-3: Migränetage/Monat, CFB, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	67 (100.0)	14.6 (5.72)							
	1-12	67 (100.0)	12.4 (7.94)	.75 (0.79)						
	13-24	66 (98.5)	12.1 (7.94)	.84 (0.83)						
EPTI 100 mg	Basln	57 (100.0)	14.2 (5.95)							
	1-12	57 (100.0)	9.88 (7.37)	-3.0 (0.82)	-2.2	0.86	[-3.9;-.55]	0.0097	-0.5	[-.83;-.12]
	13-24	53 (93.0)	8.57 (7.37)	-3.9 (0.87)	-3.1	0.95	[-5.0;-1.2]	0.0014	-0.6	[-.96;-.24]
EPTI 300 mg	Basln	62 (100.0)	14.7 (5.96)							
	1-12	62 (100.0)	10.1 (7.88)	-3.0 (0.84)	-2.3	0.85	[-4.0;-.61]	0.0080	-0.5	[-.82;-.13]
	13-24	61 (98.4)	8.31 (7.88)	-4.5 (0.88)	-3.7	0.93	[-5.5;-1.9]	0.0001	-0.7	[-1.1;-.36]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: ≤ 14 / > 14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeestimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

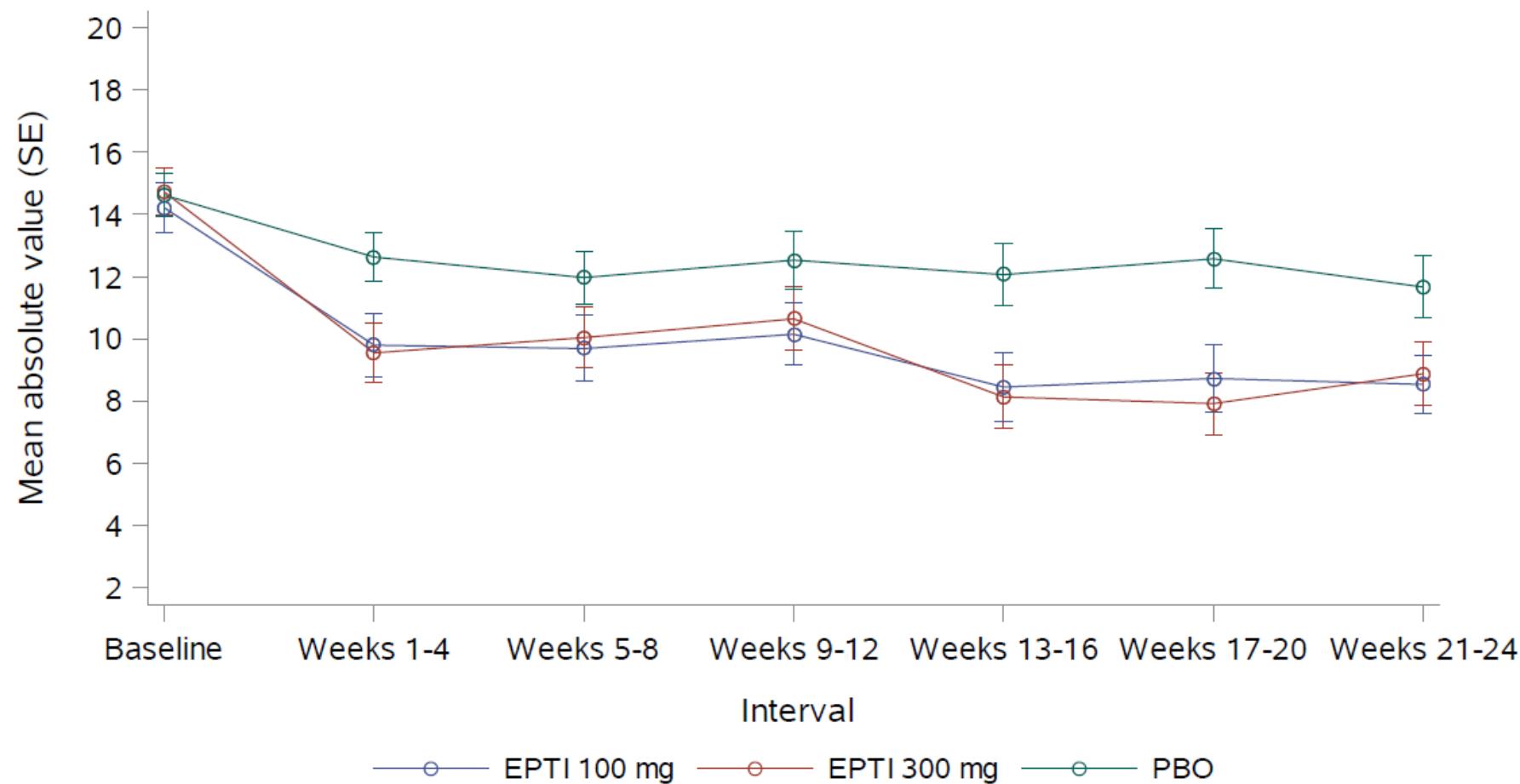
**Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) :
Age <= 35 years**

Tabelle 4G-4: Migränetage/Monat, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans				Comparison to PBO	
					Diff.	SE	CI	p-value	95% CI	
									G	CI
PBO	Basln	220 (100.0)	13.6 (5.82)							
	1-12	220 (100.0)	10.7 (6.46)	-2.5 (0.44)						
	13-24	219 (99.5)	10.2 (6.46)	-2.8 (0.46)						
EPTI 100 mg	Basln	227 (100.0)	13.7 (5.58)							
	1-12	227 (100.0)	7.85 (6.17)	-5.3 (0.43)	-2.8	0.40	[-3.6;-2.0]	<.0001	-0.7	[-.86;-.49]
	13-24	220 (96.9)	7.08 (6.17)	-5.8 (0.45)	-3.0	0.44	[-3.9;-2.2]	<.0001	-0.7	[-.85;-.48]
EPTI 300 mg	Basln	223 (100.0)	13.4 (5.30)							
	1-12	223 (100.0)	7.10 (6.02)	-5.8 (0.42)	-3.4	0.40	[-4.2;-2.6]	<.0001	-0.8	[-.99;-.61]
	13-24	217 (97.3)	6.36 (6.02)	-6.5 (0.44)	-3.7	0.44	[-4.5;-2.8]	<.0001	-0.8	[-.99;-.61]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

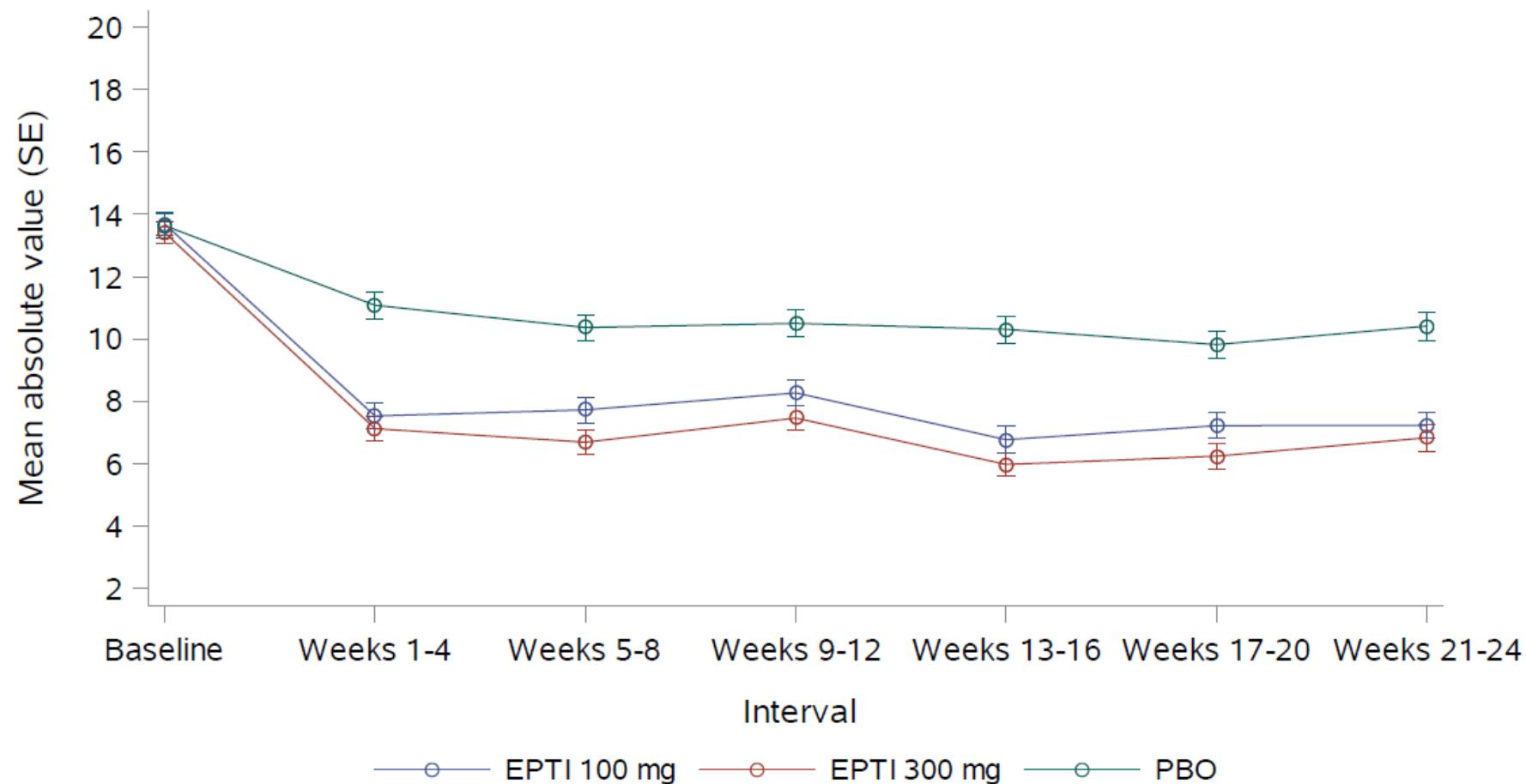
**Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) :
Age > 35 years**

Tabelle 4G-5: Migränetage/Monat, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		SMD 95% CI	
					Diff.	SE	CI	95% CI		Hedges' G	CI
								p-value			
PBO	Basln	33 (100.0)	14.8 (6.53)								
	1-12	33 (100.0)	12.3 (7.70)	-2.5 (0.99)							
	13-24	33 (100.0)	12.1 (7.70)	-2.6 (1.08)							
EPTI 100 mg	Basln	21 (100.0)	13.9 (6.58)								
	1-12	21 (100.0)	8.18 (7.54)	-5.3 (1.12)	-2.8	1.35	[-5.5;-.12]	0.0409	-0.6	[-1.1;-.02]	
	13-24	20 (95.2)	8.52 (7.54)	-4.8 (1.26)	-2.2	1.53	[-5.2;0.87]	0.1600	-0.4	[-.97;0.16]	
EPTI 300 mg	Basln	32 (100.0)	14.4 (5.03)								
	1-12	32 (100.0)	9.48 (8.06)	-5.2 (0.95)	-2.7	1.15	[-4.9;-.36]	0.0238	-0.6	[-1.1;-.08]	
	13-24	32 (100.0)	8.34 (8.06)	-6.3 (1.05)	-3.7	1.31	[-6.3;-1.1]	0.0058	-0.7	[-1.2;-.21]	

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) : Males

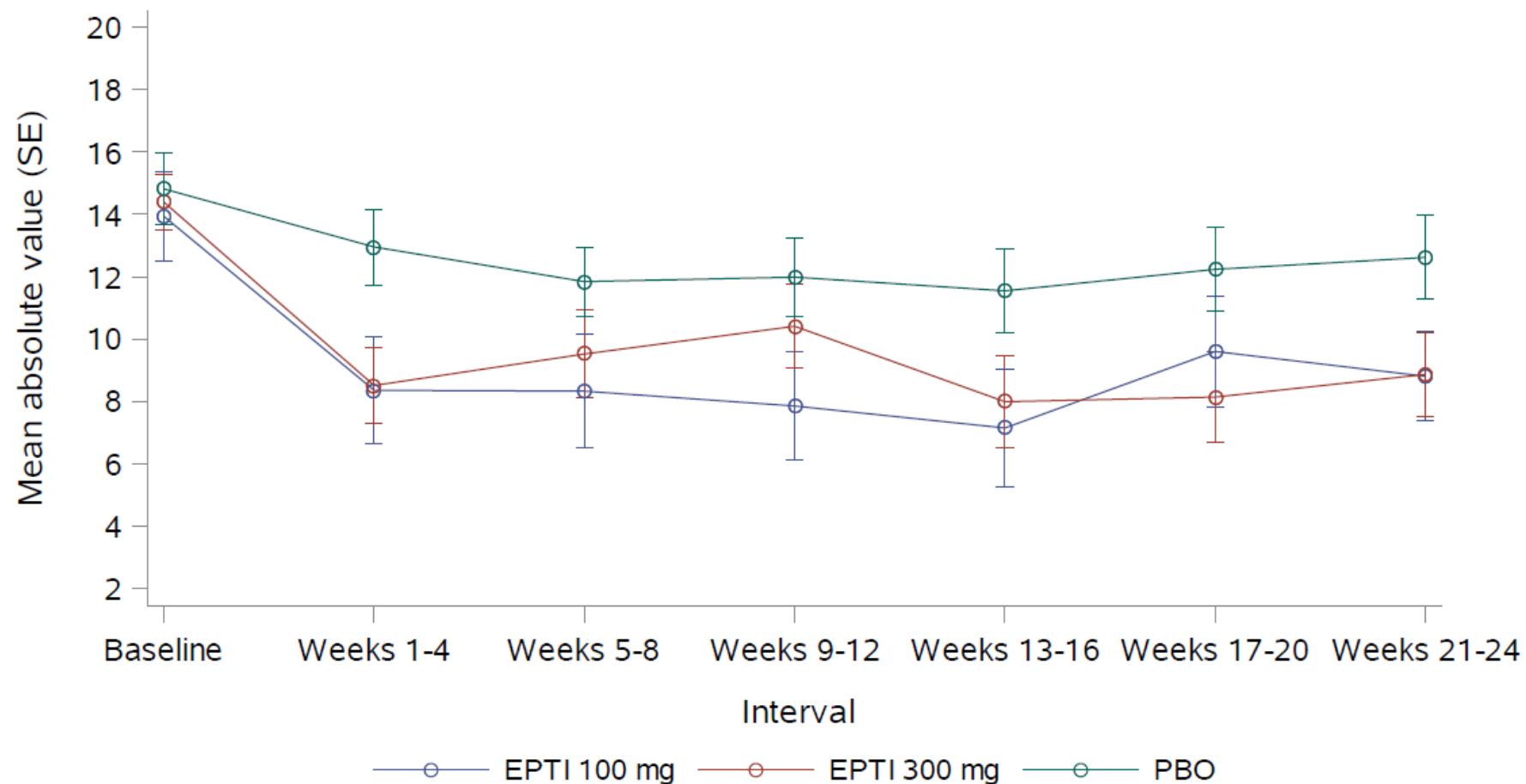


Tabelle 4G-6: Migränetage/Monat, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans				Comparison to PBO	
					Diff.	SE	CI	p-value	95% CI	
									G	CI
PBO	Basln	254 (100.0)	13.7 (5.70)		-1.7 (0.44)	0.39	[-3.4;-1.9]	<.0001	-0.6	[-.77;-.43]
	1-12	254 (100.0)	10.9 (6.74)	-2.0 (0.45)						
	13-24	252 (99.2)	10.4 (6.74)							
EPTI 100 mg	Basln	263 (100.0)	13.8 (5.58)		-4.4 (0.43)	0.39	[-3.4;-1.9]	<.0001	-0.6	[-.77;-.43]
	1-12	263 (100.0)	8.26 (6.33)	-5.1 (0.45)						
	13-24	253 (96.2)	7.27 (6.33)							
EPTI 300 mg	Basln	253 (100.0)	13.6 (5.52)		-5.0 (0.42)	0.39	[-4.1;-2.5]	<.0001	-0.8	[-.93;-.58]
	1-12	253 (100.0)	7.53 (6.27)	-5.8 (0.44)						
	13-24	246 (97.2)	6.58 (6.27)							

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

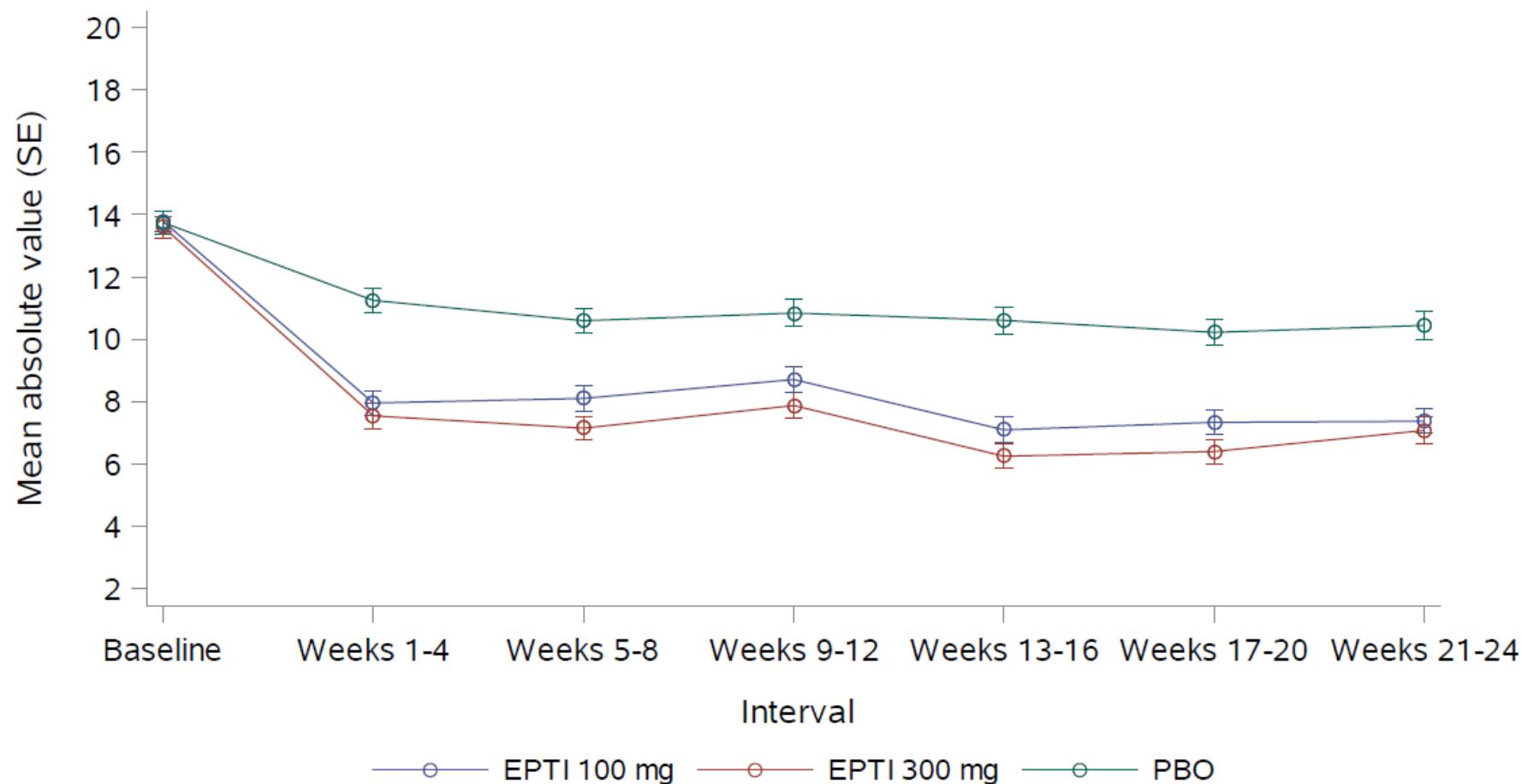
Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) : Females

Tabelle 4G-7: Migränetage/Monat, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans				Comparison to PBO	
					Diff.	SE	CI	p-value	95% CI	
									G	CI
PBO	Basln	159 (100.0)	9.63 (2.41)							
	1-12	159 (100.0)	7.73 (4.59)	-.95 (0.42)						
	13-24	159 (100.0)	7.37 (4.59)	-1.3 (0.43)						
EPTI 100 mg	Basln	154 (100.0)	9.55 (2.53)							
	1-12	154 (100.0)	5.59 (4.34)	-3.1 (0.42)	-2.1	0.39	[-2.9;-1.4]	<.0001	-0.6	[-.85;-.40]
	13-24	149 (96.8)	4.76 (4.34)	-3.8 (0.43)	-2.5	0.40	[-3.3;-1.7]	<.0001	-0.7	[-.93;-.48]
EPTI 300 mg	Basln	154 (100.0)	9.73 (2.55)							
	1-12	154 (100.0)	4.86 (3.81)	-3.9 (0.41)	-3.0	0.39	[-3.7;-2.2]	<.0001	-0.9	[-1.1;-.63]
	13-24	152 (98.7)	4.20 (3.81)	-4.5 (0.42)	-3.2	0.40	[-4.0;-2.4]	<.0001	-0.9	[-1.1;-.69]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) : Episodic Migraine

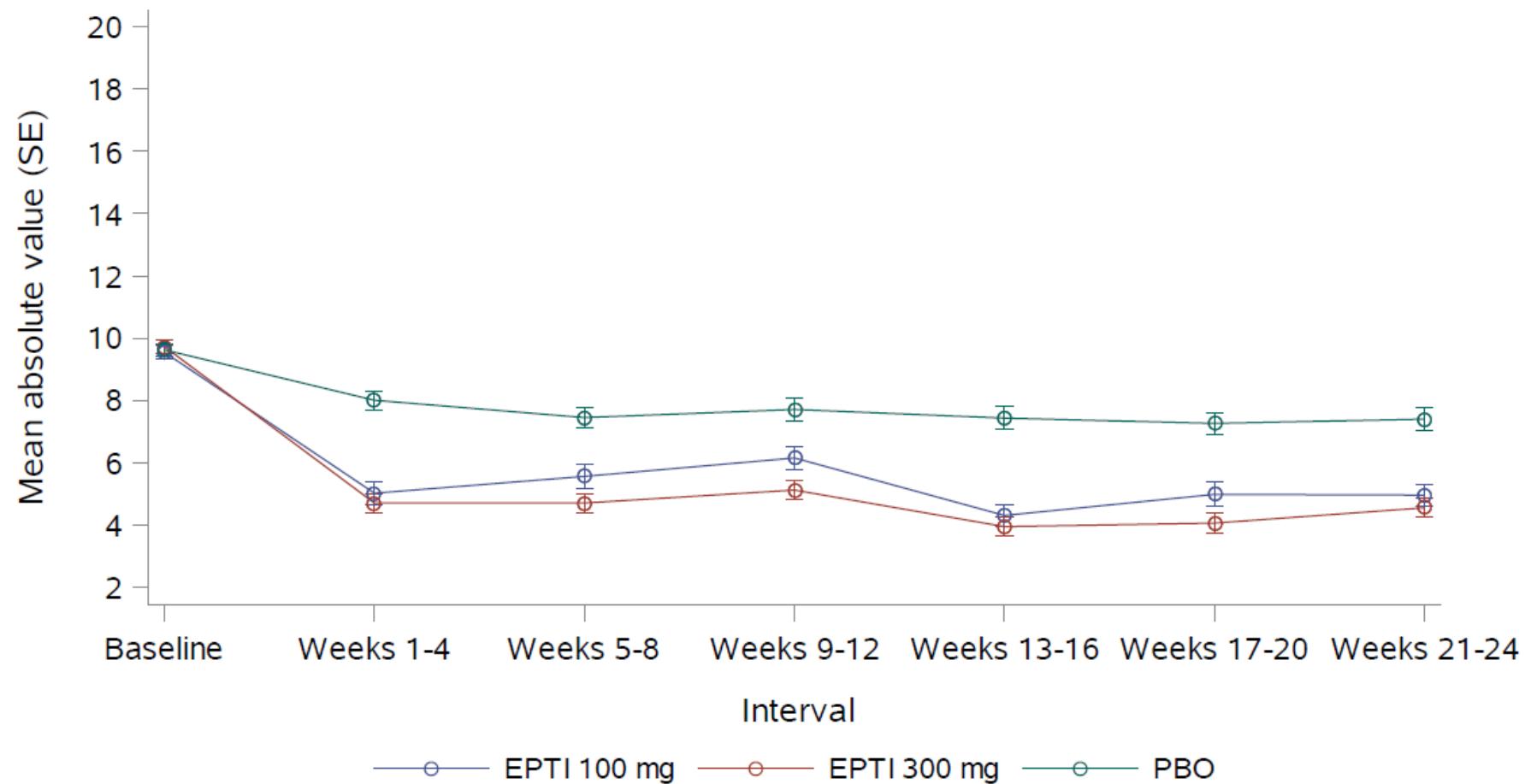


Tabelle 4G-8: Migränetage/Monat, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					CFB LSmeans			Hedges' G	CI	
					Diff.	SE	CI			
PBO	Basln	128 (100.0)	19.1 (4.28)							
	1-12	128 (100.0)	15.2 (7.06)	-2.0 (0.87)						
	13-24	126 (98.4)	14.8 (7.06)	-2.4 (0.92)						
EPTI 100 mg	Basln	130 (100.0)	18.8 (3.95)							
	1-12	130 (100.0)	11.4 (7.10)	-5.5 (0.83)	-3.5	0.66	[-4.8;-2.2]	<.0001	-0.7	[-.90;-.41]
	13-24	124 (95.4)	10.5 (7.10)	-6.2 (0.89)	-3.8	0.73	[-5.2;-2.4]	<.0001	-0.7	[-.91;-.41]
EPTI 300 mg	Basln	130 (100.0)	18.5 (3.94)							
	1-12	130 (100.0)	11.3 (7.59)	-5.3 (0.86)	-3.3	0.66	[-4.6;-2.0]	<.0001	-0.6	[-.87;-.38]
	13-24	125 (96.2)	9.85 (7.59)	-6.7 (0.91)	-4.3	0.73	[-5.7;-2.9]	<.0001	-0.7	[-.99;-.50]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. CM : Chronic Migraine.

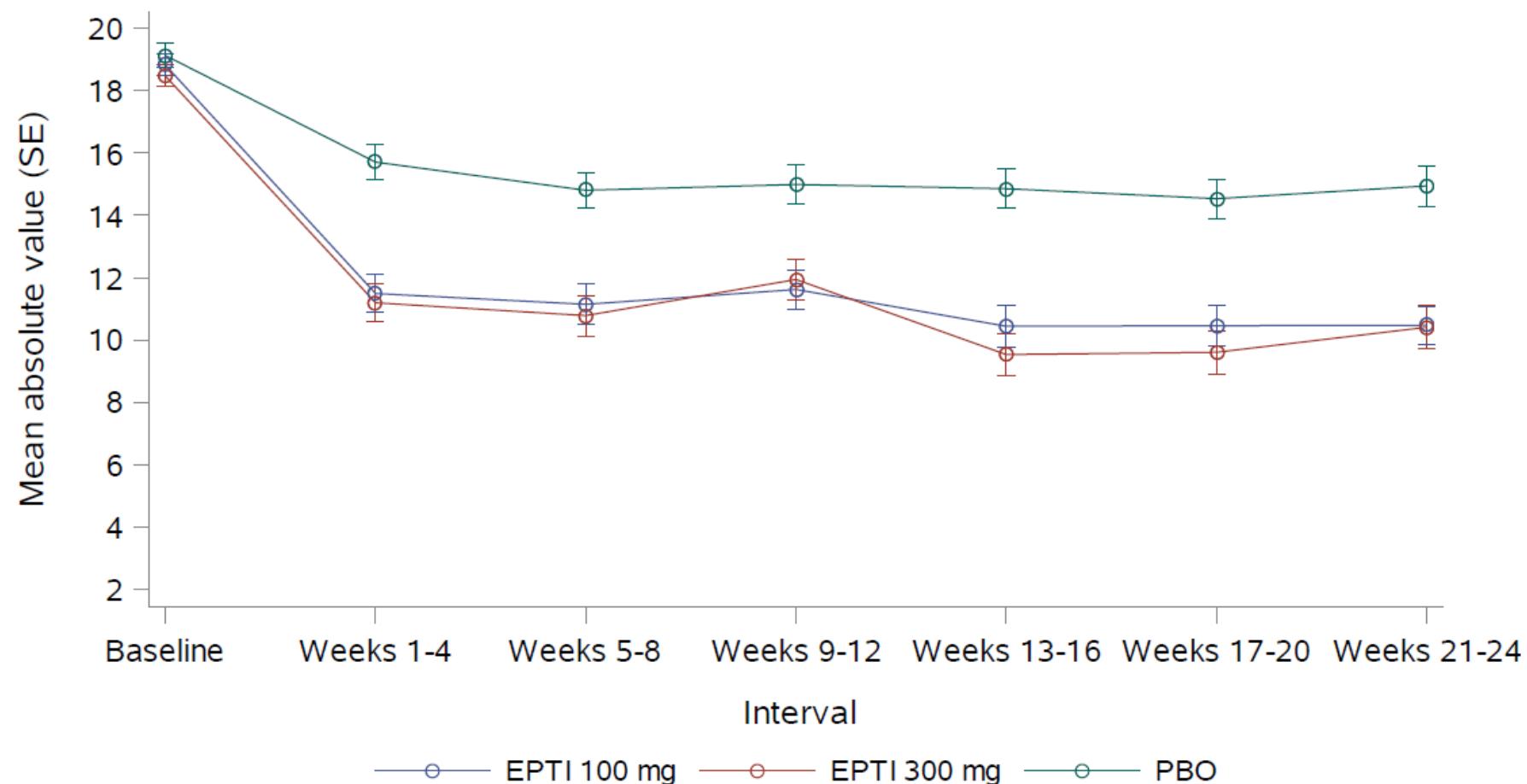
Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) : Chronic Migraine

Tabelle 4G-9: Migränetage/Monat, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		SMD 95% CI	
					Diff.	SE	CI	95% CI		Hedges' G	CI
								p-value			
PBO	Basln	35 (100.0)	19.2 (6.21)								
	1-12	35 (100.0)	16.1 (8.00)	-2.2 (1.24)							
	13-24	35 (100.0)	15.4 (8.00)	-2.5 (1.38)							
EPTI 100 mg	Basln	36 (100.0)	16.9 (5.76)								
	1-12	36 (100.0)	10.8 (7.46)	-5.5 (1.17)	-3.3	1.35	[-6.0;-.62]	0.0164	-0.6	[-1.1;-.11]	
	13-24	34 (94.4)	10.4 (7.46)	-5.6 (1.31)	-3.1	1.56	[-6.2;-.01]	0.0495	-0.5	[-.96;-.00]	
EPTI 300 mg	Basln	35 (100.0)	16.1 (5.59)								
	1-12	35 (100.0)	9.06 (7.29)	-7.2 (1.23)	-5.0	1.39	[-7.8;-.2.2]	0.0005	-0.9	[-1.3;-.39]	
	13-24	35 (100.0)	9.65 (7.29)	-6.5 (1.37)	-4.0	1.59	[-7.1;-.81]	0.0143	-0.6	[-1.1;-.12]	

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) : Medication overuse headache at baseline

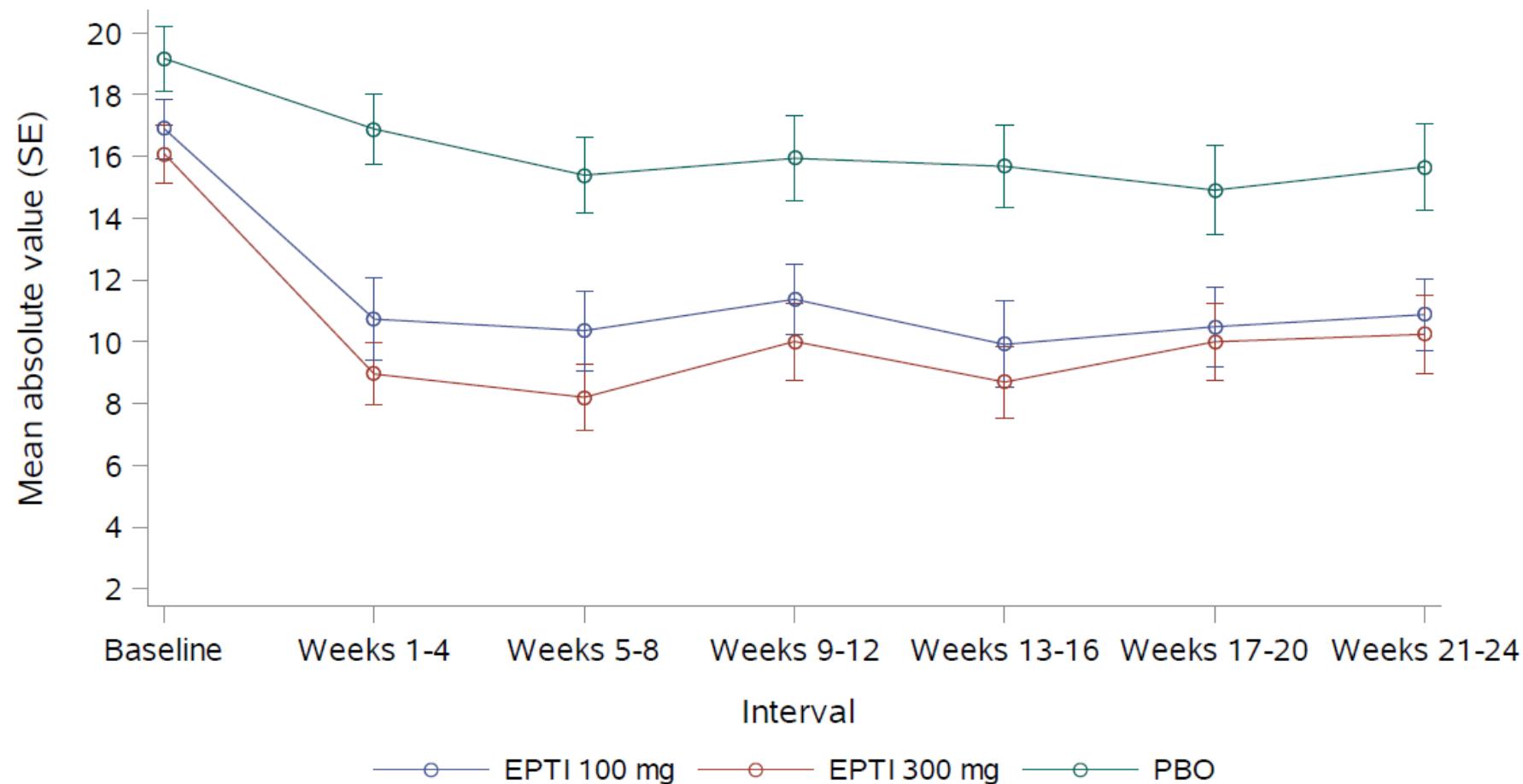


Tabelle 4G-10: Migränetage/Monat, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		SMD 95% CI	
					Diff.	SE	CI	95% CI		Hedges' G	CI
								p-value	G		
PBO	Basln	252 (100.0)	13.1 (5.35)								
	1-12	252 (100.0)	10.3 (6.45)	-1.9 (0.42)							
	13-24	250 (99.2)	9.98 (6.45)	-2.2 (0.43)							
EPTI 100 mg	Basln	248 (100.0)	13.3 (5.50)								
	1-12	248 (100.0)	7.88 (6.16)	-4.5 (0.42)	-2.6	0.38	[-3.3;-1.9]	<.0001	-0.6	[-.79;-.43]	
	13-24	239 (96.4)	6.92 (6.16)	-5.2 (0.44)	-3.0	0.41	[-3.8;-2.2]	<.0001	-0.7	[-.84;-.49]	
EPTI 300 mg	Basln	250 (100.0)	13.4 (5.38)								
	1-12	250 (100.0)	7.57 (6.30)	-4.8 (0.41)	-2.9	0.38	[-3.6;-2.1]	<.0001	-0.7	[-.85;-.50]	
	13-24	243 (97.2)	6.37 (6.30)	-5.8 (0.43)	-3.6	0.41	[-4.5;-2.8]	<.0001	-0.8	[-.98;-.62]	

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG)

No medication overuse headache at baseline

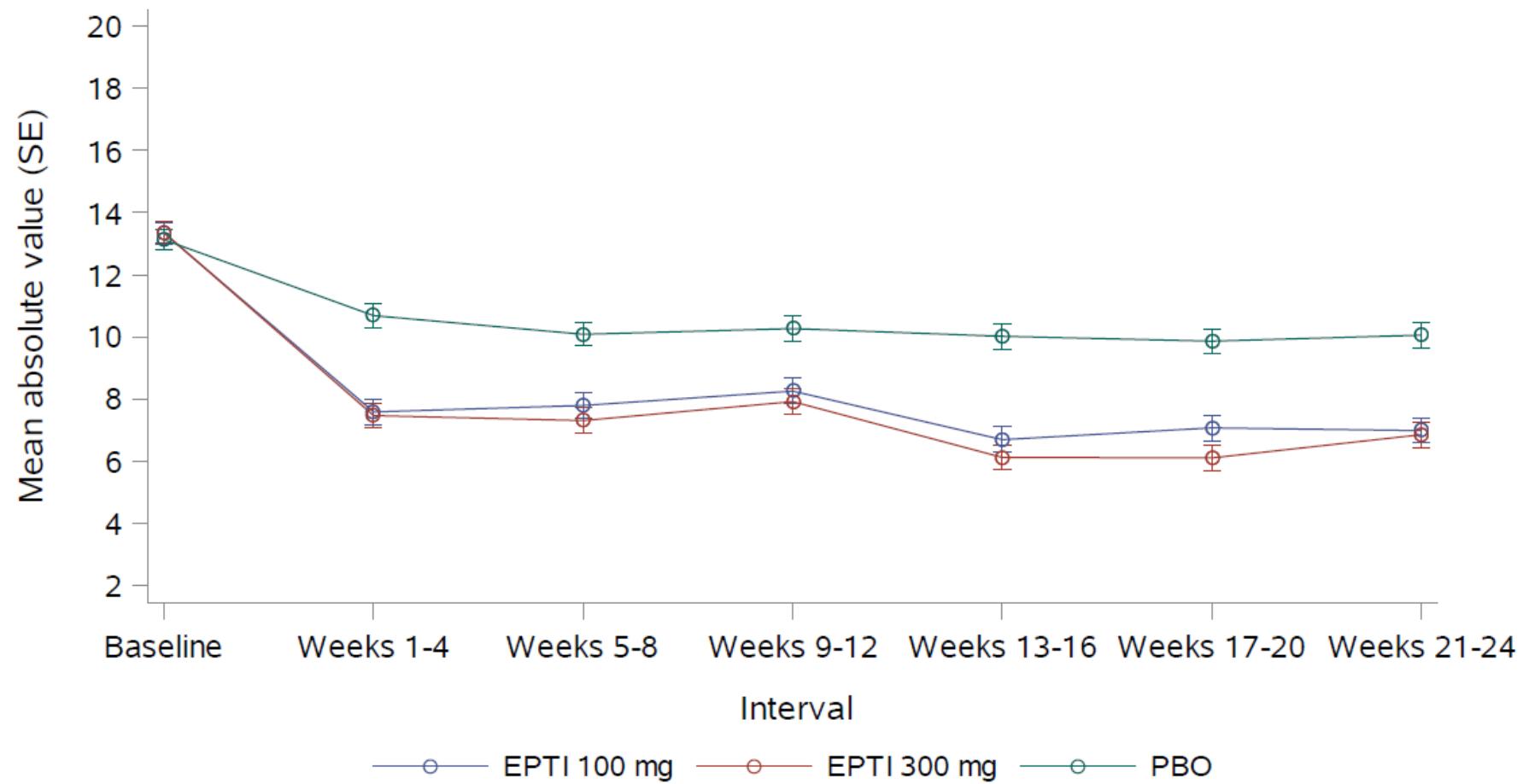


Tabelle 4G-11: Migränetage/Monat, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		SMD 95% CI	
					Diff.	SE	CI	95% CI		Hedges' G	CI
								p-value	G		
PBO	Basln	204 (100.0)	13.6 (5.73)		-2.2 (0.46)	0.44	[-3.5;-1.8]	<.0001	-0.6	[-.79;-.41]	
	1-12	204 (100.0)	10.7 (6.82)	-2.2 (0.46)							
	13-24	202 (99.0)	10.4 (6.82)	-2.3 (0.48)							
EPTI 100 mg	Basln	207 (100.0)	13.5 (5.60)		-4.9 (0.46)	0.44	[-3.5;-1.8]	<.0001	-0.6	[-.79;-.41]	
	1-12	207 (100.0)	7.85 (6.12)	-4.9 (0.46)							
	13-24	198 (95.7)	6.93 (6.12)	-5.5 (0.48)							
EPTI 300 mg	Basln	217 (100.0)	13.5 (5.49)		-5.1 (0.44)	0.43	[-3.7;-2.0]	<.0001	-0.6	[-.84;-.45]	
	1-12	217 (100.0)	7.69 (6.42)	-5.1 (0.44)							
	13-24	211 (97.2)	6.62 (6.42)	-6.0 (0.46)							

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) :
= 2 Previous Failed Treatments

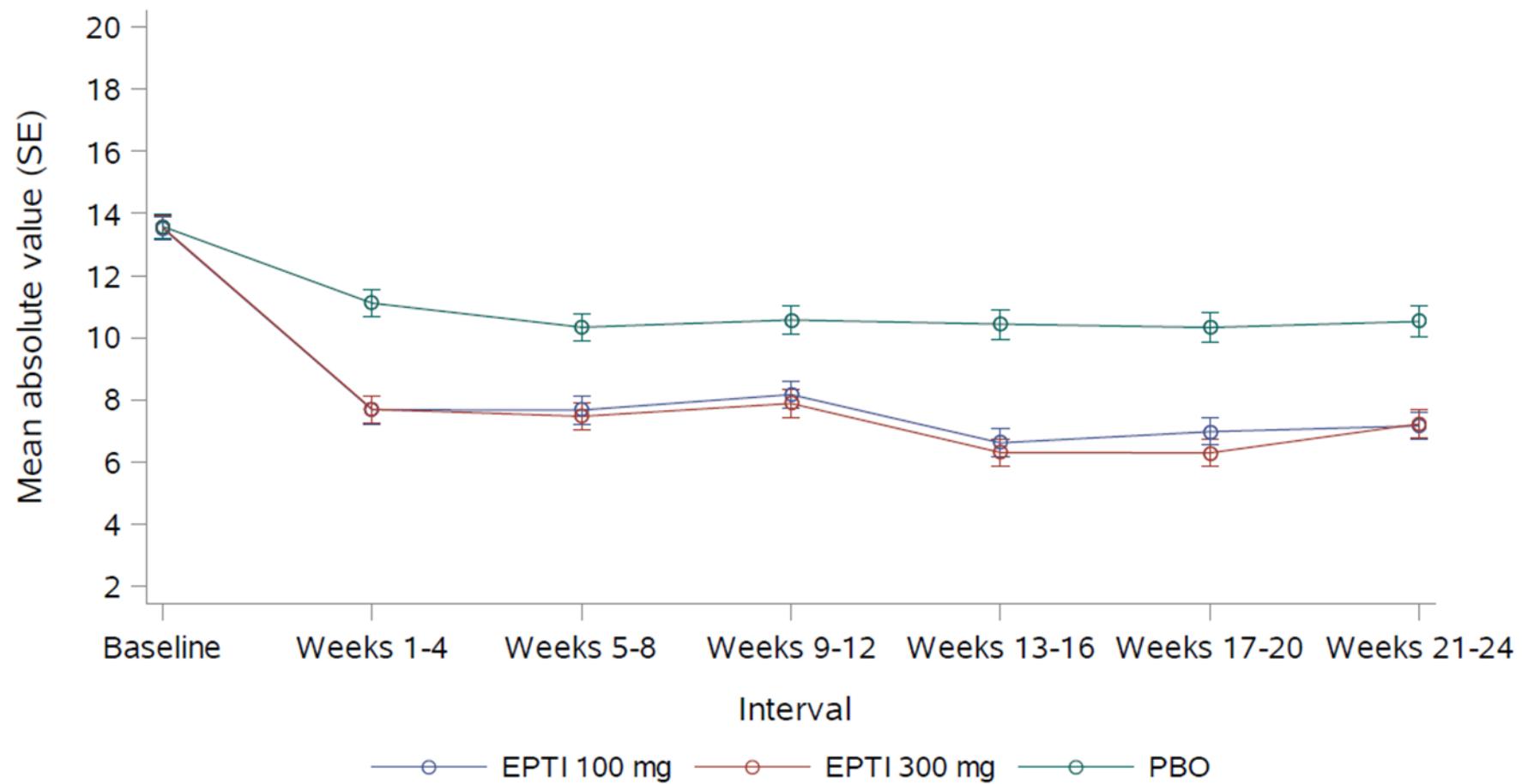


Tabelle 4G-12: Migränetage/Monat, CFB, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	83 (100.0)	14.6 (5.96)		-1.3 (0.79)	0.71	[-4.3;-1.5]	<.0001	-0.7	[-.96;-.34]	
	1-12	83 (100.0)	12.0 (6.98)	-1.6 (0.79)							
	13-24	83 (100.0)	11.1 (6.98)	-1.9 (0.83)							
EPTI 100 mg	Basln	77 (100.0)	14.5 (5.76)		-4.2 (0.77)	0.71	[-4.3;-1.5]	<.0001	-0.7	[-.96;-.34]	
	1-12	77 (100.0)	9.35 (7.07)	-5.15 (0.77)							
	13-24	75 (97.4)	8.50 (7.07)	-5.95 (0.81)							
EPTI 300 mg	Basln	68 (100.0)	14.1 (5.42)		-5.0 (0.79)	0.73	[-5.2;-2.3]	<.0001	-0.8	[-1.2;-.52]	
	1-12	68 (100.0)	7.94 (6.80)	-6.16 (0.79)							
	13-24	67 (98.5)	7.31 (6.80)	-6.79 (0.83)							

Missing eDiary data is handled using the rules provided in the SAP.

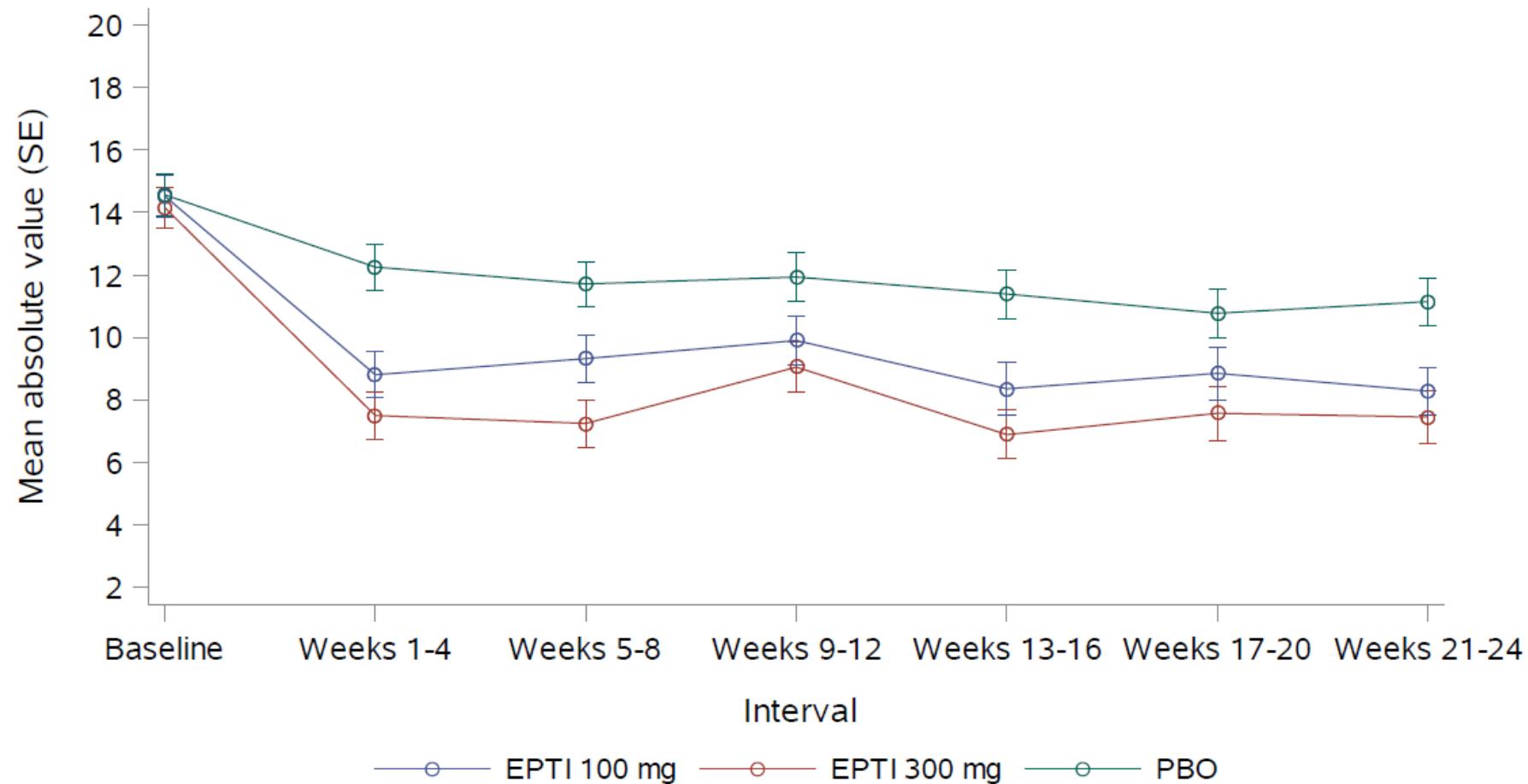
The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Monthly Migraine Days. Absolute Value: Mean (SE) by 4-Week Intervals (AMNOG) : > 2 Previous Failed Treatments



4.2.2.2 Reduktion um $\geq 50\%$

Tabelle 4G-13: Migränetage/Monat, Reduktion um $\geq 50\%$, Interaktions-p-Werte

Interval	Description	Treatment Group	
		EPTI 100 mg p-value	EPTI 300 mg p-value
Weeks 1-12	Interaction test: Age Group	0.9419	0.8786
	Interaction test: EM/CM	0.1434	0.0101
	Interaction test: MOH	0.6890	0.8020
	Interaction test: Number of FPT	0.5785	0.6176
	Interaction test: Sex	0.2446	0.8026
Weeks 13-24	Interaction test: Age Group	0.1280	0.2581
	Interaction test: EM/CM	0.1891	0.3668
	Interaction test: MOH	0.1356	0.1952
	Interaction test: Number of FPT	0.9725	0.4317
	Interaction test: Sex	0.9296	0.9282

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-14: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	67	6	(9.0)							
	13-24	66	17	(25.8)							
EPTI 100 mg	1-12	57	19	(33.3)	5.09	[1.94;15.1]	3.80	[1.59;9.07]	24.4	[10.4;38.4]	0.0007
	13-24	53	23	(43.4)	2.22	[1.02;4.96]	1.68	[1.00;2.80]	17.6	[0.63;34.6]	0.0456

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 300 mg	1-12	62	23	(37.1)	6.19	[2.42;18.1]	4.14	[1.79;9.61]	28.1	[14.3;42.0]	<.0001	
	13-24	61	32	(52.5)	3.30	[1.56;7.21]	2.03	[1.26;3.26]	26.7	[10.3;43.1]	0.0017	

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-15: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe > 35 Jahre

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	220	32	(14.5)								
	13-24	219	50	(22.8)								
EPTI 100 mg	1-12	227	104	(45.8)	5.02	[3.21;8.05]	3.15	[2.22;4.46]	31.3	[23.3;39.3]	<.0001	
	13-24	220	124	(56.4)	4.38	[2.91;6.68]	2.47	[1.89;3.24]	33.5	[24.9;42.1]	<.0001	
EPTI 300 mg	1-12	223	118	(52.9)	6.62	[4.23;10.6]	3.64	[2.58;5.13]	38.4	[30.3;46.4]	<.0001	
	13-24	217	132	(60.8)	5.26	[3.48;8.04]	2.66	[2.04;3.48]	38.0	[29.4;46.5]	<.0001	

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-16: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe männlich

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	33	3	(9.1)							
	13-24	33	6	(18.2)							
EPTI 100 mg	1-12	21	11	(52.4)	11.5	[2.80;61.8]	5.59	[1.76;17.7]	43.3	[19.8;66.8]	0.0005
	13-24	20	9	(45.0)	3.46	[0.96;13.4]	2.44	[0.95;6.25]	26.8	[1.35;52.3]	0.0575
EPTI 300 mg	1-12	32	14	(43.8)	10.5	[2.71;55.1]	5.32	[1.74;16.2]	34.7	[14.9;54.4]	0.0004
	13-24	32	17	(53.1)	7.73	[2.31;30.6]	3.07	[1.43;6.59]	34.9	[13.2;56.7]	0.0006

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-17: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe weiblich

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	254	35	(13.8)							
	13-24	252	61	(24.2)							
EPTI 100 mg	1-12	263	112	(42.6)	4.70	[3.07;7.34]	3.09	[2.20;4.33]	28.8	[21.5;36.1]	<.0001
	13-24	253	138	(54.5)	3.79	[2.60;5.58]	2.25	[1.76;2.88]	30.3	[22.2;38.4]	<.0001
EPTI 300 mg	1-12	253	127	(50.2)	6.38	[4.17;9.97]	3.65	[2.61;5.09]	36.4	[28.9;43.9]	<.0001
	13-24	246	147	(59.8)	4.69	[3.20;6.95]	2.47	[1.94;3.14]	35.5	[27.5;43.6]	<.0001

		Responders			Odds Ratio		Relative Risk		Risk Difference		
Treatment Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-18: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe EM

		Responders			Odds Ratio		Relative Risk		Risk Difference		
Treatment Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
	1-12	159	18	(11.3)							
	13-24	159	38	(23.9)							
EPTI 100 mg	1-12	154	71	(46.1)	6.72	[3.82;12.3]	4.07	[2.55;6.50]	34.8	[25.5;44.1]	<.0001
	13-24	149	89	(59.7)	4.73	[2.92;7.79]	2.50	[1.84;3.40]	35.8	[25.5;46.1]	<.0001
EPTI 300 mg	1-12	154	88	(57.1)	10.4	[5.93;19.2]	5.05	[3.20;7.96]	45.8	[36.6;55.1]	<.0001
	13-24	152	96	(63.2)	5.45	[3.36;8.99]	2.64	[1.95;3.58]	39.3	[29.1;49.4]	<.0001

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-19: Migränetage/Monat, Reduktion um $\geq 50\%$, Reduktion um $\geq 50\%$, Subgruppe CM

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	128	20	(15.6)							
	13-24	126	29	(23.0)							
EPTI 100 mg	1-12	130	52	(40.0)	3.65	[2.03;6.76]	2.55	[1.62;4.03]	24.4	[13.9;34.9]	<.0001
	13-24	124	58	(46.8)	2.93	[1.70;5.13]	2.04	[1.41;2.97]	23.8	[12.3;35.2]	<.0001
EPTI 300 mg	1-12	130	52	(40.0)	3.52	[1.96;6.51]	2.56	[1.63;4.04]	24.4	[13.9;34.9]	<.0001
	13-24	125	68	(54.4)	3.92	[2.28;6.87]	2.37	[1.66;3.39]	31.4	[20.0;42.8]	<.0001

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-20: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe MOH: ja

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	35	5	(14.3)							
	13-24	35	9	(25.7)							
EPTI 100 mg	1-12	36	15	(41.7)	4.12	[1.35;14.4]	3.13	[1.21;8.11]	27.4	[7.54;47.2]	0.0121
	13-24	34	14	(41.2)	1.85	[0.66;5.37]	1.66	[0.80;3.41]	15.5	[-6.5;37.4]	0.2403
EPTI 300 mg	1-12	35	18	(51.4)	5.89	[1.93;20.8]	3.75	[1.46;9.58]	37.1	[16.9;57.4]	0.0015
	13-24	35	17	(48.6)	2.43	[0.88;7.02]	1.88	[0.94;3.79]	22.9	[0.86;44.9]	0.0865

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-21: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe MOH: nein

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	252	33	(13.1)							
	13-24	250	58	(23.2)							
EPTI 100 mg	1-12	248	108	(43.5)	5.26	[3.40;8.32]	3.32	[2.35;4.71]	30.5	[23.0;37.9]	<.0001
	13-24	239	133	(55.6)	4.23	[2.88;6.30]	2.40	[1.87;3.09]	32.4	[24.3;40.6]	<.0001
EPTI 300 mg	1-12	250	123	(49.2)	6.63	[4.29;10.5]	3.76	[2.67;5.29]	36.1	[28.6;43.6]	<.0001
	13-24	243	147	(60.5)	5.18	[3.52;7.72]	2.61	[2.04;3.34]	37.3	[29.2;45.4]	<.0001

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-22: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe 2 Vortherapien

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	204	29	(14.2)							
	13-24	202	48	(23.8)							
EPTI 100 mg	1-12	207	97	(46.9)	5.41	[3.38;8.89]	3.30	[2.28;4.78]	32.6	[24.3;41.0]	<.0001
	13-24	198	107	(54.0)	3.80	[2.49;5.88]	2.27	[1.72;3.00]	30.3	[21.2;39.4]	<.0001
EPTI 300 mg	1-12	217	108	(49.8)	6.10	[3.83;9.98]	3.50	[2.43;5.04]	35.6	[27.4;43.8]	<.0001
	13-24	211	129	(61.1)	5.12	[3.35;7.91]	2.57	[1.97;3.37]	37.4	[28.6;46.2]	<.0001

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-23: Migränetage/Monat, Reduktion um $\geq 50\%$, Subgruppe > 2 Vortherapien

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	83	9	(10.8)							
	13-24	83	19	(22.9)							
EPTI 100 mg	1-12	77	26	(33.8)	4.14	[1.84;10.1]	3.12	[1.56;6.24]	22.9	[10.4;35.4]	0.0004
	13-24	75	40	(53.3)	3.91	[1.98;7.92]	2.35	[1.51;3.67]	30.4	[16.0;44.9]	<.0001
EPTI 300 mg	1-12	68	33	(48.5)	7.68	[3.43;18.7]	4.48	[2.30;8.69]	37.7	[24.1;51.3]	<.0001
	13-24	67	35	(52.2)	3.68	[1.84;7.58]	2.28	[1.45;3.60]	29.3	[14.4;44.3]	0.0002

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
<p>The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.</p> <p>AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.</p>											

4.2.2.3 Reduktion um $\geq 75\%$

Tabelle 4G-24: Migränetage/Monat, Reduktion um $\geq 75\%$, Interaktions-p-Werte

Interval	Description	Treatment Group	
		EPTI 100 mg	EPTI 300 mg
Weeks 1-12	Interaction test: Age Group	0.4231	0.4466
	Interaction test: EM/CM	0.9110	0.7106
	Interaction test: MOH	0.3020	0.3545
	Interaction test: Number of FPT	0.8520	0.5090
	Interaction test: Sex	0.2216	0.1886
Weeks 13-24	Interaction test: Age Group	0.3598	0.4393
	Interaction test: EM/CM	0.9200	0.9251
	Interaction test: MOH	0.4053	0.4678
	Interaction test: Number of FPT	0.4845	0.9713
	Interaction test: Sex	0.3779	0.4369

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-25: Migränetage/Monat, Reduktion um $\geq 75\%$, Subgruppe ≤ 35 Jahre

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	67	2	(3.0)							
	13-24	66	6	(9.1)							
EPTI 100 mg	1-12	57	8	(14.0)	5.19	[1.23;35.5]	4.34	[1.01;18.7]	11.1	[1.15;20.9]	0.0238
	13-24	53	11	(20.8)	2.60	[0.91;8.11]	2.25	[0.90;5.64]	11.7	[-1.3;24.6]	0.0758
EPTI 300 mg	1-12	62	10	(16.1)	6.31	[1.57;42.3]	5.35	[1.23;23.2]	13.1	[3.12;23.2]	0.0077
	13-24	61	17	(27.9)	3.92	[1.48;11.7]	3.05	[1.29;7.17]	18.8	[5.56;32.0]	0.0052

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-26: Migränetage/Monat, Reduktion um $\geq 75\%$, Subgruppe > 35 Jahre

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	220	4	(1.8)							
	13-24	219	13	(5.9)							
EPTI 100 mg	1-12	227	39	(17.2)	11.5	[4.52;39.1]	9.55	[3.47;26.3]	15.4	[10.1;20.6]	<.0001
	13-24	220	50	(22.7)	4.72	[2.55;9.36]	3.85	[2.15;6.87]	16.8	[10.4;23.2]	<.0001
EPTI 300 mg	1-12	223	44	(19.7)	13.6	[5.36;45.8]	10.9	[3.99;29.8]	17.9	[12.4;23.4]	<.0001
	13-24	217	61	(28.1)	6.28	[3.42;12.3]	4.75	[2.69;8.38]	22.2	[15.4;28.9]	<.0001

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
<p>The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.</p> <p>AMNOG: AMNOG population B.</p>												

Tabelle 4G-27: Migränetage/Monat, Reduktion um ≥ 75 %, Subgruppe männlich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	33	0	(0)								
	13-24	33	2	(6.1)								
EPTI 100 mg	1-12	21	4	(19.0)	23E4	[2.73;]		[;]		19.0	[2.25;35.8]	0.0059
	13-24	20	2	(10.0)	1.51	[0.15;14.8]	1.36	[0.22;8.50]	3.94	[-12;19.4]	0.7101	
EPTI 300 mg	1-12	32	7	(21.9)	47E4	[6.06;]		[;]		21.9	[7.55;36.2]	0.0003
	13-24	32	12	(37.5)	17.5	[3.26; 156]	7.49	[1.76;31.9]	31.4	[12.8;50.1]	0.0004	

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-28: Migränetage/Monat, Reduktion um $\geq 75\%$, Subgruppe weiblich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		1-12	254	6	(2.4)							
		13-24	252	17	(6.7)							
EPTI 100 mg		1-12	263	43	(16.3)	8.18	[3.67;21.8]	6.94	[3.01;16.0]	14.0	[9.14;18.8]	<.0001
		13-24	253	59	(23.3)	4.25	[2.44;7.74]	3.46	[2.08;5.77]	16.6	[10.5;22.6]	<.0001
EPTI 300 mg		1-12	253	47	(18.6)	9.48	[4.28;25.2]	7.79	[3.40;17.8]	16.2	[11.1;21.4]	<.0001
		13-24	246	66	(26.8)	5.09	[2.95;9.25]	3.96	[2.40;6.55]	20.1	[13.7;26.4]	<.0001

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-29: Migränetage/Monat, Reduktion um $\geq 75\%$, Subgruppe EM

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		1-12	159	4	(2.5)							
		13-24	159	13	(8.2)							
EPTI 100 mg		1-12	154	31	(20.1)	9.76	[3.74;33.5]	8.00	[2.89;22.1]	17.6	[10.8;24.4]	<.0001
		13-24	149	39	(26.2)	3.98	[2.07;8.08]	3.20	[1.78;5.76]	18.0	[9.75;26.2]	<.0001
EPTI 300 mg		1-12	154	37	(24.0)	12.3	[4.76;41.8]	9.55	[3.49;26.2]	21.5	[14.3;28.7]	<.0001
		13-24	152	51	(33.6)	5.72	[3.04;11.5]	4.10	[2.33;7.23]	25.4	[16.7;34.0]	<.0001

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. EM : Episodic Migraine

Tabelle 4G-30: Migränetage/Monat, Reduktion um $\geq 75\%$, Reduktion um $\geq 75\%$, Subgruppe CM

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	128	2	(1.6)							
	13-24	126	6	(4.8)							
EPTI 100 mg	1-12	130	16	(12.3)	8.79	[2.43;56.4]	7.17	[1.79;28.7]	10.7	[4.70;16.8]	0.0003
	13-24	124	22	(17.7)	4.28	[1.77;12.0]	3.79	[1.58;9.09]	13.0	[5.30;20.7]	0.0009
EPTI 300 mg	1-12	130	16	(12.3)	8.67	[2.40;55.7]	7.58	[1.83;31.3]	10.7	[4.70;16.8]	0.0004
	13-24	125	27	(21.6)	5.39	[2.27;14.9]	4.55	[1.94;10.7]	16.8	[8.72;25.0]	<.0001

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. CM : Chronic Migraine

Tabelle 4G-31: Migränetage/Monat, Reduktion um $\geq 75\%$, Subgruppe MOH: ja

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	35	0	(0)							
	13-24	35	2	(5.7)							
EPTI 100 mg	1-12	36	5	(13.9)	2E5	[1.85;]		[;]	13.9	[2.59;25.2]	0.0137
	13-24	34	4	(11.8)	1.64	[0.28;13.0]	1.55	[0.30;7.99]	6.05	[-7.2;19.3]	0.5878
EPTI 300 mg	1-12	35	5	(14.3)	19E4	[1.81;]		[;]	14.3	[2.69;25.9]	0.0145
	13-24	35	6	(17.1)	2.60	[0.51;19.4]	2.59	[0.59;11.5]	11.4	[-3.2;26.1]	0.2592

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-32: Migränetage/Monat, Reduktion um $\geq 75\%$, Subgruppe MOH: nein

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	252	6	(2.4)							
	13-24	250	17	(6.8)							
EPTI 100 mg	1-12	248	42	(16.9)	8.52	[3.82;22.7]	7.18	[3.11;16.6]	14.6	[9.52;19.6]	<.0001
	13-24	239	57	(23.8)	4.36	[2.50;7.97]	3.52	[2.11;5.87]	17.0	[10.8;23.3]	<.0001
EPTI 300 mg	1-12	250	49	(19.6)	10.2	[4.63;27.2]	8.33	[3.63;19.1]	17.2	[12.0;22.5]	<.0001
	13-24	243	72	(29.6)	5.88	[3.42;10.7]	4.38	[2.66;7.21]	22.8	[16.3;29.4]	<.0001

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-33: Migränetage/Monat, Reduktion um $\geq 75\%$, Subgruppe 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	204	5	(2.5)							
	13-24	202	13	(6.4)							
EPTI 100 mg	1-12	207	38	(18.4)	9.01	[3.78;26.7]	7.42	[2.99;18.4]	15.9	[10.2;21.6]	<.0001
	13-24	198	47	(23.7)	4.54	[2.43;9.04]	3.66	[2.05;6.52]	17.3	[10.5;24.1]	<.0001
EPTI 300 mg	1-12	217	41	(18.9)	9.46	[3.99;27.9]	7.75	[3.13;19.2]	16.4	[10.8;22.1]	<.0001
	13-24	211	58	(27.5)	5.60	[3.04;11.0]	4.29	[2.43;7.57]	21.1	[14.1;28.0]	<.0001

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-34: Migränetage/Monat, Reduktion um $\geq 75\%$, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	83	1	(1.2)							
	13-24	83	6	(7.2)							
EPTI 100 mg	1-12	77	9	(11.7)	11.0	[1.98; 206]	10.2	[1.29; 79.7]	10.5	[2.93; 18.0]	0.0037
	13-24	75	14	(18.7)	2.97	[1.11; 8.89]	2.59	[1.05; 6.37]	11.4	[1.01; 21.9]	0.0304
EPTI 300 mg	1-12	68	13	(19.1)	19.6	[3.70; 362]	15.8	[2.14; 117]	17.9	[8.28; 27.5]	<.0001
	13-24	67	20	(29.9)	5.49	[2.14; 16.1]	4.13	[1.76; 9.71]	22.6	[10.3; 34.9]	0.0003

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MMDs (based on the available monthly values of MMDs). The OR and p-values are based on logistic regression model including baseline MMDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MMDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.2.4 Reduktion um 100 %

Es wurden keine Interaktions-p-Werte berechnet.

Tabelle 4G-35: Reduktion der monatlichen Migränetage um 100 %, Subgruppenanalysen

	PBO		EPTI 100 mg			EPTI 300 mg		
	n	%	n	%	p-value	n	%	p-value
Week 1-12	287	1.2	284	6.3	0.0013	285	7.0	<0.0001
Week 13-24	285	3.3	273	10.5	0.0007	278	13.6	<0.0001
Sub-group analyses								
<= 35 years, week 1-12	67	1.5	57	7.0	0.14	62	7.0	0.12
<= 35 years, week 13-24	66	4.5	53	11.3	0.002	62	13.6	0.07
> 35 years, week 1-12	220	1.1	227	6.0	0.004	223	8.2	0.00033
> 35 years, week 13-24	219	2.9	220	10.3	0.2	217	14.4	<0.0001
2 failures, week 1-12	204	1.3	207	7.6	0.002	217	8.1	0.001
2 failures, week 13-24	202	3.0	198	11.6	0.0009	211	13.9	<0.0001
3+ failures, week 1-12	83	0.8	77	2.6	0.36	68	7.3	0.035
3+ failures, week 13-24	83	4.4	75	7.6	0.3	67	15.4	0.01
CM, week 1-12	128	0.5	130	4.4	0.025	130	3.1	0.2
CM, week 13-24	126	2.6	124	5.6		125	8.8	0.0005
EM, week 1-12	159	1.7	154	7.8	0.0005	154	11.4	0.0005
EM, week 13-24	159	5.0	149	14.5		152	18.6	0.0005
Female, week 1-12	254	1.2	263	6.2	0.0025	253	7.8	0.00036
Female, week 13-24	252	3.0	253	11.2	0.0003	246	13.5	<0.0001
Male, week 1-12	33	1.0	21	6.3	0.32	32	9.3	0.068
Male, week 13-24	33	5.1	20	1.7	0.5	32	19.8	0.029
MOH, week 1-12	35	0.0	36	5.6	0.24	35	4.7	0.29
MOH, week 13-24	35	1.9	34	7.9	0.4	35	9.5	0.29
No MOH, week 1-12	252	1.3	248	6.3	0.003	250	8.4	0.0002
No MOH, week 13-24	350	3.5	239	10.9	0.001	243	14.9	<0.0001

N refers to the number of subjects in the analysis at the relevant interval.

The p-values are computed separately for each active treatment group using extended CMH test, adjusting for the stratification factor (MHDs at baseline <=14/>14).

The 100% responder rate for the 12-week interval is derived from the average 100% responder rates in each of the three 4-week intervals included in the 12-week interval.

If any of the months included in the 12-week interval has a missing value of MMDs, the response status is imputed with a non-response.

4.2.3 Migräneattacken/Monat

4.2.3.1 Veränderung gegenüber dem Baselinewert

Tabelle 4G-36: Migräneattacken/Monat, CFB, Interaktions p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg p-value	EPTI 300 mg p-value
Interaction test: Age Group	0.8260	0.5088
Interaction test: EM/CM	0.5139	0.6722
Interaction test: MOH	0.1249	0.0663
Interaction test: Number of FPT	0.6076	0.0945
Interaction test: Sex	0.7578	0.2252

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-37: Migräneattacken/Monat, CFB, Interaktions p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg p-value	EPTI 300 mg p-value
Interaction test: Age Group	0.5825	0.2959
Interaction test: EM/CM	0.9840	0.6944
Interaction test: MOH	0.8057	0.7137
Interaction test: Number of FPT	0.4456	0.3378
Interaction test: Sex	0.9139	0.8172

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-38: Migräneattacken/Monat, CFB, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				Hedges' G		
					CFB LSmeans			95% CI		SMD 95% CI	
					Diff.	SE	CI	p-value	G	CI	
PBO	Basln	67 (100.0)	10.5 (5.13)								
	1-12	67 (100.0)	7.74 (5.17)	-2.1 (0.55)							
	13-24	66 (98.5)	6.99 (5.17)	-2.7 (0.59)							
EPTI 100 mg	Basln	57 (100.0)	11.0 (5.66)								
	1-12	57 (100.0)	6.15 (4.82)	-3.9 (0.58)	-1.8	0.62	[-3.1;-.61]	0.0035	-0.5	[-.89;-.18]	
	13-24	53 (93.0)	5.22 (4.82)	-4.8 (0.62)	-2.1	0.68	[-3.4;-.74]	0.0026	-0.6	[-.93;-.20]	
EPTI 300 mg	Basln	62 (100.0)	11.6 (5.96)								
	1-12	62 (100.0)	7.21 (6.42)	-3.0 (0.59)	-0.9	0.62	[-2.1;0.28]	0.1325	-0.3	[-.61;0.08]	
	13-24	61 (98.4)	5.87 (6.42)	-4.1 (0.62)	-1.4	0.67	[-2.7;-.07]	0.0397	-0.4	[-.72;-.02]	

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

Tabelle 4G-39: Migräneattacken/Monat, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				Hedges' G		
					CFB LSmeans			95% CI		SMD 95% CI	
					Diff.	SE	CI	p-value	G	CI	
PBO	Basln	220 (100.0)	11.6 (5.98)								
	1-12	220 (100.0)	8.46 (5.24)	-2.6 (0.36)							

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO					
					CFB			95% CI		
			LSmeans					SMD 95% CI		
					Diff.	SE	CI	p-value	Hedges' G	CI
EPTI 100 mg	13-24	219 (99.5)	7.75 (5.24)	-3.2 (0.38)						
	Basln	227 (100.0)	11.0 (5.44)							
	1-12	227 (100.0)	6.11 (5.27)	-4.6 (0.35)	-2.0	0.33	[-2.6;-1.3]	<.0001	-0.6	[-.75;-.38]
EPTI 300 mg	13-24	220 (96.9)	5.56 (5.27)	-5.1 (0.37)	-1.9	0.37	[-2.7;-1.2]	<.0001	-0.5	[-.69;-.32]
	Basln	223 (100.0)	10.8 (5.86)							
	1-12	223 (100.0)	5.57 (5.10)	-5.1 (0.35)	-2.4	0.33	[-3.1;-1.8]	<.0001	-0.7	[-.88;-.51]
	13-24	217 (97.3)	4.85 (5.10)	-5.8 (0.37)	-2.6	0.37	[-3.4;-1.9]	<.0001	-0.7	[-.87;-.49]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval

N: the number of patients with observations in the interval. Basln: Baseline.

Tabelle 4G-40: Migräneattacken/Monat, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO					
					CFB			95% CI		
			LSmeans					SMD 95% CI		
					Diff.	SE	CI	p-value	Hedges' G	CI
PBO	Basln	33 (100.0)	13.1 (7.49)							
	1-12	33 (100.0)	9.65 (6.32)	-2.8 (0.92)						
	13-24	33 (100.0)	9.49 (6.32)	-3.0 (1.03)						
EPTI 100 mg	Basln	21 (100.0)	12.9 (6.00)							
	1-12	21 (100.0)	7.56 (7.43)	-4.7 (1.04)	-1.8	1.24	[-4.3;0.65]	0.1456	-0.4	[-.97;0.15]
	13-24	20 (95.2)	7.87 (7.43)	-4.3 (1.21)	-1.3	1.46	[-4.2;1.60]	0.3753	-0.3	[-.82;0.31]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					CFB		95% CI		
					LSmeans	Diff.	SE	CI	p-value
EPTI 300 mg	Basln	32 (100.0)	11.5 (4.84)						
	1-12	32 (100.0)	6.73 (6.13)	-5.4 (0.89)	-2.5	1.07	[-.47;-.37]	0.0220	-0.6 [-1.1;-.09]
	13-24	32 (100.0)	5.96 (6.13)	-6.2 (1.01)	-3.2	1.28	[-5.7;-.63]	0.0151	-0.6 [-1.1;-.12]

Missing eDiary data is handled using the rules provided in the SAP.
The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.
From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval
N: the number of patients with observations in the interval. Basln: Baseline.

Tabelle 4G-41: Migräneattacken/Monat, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					CFB		95% CI		
					LSmeans	Diff.	SE	CI	p-value
PBO	Basln	254 (100.0)	11.2 (5.52)						
	1-12	254 (100.0)	8.11 (5.03)	-2.3 (0.34)					
	13-24	252 (99.2)	7.32 (5.03)	-2.9 (0.35)					
EPTI 100 mg	Basln	263 (100.0)	10.8 (5.42)						
	1-12	263 (100.0)	6.00 (4.93)	-4.2 (0.34)	-1.9	0.30	[-2.5;-.1.3]	<.0001	-0.5 [-.72;-.37]
	13-24	253 (96.2)	5.31 (4.93)	-4.9 (0.35)	-1.9	0.33	[-2.6;-.1.3]	<.0001	-0.5 [-.69;-.34]
EPTI 300 mg	Basln	253 (100.0)	10.9 (6.01)						
	1-12	253 (100.0)	5.83 (5.33)	-4.4 (0.33)	-2.1	0.31	[-2.7;-.1.5]	<.0001	-0.6 [-.79;-.44]
	13-24	246 (97.2)	4.95 (5.33)	-5.3 (0.34)	-2.3	0.33	[-3.0;-.1.7]	<.0001	-0.6 [-.80;-.44]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO								
					CFB			95% CI					
					LSmeans	Diff.	SE	CI	p-value				
Missing eDiary data is handled using the rules provided in the SAP.													
The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.													
From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval													
N: the number of patients with observations in the interval. Basln: Baseline.													

Tabelle 4G-42: Migräneattacken/Monat, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				
					CFB			95% CI	
					LSmeans	Diff.	SE	CI	p-value
PBO	Basln	159 (100.0)	8.30 (2.87)						
	1-12	159 (100.0)	6.16 (3.83)	-1.3 (0.30)					
	13-24	159 (100.0)	5.81 (3.83)	-1.6 (0.32)					
EPTI 100 mg	Basln	154 (100.0)	8.34 (2.91)						
	1-12	154 (100.0)	4.47 (3.33)	-3.0 (0.31)	-1.7	0.28	[-2.3;-1.2]	<.0001	-0.7 [-.92;-.47]
	13-24	149 (96.8)	3.89 (3.33)	-3.6 (0.32)	-1.9	0.31	[-2.5;-1.3]	<.0001	-0.7 [-.94;-.49]
EPTI 300 mg	Basln	154 (100.0)	7.82 (2.81)						
	1-12	154 (100.0)	3.75 (2.85)	-3.6 (0.30)	-2.2	0.28	[-2.8;-1.7]	<.0001	-0.9 [-1.1;-.68]
	13-24	152 (98.7)	3.20 (2.85)	-4.1 (0.31)	-2.5	0.31	[-3.1;-1.9]	<.0001	-0.9 [-1.1;-.69]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-43: Migräneattacken/Monat, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	128 (100.0)	15.2 (6.23)						
	1-12	128 (100.0)	10.9 (5.90)	-4.2 (0.72)					
	13-24	126 (98.4)	9.83 (5.90)	-5.1 (0.77)					
EPTI 100 mg	Basln	130 (100.0)	14.1 (6.12)						
	1-12	130 (100.0)	8.08 (6.25)	-6.3 (0.69)		-2.1	0.56	[-3.2;-1.0]	0.0002
	13-24	124 (95.4)	7.42 (6.25)	-7.0 (0.74)		-1.8	0.62	[-3.1;-.63]	0.0031
EPTI 300 mg	Basln	130 (100.0)	14.8 (6.33)						
	1-12	130 (100.0)	8.61 (6.79)	-6.4 (0.71)		-2.1	0.55	[-3.2;-1.0]	0.0002
	13-24	125 (96.2)	7.39 (6.79)	-7.5 (0.76)		-2.3	0.61	[-3.6;-.11]	0.0002

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				
					95% CI		SMD 95% CI	Hedges' G	CI
					CFB	LSmeans			
Missing eDiary data is handled using the rules provided in the SAP.									
The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.									
From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.									
N: the number of patients with observations in the interval. Basln: Baseline.									
AMNOG: AMNOG population B. CM : Chronic Migraine.									

Tabelle 4G-44: Migräneattacken/Monat, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				
					95% CI		SMD 95% CI	Hedges' G	CI
					CFB	LSmeans			
PBO	Basln	35 (100.0)	16.7 (7.21)						
	1-12	35 (100.0)	12.2 (6.54)	-3.3 (1.06)					
	13-24	35 (100.0)	10.8 (6.54)	-4.6 (1.16)					
EPTI 100 mg	Basln	36 (100.0)	15.6 (6.74)						
	1-12	36 (100.0)	9.31 (7.37)	-5.4 (0.99)	-2.2	1.16	[-4.5;0.13]	0.0644	-0.4
	13-24	34 (94.4)	8.97 (7.37)	-5.9 (1.09)	-1.2	1.31	[-3.9;1.35]	0.3429	-0.2
EPTI 300 mg	Basln	35 (100.0)	13.4 (5.60)						
	1-12	35 (100.0)	7.07 (5.64)	-7.4 (1.03)	-4.1	1.19	[-6.5;-1.7]	0.0009	-0.8
	13-24	35 (100.0)	6.94 (5.64)	-7.4 (1.13)	-2.8	1.34	[-5.4;-.13]	0.0402	-0.5

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-45: Migräneattacken/Monat, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	252 (100.0)	10.6 (5.18)						
	1-12	252 (100.0)	7.74 (4.90)	-2.2 (0.32)					
	13-24	250 (99.2)	7.15 (4.90)	-2.8 (0.34)					
EPTI 100 mg	Basln	248 (100.0)	10.3 (4.94)						
	1-12	248 (100.0)	5.66 (4.60)	-4.1 (0.32)		-1.9	0.29	[-2.5;-1.3]	<.0001
	13-24	239 (96.4)	5.01 (4.60)	-4.8 (0.34)		-2.0	0.33	[-2.6;-1.4]	<.0001
EPTI 300 mg	Basln	250 (100.0)	10.6 (5.85)						
	1-12	250 (100.0)	5.77 (5.35)	-4.2 (0.32)		-1.9	0.30	[-2.5;-1.3]	<.0001
	13-24	243 (97.2)	4.80 (5.35)	-5.1 (0.33)		-2.3	0.33	[-3.0;-1.7]	<.0001

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-46: Migräneattacken/Monat, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	204 (100.0)	11.1 (5.64)						
	1-12	204 (100.0)	7.92 (5.12)	-2.6 (0.37)					
	13-24	202 (99.0)	7.41 (5.12)	-3.1 (0.39)					
EPTI 100 mg	Basln	207 (100.0)	11.0 (5.55)						
	1-12	207 (100.0)	5.85 (5.12)	-4.5 (0.37)		-1.9	0.35	[-2.6;-1.2]	<.0001
	13-24	198 (95.7)	5.23 (5.12)	-5.1 (0.39)		-2.0	0.39	[-2.8;-1.2]	<.0001
EPTI 300 mg	Basln	217 (100.0)	11.0 (5.95)						
	1-12	217 (100.0)	5.89 (5.29)	-4.5 (0.35)		-1.9	0.34	[-2.6;-1.2]	<.0001
	13-24	211 (97.2)	4.95 (5.29)	-5.4 (0.37)		-2.4	0.38	[-3.1;-1.6]	<.0001

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-47: Migräneattacken/Monat, CFB, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G		
					CFB LSmeans	95% CI	SMD 95% CI	G	CI	
PBO	Basln	83 (100.0)	12.0 (6.17)							
	1-12	83 (100.0)	9.18 (5.51)	-2.0 (0.61)						
	13-24	83 (100.0)	8.00 (5.51)	-2.9 (0.63)						
EPTI 100 mg	Basln	77 (100.0)	10.9 (5.30)							
	1-12	77 (100.0)	6.84 (5.31)	-3.8 (0.59)	-1.8	0.55	[-2.9;-.75]	0.0010	-0.5	[-.84;-.21]
	13-24	75 (97.4)	6.20 (5.31)	-4.5 (0.61)	-1.6	0.61	[-2.8;-.40]	0.0092	-0.4	[-.73;-.10]
EPTI 300 mg	Basln	68 (100.0)	10.9 (5.72)							
	1-12	68 (100.0)	6.04 (5.85)	-4.4 (0.60)	-2.5	0.56	[-3.6;-1.3]	<.0001	-0.7	[-1.0;-.39]
	13-24	67 (98.5)	5.46 (5.85)	-5.0 (0.63)	-2.1	0.62	[-3.4;-.90]	0.0008	-0.6	[-.88;-.24]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		Hedges' G	
					Diff.	SE	CI	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.4 Migräneattacken mit schwerer Schmerzintensität

Tabelle 4G-48: Migräneattacken mit schwerer Schmerzintensität, CFB, Interaktions-p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.7957	0.1204
Interaction test: EM/CM	0.1247	0.0513
Interaction test: MOH	0.3239	0.3981
Interaction test: Number of FPT	0.8231	0.5475
Interaction test: Sex	0.7759	0.4522

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-49: Migräneattacken mit schwerer Schmerzintensität, Interaktions p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.9357	0.3991
Interaction test: EM/CM	0.4435	0.0398
Interaction test: MOH	0.7476	0.6860
Interaction test: Number of FPT	0.7172	0.7479
Interaction test: Sex	0.3325	0.5225

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-50: Migräneattacken mit schwerer Schmerzintensität, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G		
					CFB LSmeans			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basin	67 (100.0)	40.1 (28.8)							
	1-12	67 (100.0)	35.8 (33.1)	-4.8 (3.80)						
	13-24	66 (98.5)	34.6 (33.1)	-6.7 (4.15)						
EPTI 100 mg	Basin	57 (100.0)	47.7 (30.2)							
	1-12	57 (100.0)	36.2 (36.2)	-8.2 (3.92)	-3.4	4.15	[-12;4.82]	0.4177	-0.1	[-.50;0.21]
	13-24	53 (93.0)	31.7 (36.2)	-11 (4.38)	-4.5	4.89	[-14;5.13]	0.3566	-0.2	[-.53;0.19]
EPTI 300 mg	Basin	62 (100.0)	44.9 (26.2)							
	1-12	62 (100.0)	27.7 (33.9)	-16 (4.01)	-11.3	4.09	[-19;-3.2]	0.0064	-0.5	[-.83;-.14]
	13-24	61 (98.4)	27.4 (33.9)	-16 (4.37)	-9.7	4.72	[-19;-.38]	0.0414	-0.4	[-.72;-.01]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-51: Migräneattacken mit schwerer Schmerzintensität, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	220 (100.0)	40.5 (30.3)						
	1-12	220 (100.0)	32.1 (34.5)	-11 (2.30)					
	13-24	219 (99.5)	29.8 (34.5)	-13 (2.38)					
EPTI 100 mg	Basln	227 (100.0)	47.0 (29.7)						
	1-12	227 (100.0)	28.1 (33.0)	-19 (2.23)	-8.1	2.13	[-12;-3.9]	0.0002	-0.4
	13-24	220 (96.9)	24.7 (33.0)	-21 (2.34)	-8.6	2.31	[-13;-4.0]	0.0002	-0.4
EPTI 300 mg	Basln	223 (100.0)	43.9 (29.1)						
	1-12	223 (100.0)	23.2 (30.4)	-21 (2.21)	-10.7	2.15	[-15;-6.5]	<.0001	-0.5
	13-24	217 (97.3)	21.0 (30.4)	-23 (2.31)	-9.8	2.32	[-14;-5.3]	<.0001	-0.4

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-52: Migräneattacken mit schwerer Schmerzintensität, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G			
					CFB LSmeans	95% CI	SMD 95% CI	G	CI		
PBO	Basln	33 (100.0)	38.7 (31.2)								
	1-12	33 (100.0)	26.4 (33.5)	-11 (4.98)							
	13-24	33 (100.0)	28.7 (33.5)	-9.4 (5.58)							
EPTI 100 mg	Basln	21 (100.0)	43.0 (30.4)								
	1-12	21 (100.0)	24.2 (32.8)	-19 (5.70)		-8.6	6.84	[-22;5.03]	0.2121	-0.4	[-.91;0.21]
	13-24	20 (95.2)	26.4 (32.8)	-18 (6.62)		-8.5	8.01	[-24;7.40]	0.2897	-0.3	[-.87;0.26]
EPTI 300 mg	Basln	32 (100.0)	42.7 (29.4)								
	1-12	32 (100.0)	26.6 (32.0)	-19 (4.82)		-7.8	5.57	[-19;3.29]	0.1647	-0.3	[-.84;0.15]
	13-24	32 (100.0)	23.9 (32.0)	-21 (5.45)		-11.4	6.63	[-25;1.86]	0.0910	-0.4	[-.92;0.07]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-53: Migräneattacken mit schwerer Schmerzintensität, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G			
					CFB LSmeans	95% CI	SMD 95% CI	G	CI		
PBO	Basln	254 (100.0)	40.6 (29.7)								
	1-12	254 (100.0)	33.8 (34.3)	-8.7 (2.19)							
	13-24	252 (99.2)	31.2 (34.3)	-11 (2.28)							
EPTI 100 mg	Basln	263 (100.0)	47.5 (29.8)								
	1-12	263 (100.0)	30.1 (33.8)	-17 (2.16)		-7.8	1.99	[-12;-3.9]	0.0001	-0.3	[-.52;-.17]
	13-24	253 (96.2)	26.0 (33.8)	-20 (2.27)		-8.5	2.18	[-13;-4.2]	0.0001	-0.3	[-.52;-.17]
EPTI 300 mg	Basln	253 (100.0)	44.3 (28.4)								
	1-12	253 (100.0)	23.9 (31.2)	-21 (2.11)		-12.2	2.01	[-16;-8.2]	<.0001	-0.5	[-.71;-.36]
	13-24	246 (97.2)	22.2 (31.2)	-22 (2.22)		-10.3	2.19	[-15;-6.0]	<.0001	-0.4	[-.60;-.25]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-54: Migräneattacken mit schwerer Schmerzintensität, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	159 (100.0)	37.9 (33.0)						
	1-12	159 (100.0)	31.7 (35.0)	-8.3 (2.91)					
	13-24	159 (100.0)	28.0 (35.0)	-13 (2.97)					
EPTI 100 mg	Basln	154 (100.0)	47.2 (30.3)						
	1-12	154 (100.0)	29.1 (32.5)	-16 (2.93)		-7.9	2.72	[-13;-2.6]	0.0038
	13-24	149 (96.8)	22.5 (32.5)	-22 (3.01)		-9.1	2.86	[-15;-3.5]	0.0016
EPTI 300 mg	Basln	154 (100.0)	44.6 (29.9)						
	1-12	154 (100.0)	21.5 (30.0)	-22 (2.83)		-13.9	2.72	[-19;-8.6]	<.0001
	13-24	152 (98.7)	19.0 (30.0)	-24 (2.92)		-11.2	2.84	[-17;-5.6]	<.0001

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI CI
					CFB		95% CI		
					LSmeans	Diff.	SE	CI	p-value
<p>Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.</p> <p>From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.</p> <p>N: the number of patients with observations in the interval. Basln: Baseline.</p> <p>AMNOG: AMNOG population B. EM : Episodic Migraine.</p>									

Tabelle 4G-55: Migräneattacken mit schwerer Schmerzintensität, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI CI																														
					CFB		95% CI																																
					LSmeans	Diff.	SE	CI	p-value																														
<table border="1"> <tr> <td>PBO</td> <td>Basln</td> <td>128 (100.0)</td> <td>43.5 (25.2)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>1-12</td> <td>128 (100.0)</td> <td>34.5 (32.8)</td> <td>-10 (3.35)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>13-24</td> <td>126 (98.4)</td> <td>34.7 (32.8)</td> <td>-9.2 (3.65)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>										PBO	Basln	128 (100.0)	43.5 (25.2)								1-12	128 (100.0)	34.5 (32.8)	-10 (3.35)							13-24	126 (98.4)	34.7 (32.8)	-9.2 (3.65)					
PBO	Basln	128 (100.0)	43.5 (25.2)																																				
	1-12	128 (100.0)	34.5 (32.8)	-10 (3.35)																																			
	13-24	126 (98.4)	34.7 (32.8)	-9.2 (3.65)																																			
<table border="1"> <tr> <td>EPTI 100 mg</td> <td>Basln</td> <td>130 (100.0)</td> <td>47.0 (29.2)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>1-12</td> <td>130 (100.0)</td> <td>30.5 (34.7)</td> <td>-16 (3.18)</td> <td>-5.8</td> <td>2.57</td> <td>[-11;-71]</td> <td>0.0255</td> <td>-0.3 [-.52;-.03]</td> </tr> <tr> <td></td> <td>13-24</td> <td>124 (95.4)</td> <td>30.2 (34.7)</td> <td>-15 (3.51)</td> <td>-5.9</td> <td>2.99</td> <td>[-12;-.02]</td> <td>0.0493</td> <td>-0.2 [-.50;-.00]</td> </tr> </table>										EPTI 100 mg	Basln	130 (100.0)	47.0 (29.2)								1-12	130 (100.0)	30.5 (34.7)	-16 (3.18)	-5.8	2.57	[-11;-71]	0.0255	-0.3 [-.52;-.03]		13-24	124 (95.4)	30.2 (34.7)	-15 (3.51)	-5.9	2.99	[-12;-.02]	0.0493	-0.2 [-.50;-.00]
EPTI 100 mg	Basln	130 (100.0)	47.0 (29.2)																																				
	1-12	130 (100.0)	30.5 (34.7)	-16 (3.18)	-5.8	2.57	[-11;-71]	0.0255	-0.3 [-.52;-.03]																														
	13-24	124 (95.4)	30.2 (34.7)	-15 (3.51)	-5.9	2.99	[-12;-.02]	0.0493	-0.2 [-.50;-.00]																														
<table border="1"> <tr> <td>EPTI 300 mg</td> <td>Basln</td> <td>130 (100.0)</td> <td>43.9 (26.5)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>1-12</td> <td>130 (100.0)</td> <td>27.7 (32.5)</td> <td>-17 (3.30)</td> <td>-6.6</td> <td>2.56</td> <td>[-12;-1.5]</td> <td>0.0107</td> <td>-0.3 [-.56;-.07]</td> </tr> <tr> <td></td> <td>13-24</td> <td>125 (96.2)</td> <td>26.8 (32.5)</td> <td>-16 (3.61)</td> <td>-7.3</td> <td>2.97</td> <td>[-13;-.14]</td> <td>0.0150</td> <td>-0.3 [-.56;-.06]</td> </tr> </table>										EPTI 300 mg	Basln	130 (100.0)	43.9 (26.5)								1-12	130 (100.0)	27.7 (32.5)	-17 (3.30)	-6.6	2.56	[-12;-1.5]	0.0107	-0.3 [-.56;-.07]		13-24	125 (96.2)	26.8 (32.5)	-16 (3.61)	-7.3	2.97	[-13;-.14]	0.0150	-0.3 [-.56;-.06]
EPTI 300 mg	Basln	130 (100.0)	43.9 (26.5)																																				
	1-12	130 (100.0)	27.7 (32.5)	-17 (3.30)	-6.6	2.56	[-12;-1.5]	0.0107	-0.3 [-.56;-.07]																														
	13-24	125 (96.2)	26.8 (32.5)	-16 (3.61)	-7.3	2.97	[-13;-.14]	0.0150	-0.3 [-.56;-.06]																														

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI CI
					CFB		95% CI		
					LSmeans	Diff.	SE	CI	p-value
<p>Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.</p> <p>From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.</p> <p>N: the number of patients with observations in the interval. Basln: Baseline.</p> <p>AMNOG: AMNOG population B. CM : Chronic Migraine.</p>									

Tabelle 4G-56: Migräneattacken mit schwerer Schmerzintensität, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI CI
					CFB		95% CI		
					LSmeans	Diff.	SE	CI	p-value
PBO	Basln	35 (100.0)	43.4 (26.4)						
	1-12	35 (100.0)	35.2 (33.4)	-6.9 (4.60)					
	13-24	35 (100.0)	36.4 (33.4)	-7.3 (5.50)					
EPTI 100 mg	Basln	36 (100.0)	55.2 (31.7)						
	1-12	36 (100.0)	41.9 (37.4)	-5.5 (4.19)	1.4	5.13	[-8.8;11.5]	0.7914	0.1 [-.41;0.53]
	13-24	34 (94.4)	36.5 (37.4)	-9.8 (5.09)	-2.6	6.55	[-16;10.4]	0.6935	-0.1 [-.57;0.38]
EPTI 300 mg	Basln	35 (100.0)	41.8 (23.2)						
	1-12	35 (100.0)	28.2 (34.0)	-11 (4.38)	-4.5	5.03	[-14;5.52]	0.3772	-0.2 [-.69;0.26]
	13-24	35 (100.0)	30.5 (34.0)	-10 (5.20)	-3.2	6.37	[-16;9.45]	0.6173	-0.1 [-.59;0.35]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-57: Migräneattacken mit schwerer Schmerzintensität, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	252 (100.0)	40.0 (30.3)					<.0001	-0.4 [-.53;-.18]
	1-12	252 (100.0)	32.6 (34.3)	-10 (2.17)					
	13-24	250 (99.2)	30.2 (34.3)	-13 (2.25)					
EPTI 100 mg	Basln	248 (100.0)	45.9 (29.4)			[-12;-4.1] [-13;-4.1]	-0.4 [-.32;-.17]	<.0001 0.0001	-0.4 [-.32;-.17]
	1-12	248 (100.0)	27.9 (32.9)	-18 (2.16)					
	13-24	239 (96.4)	24.6 (32.9)	-21 (2.26)					
EPTI 300 mg	Basln	250 (100.0)	44.4 (29.1)			[-15;-7.3] [-14;-5.9]	-0.5 [-.60;-.24]	<.0001 <.0001	-0.5 [-.60;-.24]
	1-12	250 (100.0)	23.6 (30.8)	-22 (2.12)					
	13-24	243 (97.2)	21.2 (30.8)	-23 (2.22)					

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-58: Migräneattacken mit schwerer Schmerzintensität, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	204 (100.0)	38.8 (30.0)		-9.7 (2.37)				
	1-12	204 (100.0)	31.2 (34.6)	-2.6 (2.37)					
	13-24	202 (99.0)	29.1 (34.6)	-9.7 (2.45)					
EPTI 100 mg	Basln	207 (100.0)	45.9 (29.7)		-17 (2.34)				
	1-12	207 (100.0)	28.0 (32.5)	-17.9 (2.34)		-7.2	2.27	[-12;-2.7]	0.0016
	13-24	198 (95.7)	24.0 (32.5)	-14.0 (2.46)		-8.2	2.45	[-13;-3.4]	0.0009
EPTI 300 mg	Basln	217 (100.0)	45.1 (29.5)		-19 (2.26)				
	1-12	217 (100.0)	25.5 (31.5)	-19.6 (2.26)		-9.2	2.25	[-14;-4.8]	<.0001
	13-24	211 (97.2)	22.3 (31.5)	-12.8 (2.36)		-9.0	2.41	[-14;-4.2]	0.0002

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI CI
					CFB		95% CI		
					LSmeans	Diff.	SE	CI	p-value
<p>Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.</p> <p>From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.</p> <p>N: the number of patients with observations in the interval. Basln: Baseline.</p> <p>AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.</p>									

Tabelle 4G-59: Migräneattacken mit schwerer Schmerzintensität, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI CI																														
					CFB		95% CI																																
					LSmeans	Diff.	SE	CI	p-value																														
<table border="1"> <tr> <td>PBO</td> <td>Basln</td> <td>83 (100.0)</td> <td>44.4 (29.3)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>1-12</td> <td>83 (100.0)</td> <td>37.2 (33.0)</td> <td>-9.7 (3.81)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>13-24</td> <td>83 (100.0)</td> <td>35.5 (33.0)</td> <td>-12 (4.06)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>										PBO	Basln	83 (100.0)	44.4 (29.3)								1-12	83 (100.0)	37.2 (33.0)	-9.7 (3.81)							13-24	83 (100.0)	35.5 (33.0)	-12 (4.06)					
PBO	Basln	83 (100.0)	44.4 (29.3)																																				
	1-12	83 (100.0)	37.2 (33.0)	-9.7 (3.81)																																			
	13-24	83 (100.0)	35.5 (33.0)	-12 (4.06)																																			
<table border="1"> <tr> <td>EPTI 100 mg</td> <td>Basln</td> <td>77 (100.0)</td> <td>50.4 (29.9)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>1-12</td> <td>77 (100.0)</td> <td>34.1 (36.3)</td> <td>-17 (3.70)</td> <td>-7.1</td> <td>3.50</td> <td>[-14;-19]</td> <td>0.0441</td> <td>-0.3 [-.63;-.01]</td> </tr> <tr> <td></td> <td>13-24</td> <td>75 (97.4)</td> <td>31.5 (36.3)</td> <td>-18 (3.98)</td> <td>-6.7</td> <td>4.03</td> <td>[-15;1.21]</td> <td>0.0962</td> <td>-0.3 [-.58;0.05]</td> </tr> </table>										EPTI 100 mg	Basln	77 (100.0)	50.4 (29.9)								1-12	77 (100.0)	34.1 (36.3)	-17 (3.70)	-7.1	3.50	[-14;-19]	0.0441	-0.3 [-.63;-.01]		13-24	75 (97.4)	31.5 (36.3)	-18 (3.98)	-6.7	4.03	[-15;1.21]	0.0962	-0.3 [-.58;0.05]
EPTI 100 mg	Basln	77 (100.0)	50.4 (29.9)																																				
	1-12	77 (100.0)	34.1 (36.3)	-17 (3.70)	-7.1	3.50	[-14;-19]	0.0441	-0.3 [-.63;-.01]																														
	13-24	75 (97.4)	31.5 (36.3)	-18 (3.98)	-6.7	4.03	[-15;1.21]	0.0962	-0.3 [-.58;0.05]																														
<table border="1"> <tr> <td>EPTI 300 mg</td> <td>Basln</td> <td>68 (100.0)</td> <td>41.0 (24.7)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>1-12</td> <td>68 (100.0)</td> <td>19.8 (30.8)</td> <td>-25 (3.84)</td> <td>-15.6</td> <td>3.55</td> <td>[-23;-8.6]</td> <td><.0001</td> <td>-0.7 [-1.0;-.40]</td> </tr> <tr> <td></td> <td>13-24</td> <td>67 (98.5)</td> <td>22.6 (30.8)</td> <td>-23 (4.13)</td> <td>-11.6</td> <td>4.10</td> <td>[-20;-3.5]</td> <td>0.0053</td> <td>-0.5 [-.79;-.14]</td> </tr> </table>										EPTI 300 mg	Basln	68 (100.0)	41.0 (24.7)								1-12	68 (100.0)	19.8 (30.8)	-25 (3.84)	-15.6	3.55	[-23;-8.6]	<.0001	-0.7 [-1.0;-.40]		13-24	67 (98.5)	22.6 (30.8)	-23 (4.13)	-11.6	4.10	[-20;-3.5]	0.0053	-0.5 [-.79;-.14]
EPTI 300 mg	Basln	68 (100.0)	41.0 (24.7)																																				
	1-12	68 (100.0)	19.8 (30.8)	-25 (3.84)	-15.6	3.55	[-23;-8.6]	<.0001	-0.7 [-1.0;-.40]																														
	13-24	67 (98.5)	22.6 (30.8)	-23 (4.13)	-11.6	4.10	[-20;-3.5]	0.0053	-0.5 [-.79;-.14]																														

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO			SMD 95% CI	
					Diff.	SE	CI	p-value	Hedges' G			
									95% CI	G	CI	
<p>Missing eDiary data is handled using the rules provided in the SAP. Patients with no migraine attacks are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.</p> <p>From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.</p> <p>N: the number of patients with observations in the interval. Basln: Baseline.</p> <p>AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.</p>												

4.2.5 Patienten mit Migräne am Tag nach erster Dosierung

Keine Interaktions-p-Werte berechnet

Tabelle 4G-60: Patienten mit Migräne an Tag 1 nach erster Dosierung, Ergebnisse der Subgruppenanalysen

	PBO		EPTI 100 mg		p-value	EPTI 300 mg	
	n	%	n	%		n	%
MMDs baseline	287	49.5	284	49.2		285	48.9
Infusion V2 + 1 day		43.7		26.1	<0.0001		24.7
Sub-group analyses							
<= 35 years, baseline	67	52.2	57	50.8		62	52.5
<= 35 years, infusion V2 + 1 day		45.2		29.8	0.12		33.9
> 35 years, baseline	220	48.7	227	48.8		223	47.9
> 35 years, infusion V2 + 1 day		43.2		25.1	<0.0001		22.2
2 failures, baseline	204	48.5	207	48.3		217	48.4
2 failures, infusion V2 + 1 day		42.0		23.1	<0.0001		25.0
3+ failures, baseline	83	52.0	77	51.8		68	50.6
3+ failures, infusion V2 + 1 day		47.9		33.9	0.05		23.8
CM, baseline	128	68.3	130	67.2		130	66.0
CM, infusion V2 + 1 day		58.9		38.4	0.004		36.3
EM, baseline	159	34.4	154	34.0		154	34.7
EM, infusion V2 + 1 day		31.4		15.7	0.0005		15.1
Female, baseline	254	49.1	263	49.2		253	48.6
Female, infusion V2 + 1 day		43.4		26.6	<0.0001		23.8
Male, baseline	33	52.9	21	49.7		32	51.3
Male, infusion V2 + 1 day		45.6		19.5	0.068		32.0
MOH, baseline	35	68.5	36	60.3		35	57.4
MOH, infusion V2 + 1 day		65.7		31.5	0.0092		35.5
No MOH, baseline	252	46.9	248	47.6		250	47.7
No MOH, infusion V2 + 1 day		40.6		25.3	0.0001		23.2
							<0.0001

N refers to the number of subjects in the analysis at the relevant timepoint.

The p-values are computed separately for each active treatment group using extended CMH test, adjusting for the stratification factor (MHDs at baseline <=14/>14).

Baseline is the average percentage of patients with migraine across the first 28 days.

The percentage of patients with a migraine on the day after first dosing is derived based on available eDiary data on Day 1.

If eDiary data on Day 1 missing, the migraine rate for the patient is imputed as described in the SAP section 19.1.1.3.

4.2.6 Tage mit Verwendung akuter Migränemedikation

Tabelle 4G-61: Tage mit Verwendung akuter Migränemedikation, CFB, Interaktions-p-Werte

Description	Treatment Group	
	EPTI 100 mg p-value	EPTI 300 mg p-value
Week 1-12		
Interaction test: Age Group	0.8744	0.9301
Interaction test: EM/CM	0.2191	0.6205
Interaction test: MOH	0.7536	0.2900
Interaction test: Number of FPT	0.8834	0.0972
Interaction test: Sex	0.3696	0.0120
Week 13-24		
Interaction test: Age Group	0.9655	0.9021
Interaction test: EM/CM	0.1681	0.5127
Interaction test: MOH	0.9865	0.5308
Interaction test: Number of FPT	0.6335	0.3840
Interaction test: Sex	0.7472	0.9374

Tabelle 4G-62: Tage mit Verwendung akuter Migränemedikation, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO			Hedges' G		
								95% CI			SMD 95% CI		
					Diff.	SE	CI	p-value	G	CI			
PBO	Basln	67 (100.0)	9.87 (5.83)										
	1-12	67 (100.0)	8.75 (6.84)	-.38 (0.64)									
	13-24	65 (97.0)	8.44 (6.84)	-.10 (0.71)									
EPTI 100 mg	Basln	56 (100.0)	9.82 (5.49)										
	1-12	56 (100.0)	6.41 (5.42)	-2.7 (0.65)	-2.3	0.67	[-3.6;-.96]	0.0009	-0.6	[-.97;-.26]			

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI		
					CFB						
					LSmeans	Diff.	95% CI				
	13-24	53 (94.6)	5.56 (5.42)	-3.1 (0.74)	-3.0	0.82	[-4.7;-1.4]	0.0003	-0.7 [-1.0;-.32]		
EPTI 300 mg	Basln	61 (100.0)	10.6 (5.48)								
	1-12	61 (100.0)	6.72 (6.98)	-2.9 (0.68)	-2.5	0.67	[-3.9;-1.2]	0.0002	-0.7 [-1.0;-.32]		
	13-24	60 (98.4)	6.17 (6.98)	-3.5 (0.75)	-3.4	0.81	[-5.0;-1.8]	<.0001	-0.8 [-1.1;-.40]		

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-63: Tage mit Verwendung akuter Migränemedikation, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI		
					CFB						
					LSmeans	Diff.	95% CI				
PBO	Basln	220 (100.0)	11.6 (6.01)								
EPTI 100 mg	1-12	220 (100.0)	9.17 (6.57)	-2.1 (0.41)							
	13-24	219 (99.5)	8.96 (6.57)	-2.3 (0.43)							
	Basln	227 (100.0)	11.5 (5.39)								
EPTI 300 mg	1-12	227 (100.0)	6.44 (5.48)	-4.7 (0.41)	-2.6	0.38	[-3.3;-1.9]	<.0001	-0.6 [-.83;-.46]		
	13-24	220 (96.9)	5.88 (5.48)	-5.1 (0.43)	-2.9	0.42	[-3.7;-2.1]	<.0001	-0.7 [-.85;-.47]		
	Basln	221 (100.0)	11.2 (5.17)								

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO						
					CFB			95% CI		SMD 95% CI	
					LSmeans	Diff.	SE	CI	p-value	G	CI
1-12	221 (100.0)	5.78 (5.56)	-5.2 (0.40)	-3.1	0.38	[-3.8;-2.3]	<.0001	-0.8	[-.95;-.58]		
	13-24	217 (98.2)	5.12 (5.56)	-5.8 (0.42)	-3.5	0.42	[-4.3;-2.7]	<.0001	-0.8	[-.99;-.61]	

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-64: Tage mit Verwendung akuter Migränemedikation, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO						
					CFB			95% CI		SMD 95% CI	
					LSmeans	Diff.	SE	CI	p-value	G	CI
PBO	Basln	33 (100.0)	11.8 (7.80)								
	1-12	33 (100.0)	10.3 (7.93)	-1.2 (1.17)							
	13-24	33 (100.0)	10.5 (7.93)	-1.1 (1.26)							
EPTI 100 mg	Basln	21 (100.0)	12.6 (6.70)								
	1-12	21 (100.0)	7.20 (7.52)	-4.0 (1.34)	-2.8	1.61	[-6.0;0.38]	0.0836	-0.5	[-1.0;0.07]	
	13-24	20 (95.2)	7.78 (7.52)	-3.3 (1.49)	-2.2	1.79	[-5.8;1.33]	0.2156	-0.4	[-.92;0.21]	
EPTI 300 mg	Basln	32 (100.0)	12.2 (4.86)								
	1-12	32 (100.0)	7.64 (6.40)	-4.3 (1.14)	-3.1	1.32	[-5.7;-.46]	0.0221	-0.6	[-1.1;-.09]	
	13-24	32 (100.0)	6.59 (6.40)	-5.4 (1.24)	-4.3	1.49	[-7.2;-.13]	0.0055	-0.7	[-1.2;-.22]	

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-65: Tage mit Verwendung akuter Migränemedikation, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	254 (100.0)	11.1 (5.75)		-1.6 (0.39)			<.0001	[-.6;-.47]
	1-12	254 (100.0)	8.92 (6.42)	-1.6 (0.39)					
	13-24	251 (98.8)	8.63 (6.42)	-1.7 (0.41)					
EPTI 100 mg	Basln	262 (100.0)	11.1 (5.33)		-4.1 (0.39)	-2.5	0.34	<.0001	[-.6;-.47]
	1-12	262 (100.0)	6.38 (5.25)	-4.1 (0.39)		-2.5	0.34		
	13-24	253 (96.6)	5.66 (5.25)	-4.6 (0.41)		-2.9	0.38		
EPTI 300 mg	Basln	250 (100.0)	10.9 (5.27)		-4.6 (0.38)	-3.0	0.34	<.0001	[-.8;-.61]
	1-12	250 (100.0)	5.77 (5.82)	-4.6 (0.38)		-3.0	0.34		
	13-24	245 (98.0)	5.19 (5.82)	-5.2 (0.40)		-3.5	0.38		

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-66: Tage mit Verwendung akuter Migränemedikation, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	159 (100.0)	7.94 (3.21)					<.0001	-0.6 [-.86;-.42]
	1-12	159 (100.0)	6.58 (4.91)	-.82 (0.39)					
	13-24	159 (100.0)	6.43 (4.91)	-.91 (0.41)					
EPTI 100 mg	Basln	154 (100.0)	8.06 (2.89)			[-2.7;-1.3] [-3.3;-1.7]	<.0001 <.0001	-0.6 -0.7 [-.93;-.49]	[-.86;-.42] [-.93;-.49]
	1-12	154 (100.0)	4.62 (3.80)	-2.8 (0.40)					
	13-24	149 (96.8)	3.98 (3.80)	-3.4 (0.42)					
EPTI 300 mg	Basln	154 (100.0)	8.19 (3.19)			[-3.4;-2.0] [-3.9;-2.3]	<.0001 <.0001	-0.9 -0.9 [-1.1;-.64]	[-.86;-.42] [-.93;-.49]
	1-12	154 (100.0)	3.97 (4.22)	-3.6 (0.38)					
	13-24	152 (98.7)	3.54 (4.22)	-4.0 (0.40)					

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-67: Tage mit Verwendung akuter Migränemedikation, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	128 (100.0)	15.2 (6.21)						
	1-12	128 (100.0)	12.2 (7.25)	-2.0 (0.79)					
	13-24	125 (97.7)	11.9 (7.25)	-2.6 (0.85)					
EPTI 100 mg	Basln	129 (100.0)	14.9 (5.43)						
	1-12	129 (100.0)	8.62 (6.28)	-5.3 (0.76)	-3.3	0.60	[-4.5;-2.1]	<.0001	-0.7
	13-24	124 (96.1)	8.02 (6.28)	-6.2 (0.82)	-3.6	0.67	[-4.9;-2.3]	<.0001	-0.7
EPTI 300 mg	Basln	127 (100.0)	14.6 (5.04)						
	1-12	127 (100.0)	8.41 (6.87)	-5.4 (0.79)	-3.3	0.60	[-4.5;-2.2]	<.0001	-0.7
	13-24	124 (97.6)	7.53 (6.87)	-6.7 (0.84)	-4.1	0.67	[-5.4;-2.8]	<.0001	-0.8

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-68: Tage mit Verwendung akuter Migränemedikation, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G		
					CFB LSmeans	95% CI	SMD 95% CI	G	CI	
PBO	Basln	35 (100.0)	16.7 (7.72)							
	1-12	35 (100.0)	13.8 (8.15)	-1.0 (1.22)						
	13-24	34 (97.1)	12.9 (8.15)	-1.6 (1.29)						
EPTI 100 mg	Basln	35 (100.0)	14.8 (6.31)							
	1-12	35 (100.0)	9.65 (7.43)	-4.1 (1.14)	-3.1	1.36	[-5.8;-.39]	0.0252	-0.5	[-1.0;-.07]
	13-24	34 (97.1)	9.36 (7.43)	-4.8 (1.20)	-3.2	1.46	[-6.1;-.29]	0.0315	-0.5	[-1.0;-.05]
EPTI 300 mg	Basln	35 (100.0)	12.9 (4.76)							
	1-12	35 (100.0)	7.05 (5.36)	-6.0 (1.21)	-5.0	1.40	[-7.7;-2.2]	0.0006	-0.8	[-1.3;-.37]
	13-24	34 (97.1)	6.76 (5.36)	-6.5 (1.27)	-4.9	1.50	[-7.9;-.19]	0.0016	-0.8	[-1.3;-.31]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-69: Tage mit Verwendung akuter Migränemedikation, Subgruppe MOH:nein

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	252 (100.0)	10.4 (5.31)		-1.7 (0.38)			-0.7	[-.85;-.50]
	1-12	252 (100.0)	8.40 (6.25)	-1.7 (0.38)					
	13-24	250 (99.2)	8.33 (6.25)	-1.7 (0.40)					
EPTI 100 mg	Basln	248 (100.0)	10.7 (5.12)		-4.2 (0.38)			<.0001	[-.87;-.52]
	1-12	248 (100.0)	5.99 (4.94)	-4.2 (0.38)		-2.5	0.34		
	13-24	239 (96.4)	5.32 (4.94)	-4.6 (0.40)		-2.9	0.38		
EPTI 300 mg	Basln	247 (100.0)	10.8 (5.26)		-4.5 (0.37)			<.0001	[-.97;-.62]
	1-12	247 (100.0)	5.84 (5.95)	-4.5 (0.37)		-2.8	0.34		
	13-24	243 (98.4)	5.15 (5.95)	-5.1 (0.40)		-3.4	0.38		

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-70: Tage mit Verwendung akuter Migränemedikation, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	204 (100.0)	11.1 (6.06)						
	1-12	204 (100.0)	8.74 (6.58)	-1.9 (0.41)					
	13-24	202 (99.0)	8.75 (6.58)	-1.8 (0.43)					
EPTI 100 mg	Basln	206 (100.0)	11.1 (5.47)						
	1-12	206 (100.0)	6.11 (5.37)	-4.3 (0.41)	-2.4	0.38	[-3.2;-1.7]	<.0001	-0.6
	13-24	198 (96.1)	5.51 (5.37)	-4.8 (0.43)	-3.0	0.43	[-3.8;-2.1]	<.0001	-0.7
EPTI 300 mg	Basln	214 (100.0)	10.9 (5.07)						
	1-12	214 (100.0)	5.78 (5.43)	-4.7 (0.39)	-2.8	0.37	[-3.5;-2.0]	<.0001	-0.7
	13-24	210 (98.1)	5.06 (5.43)	-5.3 (0.42)	-3.5	0.42	[-4.4;-2.7]	<.0001	-0.8

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-71: Tage mit Verwendung akuter Migränemedikation, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	83 (100.0)	11.5 (5.89)						
	1-12	83 (100.0)	9.89 (6.78)	-.52 (0.77)					
	13-24	82 (98.8)	9.06 (6.78)	-1.0 (0.81)					
EPTI 100 mg	Basln	77 (100.0)	11.5 (5.40)						
	1-12	77 (100.0)	7.32 (5.65)	-3.3 (0.75)	-2.8	0.69	[-4.1;-1.4]	<.0001	-0.6
	13-24	75 (97.4)	6.63 (5.65)	-3.8 (0.80)	-2.8	0.78	[-4.4;-1.3]	0.0004	-0.6
EPTI 300 mg	Basln	68 (100.0)	11.6 (5.74)						
	1-12	68 (100.0)	6.63 (7.12)	-4.0 (0.77)	-3.4	0.71	[-4.8;-2.0]	<.0001	-0.8
	13-24	67 (98.5)	6.23 (7.12)	-4.3 (0.82)	-3.3	0.80	[-4.8;-1.7]	<.0001	-0.7

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					95% CI		Diff.	SE	CI
					CFB	LSmeans			

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.
N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.7 Kopfschmerztag/Monat

4.2.7.1 Veränderung gegenüber dem Baseline-Wert

Tabelle 4G-72: Kopfschmerztag/Monat, CFB, Interaktions p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.7187	0.2280
Interaction test: EM/CM	0.3458	0.5766
Interaction test: MOH	0.7219	0.2918
Interaction test: Number of FPT	0.8941	0.0664
Interaction test: Sex	0.6387	0.3285

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-73: Kopfschmerztage/Monat, CFB, Interaktions p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.4946	0.2423
Interaction test: EM/CM	0.1718	0.4725
Interaction test: MOH	0.9961	0.4191
Interaction test: Number of FPT	0.6040	0.2715
Interaction test: Sex	0.7759	0.9087

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-74: Kopfschmerztage/Monat, CFB, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					CFB LSmeans				95% CI	
					Diff.	SE	CI	p-value	G	CI
PBO	BasIn	67 (100.0)	15.3 (5.73)							
	1-12	67 (100.0)	12.8 (7.99)	-.83 (0.79)						
	13-24	66 (98.5)	12.3 (7.99)	-1.2 (0.83)						
EPTI 100 mg	BasIn	57 (100.0)	14.8 (6.07)							
	1-12	57 (100.0)	10.3 (7.41)	-3.1 (0.81)	-2.3	0.86	[-4.0;-.55]	0.0097	-0.5	[-.83;-.12]
	13-24	53 (93.0)	8.80 (7.41)	-4.3 (0.87)	-3.1	0.96	[-5.0;-1.2]	0.0015	-0.6	[-.96;-.23]
EPTI 300 mg	BasIn	62 (100.0)	15.4 (6.07)							
	1-12	62 (100.0)	10.8 (8.16)	-2.8 (0.84)	-2.0	0.86	[-3.7;-.31]	0.0207	-0.4	[-.76;-.06]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI		
					CFB						
					LSmeans	Diff.	95% CI				
	13-24	61 (98.4)	8.92 (8.16)	-4.5 (0.88)		-3.3	0.94 [-5.1;-1.4]	0.0006	-0.6 [-.97;-.27]		

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-75: Kopfschmerztag/Monat, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI		
					CFB						
					LSmeans	Diff.	95% CI				
PBO	Basln	220 (100.0)	14.3 (5.91)					<.0001	-0.6 [-.82;-.45]		
	1-12	220 (100.0)	11.1 (6.58)	-2.4 (0.44)							
	13-24	219 (99.5)	10.5 (6.58)	-2.9 (0.46)							
EPTI 100 mg	Basln	227 (100.0)	14.4 (5.59)					<.0001	-0.6 [-.86;-.49]		
	1-12	227 (100.0)	8.49 (6.22)	-5.1 (0.43)		-2.7	0.41 [-3.5;-1.9]				
	13-24	220 (96.9)	7.39 (6.22)	-6.0 (0.45)		-3.1	0.44 [-4.0;-2.3]				
EPTI 300 mg	Basln	223 (100.0)	14.1 (5.28)					<.0001	-0.8 [-.94;-.56]		
	1-12	223 (100.0)	7.78 (6.13)	-5.6 (0.43)		-3.2	0.41 [-4.1;-2.4]				
	13-24	217 (97.3)	6.74 (6.13)	-6.6 (0.44)		-3.7	0.44 [-4.6;-2.8]				

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO								
					95% CI			SMD 95% CI					
					CFB	LSmeans	Hedges'	G	CI				
Missing eDiary data is handled using the rules provided in the SAP.													
The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.													
From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.													
N: the number of patients with observations in the interval. Basln: Baseline.													
AMNOG: AMNOG population B.													

Tabelle 4G-76: Kopfschmerztag/Monat, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				
					95% CI			SMD 95% CI	
					CFB	LSmeans	Hedges'	G	CI
PBO									
PBO	Basln	33 (100.0)	15.1 (6.58)						
	1-12	33 (100.0)	12.7 (7.77)	-2.7 (0.99)					
	13-24	33 (100.0)	12.3 (7.77)	-3.1 (1.07)					
EPTI 100 mg									
EPTI 100 mg	Basln	21 (100.0)	14.3 (6.53)						
	1-12	21 (100.0)	8.76 (7.34)	-5.4 (1.13)	-2.7	1.39	[-5.5;0.05]	0.0544	-0.5 [-1.1;0.01]
	13-24	20 (95.2)	8.78 (7.34)	-5.3 (1.25)	-2.2	1.54	[-5.2;0.89]	0.1616	-0.4 [-.96;0.16]
EPTI 300 mg									
EPTI 300 mg	Basln	32 (100.0)	15.1 (4.75)						
	1-12	32 (100.0)	9.98 (8.32)	-5.4 (0.97)	-2.7	1.12	[-5.0;-.48]	0.0182	-0.6 [-1.1;-.11]
	13-24	32 (100.0)	8.53 (8.32)	-6.9 (1.05)	-3.8	1.26	[-6.3;-1.3]	0.0035	-0.7 [-1.2;-.25]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO									
					CFB			95% CI		SMD 95% CI				
					LSmeans	Diff.	SE	CI	p-value	G	CI			
Missing eDiary data is handled using the rules provided in the SAP.														
The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.														
From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.														
N: the number of patients with observations in the interval. Basln: Baseline.														
AMNOG: AMNOG population B.														

Tabelle 4G-77: Kopfschmerztag/Monat, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO									
					CFB			95% CI		SMD 95% CI				
					LSmeans	Diff.	SE	CI	p-value	G	CI			
PBO														
Basln														
1-12														
13-24														
EPTI 100 mg														
Basln														
1-12														
13-24														
EPTI 300 mg														
Basln														
1-12														
13-24														

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-78: Kopfschmerztag/Monat, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	159 (100.0)	10.2 (2.48)						
	1-12	159 (100.0)	8.05 (4.60)	-1.2 (0.42)					
	13-24	159 (100.0)	7.60 (4.60)	-1.6 (0.43)					
EPTI 100 mg	Basln	154 (100.0)	10.1 (2.50)						
	1-12	154 (100.0)	6.08 (4.37)	-3.2 (0.42)	-2.0	0.39	[-2.7;-1.2]	<.0001	-0.6
	13-24	149 (96.8)	5.00 (4.37)	-4.1 (0.43)	-2.5	0.40	[-3.3;-1.7]	<.0001	-0.7
EPTI 300 mg	Basln	154 (100.0)	10.3 (2.54)						
	1-12	154 (100.0)	5.32 (3.85)	-4.0 (0.41)	-2.8	0.39	[-3.6;-2.1]	<.0001	-0.8
	13-24	152 (98.7)	4.50 (3.85)	-4.8 (0.42)	-3.2	0.40	[-4.0;-2.4]	<.0001	-0.9

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-79: Kopfschmerztag/Monat, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	128 (100.0)	19.9 (4.13)						
	1-12	128 (100.0)	15.9 (7.14)	-2.7 (0.74)					
	13-24	126 (98.4)	15.2 (7.14)	-3.2 (0.78)					
EPTI 100 mg	Basln	130 (100.0)	19.7 (3.60)						
	1-12	130 (100.0)	12.2 (7.12)	-6.1 (0.72)	-3.5	0.66	[-4.8;-2.2]	<.0001	-0.7
	13-24	124 (95.4)	10.8 (7.12)	-7.1 (0.76)	-3.9	0.73	[-5.3;-2.5]	<.0001	-0.7
EPTI 300 mg	Basln	130 (100.0)	19.3 (3.73)						
	1-12	130 (100.0)	12.1 (7.77)	-5.9 (0.74)	-3.2	0.66	[-4.5;-1.9]	<.0001	-0.6
	13-24	125 (96.2)	10.4 (7.77)	-7.3 (0.77)	-4.1	0.73	[-5.6;-2.7]	<.0001	-0.7

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				
					CFB LSmeans	95% CI	SMD 95% CI	Hedges' G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-80: Kopfschmerztag/Monat, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				
					CFB LSmeans	95% CI	SMD 95% CI	Hedges' G	CI
PBO	Basln	35 (100.0)	19.9 (5.89)						
	1-12	35 (100.0)	16.7 (8.07)	-2.0 (1.35)					
	13-24	35 (100.0)	15.7 (8.07)	-2.9 (1.38)					
EPTI 100 mg	Basln	36 (100.0)	17.3 (5.71)						
	1-12	36 (100.0)	11.0 (7.51)	-5.6 (1.27)		-3.6	1.51	[-6.6;-.61]	0.0190
	13-24	34 (94.4)	10.5 (7.51)	-5.8 (1.31)		-2.9	1.57	[-6.1;0.19]	0.0658
EPTI 300 mg	Basln	35 (100.0)	16.6 (5.20)						
	1-12	35 (100.0)	10.5 (7.53)	-6.6 (1.31)		-4.6	1.55	[-7.7;-1.5]	0.0038
	13-24	35 (100.0)	10.0 (7.53)	-6.8 (1.33)		-4.0	1.60	[-7.1;-.77]	0.0156

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				
					CFB LSmeans	95% CI	SMD 95% CI	Hedges' G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-81: Kopfschmerztag/Monat, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				
					CFB LSmeans	95% CI	SMD 95% CI	Hedges' G	CI
PBO	Basln	252 (100.0)	13.8 (5.48)						
	1-12	252 (100.0)	10.8 (6.56)	-1.9 (0.41)					
	13-24	250 (99.2)	10.3 (6.56)	-2.4 (0.43)					
EPTI 100 mg	Basln	248 (100.0)	14.1 (5.57)						
	1-12	248 (100.0)	8.56 (6.22)	-4.4 (0.41)		-2.5	0.38	[-3.2;-1.7]	<.0001
	13-24	239 (96.4)	7.25 (6.22)	-5.4 (0.43)		-3.1	0.41	[-3.9;-2.3]	<.0001
EPTI 300 mg	Basln	250 (100.0)	14.1 (5.45)						
	1-12	250 (100.0)	8.17 (6.45)	-4.7 (0.41)		-2.8	0.38	[-3.6;-2.1]	<.0001
	13-24	243 (97.2)	6.81 (6.45)	-6.0 (0.42)		-3.6	0.41	[-4.4;-2.8]	<.0001

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-82: Kopfschmerztag/Monat, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	204 (100.0)	14.2 (5.80)						
	1-12	204 (100.0)	11.2 (6.96)	-2.2 (0.47)					
	13-24	202 (99.0)	10.8 (6.96)	-2.5 (0.48)					
EPTI 100 mg	Basln	207 (100.0)	14.2 (5.60)						
	1-12	207 (100.0)	8.40 (6.14)	-4.8 (0.47)		-2.6	0.45	[-3.5;-1.7]	<.0001
	13-24	198 (95.7)	7.18 (6.14)	-5.7 (0.48)		-3.2	0.48	[-4.1;-2.2]	<.0001
EPTI 300 mg	Basln	217 (100.0)	14.2 (5.50)						
	1-12	217 (100.0)	8.41 (6.65)	-4.8 (0.45)		-2.6	0.44	[-3.5;-1.8]	<.0001
	13-24	211 (97.2)	7.06 (6.65)	-6.0 (0.47)		-3.5	0.47	[-4.5;-2.6]	<.0001

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-83: Kopfschmerztag/Monat, CFB, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI
PBO	Basln	83 (100.0)	15.2 (6.04)						
	1-12	83 (100.0)	12.4 (6.99)	-1.4 (0.79)					
	13-24	83 (100.0)	11.4 (6.99)	-2.2 (0.82)					
EPTI 100 mg	Basln	77 (100.0)	15.2 (5.87)						
	1-12	77 (100.0)	10.1 (7.15)	-4.1 (0.77)	-2.8	0.71	[-4.2;-1.4]	0.0001	-0.6
	13-24	75 (97.4)	8.89 (7.15)	-5.2 (0.81)	-3.1	0.79	[-4.6;-1.5]	0.0001	-0.6
EPTI 300 mg	Basln	68 (100.0)	14.9 (5.40)						
	1-12	68 (100.0)	8.56 (6.78)	-5.1 (0.79)	-3.8	0.73	[-5.2;-2.4]	<.0001	-0.9
	13-24	67 (98.5)	7.69 (6.78)	-5.9 (0.83)	-3.7	0.81	[-5.3;-2.2]	<.0001	-0.8

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB LSmeans	95% CI	SMD 95% CI	G	CI

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans estimate using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.7.2 Reduktion um $\geq 50\%$

Tabelle 4G-84: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Interaktions-p-Werte

Interval	Description	Treatment Group	
		EPTI 100 mg	EPTI 300 mg
Weeks 1-12	Interaction test: Age Group	0.9645	0.6918
	Interaction test: EM/CM	0.6434	0.1848
	Interaction test: MOH	0.7223	0.6957
	Interaction test: Number of FPT	0.3411	0.6451
	Interaction test: Sex	0.3232	0.8450
Weeks 13-24	Interaction test: Age Group	0.1045	0.1959
	Interaction test: EM/CM	0.1357	0.1842
	Interaction test: MOH	0.1811	0.2097
	Interaction test: Number of FPT	0.8342	0.7103

Interval	Description	Treatment Group	
		EPTI 100 mg	EPTI 300 mg
		p-value	p-value
	Interaction test: Sex	0.5767	0.8936

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-85: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	67	6	(9.0)							
	13-24	66	17	(25.8)							
EPTI 100 mg	1-12	57	18	(31.6)	4.81	[1.82;14.4]	3.61	[1.51;8.65]	22.6	[8.75;36.5]	0.0012
	13-24	53	21	(39.6)	1.91	[0.86;4.31]	1.53	[0.90;2.59]	13.9	[-3.0;30.7]	0.1128
EPTI 300 mg	1-12	62	20	(32.3)	5.09	[1.96;15.0]	3.60	[1.53;8.48]	23.3	[9.81;36.8]	0.0006
	13-24	61	30	(49.2)	2.96	[1.38;6.51]	1.90	[1.17;3.08]	23.4	[7.03;39.8]	0.0049

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline: ≤ 14 / > 14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-86: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Subgruppe > 35 Jahre

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		1-12	220	31	(14.1)							
		13-24	219	53	(24.2)							
EPTI 100 mg		1-12	227	97	(42.7)	4.65	[2.95;7.49]	3.04	[2.13;4.36]	28.6	[20.7;36.5]	<.0001
		13-24	220	122	(55.5)	3.93	[2.62;5.95]	2.29	[1.77;2.98]	31.3	[22.6;39.9]	<.0001
EPTI 300 mg		1-12	223	112	(50.2)	6.22	[3.95;10.0]	3.57	[2.51;5.07]	36.1	[28.1;44.1]	<.0001
		13-24	217	133	(61.3)	4.97	[3.30;7.57]	2.53	[1.96;3.28]	37.1	[28.5;45.7]	<.0001

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-87: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Subgruppe männlich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		1-12	33	3	(9.1)							
		13-24	33	7	(21.2)							
EPTI 100 mg		1-12	21	10	(47.6)	9.40	[2.27;50.3]	5.10	[1.59;16.4]	38.5	[15.0;62.0]	0.0016
		13-24	20	8	(40.0)	2.24	[0.63;8.30]	1.82	[0.75;4.43]	18.8	[-6.8;44.4]	0.2134
EPTI 300 mg		1-12	32	13	(40.6)	9.38	[2.41;48.8]	5.01	[1.65;15.2]	31.5	[11.9;51.2]	0.0008
		13-24	32	17	(53.1)	6.17	[1.92;22.9]	2.69	[1.33;5.43]	31.9	[9.70;54.1]	0.0018

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B.

Tabelle 4G-88: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Subgruppe weiblich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	254	34	(13.4)								
	13-24	252	63	(25.0)								
EPTI 100 mg	1-12	263	105	(39.9)	4.40	[2.86;6.91]	2.98	[2.11;4.22]	26.5	[19.3;33.8]	<.0001	
	13-24	253	135	(53.4)	3.49	[2.39;5.12]	2.14	[1.68;2.72]	28.4	[20.2;36.5]	<.0001	
EPTI 300 mg	1-12	253	119	(47.0)	5.86	[3.81;9.22]	3.51	[2.50;4.93]	33.6	[26.2;41.1]	<.0001	
	13-24	246	146	(59.3)	4.45	[3.04;6.57]	2.37	[1.87;3.01]	34.3	[26.2;42.5]	<.0001	

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B.

Tabelle 4G-89: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Subgruppe EM

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	159	21	(13.2)							
	13-24	159	39	(24.5)							
EPTI 100 mg	1-12	154	67	(43.5)	5.06	[2.94;9.02]	3.29	[2.13;5.10]	30.3	[20.9;39.7]	<.0001
	13-24	149	87	(58.4)	4.31	[2.67;7.08]	2.38	[1.76;3.23]	33.9	[23.5;44.2]	<.0001
EPTI 300 mg	1-12	154	82	(53.2)	7.49	[4.36;13.3]	4.03	[2.64;6.17]	40.0	[30.6;49.5]	<.0001
	13-24	152	97	(63.8)	5.43	[3.35;8.95]	2.60	[1.93;3.50]	39.3	[29.1;49.4]	<.0001

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. EM: Episodic Migraine

Tabelle 4G-90: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Reduktion um $\geq 50\%$, Subgruppe CM

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	128	16	(12.5)							
	13-24	126	31	(24.6)							
EPTI 100 mg	1-12	130	48	(36.9)	4.29	[2.30;8.39]	2.93	[1.76;4.90]	24.4	[14.3;34.5]	<.0001
	13-24	124	56	(45.2)	2.52	[1.47;4.39]	1.83	[1.27;2.63]	20.6	[9.01;32.1]	0.0007
EPTI 300 mg	1-12	130	50	(38.5)	4.32	[2.32;8.42]	3.08	[1.86;5.12]	26.0	[15.8;36.1]	<.0001
	13-24	125	66	(52.8)	3.36	[1.96;5.85]	2.15	[1.52;3.04]	28.2	[16.7;39.7]	<.0001

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. CM : Chronic Migraine

Tabelle 4G-91: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Subgruppe MOH: ja

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	35	5	(14.3)							
	13-24	35	9	(25.7)							
EPTI 100 mg	1-12	36	15	(41.7)	4.08	[1.33;14.3]	3.13	[1.21;8.11]	27.4	[7.54;47.2]	0.0131
	13-24	34	14	(41.2)	1.74	[0.61;5.09]	1.66	[0.80;3.41]	15.5	[-6.5;37.4]	0.2966
EPTI 300 mg	1-12	35	17	(48.6)	5.14	[1.67;18.3]	3.58	[1.40;9.12]	34.3	[14.1;54.5]	0.0039
	13-24	35	17	(48.6)	2.26	[0.81;6.55]	1.88	[0.94;3.79]	22.9	[0.86;44.9]	0.1211

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-92: Kopfschmerztage/Monat, Reduktion um $\geq 50\%$, Subgruppe MOH: nein

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	252	32	(12.7)							
	13-24	250	61	(24.4)							
EPTI 100 mg	1-12	248	100	(40.3)	4.86	[3.12;7.74]	3.19	[2.23;4.55]	27.6	[20.3;35.0]	<.0001
	13-24	239	129	(54.0)	3.75	[2.55;5.55]	2.22	[1.73;2.84]	29.6	[21.3;37.8]	<.0001
EPTI 300 mg	1-12	250	115	(46.0)	6.15	[3.96;9.78]	3.64	[2.57;5.16]	33.3	[25.9;40.7]	<.0001
	13-24	243	146	(60.1)	4.82	[3.28;7.16]	2.47	[1.94;3.14]	35.7	[27.5;43.8]	<.0001

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-93: Kopfschmerztage/Monat, Reduktion um $\geq 50\%$, Subgruppe 2 Vortherapien

Treatment		Responders			Odds Ratio		Relative Risk		Risk Difference		
Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	204	27	(13.2)							
	13-24	202	50	(24.8)							
EPTI 100 mg	1-12	207	91	(44.0)	5.29	[3.27;8.80]	3.32	[2.26;4.87]	30.7	[22.5;38.9]	<.0001
	13-24	198	103	(52.0)	3.35	[2.19;5.17]	2.10	[1.59;2.77]	27.3	[18.1;36.4]	<.0001
EPTI 300 mg	1-12	217	99	(45.6)	5.66	[3.51;9.37]	3.45	[2.36;5.05]	32.4	[24.3;40.5]	<.0001
	13-24	211	126	(59.7)	4.60	[3.02;7.09]	2.41	[1.85;3.15]	35.0	[26.1;43.9]	<.0001

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-94: Kopfschmerztag/Monat, Reduktion um $\geq 50\%$, Subgruppe > 2 Vortherapien

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	83	10	(12.0)								
	13-24	83	20	(24.1)								
EPTI 100 mg	1-12	77	24	(31.2)	3.28	[1.47;7.76]	2.60	[1.33;5.09]	19.1	[6.63;31.6]	0.0033	
	13-24	75	40	(53.3)	3.65	[1.86;7.33]	2.24	[1.45;3.45]	29.2	[14.7;43.8]	0.0001	
EPTI 300 mg	1-12	68	33	(48.5)	7.00	[3.17;16.6]	4.03	[2.14;7.57]	36.5	[22.7;50.3]	<.0001	
	13-24	67	37	(55.2)	3.91	[1.96;7.99]	2.29	[1.48;3.56]	31.1	[16.1;46.2]	<.0001	

The 50% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.7.3 Reduktion um $\geq 75\%$ Tabelle 4G-95: Kopfschmerztag/Monat, Reduktion um $\geq 75\%$, Interaktions-p-Werte

Interval	Description	Treatment Group	
		EPTI 100 mg p-value	EPTI 300 mg p-value
Weeks 1-12	Interaction test: Age Group	0.7130	0.4016
	Interaction test: EM/CM	0.9849	0.9045
	Interaction test: MOH	0.2750	0.4101
	Interaction test: Number of FPT	0.4245	0.7351
	Interaction test: Sex	0.7216	0.8381
Weeks 13-24	Interaction test: Age Group	0.8595	0.8356
	Interaction test: EM/CM	0.9428	0.9205
	Interaction test: MOH	0.4824	0.5185
	Interaction test: Number of FPT	0.2571	0.5186
	Interaction test: Sex	0.2060	0.2441

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-96: Kopfschmerztag/Monat, Reduktion um $\geq 75\%$, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	1-12	67	2	(3.0)							
	13-24	66	5	(7.6)							
EPTI 100 mg	1-12	57	9	(15.8)	5.95	[1.44;40.5]	4.85	[1.15;20.5]	12.8	[2.50;23.1]	0.0122
	13-24	53	11	(20.8)	3.19	[1.07;10.8]	2.72	[1.01;7.31]	13.2	[0.53;25.8]	0.0374

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 300 mg	1-12	62	7	(11.3)	4.21	[0.96;29.2]	3.74	[0.82;17.0]	8.31	[-.56;17.2]	0.0568
	13-24	61	16	(26.2)	4.41	[1.59;14.4]	3.45	[1.35;8.82]	18.7	[5.90;31.4]	0.0038

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B.

Tabelle 4G-97: Kopfschmerztag/Monat, Reduktion um ≥ 75 %, Subgruppe > 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	220	5	(2.3)							
	13-24	219	15	(6.8)							
EPTI 100 mg	1-12	227	36	(15.9)	8.34	[3.49;24.7]	7.08	[2.83;17.7]	13.6	[8.44;18.7]	<.0001
	13-24	220	45	(20.5)	3.57	[1.96;6.84]	3.01	[1.73;5.22]	13.6	[7.31;19.9]	<.0001
EPTI 300 mg	1-12	223	40	(17.9)	9.59	[4.05;28.3]	7.93	[3.19;19.7]	15.7	[10.3;21.1]	<.0001
	13-24	217	58	(26.7)	5.05	[2.82;9.58]	3.92	[2.29;6.68]	19.9	[13.1;26.7]	<.0001

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B.

Tabelle 4G-98: Kopfschmerztag/Monat, Reduktion um $\geq 75\%$, Subgruppe männlich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		1-12	33	1	(3.0)							
		13-24	33	2	(6.1)							
EPTI 100 mg		1-12	21	3	(14.3)	5.16	[0.56; 114]	4.07	[0.47;35.1]	11.3	[-4.8;27.3]	0.1501
		13-24	20	1	(5.0)	0.71	[0.03;8.74]	0.68	[0.07;6.76]	-1.1	[-14;11.5]	0.7892
EPTI 300 mg		1-12	32	7	(21.9)	16.7	[2.31; 355]	9.17	[1.20;70.0]	18.8	[3.37;34.3]	0.0034
		13-24	32	13	(40.6)	26.4	[4.60; 271]	8.17	[1.96;34.1]	34.6	[15.7;53.4]	<.0001

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline: ≤ 14 / > 14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B.

Tabelle 4G-99: Kopfschmerztag/Monat, Reduktion um $\geq 75\%$, Subgruppe weiblich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		1-12	254	6	(2.4)							
		13-24	252	18	(7.1)							
EPTI 100 mg		1-12	263	42	(16.0)	7.98	[3.58;21.3]	6.79	[2.94;15.7]	13.6	[8.80;18.4]	<.0001
		13-24	253	55	(21.7)	3.66	[2.11;6.61]	3.05	[1.85;5.04]	14.6	[8.60;20.6]	<.0001
EPTI 300 mg		1-12	253	40	(15.8)	7.80	[3.48;20.8]	6.63	[2.87;15.3]	13.4	[8.58;18.3]	<.0001
		13-24	246	61	(24.8)	4.31	[2.50;7.75]	3.46	[2.11;5.67]	17.7	[11.4;23.9]	<.0001

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B.

Tabelle 4G-100: Kopfschmerztag/Monat, Reduktion um ≥ 75 %, Subgruppe EM

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	159	5	(3.1)								
	13-24	159	14	(8.8)								
EPTI 100 mg	1-12	154	31	(20.1)	7.74	[3.18;23.2]	6.40	[2.56;16.0]	17.0	[10.1;23.9]	<.0001	
	13-24	149	37	(24.8)	3.42	[1.80;6.84]	2.82	[1.59;5.00]	16.0	[7.81;24.2]	0.0001	
EPTI 300 mg	1-12	154	33	(21.4)	8.44	[3.48;25.3]	6.81	[2.73;17.0]	18.3	[11.3;25.3]	<.0001	
	13-24	152	48	(31.6)	4.83	[2.59;9.54]	3.59	[2.06;6.23]	22.8	[14.2;31.4]	<.0001	

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B. EM: Episodic Migraine

Tabelle 4G-101: Kopfschmerztag/Monat, Reduktion um ≥ 75 %, Reduktion um ≥ 75 %, Subgruppe CM

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		1-12	128	2	(1.6)							
		13-24	126	6	(4.8)							
EPTI 100 mg		1-12	130	14	(10.8)	7.55	[2.05;48.8]	6.25	[1.54;25.3]	9.21	[3.46;15.0]	0.0012
		13-24	124	19	(15.3)	3.60	[1.46;10.2]	3.26	[1.33;7.96]	10.6	[3.21;17.9]	0.0047
EPTI 300 mg		1-12	130	14	(10.8)	7.45	[2.02;48.2]	6.63	[1.59;27.7]	9.21	[3.46;15.0]	0.0014
		13-24	125	26	(20.8)	5.14	[2.16;14.3]	4.39	[1.87;10.3]	16.0	[8.01;24.1]	0.0001

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. CM: Chronic Migraine

Tabelle 4G-102: Kopfschmerztage/Monat, Reduktion um ≥ 75 %, Subgruppe MOH: ja

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		1-12	35	0	(0)							
		13-24	35	2	(5.7)							
EPTI 100 mg		1-12	36	5	(13.9)	24E4	[1.83;]		[;]	13.9	[2.59;25.2]	0.0142
		13-24	34	4	(11.8)	1.49	[0.25;11.9]	1.55	[0.30;7.99]	6.05	[-7.2;19.3]	0.6677
EPTI 300 mg		1-12	35	3	(8.6)	14E4	[0.91;]		[;]	8.57	[-.70;17.8]	0.0583
		13-24	35	6	(17.1)	2.38	[0.46;17.9]	2.59	[0.59;11.5]	11.4	[-3.2;26.1]	0.3103

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-103: Kopfschmerztage/Monat, Reduktion um ≥ 75 %, Subgruppe MOH: nein

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	252	7	(2.8)								
	13-24	250	18	(7.2)								
EPTI 100 mg	1-12	248	40	(16.1)	6.92	[3.22;17.2]	5.87	[2.68;12.8]	13.4	[8.34;18.4]	<.0001	
	13-24	239	52	(21.8)	3.66	[2.10;6.64]	3.04	[1.83;5.04]	14.6	[8.42;20.7]	<.0001	
EPTI 300 mg	1-12	250	44	(17.6)	7.71	[3.61;19.1]	6.42	[2.94;14.0]	14.8	[9.68;20.0]	<.0001	
	13-24	243	68	(28.0)	5.13	[3.00;9.20]	3.91	[2.40;6.37]	20.8	[14.3;27.3]	<.0001	

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-104: Kopfschmerztag/Monat, Reduktion um $\geq 75\%$, Subgruppe 2 Vortherapien

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	204	5	(2.5)							
	13-24	202	13	(6.4)							
EPTI 100 mg	1-12	207	38	(18.4)	9.07	[3.80;26.9]	7.41	[2.99;18.4]	15.9	[10.2;21.6]	<.0001
	13-24	198	44	(22.2)	4.18	[2.22;8.35]	3.42	[1.91;6.13]	15.8	[9.08;22.5]	<.0001
EPTI 300 mg	1-12	217	38	(17.5)	8.65	[3.63;25.6]	7.19	[2.89;17.9]	15.1	[9.58;20.5]	<.0001
	13-24	211	57	(27.0)	5.47	[2.96;10.8]	4.21	[2.38;7.44]	20.6	[13.7;27.5]	<.0001

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs).

The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-105: Kopfschmerztag/Monat, Reduktion um $\geq 75\%$, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	1-12	83	2	(2.4)							
	13-24	83	7	(8.4)							
EPTI 100 mg	1-12	77	7	(9.1)	4.12	[0.95;28.4]	3.96	[0.85;18.6]	6.68	[-.54;13.9]	0.0587
	13-24	75	12	(16.0)	2.09	[0.78;5.99]	1.91	[0.80;4.59]	7.57	[-2.7;17.8]	0.1415
EPTI 300 mg	1-12	68	9	(13.2)	6.27	[1.54;42.3]	5.48	[1.23;24.5]	10.8	[2.12;19.5]	0.0088
	13-24	67	17	(25.4)	3.79	[1.50;10.6]	3.01	[1.33;6.82]	16.9	[4.93;29.0]	0.0044

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The 75% response variable across the three 4-week intervals is calculated as the average percentage change in MHDs (based on the available monthly values of MHDs). The OR and p-values are based on logistic regression model including baseline MHDs as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. If the MHDs value is missing for a given month, the responder status is derived based on the available values.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.7.4 Reduktion um 100 %

Es wurden keine Interaktions-p-Werte berechnet.

Tabelle 4G-106: Reduktion der monatlichen Kopfschmerztage um 100 %, Subgruppenanalysen

Table 3 Analysis of Proportion of Patients with 100% Reduction in Monthly Headache Days (AMNOG)

	PBO		EPTI 100 mg		p-value	EPTI 300 mg		p-value
	n	%	n	%		n	%	
Week 1-12	287	1.2	284	4.3	0.020	285	5.5	0.0037
Week 13-24	285	3.3	273	9.3	0.0032	278	11.7	0.0001
Sub-group analyses								
<= 35 years, week 1-12	67	1.5	57	5.2	0.28	62	4.8	0.28
<= 35 years, week 13-24	66	4.5	53	10.7	0.23	62	10.9	0.18
> 35 years, week 1-12	220	1.1	227	4.1	0.041	223	5.7	0.007
> 35 years, week 13-24	219	2.9	220	8.9	0.0065	217	12.0	0.00029
2 failures, week 1-12	204	1.3	207	5.3	0.025	217	5.8	0.013
2 failures, week 13-24	202	3.0	198	10.6	0.0026	211	12.0	0.00049
3+ failures, week 1-12	83	0.8	77	1.7	0.57	68	4.4	0.15
3+ failures, week 13-24	83	4.4	75	5.8	0.57	67	10.9	0.10
CM, week 1-12	128	0.5	130	3.3	0.14	130	2.6	0.45
CM, week 13-24	126	2.6	124	5.1	0.062	125	8.2	0.003
EM, week 1-12	159	1.7	154	5.2	0.014	154	8.0	0.0005
EM, week 13-24	159	5.0	149	12.7	0.001	152	14.7	0.003
Female, week 1-12	254	1.2	263	4.3	0.03	253	5.1	0.012
Female, week 13-24	252	3.0	253	9.9	0.0016	246	10.8	0.00064
Male, week 1-12	33	1.0	21	4.7	0.45	32	8.3	0.0923
Male, week 13-24	33	5.1	20	1.7	0.45	32	18.7	0.039
MOH, week 1-12	35	0.0	36	4.6	0.28	35	1.9	0.52
MOH, week 13-24	35	1.9	34	7.9	0.39	35	6.6	0.47
No MOH, week 1-12	252	1.3	248	4.3	0.042	250	6.0	0.0047
No MOH, week 13-24	350	3.5	239	9.5	0.0056	243	12.5	0.00019

N refers to the number of subjects in the analysis at the relevant interval.

The p-values are computed separately for each active treatment group using extended CMH test, adjusting for the stratification factor (MHDs at baseline <=14/>14).

The 100% responder rate for the 12-week interval is derived based on the average 100% responder status for the 4-week intervals included in the interval.

If any of the months included in the 12-week interval has a missing value of MHDs, the response status is imputed with a non-response.

4.2.8 Kopfschmerzepisoden/Monat

Tabelle 4G-107: Kopfschmerzepisoden/Monat, CFB, Interaktions p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.8756	0.6109
Interaction test: EM/CM	0.2207	0.6057
Interaction test: MOH	0.0188	0.0624
Interaction test: Number of FPT	0.6162	0.0700
Interaction test: Sex	0.8432	0.1809

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-108: Kopfschmerzepisoden/Monat, CFB, Interaktions p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.7454	0.3854
Interaction test: EM/CM	0.9920	0.6256
Interaction test: MOH	0.7606	0.6873
Interaction test: Number of FPT	0.4534	0.2928
Interaction test: Sex	0.9526	0.8442

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-109: Kopfschmerzepisoden/Monat, CFB, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		SMD 95% CI	
					Diff.	SE	CI	95% CI		G	CI
								G	CI		
PBO	Basln	67 (100.0)	11.2 (5.40)								
	1-12	67 (100.0)	8.18 (5.30)	-2.4 (0.57)							
	13-24	66 (98.5)	7.22 (5.30)	-3.2 (0.60)							
EPTI 100 mg	Basln	57 (100.0)	11.7 (5.93)								
	1-12	57 (100.0)	6.62 (4.85)	-4.2 (0.60)	-1.9	0.64	[-3.1;-.62]		0.0036	-0.5	[-.89;-.18]
	13-24	53 (93.0)	5.41 (4.85)	-5.4 (0.63)	-2.2	0.69	[-3.6;-.83]		0.0018	-0.6	[-.95;-.22]
EPTI 300 mg	Basln	62 (100.0)	12.4 (6.16)								
	1-12	62 (100.0)	7.89 (6.63)	-3.1 (0.61)	-0.8	0.63	[-2.0;0.48]		0.2234	-0.2	[-.56;0.13]
	13-24	61 (98.4)	6.34 (6.63)	-4.4 (0.64)	-1.2	0.68	[-2.6;0.14]		0.0774	-0.3	[-.67;0.04]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-110: Kopfschmerzepisoden/Monat, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB			Comparison to PBO		SMD 95% CI	
					LSmeans			95% CI			
					Diff.			SE	CI	p-value	G
PBO	Basln	220 (100.0)	12.4 (6.52)								
	1-12	220 (100.0)	9.10 (5.54)	-2.7 (0.38)							
	13-24	219 (99.5)	8.13 (5.54)	-3.5 (0.39)							
EPTI 100 mg	Basln	227 (100.0)	11.8 (5.74)								
	1-12	227 (100.0)	6.75 (5.41)	-4.7 (0.37)	-2.0	0.35	[-2.7;-1.3]	<.0001		-0.5	[-.72;-.35]
	13-24	220 (96.9)	5.88 (5.41)	-5.5 (0.38)	-2.0	0.38	[-2.7;-1.3]	<.0001		-0.5	[-.69;-.32]
EPTI 300 mg	Basln	223 (100.0)	11.5 (5.90)								
	1-12	223 (100.0)	6.10 (5.26)	-5.2 (0.36)	-2.5	0.35	[-3.2;-1.8]	<.0001		-0.7	[-.85;-.48]
	13-24	217 (97.3)	5.21 (5.26)	-6.1 (0.38)	-2.6	0.38	[-3.3;-1.8]	<.0001		-0.7	[-.84;-.46]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.
N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-111: Kopfschmerzepisoden/Monat, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	33 (100.0)	13.6 (7.70)								
	1-12	33 (100.0)	10.1 (6.49)	-3.0 (0.99)							
	13-24	33 (100.0)	9.69 (6.49)	-3.4 (1.07)							
EPTI 100 mg	Basln	21 (100.0)	13.4 (6.03)								
	1-12	21 (100.0)	8.21 (7.25)	-4.6 (1.13)	-1.5	1.34	[-4.2;1.15]	0.2599	-0.3	[-.87;0.24]	
	13-24	20 (95.2)	8.15 (7.25)	-4.6 (1.25)	-1.2	1.50	[-4.1;1.82]	0.4414	-0.2	[-.78;0.34]	
EPTI 300 mg	Basln	32 (100.0)	12.3 (4.71)								
	1-12	32 (100.0)	7.22 (6.57)	-5.5 (0.96)	-2.5	1.15	[-4.8;-.17]	0.0353	-0.5	[-1.0;-.04]	
	13-24	32 (100.0)	6.16 (6.57)	-6.6 (1.04)	-3.2	1.29	[-5.7;-.59]	0.0167	-0.6	[-1.1;-.11]	

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-112: Kopfschmerzepisoden/Monat, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB			Comparison to PBO		SMD 95% CI	
					LSmeans			95% CI		Hedges'	
					Diff.	SE	CI	p-value	G	CI	
PBO	Basln	254 (100.0)	12.0 (6.07)								
	1-12	254 (100.0)	8.72 (5.32)	-2.4 (0.35)							
	13-24	252 (99.2)	7.69 (5.32)	-3.3 (0.36)							
EPTI 100 mg	Basln	263 (100.0)	11.6 (5.74)								
	1-12	263 (100.0)	6.60 (5.08)	-4.3 (0.35)	-1.9	0.32	[-2.5;-1.3]	<.0001	-0.5	[-.70;-.35]	
	13-24	253 (96.2)	5.61 (5.08)	-5.3 (0.36)	-2.0	0.34	[-2.6;-1.3]	<.0001	-0.5	[-.69;-.34]	
EPTI 300 mg	Basln	253 (100.0)	11.6 (6.10)								
	1-12	253 (100.0)	6.40 (5.47)	-4.5 (0.34)	-2.1	0.32	[-2.7;-1.5]	<.0001	-0.6	[-.76;-.41]	
	13-24	246 (97.2)	5.36 (5.47)	-5.5 (0.35)	-2.2	0.34	[-2.9;-1.5]	<.0001	-0.6	[-.76;-.41]	

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-113: Kopfschmerzepisoden/Monat, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	159 (100.0)	8.83 (2.93)		-1.5 (0.31)	0.28	[-2.1;-.99]	<.0001	-0.6	[-.84;-.39]	
	1-12	159 (100.0)	6.47 (3.89)	-1.5 (0.31)							
	13-24	159 (100.0)	6.02 (3.89)	-2.0 (0.32)							
EPTI 100 mg	Basln	154 (100.0)	8.91 (3.03)		-3.1 (0.31)	0.31	[-2.5;-1.3]	<.0001	-0.7	[-.93;-.48]	
	1-12	154 (100.0)	4.97 (3.42)	-3.1 (0.31)							
	13-24	149 (96.8)	4.14 (3.42)	-3.9 (0.33)							
EPTI 300 mg	Basln	154 (100.0)	8.39 (2.76)		-3.6 (0.30)	0.29	[-2.7;-1.5]	<.0001	-0.8	[-1.1;-.61]	
	1-12	154 (100.0)	4.19 (2.92)	-3.6 (0.30)							
	13-24	152 (98.7)	3.48 (2.92)	-4.4 (0.32)							

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-114: Kopfschmerzepisoden/Monat, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	128 (100.0)	16.3 (6.88)		-4.2 (0.75)			0.0001	-0.5	[-.73;-.24]	
	1-12	128 (100.0)	11.9 (6.26)	-4.2 (0.75)							
	13-24	126 (98.4)	10.3 (6.26)	-5.5 (0.79)							
EPTI 100 mg	Basln	130 (100.0)	15.2 (6.37)		-6.5 (0.72)	0.58	[-3.4;-1.1]	0.0001	-0.5	[-.73;-.24]	
	1-12	130 (100.0)	8.80 (6.39)	-6.5 (0.72)		-2.3					
	13-24	124 (95.4)	7.77 (6.39)	-7.5 (0.76)		-2.0	0.64	[-3.3;-.75]	0.0018	-0.4	[-.65;-.15]
EPTI 300 mg	Basln	130 (100.0)	15.6 (6.34)		-6.4 (0.74)	0.58	[-3.3;-1.1]	0.0002	-0.5	[-.72;-.23]	
	1-12	130 (100.0)	9.32 (6.98)	-6.4 (0.74)		-2.2					
	13-24	125 (96.2)	7.90 (6.98)	-7.7 (0.78)		-2.2	0.63	[-3.5;-.98]	0.0005	-0.4	[-.69;-.20]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.
N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-115: Kopfschmerzepisoden/Monat, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	35 (100.0)	17.6 (7.27)								
	1-12	35 (100.0)	12.9 (6.85)	-3.2 (1.13)							
	13-24	35 (100.0)	11.1 (6.85)	-4.9 (1.21)							
EPTI 100 mg	Basln	36 (100.0)	16.1 (6.64)								
	1-12	36 (100.0)	9.47 (7.46)	-5.7 (1.05)	-2.5	1.23	[-4.9;-.04]	0.0468	-0.5	[-.95;-.01]	
	13-24	34 (94.4)	9.07 (7.46)	-6.1 (1.13)	-1.2	1.35	[-3.9;1.49]	0.3793	-0.2	[-.69;0.27]	
EPTI 300 mg	Basln	35 (100.0)	13.9 (5.75)								
	1-12	35 (100.0)	7.72 (6.15)	-7.2 (1.10)	-4.0	1.28	[-6.6;-1.5]	0.0022	-0.8	[-1.2;-.28]	
	13-24	35 (100.0)	7.30 (6.15)	-7.5 (1.18)	-2.5	1.40	[-5.3;0.24]	0.0734	-0.4	[-.91;0.04]	

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-116: Kopfschmerzepisoden/Monat, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								G	CI	
PBO	Basln	252 (100.0)	11.4 (5.75)							
	1-12	252 (100.0)	8.31 (5.16)	-2.4 (0.33)						
	13-24	250 (99.2)	7.50 (5.16)	-3.1 (0.35)						
EPTI 100 mg	Basln	248 (100.0)	11.1 (5.36)							
	1-12	248 (100.0)	6.32 (4.77)	-4.2 (0.33)	-1.8	0.31	[-2.4;-1.2]	<.0001	-0.5	[-.70;-.35]
	13-24	239 (96.4)	5.33 (4.77)	-5.2 (0.35)	-2.1	0.34	[-2.7;-1.4]	<.0001	-0.6	[-.73;-.38]
EPTI 300 mg	Basln	250 (100.0)	11.4 (5.93)							
	1-12	250 (100.0)	6.32 (5.48)	-4.3 (0.33)	-1.9	0.31	[-2.5;-1.3]	<.0001	-0.6	[-.74;-.39]
	13-24	243 (97.2)	5.19 (5.48)	-5.4 (0.34)	-2.3	0.34	[-3.0;-1.6]	<.0001	-0.6	[-.80;-.44]

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-117: Kopfschmerzepisoden/Monat, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	204 (100.0)	11.9 (6.22)		-2.7 (0.38)	0.36	[-2.7;-1.2]	<.0001	-0.5	[-.72;-.34]	
	1-12	204 (100.0)	8.55 (5.44)								
	13-24	202 (99.0)	7.78 (5.44)								
EPTI 100 mg	Basln	207 (100.0)	11.8 (5.79)		-4.7 (0.38)	0.39	[-2.9;-1.3]	<.0001	-0.5	[-.73;-.34]	
	1-12	207 (100.0)	6.39 (5.18)								
	13-24	198 (95.7)	5.49 (5.18)								
EPTI 300 mg	Basln	217 (100.0)	11.7 (6.02)		-4.6 (0.37)	0.36	[-2.6;-1.2]	<.0001	-0.5	[-.71;-.32]	
	1-12	217 (100.0)	6.45 (5.54)								
	13-24	211 (97.2)	5.34 (5.54)								

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-118: Kopfschmerzepisoden/Monat, CFB, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		SMD 95% CI	
					Diff.	SE	CI	95% CI		Hedges' G	CI
								p-value			
PBO	Basln	83 (100.0)	12.7 (6.45)		-2.3 (0.64)	0.58	[-2.8;-.52]	0.0044	-0.5 [-.77;-.14]		
	1-12	83 (100.0)	9.69 (5.65)	-2.3 (0.64)							
	13-24	83 (100.0)	8.27 (5.65)	-3.4 (0.66)							
EPTI 100 mg	Basln	77 (100.0)	11.7 (5.73)		-3.9 (0.61)	0.58	[-2.8;-.52]	0.0044	-0.5 [-.77;-.14]		
	1-12	77 (100.0)	7.60 (5.59)	-3.9 (0.61)							
	13-24	75 (97.4)	6.60 (5.59)	-5.0 (0.64)							
EPTI 300 mg	Basln	68 (100.0)	11.7 (5.81)		-4.8 (0.63)	0.59	[-3.7;-.1.3]	<.0001	-0.7 [-1.0;-.37]		
	1-12	68 (100.0)	6.62 (5.82)	-4.8 (0.63)							
	13-24	67 (98.5)	5.82 (5.82)	-5.6 (0.66)							

Missing eDiary data is handled using the rules provided in the SAP.

The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.9 Kopfschmerzepisoden mit schwerer Schmerzintensität

Tabelle 4G-119: Kopfschmerzepisoden mit schwerer Schmerzintensität, CFB, Interaktions p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.7361	0.0754
Interaction test: EM/CM	0.1164	0.0827

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: MOH	0.2528	0.4480
Interaction test: Number of FPT	0.8587	0.6439
Interaction test: Sex	0.9449	0.3723

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-120: Kopfschmerzepisoden mit schwerer Schmerzintensität, Interaktions p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.9267	0.2635
Interaction test: EM/CM	0.3320	0.0534
Interaction test: MOH	0.6881	0.6393
Interaction test: Number of FPT	0.7638	0.8544
Interaction test: Sex	0.6601	0.3896

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-121: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Diff.	SE	CI	p-value	Comparison to PBO	
									CFB LSmeans	
									Hedges' G	SMD 95% CI
PBO	Basln	67 (100.0)	38.5 (28.6)							
	1-12	67 (100.0)	35.1 (33.1)	-3.3 (3.73)						
	13-24	66 (98.5)	34.2 (33.1)	-4.7 (4.06)						
EPTI 100 mg	Basln	57 (100.0)	45.2 (29.2)							
	1-12	57 (100.0)	34.7 (35.9)	-6.8 (3.83)	-3.5	4.06	[-11;4.53]	0.3920	-0.2	[-.51;0.20]
	13-24	53 (93.0)	31.0 (35.9)	-9.0 (4.28)	-4.3	4.77	[-14;5.12]	0.3699	-0.2	[-.53;0.20]
EPTI 300 mg	Basln	62 (100.0)	41.9 (25.0)							
	1-12	62 (100.0)	26.8 (33.3)	-14 (3.93)	-10.4	4.00	[-18;-2.5]	0.0103	-0.5	[-.80;-.11]
	13-24	61 (98.4)	26.4 (33.3)	-14 (4.28)	-9.5	4.60	[-19;-.38]	0.0412	-0.4	[-.72;-.01]

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-122: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			SMD 95% CI		
					CFB			95% CI		
			LSmeans			Diff.	SE	CI	p-value	Hedges' G
PBO	Basln	220 (100.0)	38.5 (29.6)							
	1-12	220 (100.0)	30.7 (34.3)	-9.5 (2.21)						
	13-24	219 (99.5)	29.1 (34.3)	-11 (2.32)						
EPTI 100 mg	Basln	227 (100.0)	43.9 (28.3)							
	1-12	227 (100.0)	26.8 (32.0)	-17 (2.15)	-7.5	2.05	[-12;-3.5]	0.0003	-0.3	[-.53;-.16]
	13-24	220 (96.9)	23.8 (32.0)	-19 (2.27)	-8.4	2.27	[-13;-4.0]	0.0002	-0.4	[-.54;-.17]
EPTI 300 mg	Basln	223 (100.0)	41.0 (27.6)							
	1-12	223 (100.0)	21.7 (29.5)	-20 (2.13)	-10.3	2.06	[-14;-6.3]	<.0001	-0.5	[-.66;-.29]
	13-24	217 (97.3)	20.1 (29.5)	-21 (2.25)	-9.6	2.28	[-14;-5.1]	<.0001	-0.4	[-.59;-.22]

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.
N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-123: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		SMD 95% CI	
					Diff.	SE	CI	95% CI		G	CI
								G	CI		
PBO	Basln	33 (100.0)	37.2 (30.2)								
	1-12	33 (100.0)	26.0 (33.5)	-10 (4.73)							
	13-24	33 (100.0)	28.4 (33.5)	-8.6 (5.43)							
EPTI 100 mg	Basln	21 (100.0)	42.2 (30.9)								
	1-12	21 (100.0)	22.6 (30.0)	-20 (5.41)	-9.6	6.47	[-22;3.34]		0.1438	-0.4	[-.97;0.14]
	13-24	20 (95.2)	23.6 (30.0)	-19 (6.45)	-10.8	7.81	[-26;4.76]		0.1709	-0.4	[-.96;0.17]
EPTI 300 mg	Basln	32 (100.0)	39.5 (27.9)								
	1-12	32 (100.0)	25.4 (31.8)	-17 (4.59)	-6.5	5.26	[-17;4.02]		0.2224	-0.3	[-.80;0.19]
	13-24	32 (100.0)	23.6 (31.8)	-18 (5.32)	-9.6	6.50	[-23;3.41]		0.1460	-0.4	[-.86;0.13]

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-124: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB			Comparison to PBO		SMD 95% CI	
					LSmeans			95% CI			
								Diff.	SE	CI	p-value
PBO	Basln	254 (100.0)	38.7 (29.3)								
	1-12	254 (100.0)	32.5 (34.1)	-7.3 (2.13)							
	13-24	252 (99.2)	30.5 (34.1)	-9.1 (2.23)							
EPTI 100 mg	Basln	263 (100.0)	44.3 (28.3)								
	1-12	263 (100.0)	28.8 (33.1)	-15 (2.10)	-7.3	1.92	[-11;-3.5]	0.0002		-0.3	[-.51;-.16]
	13-24	253 (96.2)	25.3 (33.1)	-17 (2.21)	-8.2	2.14	[-12;-4.0]	0.0001		-0.3	[-.52;-.17]
EPTI 300 mg	Basln	253 (100.0)	41.4 (26.9)								
	1-12	253 (100.0)	22.5 (30.3)	-19 (2.05)	-11.8	1.94	[-16;-8.0]	<.0001		-0.5	[-.71;-.36]
	13-24	246 (97.2)	21.2 (30.3)	-19 (2.17)	-10.3	2.15	[-15;-6.1]	<.0001		-0.4	[-.61;-.25]

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.
N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B.

Tabelle 4G-125: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			SMD 95% CI		
					CFB LSmeans			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	159 (100.0)	36.2 (32.2)							
	1-12	159 (100.0)	30.6 (34.9)	-6.1 (2.83)						
	13-24	159 (100.0)	27.6 (34.9)	-9.8 (2.90)						
EPTI 100 mg	Basln	154 (100.0)	44.2 (28.8)							
	1-12	154 (100.0)	27.9 (31.4)	-14 (2.84)	-7.5	2.63	[-13;-2.3]	0.0045	-0.3	[-.54;-.10]
	13-24	149 (96.8)	21.5 (31.4)	-19 (2.94)	-9.5	2.80	[-15;-4.0]	0.0008	-0.4	[-.61;-.16]
EPTI 300 mg	Basln	154 (100.0)	40.6 (27.3)							
	1-12	154 (100.0)	20.1 (29.2)	-19 (2.75)	-13.2	2.63	[-18;-8.1]	<.0001	-0.6	[-.79;-.35]
	13-24	152 (98.7)	18.3 (29.2)	-21 (2.86)	-10.8	2.78	[-16;-5.3]	0.0001	-0.4	[-.66;-.22]

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-126: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB			Comparison to PBO		SMD 95% CI	
					LSmeans			95% CI			
								Hedges'			G
PBO	Basln	128 (100.0)	41.4 (25.2)								
	1-12	128 (100.0)	33.0 (32.5)	-9.8 (3.23)							
	13-24	126 (98.4)	33.7 (32.5)	-8.8 (3.57)							
EPTI 100 mg	Basln	130 (100.0)	44.0 (28.1)								
	1-12	130 (100.0)	29.0 (34.2)	-15 (3.07)	-5.2	2.48	[-10;-.29]	0.0378		-0.3 [-.50;-.01]	
	13-24	124 (95.4)	29.5 (34.2)	-14 (3.43)	-5.0	2.94	[-11;0.80]	0.0912		-0.2 [-.46;.03]	
EPTI 300 mg	Basln	130 (100.0)	42.2 (26.6)								
	1-12	130 (100.0)	26.3 (31.6)	-17 (3.19)	-6.7	2.47	[-12;-.18]	0.0070		-0.3 [-.58;-.09]	
	13-24	125 (96.2)	25.5 (31.6)	-17 (3.53)	-7.8	2.93	[-14;-.20]	0.0083		-0.3 [-.58;-.09]	

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.
N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-127: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								G	CI	
PBO	Basln	35 (100.0)	41.9 (26.2)							
	1-12	35 (100.0)	34.0 (33.1)	-8.7 (4.58)						
	13-24	35 (100.0)	35.6 (33.1)	-8.6 (5.50)						
EPTI 100 mg	Basln	36 (100.0)	53.6 (31.2)							
	1-12	36 (100.0)	41.5 (37.5)	-5.7 (4.18)	2.9	5.11	[-7.2;13.1]	0.5669	0.1	[-.33;0.61]
	13-24	34 (94.4)	36.4 (37.5)	-9.9 (5.10)	-1.3	6.56	[-14;11.8]	0.8478	-0.0	[-.52;0.43]
EPTI 300 mg	Basln	35 (100.0)	40.6 (22.9)							
	1-12	35 (100.0)	26.5 (34.0)	-13 (4.36)	-4.5	5.01	[-14;5.48]	0.3749	-0.2	[-.69;0.26]
	13-24	35 (100.0)	29.7 (34.0)	-11 (5.20)	-2.5	6.39	[-15;10.1]	0.6926	-0.1	[-.57;0.38]

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-128: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			SMD 95% CI		
					CFB			95% CI		
			LSmeans			Diff.	SE	CI	p-value	Hedges' G
PBO	Basln	252 (100.0)	38.1 (29.8)							
	1-12	252 (100.0)	31.4 (34.1)	-8.6 (2.11)						
	13-24	250 (99.2)	29.6 (34.1)	-10 (2.19)						
EPTI 100 mg	Basln	248 (100.0)	42.7 (27.8)							
	1-12	248 (100.0)	26.5 (31.9)	-16 (2.10)	-7.8	1.95	[-12;-4.0]	<.0001	-0.4	[-.53;-.18]
	13-24	239 (96.4)	23.5 (31.9)	-19 (2.20)	-8.3	2.13	[-13;-4.1]	0.0001	-0.4	[-.53;-.18]
EPTI 300 mg	Basln	250 (100.0)	41.3 (27.6)							
	1-12	250 (100.0)	22.3 (29.8)	-19 (2.06)	-10.7	1.95	[-15;-6.9]	<.0001	-0.5	[-.67;-.32]
	13-24	243 (97.2)	20.3 (29.8)	-20 (2.16)	-10.0	2.12	[-14;-5.9]	<.0001	-0.4	[-.60;-.25]

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval. N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-129: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			SMD 95% CI		
					CFB LSmeans			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	204 (100.0)	36.9 (29.4)							
	1-12	204 (100.0)	30.0 (34.4)	-8.2 (2.30)						
	13-24	202 (99.0)	28.4 (34.4)	-9.8 (2.39)						
EPTI 100 mg	Basln	207 (100.0)	43.0 (28.3)							
	1-12	207 (100.0)	26.9 (31.9)	-15 (2.27)	-6.7	2.20	[-11;-2.4]	0.0024	-0.3	[-.49;-.11]
	13-24	198 (95.7)	23.2 (31.9)	-18 (2.39)	-7.9	2.39	[-13;-3.2]	0.0010	-0.3	[-.53;-.14]
EPTI 300 mg	Basln	217 (100.0)	42.4 (28.2)							
	1-12	217 (100.0)	24.2 (30.6)	-17 (2.19)	-8.9	2.18	[-13;-4.7]	<.0001	-0.4	[-.59;-.21]
	13-24	211 (97.2)	21.4 (30.6)	-19 (2.30)	-8.9	2.36	[-14;-4.3]	0.0002	-0.4	[-.57;-.18]

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.
N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-130: Kopfschmerzepisoden mit schwerer Schmerzintensität, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Diff.	SE	CI	p-value	Comparison to PBO		SMD 95% CI	
									CFB LSmeans			
									G	CI		
PBO	Basln	83 (100.0)	42.5 (29.0)									
	1-12	83 (100.0)	36.0 (32.8)	-7.9 (3.68)								
	13-24	83 (100.0)	34.9 (32.8)	-9.0 (3.97)								
EPTI 100 mg	Basln	77 (100.0)	47.1 (28.6)									
	1-12	77 (100.0)	32.4 (35.1)	-15 (3.57)	-7.0	3.35	[-14;-.45]	0.0365	-0.3	[-.64;-.02]		
	13-24	75 (97.4)	30.1 (35.1)	-16 (3.89)	-7.1	3.98	[-15;0.71]	0.0744	-0.3	[-.60;0.03]		
EPTI 300 mg	Basln	68 (100.0)	37.3 (22.4)									
	1-12	68 (100.0)	18.5 (30.1)	-23 (3.72)	-14.7	3.41	[-21;-7.9]	<.0001	-0.7	[-1.0;-.38]		
	13-24	67 (98.5)	21.6 (30.1)	-20 (4.06)	-11.2	4.06	[-19;-3.2]	0.0065	-0.5	[-.78;-.13]		

Missing eDiary data is handled using the rules provided in the SAP. Patients with no headache episodes are included with a rate of 0. The estimated means, mean differences from PBO, and 95% confidence intervals are from an MMRM with month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24), country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction.

From the MMRM, estimates and tests across multiple 4-week intervals are computed via SAS lsmeans using equal weights for each 4-week interval.

N: the number of patients with observations in the interval. Basln: Baseline.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.10 MBS (Most Bothersome Symptom)

Tabelle 4G-131: MBS, Gruppendifferenz, Interaktions-p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.6769	0.1791
Interaction test: EM/CM	0.6240	0.5069
Interaction test: MOH	0.4657	0.0653

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Number of FPT	0.7257	0.5360
Interaction test: Sex	0.3533	0.2413

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-132: MBS, Gruppendifferenz, Interaktions-p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.8307	0.2718
Interaction test: EM/CM	0.3753	0.8562
Interaction test: MOH	0.1785	0.0431
Interaction test: Number of FPT	0.4633	0.2371
Interaction test: Sex	0.2517	0.0980

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-133: MBS, Gruppendifferenz, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					Diff.	SE	95% CI		
PBO	Basln	66 (100.0)							
	12	66 (100.0)	3.53 (1.17)	3.83 (0.18)					
	24	65 (98.5)	3.65 (1.22)	3.95 (0.18)					
EPTI 100 mg	Basln	54 (100.0)							
	12	54 (100.0)	2.81 (1.12)	3.04 (0.19)	-0.8	0.20	[-1.2;-39]	0.0001	-0.7 [-1.1;-.35]
	24	50 (92.6)	2.76 (1.04)	3.00 (0.19)	-0.9	0.20	[-1.3;-.55]	<.0001	-0.9 [-1.3;-.51]
EPTI 300 mg	Basln	62 (100.0)							
	12	61 (98.4)	2.67 (1.06)	2.88 (0.19)	-1.0	0.20	[-1.3;-.56]	<.0001	-0.9 [-1.2;-.51]
	24	60 (96.8)	2.48 (1.03)	2.69 (0.19)	-1.3	0.19	[-1.6;-.88]	<.0001	-1.2 [-1.5;-.81]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

Tabelle 4G-134: MBS, Gruppendifferenz, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					Diff.	SE	95% CI		
PBO	Basln	216 (100.0)							
	12	216 (100.0)	3.46 (1.09)	3.57 (0.11)					
	24	207 (95.8)	3.30 (1.09)	3.45 (0.11)					
EPTI 100 mg	Basln	223 (100.0)							

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	
					Diff.	SE	p-value			
	12	222 (99.6)	2.57 (1.12)	2.67 (0.11)	-0.9	0.11	[-1.1;-68]	<.0001	-0.8	[-.98;-.61]
	24	215 (96.4)	2.44 (1.08)	2.59 (0.11)	-0.9	0.11	[-1.1;-65]	<.0001	-0.8	[-.98;-.60]
EPTI 300 mg	Basln	219 (100.0)								
	12	219 (100.0)	2.47 (1.15)	2.59 (0.11)	-1.0	0.11	[-1.2;-.77]	<.0001	-0.9	[-.11;-.68]
	24	212 (96.8)	2.34 (1.14)	2.49 (0.11)	-1.0	0.11	[-1.2;-.74]	<.0001	-0.9	[-.11;-.67]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

Tabelle 4G-135: MBS, Gruppendifferenz, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	
					Diff.	SE	p-value			
PBO	Basln	30 (100.0)								
	12	30 (100.0)	3.80 (1.00)	3.92 (0.28)						
	24	29 (96.7)	3.93 (1.07)	4.07 (0.28)						
EPTI 100 mg	Basln	21 (100.0)								
	12	21 (100.0)	2.67 (1.20)	2.84 (0.31)	-1.1	0.38	[-1.9;-.32]	0.0061	-0.8	[-.14;-.24]
	24	19 (90.5)	2.84 (1.30)	3.05 (0.31)	-1.0	0.38	[-1.8;-.25]	0.0097	-0.8	[-.14;-.20]
EPTI 300 mg	Basln	32 (100.0)								
	12	32 (100.0)	2.56 (1.29)	2.60 (0.26)	-1.3	0.32	[-1.9;-.69]	<.0001	-1.1	[-.16;-.56]
	24	32 (100.0)	2.47 (1.16)	2.51 (0.26)	-1.6	0.31	[-2.2;-.94]	<.0001	-1.3	[-.18;-.77]

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					Diff.	SE	95% CI		

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

Tabelle 4G-136: MBS, Gruppendifferenz, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					Diff.	SE	95% CI		
PBO	Basln	252 (100.0)							
	12	252 (100.0)	3.44 (1.11)	3.58 (0.11)					
	24	243 (96.4)	3.32 (1.12)	3.49 (0.11)					
EPTI 100 mg	Basln	256 (100.0)							
	12	255 (99.6)	2.61 (1.12)	2.75 (0.11)	-0.8	0.10	[-1.0;-64]	<.0001	-0.7 [-.92;-.57]
	24	246 (96.1)	2.48 (1.06)	2.65 (0.11)	-0.8	0.10	[-1.0;-.65]	<.0001	-0.8 [-.96;-.60]
EPTI 300 mg	Basln	249 (100.0)							
	12	248 (99.6)	2.51 (1.12)	2.65 (0.10)	-0.9	0.10	[-1.1;-.73]	<.0001	-0.8 [-1.0;-.66]
	24	240 (96.4)	2.36 (1.11)	2.54 (0.10)	-1.0	0.10	[-1.1;-.76]	<.0001	-0.9 [-1.1;-.70]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

Tabelle 4G-137: MBS, Gruppendifferenz, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					Diff.	SE	95% CI		
PBO	Basln	154 (100.0)							
	12	154 (100.0)	3.36 (1.11)	3.53 (0.13)					
	24	151 (98.1)	3.17 (1.11)	3.34 (0.13)					
EPTI 100 mg	Basln	150 (100.0)							
	12	150 (100.0)	2.55 (1.01)	2.70 (0.13)	-0.8	0.12	[-1.1;-.59]	<.0001	-0.8 [-1.0;-.56]
	24	142 (94.7)	2.35 (1.05)	2.53 (0.13)	-0.8	0.12	[-1.1;-.56]	<.0001	-0.8 [-.99;-.53]
EPTI 300 mg	Basln	154 (100.0)							
	12	154 (100.0)	2.34 (1.04)	2.50 (0.12)	-1.0	0.12	[-1.3;-.80]	<.0001	-1.0 [-1.2;-.75]
	24	150 (97.4)	2.18 (1.03)	2.34 (0.13)	-1.0	0.12	[-1.2;-.76]	<.0001	-0.9 [-1.2;-.71]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-138: MBS, Gruppendifferenz, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					Diff.	SE	95% CI		
PBO	Basln	128 (100.0)							
	12	128 (100.0)	3.61 (1.08)	3.93 (0.19)					
	24	121 (94.5)	3.65 (1.10)	3.92 (0.19)					
EPTI 100 mg	Basln	127 (100.0)							
	12	126 (99.2)	2.70 (1.24)	2.99 (0.18)	-0.9	0.15	[-1.2;-.64]	<.0001	-0.8 [-1.0;-.53]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			p-value	SMD 95% CI		
					95% CI				Hedges'		
					LSmeans	Diff.	SE		G	CI	
	24	123 (96.9)	2.67 (1.10)	2.92 (0.18)	-1.0	0.14	[-1.3;-72]	<.0001	-0.9	[-1.1;-.64]	
EPTI 300 mg	Basln	127 (100.0)									
	12	126 (99.2)	2.72 (1.21)	3.03 (0.19)	-0.9	0.15	[-1.2;-.61]	<.0001	-0.8	[-1.0;-.51]	
	24	122 (96.1)	2.61 (1.17)	2.88 (0.19)	-1.0	0.14	[-1.3;-.76]	<.0001	-0.9	[-1.2;-.69]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-139: MBS, Gruppendifferenz, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			p-value	SMD 95% CI		
					95% CI				Hedges'		
					LSmeans	Diff.	SE		G	CI	
PBO	Basln	34 (100.0)									
	12	34 (100.0)	3.44 (1.08)	3.45 (0.26)							
	24	31 (91.2)	3.26 (1.18)	3.18 (0.26)							
EPTI 100 mg	Basln	36 (100.0)									
	12	36 (100.0)	2.75 (1.16)	2.84 (0.24)	-0.6	0.29	[-1.2;-.04]	0.0362	-0.5	[-.98;-.03]	
	24	35 (97.2)	2.74 (1.15)	2.76 (0.24)	-0.4	0.29	[-.99;0.15]	0.1468	-0.4	[-.85;0.13]	
EPTI 300 mg	Basln	33 (100.0)									
	12	33 (100.0)	2.55 (1.12)	2.58 (0.25)	-0.9	0.28	[-1.4;-.30]	0.0031	-0.7	[-1.2;-.26]	
	24	33 (100.0)	2.76 (1.09)	2.70 (0.25)	-0.5	0.28	[-1.0;0.09]	0.0980	-0.4	[-.92;0.08]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-140: MBS, Gruppendifferenz, Subgruppe MOH: nein

		Comparison to PBO								
		95% CI			SMD 95% CI					
Treatment Group	Weeks	LSmeans			Diff.	SE	CI	Hedges' G		
		Mean (SD)	(SE)					p-value	CI	
PBO	Basln	248 (100.0)								
	12	248 (100.0)	3.48 (1.11)	3.63 (0.11)						
	24	241 (97.2)	3.40 (1.13)	3.58 (0.11)						
EPTI 100 mg	Basln	241 (100.0)								
	12	240 (99.6)	2.60 (1.12)	2.75 (0.11)	-0.9	0.10	[-1.1;-.69]	<.0001	-0.8	[-.97;-.62]
	24	230 (95.4)	2.47 (1.07)	2.66 (0.11)	-0.9	0.10	[-1.1;-.73]	<.0001	-0.9	[-1.0;-.67]
EPTI 300 mg	Basln	248 (100.0)								
	12	247 (99.6)	2.51 (1.14)	2.67 (0.10)	-1.0	0.10	[-1.2;-.77]	<.0001	-0.9	[-1.0;-.69]
	24	239 (96.4)	2.32 (1.11)	2.52 (0.10)	-1.1	0.10	[-1.3;-.87]	<.0001	-1.0	[-1.2;-.80]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-141: MBS, Gruppendifferenz, Subgruppe 2 Vortherapien

		Comparison to PBO							
		95% CI			SMD 95% CI				
Treatment Group	Weeks	LSmeans			Diff.	SE	CI	Hedges' G	
		Mean (SD)	(SE)					p-value	CI
PBO	Basln	199 (100.0)							
	12	199 (100.0)	3.39 (1.09)	3.56 (0.11)					
	24	193 (97.0)	3.30 (1.11)	3.49 (0.11)					

Treatment	Group	Weeks	N (%)	LSmeans					Comparison to PBO			
				Mean (SD)	(SE)	Diff.	SE	CI	p-value	G	Hedges'	SMD 95% CI
EPTI 100 mg		Basln	202 (100.0)									
		12	201 (99.5)	2.54 (1.06)	2.73 (0.11)	-0.8	0.11	[-1.0;- .62]	<.0001	-0.8	[-.97;-.58]	
		24	191 (94.6)	2.43 (1.04)	2.67 (0.11)	-0.8	0.11	[-1.0;-.61]	<.0001	-0.8	[-.98;-.58]	
EPTI 300 mg		Basln	215 (100.0)									
		12	214 (99.5)	2.48 (1.11)	2.68 (0.10)	-0.9	0.10	[-1.1;-.67]	<.0001	-0.8	[-1.0;-.63]	
		24	208 (96.7)	2.35 (1.09)	2.56 (0.10)	-0.9	0.11	[-1.1;-.72]	<.0001	-0.9	[-1.1;-.68]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-142: MBS, Gruppendifferenz, Subgruppe > 2 Vortherapien

Treatment	Group	Weeks	N (%)	LSmeans					Comparison to PBO			
				Mean (SD)	(SE)	Diff.	SE	CI	p-value	G	Hedges'	SMD 95% CI
PBO		Basln	83 (100.0)									
		12	83 (100.0)	3.67 (1.12)	3.85 (0.20)							
		24	79 (95.2)	3.59 (1.15)	3.81 (0.21)							
EPTI 100 mg		Basln	75 (100.0)									
		12	75 (100.0)	2.83 (1.26)	2.97 (0.20)	-0.9	0.20	[-1.3;-.50]	<.0001	-0.7	[-1.0;-.40]	
		24	74 (98.7)	2.68 (1.16)	2.85 (0.20)	-1.0	0.19	[-1.3;-.58]	<.0001	-0.8	[-1.1;-.48]	
EPTI 300 mg		Basln	66 (100.0)									
		12	66 (100.0)	2.62 (1.21)	2.81 (0.21)	-1.0	0.20	[-1.4;-.64]	<.0001	-0.8	[-1.2;-.52]	
		24	64 (97.0)	2.47 (1.19)	2.71 (0.21)	-1.1	0.20	[-1.5;-.70]	<.0001	-0.9	[-1.3;-.59]	

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Diff.	SE	CI	p-value	Comparison to PBO		SMD 95% CI Hedges'
									95% CI	G	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.11 PGIC (Patient Global Impression of Change)

Tabelle 4G-143: PGIC, Gruppendifferenz, Interaktions p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.9927	0.7806
Interaction test: EM/CM	0.1849	0.1678
Interaction test: MOH	0.0783	0.3567
Interaction test: Number of FPT	0.7883	0.2957
Interaction test: Sex	0.4066	0.2332

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-144: PGIC, Gruppendifferenz, Interaktions p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.8131	0.6553
Interaction test: EM/CM	0.3417	0.1717
Interaction test: MOH	0.1789	0.3363
Interaction test: Number of FPT	0.7938	0.7008
Interaction test: Sex	0.2872	0.2247

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-145: PGIC, Gruppendifferenz, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			SMD 95% CI	Hedges' G	CI
					Diff.	SE	95% CI			
							p-value			
PBO	Basln	67 (100.0)			-1.0	0.17	[-1.4;-.70]	<.0001	-1.1	[-1.5;-.74]
	4	66 (98.5)	3.38 (0.87)	3.67 (0.16)						
	12	67 (100.0)	3.55 (1.22)	3.85 (0.17)						
	24	65 (97.0)	3.40 (1.31)	3.72 (0.17)						
EPTI 100 mg	Basln	56 (100.0)			-1.1	0.20	[-1.4;-.66]	<.0001	-1.0	[-1.3;-.60]
	4	54 (96.4)	2.37 (1.03)	2.63 (0.17)						
	12	55 (98.2)	2.51 (1.09)	2.79 (0.18)						
	24	51 (91.1)	2.41 (0.98)	2.70 (0.18)						
EPTI 300 mg	Basln	62 (100.0)								

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	
					Diff.	SE	CI		p-value	
	4	58 (93.5)	2.43 (0.99)	2.69 (0.17)	-1.0	0.17	[-1.3;-.64]	<.0001	-1.0	[-1.4;-.68]
	12	61 (98.4)	2.44 (1.03)	2.71 (0.18)	-1.1	0.20	[-1.5;-.75]	<.0001	-1.0	[-1.4;-.68]
	24	60 (96.8)	2.23 (1.05)	2.50 (0.18)	-1.2	0.19	[-1.6;-.83]	<.0001	-1.1	[-1.5;-.77]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

Tabelle 4G-146: PGIC, Gruppendifferenz, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	
					Diff.	SE	CI		p-value	
PBO	Basln	220 (100.0)								
	4	208 (94.5)	3.36 (1.08)	3.50 (0.11)						
	12	219 (99.5)	3.40 (1.11)	3.53 (0.11)						
	24	211 (95.9)	3.25 (1.18)	3.42 (0.11)						
EPTI 100 mg	Basln	226 (100.0)								
	4	215 (95.1)	2.35 (1.11)	2.49 (0.10)	-1.0	0.10	[-1.2;-.80]	<.0001	-0.9	[-1.1;-.75]
	12	223 (98.7)	2.39 (1.13)	2.53 (0.11)	-1.0	0.11	[-1.2;-.79]	<.0001	-0.9	[-1.1;-.71]
	24	216 (95.6)	2.30 (1.06)	2.47 (0.11)	-0.9	0.11	[-1.2;-.74]	<.0001	-0.9	[-1.1;-.68]
EPTI 300 mg	Basln	222 (100.0)								
	4	214 (96.4)	2.30 (1.06)	2.43 (0.10)	-1.1	0.10	[-1.3;-.86]	<.0001	-1.0	[-1.2;-.80]
	12	221 (99.5)	2.29 (1.11)	2.42 (0.10)	-1.1	0.11	[-1.3;-.90]	<.0001	-1.0	[-1.2;-.80]
	24	214 (96.4)	2.19 (1.09)	2.36 (0.10)	-1.1	0.11	[-1.3;-.85]	<.0001	-1.0	[-1.2;-.77]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			SMD 95% CI Hedges' G CI
					LSmeans	Diff.	95% CI SE CI p-value	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

Tabelle 4G-147: PGIC, Gruppendifferenz, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			SMD 95% CI Hedges' G CI
					LSmeans	Diff.	95% CI SE CI p-value	
PBO	Basln	33 (100.0)						
	4	31 (93.9)	3.74 (0.93)	3.83 (0.23)				
	12	32 (97.0)	3.75 (1.11)	3.78 (0.25)				
	24	32 (97.0)	3.72 (1.40)	3.82 (0.25)				
EPTI 100 mg	Basln	21 (100.0)						
	4	21 (100.0)	2.43 (0.98)	2.83 (0.26)	-1.0	0.32	[-1.6;-37]	0.0023 -0.9 [-1.5;-33]
	12	21 (100.0)	2.29 (1.01)	2.69 (0.29)	-1.1	0.35	[-1.8;-39]	0.0027 -0.9 [-1.4;-31]
	24	19 (90.5)	2.53 (1.07)	2.95 (0.30)	-0.9	0.35	[-1.6;-17]	0.0159 -0.7 [-1.3;-14]
EPTI 300 mg	Basln	32 (100.0)						
	4	32 (100.0)	2.28 (1.28)	2.36 (0.22)	-1.5	0.26	[-2.0;-95]	<.0001 -1.4 [-1.9;-91]
	12	32 (100.0)	2.44 (1.34)	2.51 (0.24)	-1.3	0.29	[-1.9;-68]	<.0001 -1.1 [-1.6;-58]
	24	32 (100.0)	2.34 (1.12)	2.39 (0.24)	-1.4	0.29	[-2.0;-84]	<.0001 -1.2 [-1.7;-72]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

Tabelle 4G-148: PGIC, Gruppendifferenz, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					LSmeans	95% CI	p-value		
PBO	Basln	254 (100.0)							
	4	243 (95.7)	3.32 (1.03)	3.50 (0.10)					
	12	254 (100.0)	3.40 (1.14)	3.58 (0.10)					
	24	244 (96.1)	3.23 (1.18)	3.45 (0.10)					
EPTI 100 mg	Basln	261 (100.0)							
	4	248 (95.0)	2.35 (1.10)	2.53 (0.10)	-1.0	0.09	[-1.2;-.79]	<.0001	-0.9 [-1.1;-.76]
	12	257 (98.5)	2.43 (1.13)	2.62 (0.10)	-1.0	0.10	[-1.2;-.77]	<.0001	-0.9 [-1.0;-.70]
	24	248 (95.0)	2.31 (1.05)	2.52 (0.10)	-0.9	0.10	[-1.1;-.73]	<.0001	-0.9 [-1.0;-.68]
EPTI 300 mg	Basln	252 (100.0)							
	4	240 (95.2)	2.33 (1.02)	2.51 (0.10)	-1.0	0.09	[-1.2;-.80]	<.0001	-0.9 [-1.1;-.77]
	12	250 (99.2)	2.31 (1.06)	2.49 (0.10)	-1.1	0.10	[-1.3;-.90]	<.0001	-1.0 [-1.2;-.81]
	24	242 (96.0)	2.18 (1.07)	2.40 (0.10)	-1.1	0.10	[-1.2;-.86]	<.0001	-1.0 [-1.1;-.79]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

Tabelle 4G-149: PGIC, Gruppendifferenz, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					LSmeans	95% CI	p-value		
PBO	Basln	159 (100.0)							
	4	152 (95.6)	3.27 (1.03)	3.42 (0.12)					
	12	158 (99.4)	3.33 (1.12)	3.46 (0.12)					
	24	155 (97.5)	3.01 (1.13)	3.16 (0.12)					

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	SMD 95% CI
					Diff.	SE	p-value			
EPTI 100 mg	Basln	152 (100.0)								
	4	148 (97.4)	2.17 (0.99)	2.30 (0.12)	-1.1	0.12	[-1.3;-.89]	<.0001	-1.1	[-1.3;-.89]
	12	150 (98.7)	2.27 (1.00)	2.41 (0.12)	-1.0	0.12	[-1.3;-.82]	<.0001	-1.0	[-1.3;-.80]
	24	142 (93.4)	2.11 (0.90)	2.25 (0.12)	-0.9	0.12	[-1.1;-.67]	<.0001	-0.9	[-1.1;-.67]
EPTI 300 mg	Basln	155 (100.0)								
	4	148 (95.5)	2.21 (1.01)	2.33 (0.11)	-1.1	0.12	[-1.3;-.86]	<.0001	-1.1	[-1.3;-.86]
	12	154 (99.4)	2.16 (0.95)	2.28 (0.11)	-1.2	0.12	[-1.4;-.95]	<.0001	-1.2	[-1.4;-.93]
	24	150 (96.8)	2.03 (0.98)	2.15 (0.12)	-1.0	0.12	[-1.2;-.77]	<.0001	-1.0	[-1.2;-.76]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-150: PGIC, Gruppendifferenz, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	SMD 95% CI
					Diff.	SE	p-value			
PBO	Basln	128 (100.0)								
	4	122 (95.3)	3.48 (1.02)	3.83 (0.18)						
	12	128 (100.0)	3.57 (1.15)	3.88 (0.19)						
	24	121 (94.5)	3.64 (1.22)	3.86 (0.18)						
EPTI 100 mg	Basln	130 (100.0)								
	4	121 (93.1)	2.58 (1.17)	2.92 (0.17)	-0.9	0.14	[-1.2;-.63]	<.0001	-0.8	[-1.1;-.59]
	12	128 (98.5)	2.59 (1.23)	2.89 (0.18)	-1.0	0.15	[-1.3;-.69]	<.0001	-0.8	[-1.1;-.58]
	24	125 (96.2)	2.57 (1.15)	2.79 (0.18)	-1.1	0.15	[-1.4;-.78]	<.0001	-0.9	[-1.2;-.66]
EPTI 300 mg	Basln	128 (100.0)								

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	
					Diff.	SE	p-value			
	4	124 (96.9)	2.47 (1.09)	2.80 (0.17)	-1.0	0.14	[-1.3;-.76]	<.0001	-1.0	[-1.2;-.71]
	12	127 (99.2)	2.50 (1.21)	2.80 (0.18)	-1.1	0.15	[-1.4;-.78]	<.0001	-0.9	[-1.1;-.65]
	24	123 (96.1)	2.41 (1.16)	2.61 (0.18)	-1.2	0.15	[-1.5;-.95]	<.0001	-1.1	[-1.3;-.81]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-151: PGIC, Gruppendifferenz, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	
					Diff.	SE	p-value			
PBO	Basln	35 (100.0)								
	4	32 (91.4)	3.28 (0.89)	3.32 (0.23)						
	12	35 (100.0)	3.43 (1.17)	3.50 (0.25)						
	24	31 (88.6)	3.35 (1.38)	3.28 (0.26)						
EPTI 100 mg	Basln	36 (100.0)								
	4	33 (91.7)	2.82 (1.13)	2.96 (0.22)	-0.4	0.26	[-.88;0.16]	0.1706	-0.3	[-.84;0.15]
	12	36 (100.0)	2.67 (1.12)	2.82 (0.23)	-0.7	0.29	[-1.2;-.11]	0.0205	-0.6	[-1.0;-.09]
	24	35 (97.2)	2.71 (1.07)	2.80 (0.23)	-0.5	0.29	[-1.1;0.10]	0.1012	-0.4	[-.90;0.08]
EPTI 300 mg	Basln	35 (100.0)								
	4	32 (91.4)	2.28 (0.96)	2.36 (0.22)	-1.0	0.26	[-1.5;-.44]	0.0004	-0.9	[-1.4;-.42]
	12	34 (97.1)	2.21 (1.12)	2.30 (0.24)	-1.2	0.29	[-1.8;-.62]	<.0001	-1.0	[-1.5;-.52]
	24	34 (97.1)	2.53 (1.11)	2.51 (0.24)	-0.8	0.29	[-1.4;-.20]	0.0091	-0.7	[-1.2;-.17]

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			SMD 95% CI						
					Diff.	SE	95% CI	Hedges' G	CI					
The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.														
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.														

Tabelle 4G-152: PGIC, Gruppendifferenz, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			SMD 95% CI						
					Diff.	SE	95% CI	Hedges' G	CI					
PBO														
Basln 252 (100.0)														
4 242 (96.0)														
12 251 (99.6)														
24 245 (97.2)														
EPTI 100 mg														
Basln 246 (100.0)														
4 236 (95.9)														
12 242 (98.4)														
24 232 (94.3)														
EPTI 300 mg														
Basln 249 (100.0)														
4 240 (96.4)														
12 248 (99.6)														
24 240 (96.4)														

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-153: PGIC, Gruppendifferenz, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	Lsmeans		Comparison to PBO			SMD 95% CI	
				(SE)	Diff.	SE	CI	p-value	G	CI
PBO	Basln	204 (100.0)								
	4	194 (95.1)	3.29 (1.01)	3.47 (0.10)						
	12	203 (99.5)	3.32 (1.09)	3.49 (0.10)						
	24	197 (96.6)	3.23 (1.22)	3.44 (0.11)						
EPTI 100 mg	Basln	206 (100.0)								
	4	197 (95.6)	2.28 (1.07)	2.50 (0.10)	-1.0	0.10	[-1.2;-.77]	<.0001	-0.9	[-1.1;-.75]
	12	203 (98.5)	2.32 (1.03)	2.53 (0.10)	-1.0	0.10	[-1.2;-.76]	<.0001	-0.9	[-1.1;-.72]
	24	193 (93.7)	2.23 (0.98)	2.48 (0.11)	-1.0	0.11	[-1.2;-.76]	<.0001	-0.9	[-1.1;-.72]
EPTI 300 mg	Basln	216 (100.0)								
	4	205 (94.9)	2.33 (1.04)	2.52 (0.10)	-1.0	0.10	[-1.2;-.75]	<.0001	-0.9	[-1.1;-.73]
	12	215 (99.5)	2.28 (1.07)	2.48 (0.10)	-1.0	0.10	[-1.2;-.82]	<.0001	-1.0	[-1.2;-.78]
	24	209 (96.8)	2.16 (1.08)	2.38 (0.10)	-1.1	0.11	[-1.3;-.85]	<.0001	-1.0	[-1.2;-.80]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-154: PGIC, Gruppendifferenz, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	Lsmeans		Comparison to PBO			SMD 95% CI	
				(SE)	Diff.	SE	CI	p-value	G	CI
PBO	Basln	83 (100.0)								
	4	80 (96.4)	3.54 (1.05)	3.76 (0.19)						
	12	83 (100.0)	3.72 (1.20)	3.94 (0.20)						
	24	79 (95.2)	3.41 (1.19)	3.68 (0.19)						

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					95% CI			Hedges' G	CI	
					Diff.	SE	p-value			
EPTI 100 mg	Basln	76 (100.0)								
	4	72 (94.7)	2.54 (1.13)	2.74 (0.18)	-1.0	0.18	[-1.4;-.67]	<.0001	-0.9	[-1.3;-.62]
	12	75 (98.7)	2.69 (1.29)	2.90 (0.19)	-1.0	0.20	[-1.4;-.66]	<.0001	-0.8	[-1.2;-.53]
	24	74 (97.4)	2.57 (1.17)	2.79 (0.19)	-0.9	0.19	[-1.3;-.52]	<.0001	-0.8	[-1.1;-.44]
EPTI 300 mg	Basln	68 (100.0)								
	4	67 (98.5)	2.31 (1.09)	2.55 (0.19)	-1.2	0.18	[-1.6;-.86]	<.0001	-1.1	[-1.4;-.79]
	12	67 (98.5)	2.46 (1.15)	2.69 (0.20)	-1.3	0.20	[-1.7;-.85]	<.0001	-1.0	[-1.3;-.69]
	24	65 (95.6)	2.32 (1.06)	2.60 (0.20)	-1.1	0.20	[-1.5;-.70]	<.0001	-0.9	[-1.3;-.60]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, treatment-by-visit interaction, and stratum-by-visit interaction.
 N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.12 EQ-5D VAS (Gesundheitszustand)

4.2.12.1 Veränderung gegenüber dem Baseline-Wert

Tabelle 4G-155: EQ-5D VAS, CFB, Interaktions-p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.8590	0.2494
Interaction test: EM/CM	0.0177	0.0003
Interaction test: MOH	0.5960	0.6775
Interaction test: Number of FPT	0.0496	0.2945

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Sex	0.1711	0.0019

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-156: EQ-5D VAS, CFB, Interaktions-p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.7293	0.0973
Interaction test: EM/CM	0.0157	<.0001
Interaction test: MOH	0.9339	0.3237
Interaction test: Number of FPT	0.4007	0.1802
Interaction test: Sex	0.0830	0.0016

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model. The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-157: EQ-5D VAS, CFB, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	64 (100.0)	75.0 (17.6)								
	4	63 (98.4)	68.9 (22.4)	-7.1 (2.96)							
	8	62 (96.9)	70.4 (23.1)	-5.7 (3.14)							
	12	64 (100.0)	68.4 (24.7)	-7.9 (3.06)							
	16	62 (96.9)	69.7 (26.0)	-6.6 (3.05)							
	20	61 (95.3)	68.9 (25.9)	-7.2 (3.22)							
	24	62 (96.9)	69.4 (22.5)	-6.4 (2.93)							
EPTI 100 mg	Basln	54 (100.0)	70.0 (21.5)								
	4	52 (96.3)	73.9 (20.9)	0.16 (3.12)	7.3	3.45	[0.49;14.1]	0.0359	0.4	[0.03;0.77]	
	8	52 (96.3)	73.4 (21.8)	-.65 (3.30)	5.1	3.76	[-2.3;12.5]	0.1778	0.3	[-.12;0.63]	
	12	53 (98.1)	75.9 (19.7)	2.28 (3.23)	10.2	3.64	[3.03;17.4]	0.0056	0.5	[0.15;0.89]	
	16	52 (96.3)	76.9 (19.0)	2.48 (3.21)	9.0	3.61	[1.92;16.2]	0.0131	0.5	[0.10;0.84]	
	20	49 (90.7)	76.6 (17.6)	1.88 (3.43)	9.1	3.94	[1.34;16.9]	0.0219	0.4	[0.07;0.82]	
	24	49 (90.7)	73.6 (19.2)	-.80 (3.08)	5.6	3.38	[-1.1;12.3]	0.0994	0.3	[-.06;0.69]	
EPTI 300 mg	Basln	61 (100.0)	76.2 (20.4)								
	4	57 (93.4)	79.4 (18.5)	3.28 (3.12)	10.4	3.37	[3.77;17.1]	0.0023	0.6	[0.20;0.93]	
	8	57 (93.4)	81.7 (19.4)	5.87 (3.27)	11.6	3.66	[4.40;18.8]	0.0018	0.6	[0.22;0.95]	
	12	60 (98.4)	79.4 (21.3)	3.01 (3.18)	10.9	3.53	[3.98;17.9]	0.0022	0.6	[0.20;0.91]	
	16	58 (95.1)	82.1 (18.9)	6.05 (3.17)	12.6	3.50	[5.71;19.5]	0.0004	0.7	[0.30;1.02]	
	20	58 (95.1)	78.3 (23.0)	1.94 (3.32)	9.2	3.77	[1.74;16.6]	0.0160	0.4	[0.08;0.81]	
	24	59 (96.7)	83.3 (16.3)	7.28 (3.01)	13.7	3.25	[7.26;20.1]	<.0001	0.8	[0.41;1.12]	

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	CI		
					CFB		95% CI				
					LSmeans	Diff.					

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.
N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

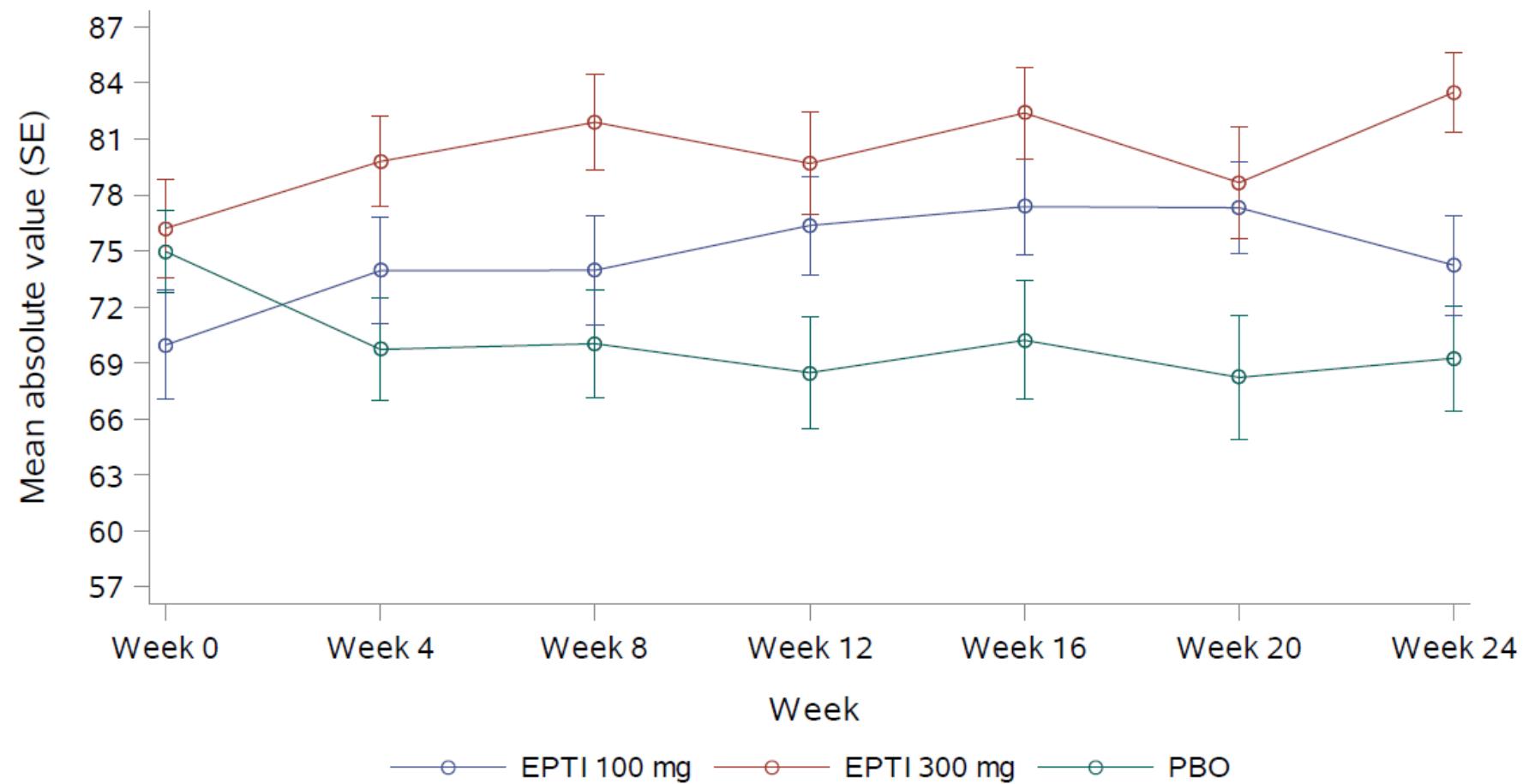
EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Age <= 35 years

Tabelle 4G-158: EQ-5D VAS, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' SMD 95% CI		
					CFB			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	212 (100.0)	73.6 (21.4)							
	4	203 (95.8)	75.2 (18.5)	-1.7 (1.58)						
	8	204 (96.2)	75.1 (20.8)	-2.1 (1.68)						
	12	212 (100.0)	75.3 (21.1)	-1.5 (1.61)						
	16	205 (96.7)	76.0 (20.1)	-1.0 (1.64)						
	20	202 (95.3)	75.2 (20.8)	-2.0 (1.68)						
	24	204 (96.2)	75.4 (21.1)	-1.1 (1.60)						
EPTI 100 mg	Basln	208 (100.0)	77.5 (18.1)							
	4	200 (96.2)	80.4 (17.4)	2.46 (1.58)	4.1	1.65	[0.90;7.36]	0.0123	0.3	[0.05;0.45]
	8	202 (97.1)	79.5 (19.6)	1.12 (1.68)	3.2	1.83	[-.40;6.81]	0.0810	0.2	[-.02;0.37]
	12	205 (98.6)	80.6 (17.8)	2.61 (1.61)	4.2	1.71	[0.79;7.52]	0.0155	0.2	[0.05;0.43]
	16	200 (96.2)	81.9 (18.7)	3.65 (1.65)	4.7	1.76	[1.20;8.11]	0.0084	0.3	[0.07;0.46]
	20	197 (94.7)	82.0 (16.7)	3.59 (1.69)	5.6	1.83	[1.96;9.15]	0.0025	0.3	[0.11;0.50]
	24	198 (95.2)	81.3 (17.1)	3.17 (1.62)	4.3	1.69	[0.96;7.60]	0.0117	0.3	[0.06;0.45]
EPTI 300 mg	Basln	215 (100.0)	74.1 (20.6)							
	4	209 (97.2)	78.8 (18.9)	1.73 (1.53)	3.4	1.63	[0.20;6.61]	0.0372	0.2	[0.01;0.40]
	8	210 (97.7)	80.2 (19.9)	2.90 (1.63)	5.0	1.82	[1.41;8.55]	0.0063	0.3	[0.08;0.46]
	12	214 (99.5)	81.8 (18.0)	4.64 (1.57)	6.2	1.70	[2.86;9.52]	0.0003	0.4	[0.16;0.54]
	16	205 (95.3)	81.4 (19.2)	3.97 (1.60)	5.0	1.75	[1.54;8.40]	0.0046	0.3	[0.09;0.48]
	20	204 (94.9)	80.2 (20.5)	2.65 (1.64)	4.6	1.81	[1.06;8.18]	0.0111	0.3	[0.06;0.45]
	24	207 (96.3)	81.8 (18.0)	4.97 (1.56)	6.1	1.67	[2.80;9.37]	0.0003	0.4	[0.17;0.55]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		
					Diff.	SE	CI	95% CI	SMD	95% CI
									Hedges' G	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

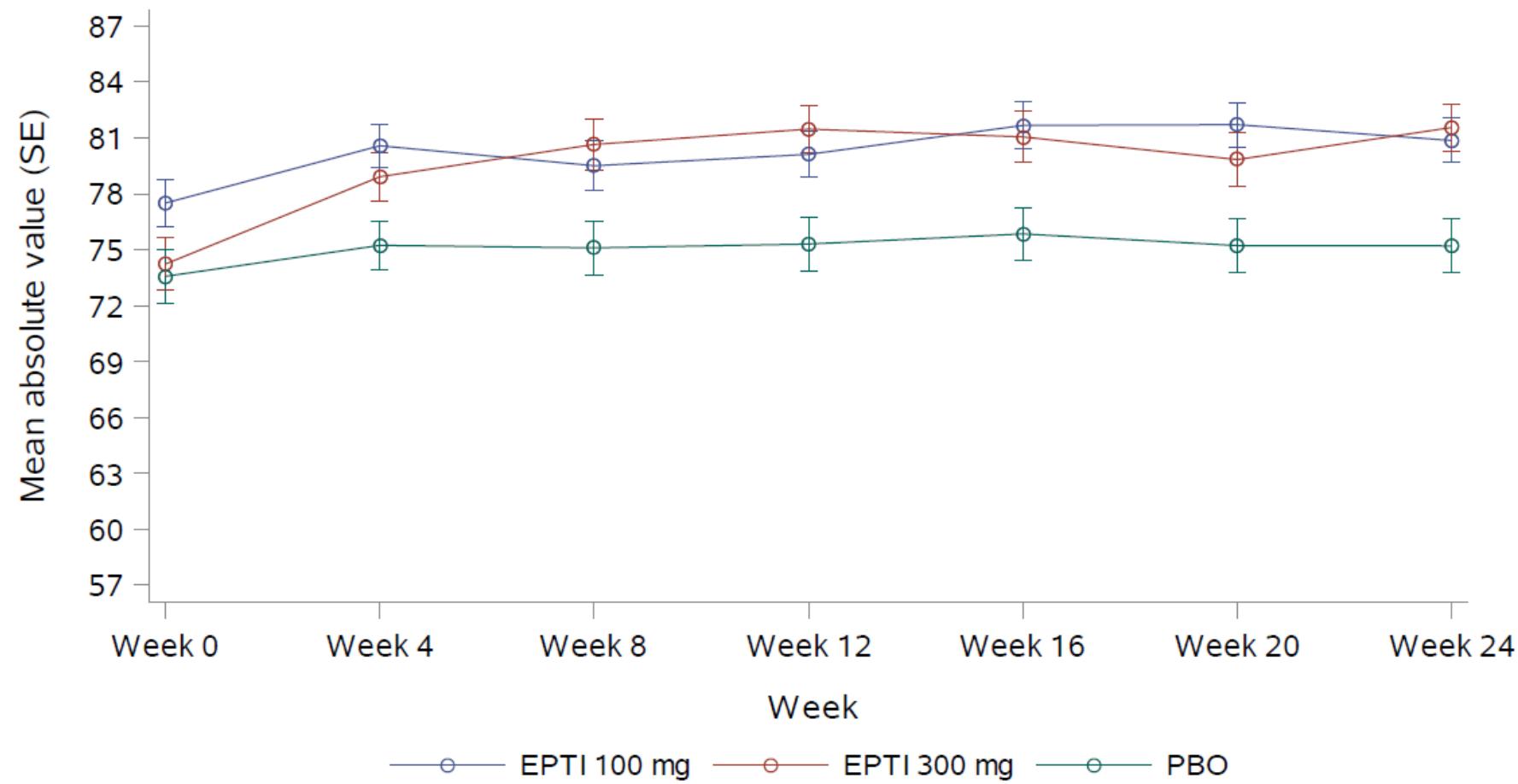
EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Age > 35 years

Tabelle 4G-159: EQ-5D VAS, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	28 (100.0)	73.3 (19.8)							
	4	28 (100.0)	65.7 (23.8)	-8.6 (4.05)						
	8	26 (92.9)	71.4 (23.9)	-2.8 (3.77)						
	12	28 (100.0)	68.5 (22.2)	-5.9 (4.01)						
	16	28 (100.0)	68.2 (26.5)	-6.1 (4.22)						
	20	26 (92.9)	73.4 (24.2)	-.90 (4.80)						
	24	28 (100.0)	63.8 (28.4)	-11 (3.97)						
EPTI 100 mg	Basln	20 (100.0)	75.6 (16.2)							
	4	20 (100.0)	78.4 (12.2)	1.39 (4.50)	10.0	5.60	[-1.2;21.1]	0.0787	0.5	[-.06;1.11]
	8	20 (100.0)	79.5 (12.5)	2.17 (4.05)	4.9	5.06	[-5.1;15.0]	0.3321	0.3	[-.30;0.88]
	12	20 (100.0)	81.9 (12.6)	4.22 (4.43)	10.1	5.51	[-.86;21.1]	0.0703	0.5	[-.05;1.12]
	16	20 (100.0)	81.6 (13.0)	4.89 (4.72)	11.0	5.89	[-.76;22.7]	0.0664	0.5	[-.04;1.13]
	20	20 (100.0)	78.3 (13.9)	-.17 (5.35)	0.7	6.82	[-13;14.3]	0.9144	0.0	[-.56;0.62]
	24	18 (90.0)	78.2 (13.2)	0.03 (4.55)	10.9	5.55	[-16;21.9]	0.0532	0.6	[-.01;1.20]
EPTI 300 mg	Basln	31 (100.0)	72.3 (21.3)							
	4	30 (96.8)	79.4 (19.8)	6.16 (3.78)	14.7	4.77	[5.23;24.3]	0.0029	0.8	[0.29;1.34]
	8	31 (100.0)	77.6 (21.2)	5.38 (3.42)	8.2	4.24	[-.32;16.6]	0.0589	0.5	[-.02;1.04]
	12	31 (100.0)	75.8 (22.1)	3.56 (3.70)	9.5	4.67	[0.15;18.8]	0.0466	0.5	[0.01;1.05]
	16	31 (100.0)	80.0 (18.6)	7.48 (3.91)	13.6	5.02	[3.55;23.6]	0.0087	0.7	[0.18;1.22]
	20	29 (93.5)	72.6 (31.6)	-1.5 (4.47)	-0.6	5.92	[-12;11.2]	0.9211	-0.0	[-.57;0.51]
	24	31 (100.0)	82.0 (18.3)	10.1 (3.66)	20.9	4.61	[11.7;30.1]	<.0001	1.2	[0.66;1.70]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB			Comparison to PBO			
					LSmeans			95% CI		SMD 95% CI	
					Diff.	SE	CI	p-value	G	CI	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

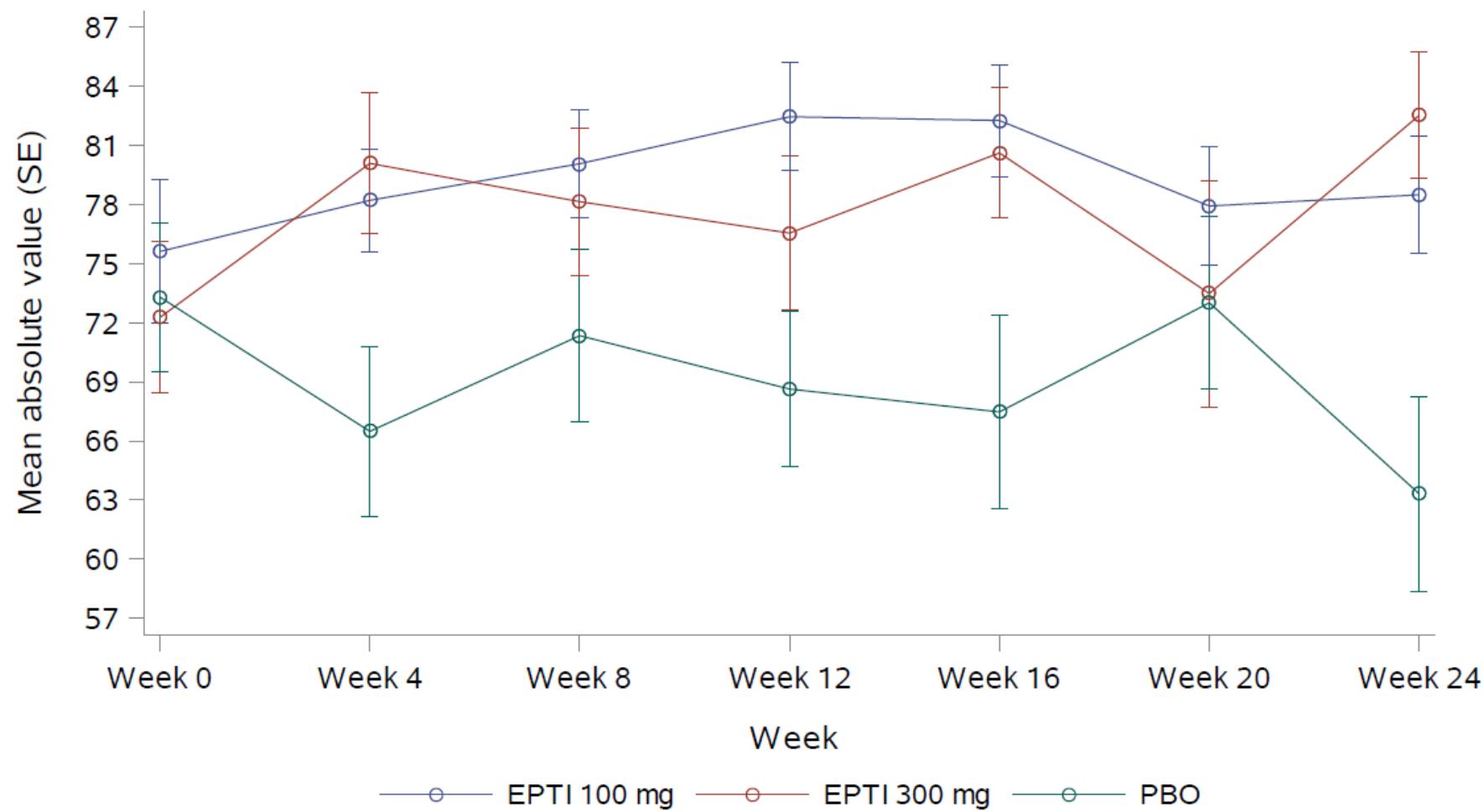
EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Males

Tabelle 4G-160: EQ-5D VAS, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' SMD 95% CI		
					CFB			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	248 (100.0)	74.0 (20.7)							
	4	238 (96.0)	74.6 (18.9)	-2.4 (1.52)						
	8	240 (96.8)	74.3 (21.1)	-3.1 (1.62)						
	12	248 (100.0)	74.2 (22.1)	-2.8 (1.57)						
	16	239 (96.4)	75.2 (21.0)	-2.1 (1.58)						
	20	237 (95.6)	73.8 (22.0)	-3.5 (1.60)						
	24	238 (96.0)	75.2 (20.3)	-1.6 (1.53)						
EPTI 100 mg	Basln	242 (100.0)	76.0 (19.3)							
	4	232 (95.9)	79.2 (18.8)	1.50 (1.53)	3.9	1.55	[0.89;6.97]	0.0114	0.2	[0.05;0.42]
	8	234 (96.7)	78.1 (20.7)	0.21 (1.63)	3.3	1.74	[-.08;6.73]	0.0558	0.2	[-.00;0.36]
	12	238 (98.3)	79.4 (18.6)	1.80 (1.58)	4.6	1.64	[1.41;7.85]	0.0049	0.3	[0.08;0.43]
	16	232 (95.9)	80.8 (19.2)	2.79 (1.59)	4.9	1.65	[1.65;8.14]	0.0032	0.3	[0.09;0.45]
	20	226 (93.4)	81.1 (17.3)	2.93 (1.62)	6.5	1.70	[3.12;9.80]	0.0002	0.4	[0.17;0.54]
	24	229 (94.6)	79.9 (18.1)	2.08 (1.55)	3.7	1.57	[0.64;6.81]	0.0179	0.2	[0.04;0.40]
EPTI 300 mg	Basln	245 (100.0)	74.9 (20.5)							
	4	236 (96.3)	78.8 (18.7)	1.75 (1.48)	4.2	1.54	[1.14;7.21]	0.0070	0.2	[0.07;0.43]
	8	236 (96.3)	80.9 (19.6)	3.42 (1.59)	6.5	1.73	[3.13;9.93]	0.0002	0.3	[0.17;0.53]
	12	243 (99.2)	82.0 (18.3)	4.62 (1.53)	7.5	1.63	[4.24;10.7]	<.0001	0.4	[0.23;0.59]
	16	232 (94.7)	81.8 (19.2)	4.05 (1.55)	6.2	1.65	[2.91;9.39]	0.0002	0.3	[0.16;0.52]
	20	233 (95.1)	80.7 (19.3)	3.20 (1.57)	6.7	1.69	[3.41;10.1]	<.0001	0.4	[0.19;0.55]
	24	235 (95.9)	82.2 (17.6)	5.06 (1.50)	6.7	1.56	[3.63;9.76]	<.0001	0.4	[0.21;0.58]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					95% CI			SMD 95% CI	
					CFB	LSmeans	Diff.	SE	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

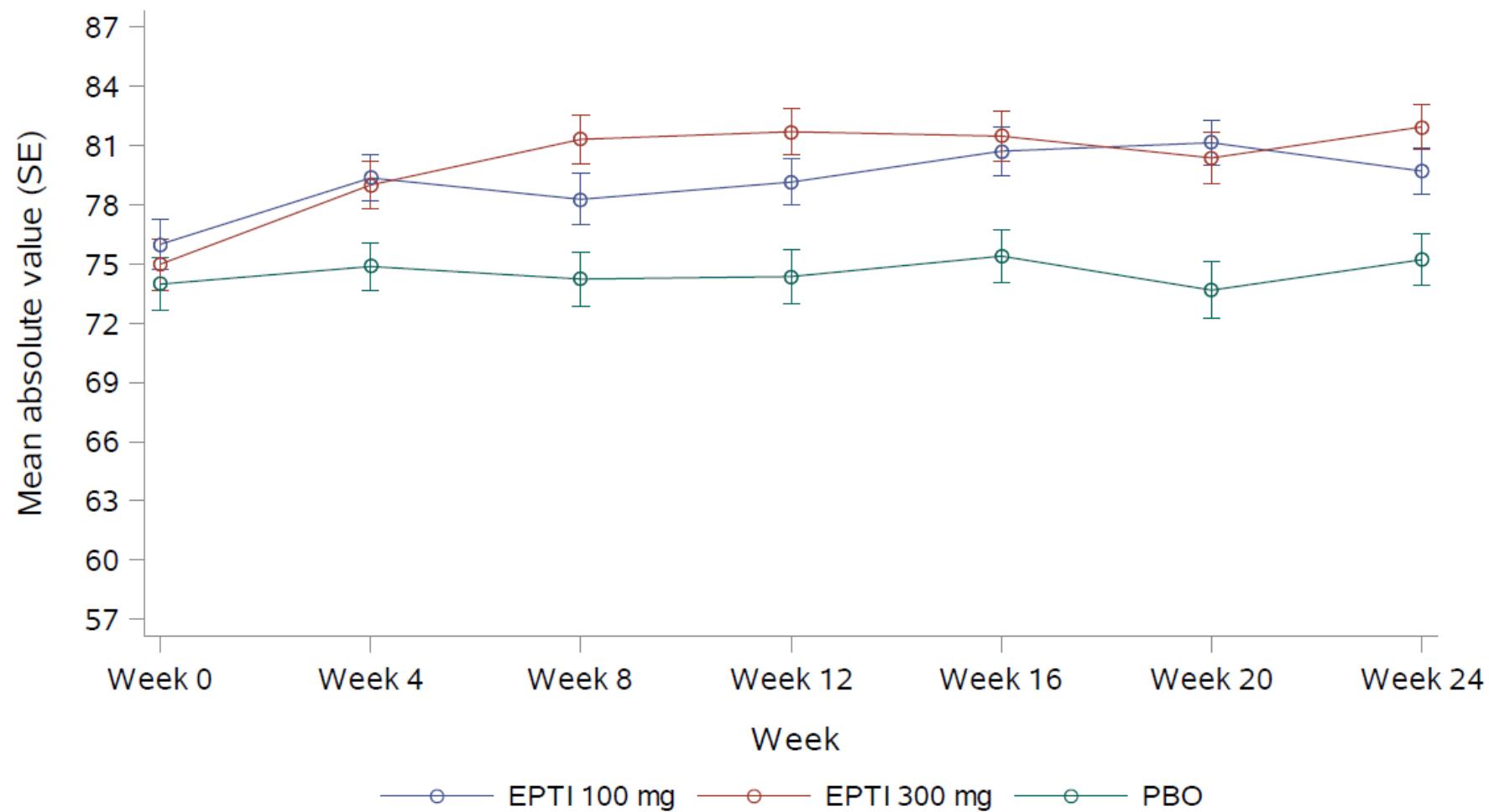
EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Females

Tabelle 4G-161: EQ-5D VAS, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	149 (100.0)	78.9 (18.7)								
	4	143 (96.0)	78.7 (18.3)	-.62 (1.72)							
	8	145 (97.3)	81.4 (16.6)	2.15 (1.78)							
	12	149 (100.0)	81.1 (18.1)	2.06 (1.73)							
	16	147 (98.7)	82.1 (15.6)	3.01 (1.73)							
	20	144 (96.6)	79.1 (18.1)	0.08 (1.82)							
	24	145 (97.3)	81.0 (16.9)	2.11 (1.69)							
EPTI 100 mg	Basln	146 (100.0)	77.9 (18.8)								
	4	142 (97.3)	82.5 (16.8)	3.98 (1.73)	4.6	1.82	[1.02;8.19]	0.0119	0.3	[0.07;0.53]	
	8	143 (97.9)	81.7 (18.2)	2.98 (1.80)	0.8	1.93	[-3.0;4.63]	0.6691	0.1	[-18;0.28]	
	12	144 (98.6)	82.3 (16.3)	3.80 (1.75)	1.7	1.84	[-1.9;5.37]	0.3435	0.1	[-12;0.34]	
	16	143 (97.9)	84.5 (15.7)	5.96 (1.75)	2.9	1.84	[-6.7;6.57]	0.1101	0.2	[-04;0.42]	
	20	139 (95.2)	84.0 (15.0)	5.17 (1.84)	5.1	2.01	[1.14;9.04]	0.0117	0.3	[0.07;0.53]	
	24	136 (93.2)	81.6 (17.4)	2.69 (1.73)	0.6	1.78	[-2.9;4.08]	0.7451	0.0	[-20;0.27]	
EPTI 300 mg	Basln	151 (100.0)	78.7 (17.3)								
	4	145 (96.0)	82.8 (15.5)	3.94 (1.66)	4.6	1.81	[1.00;8.13]	0.0123	0.3	[0.06;0.53]	
	8	146 (96.7)	83.4 (17.8)	4.45 (1.73)	2.3	1.92	[-1.5;6.08]	0.2319	0.1	[-09;0.37]	
	12	150 (99.3)	84.9 (16.8)	5.89 (1.67)	3.8	1.83	[0.24;7.42]	0.0364	0.2	[0.02;0.47]	
	16	145 (96.0)	83.4 (18.9)	4.43 (1.69)	1.4	1.83	[-2.2;5.02]	0.4404	0.1	[-14;0.32]	
	20	143 (94.7)	83.2 (20.0)	4.19 (1.78)	4.1	1.99	[0.19;8.04]	0.0398	0.2	[0.01;0.48]	
	24	146 (96.7)	84.3 (16.3)	5.55 (1.66)	3.4	1.75	[-.01;6.88]	0.0507	0.2	[-.00;0.46]	

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		Hedges' G	
					Diff.	SE	CI	95% CI	SMD 95% CI	G	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. EM : Episodic Migraine.

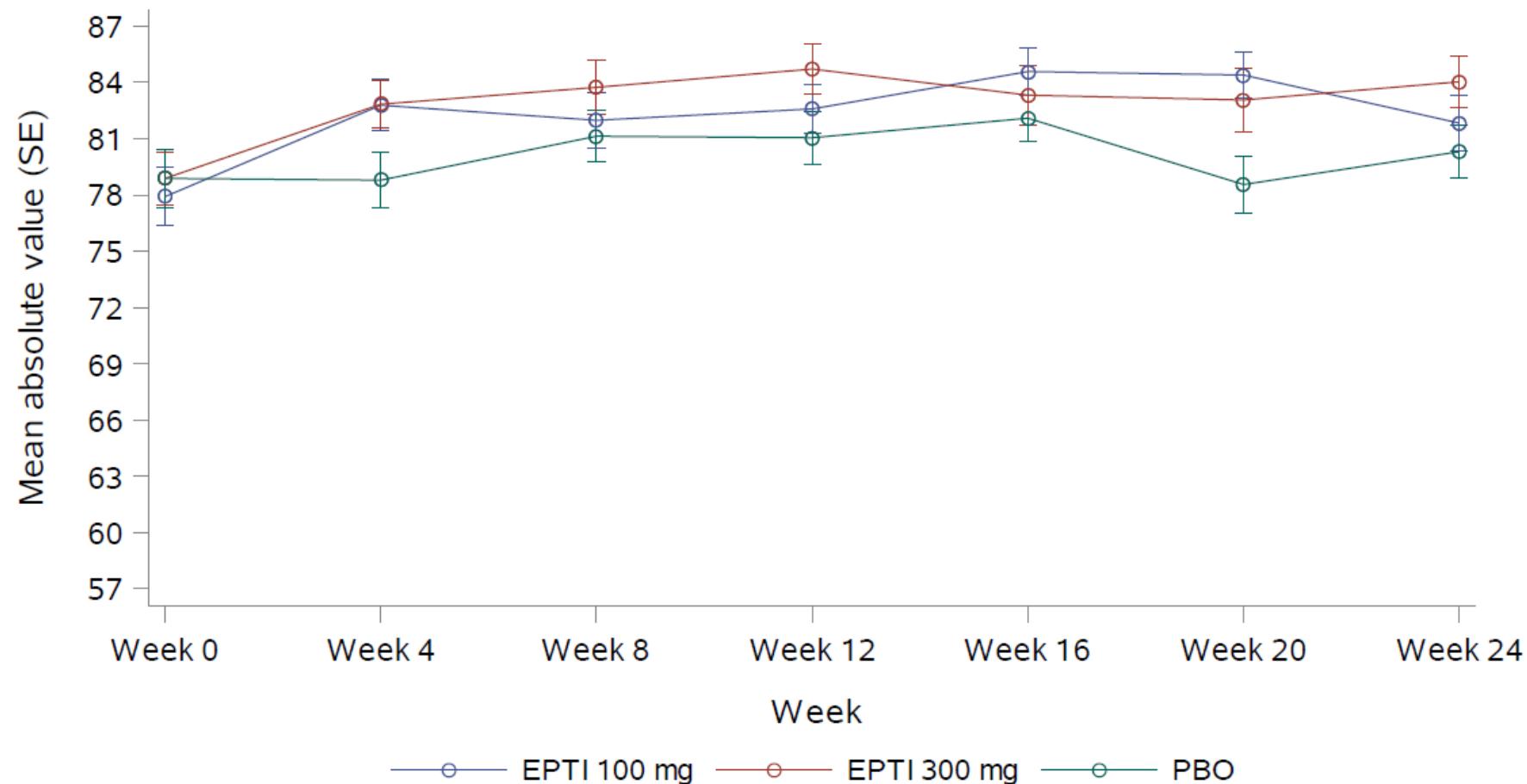
EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Episodic Migraine

Tabelle 4G-162: EQ-5D VAS, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	127 (100.0)	68.0 (21.2)							
	4	123 (96.9)	67.9 (19.6)	-5.3 (2.96)						
	8	121 (95.3)	65.1 (23.1)	-6.1 (3.24)						
	12	127 (100.0)	64.9 (23.4)	-6.9 (3.09)						
	16	120 (94.5)	65.2 (24.4)	-6.2 (3.15)						
	20	119 (93.7)	67.3 (24.9)	-3.5 (3.20)						
	24	121 (95.3)	65.6 (23.4)	-5.8 (3.01)						
EPTI 100 mg	Basln	116 (100.0)	73.5 (19.2)							
	4	110 (94.8)	74.7 (19.3)	-.59 (2.92)	4.7	2.44	[-10;9.51]	0.0550	0.3	[-.01;0.51]
	8	111 (95.7)	73.7 (21.7)	0.71 (3.25)	6.8	2.76	[1.35;12.2]	0.0146	0.3	[0.06;0.58]
	12	114 (98.3)	76.2 (20.0)	2.73 (3.05)	9.7	2.62	[4.51;14.8]	0.0003	0.5	[0.22;0.73]
	16	109 (94.0)	76.0 (21.3)	2.32 (3.14)	8.5	2.69	[3.21;13.8]	0.0017	0.4	[0.16;0.68]
	20	107 (92.2)	76.9 (18.6)	3.71 (3.19)	7.2	2.77	[1.73;12.6]	0.0100	0.3	[0.08;0.61]
	24	111 (95.7)	77.5 (18.1)	3.79 (3.00)	9.6	2.52	[4.67;14.6]	0.0002	0.5	[0.24;0.76]
EPTI 300 mg	Basln	125 (100.0)	69.6 (23.0)							
	4	121 (96.8)	74.2 (21.2)	0.19 (2.94)	5.5	2.36	[0.83;10.1]	0.0210	0.3	[0.05;0.55]
	8	121 (96.8)	77.1 (21.6)	5.24 (3.23)	11.3	2.69	[6.03;16.6]	<.0001	0.5	[0.29;0.79]
	12	124 (99.2)	76.9 (20.2)	4.56 (3.08)	11.5	2.54	[6.49;16.5]	<.0001	0.6	[0.32;0.82]
	16	118 (94.4)	79.3 (19.1)	6.95 (3.14)	13.1	2.62	[7.99;18.3]	<.0001	0.7	[0.40;0.91]
	20	119 (95.2)	75.8 (21.7)	3.96 (3.19)	7.4	2.68	[2.15;12.7]	0.0059	0.4	[0.10;0.61]
	24	120 (96.0)	79.5 (18.8)	7.14 (3.00)	13.0	2.45	[8.16;17.8]	<.0001	0.7	[0.43;0.94]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		Hedges' G	
					Diff.	SE	CI	95% CI	SMD 95% CI	p-value	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. CM : Chronic Migraine.

EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Chronic Migraine

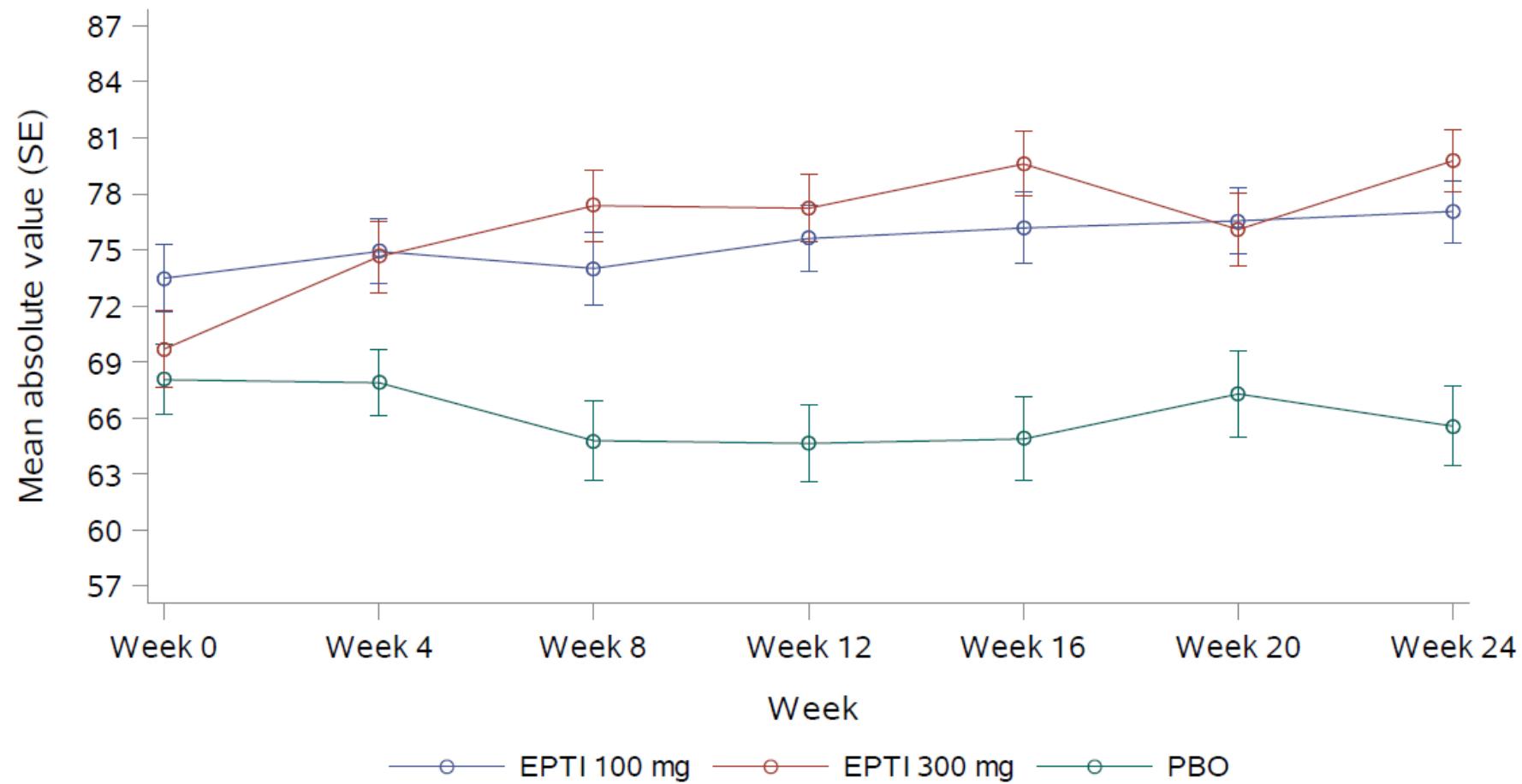


Tabelle 4G-163: EQ-5D VAS, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	33 (100.0)	64.2 (21.8)							
	4	32 (97.0)	65.9 (17.2)	2.17 (4.16)						
	8	31 (93.9)	64.8 (25.8)	2.54 (4.51)						
	12	33 (100.0)	65.5 (23.5)	4.89 (4.59)						
	16	32 (97.0)	63.7 (26.5)	1.97 (4.74)						
	20	31 (93.9)	63.4 (24.6)	1.67 (4.59)						
	24	31 (93.9)	63.8 (26.3)	0.88 (4.65)						
EPTI 100 mg	Basln	33 (100.0)	68.2 (19.7)							
	4	30 (90.9)	67.7 (18.6)	0.79 (3.99)	-1.4	4.44	[-10;7.47]	0.7573	-0.1	[-.58;0.43]
	8	31 (93.9)	73.3 (17.4)	7.92 (4.38)	5.4	5.04	[-4.6;15.4]	0.2889	0.3	[-.23;0.78]
	12	32 (97.0)	71.7 (19.8)	7.96 (4.42)	3.1	5.16	[-7.2;13.3]	0.5538	0.1	[-.35;0.64]
	16	32 (97.0)	73.6 (19.8)	8.55 (4.55)	6.6	5.39	[-4.1;17.3]	0.2255	0.3	[-.19;0.80]
	20	31 (93.9)	70.3 (18.3)	5.99 (4.41)	4.3	5.17	[-6.0;14.6]	0.4058	0.2	[-.29;0.72]
	24	32 (97.0)	70.6 (19.1)	5.95 (4.43)	5.1	5.25	[-5.4;15.5]	0.3369	0.2	[-.26;0.74]
EPTI 300 mg	Basln	33 (100.0)	67.5 (23.8)							
	4	31 (93.9)	76.5 (19.9)	12.0 (4.02)	9.8	4.37	[1.13;18.5]	0.0272	0.6	[0.07;1.07]
	8	32 (97.0)	75.1 (22.2)	11.7 (4.34)	9.2	4.99	[-.77;19.1]	0.0701	0.5	[-.04;0.96]
	12	32 (97.0)	78.4 (20.8)	16.2 (4.45)	11.4	5.11	[1.20;21.5]	0.0289	0.6	[0.06;1.04]
	16	33 (100.0)	78.4 (18.8)	15.3 (4.55)	13.3	5.33	[2.76;23.9]	0.0140	0.6	[0.13;1.11]
	20	32 (97.0)	77.4 (20.6)	14.9 (4.42)	13.2	5.10	[3.08;23.3]	0.0112	0.7	[0.15;1.15]
	24	32 (97.0)	77.3 (19.1)	14.4 (4.49)	13.6	5.18	[3.27;23.9]	0.0104	0.7	[0.16;1.16]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		Hedges' G	
					Diff.	SE	CI	95% CI	SMD 95% CI	G	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

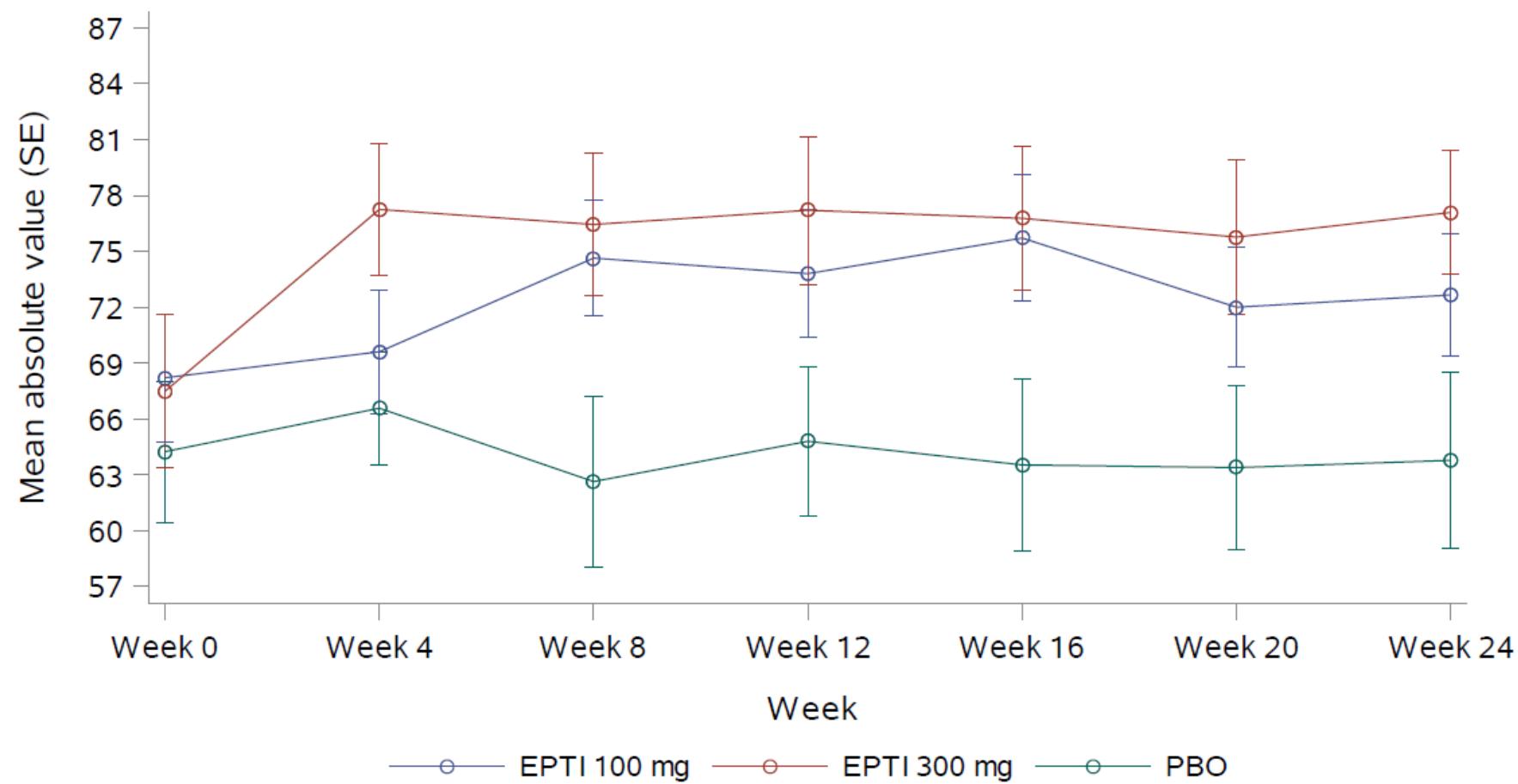
EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Medication overuse headache at baseline

Tabelle 4G-164: EQ-5D VAS, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' SMD 95% CI		
					CFB			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	243 (100.0)	75.2 (20.1)							
	4	234 (96.3)	74.8 (19.8)	-3.6 (1.51)						
	8	235 (96.7)	75.2 (20.5)	-3.5 (1.59)						
	12	243 (100.0)	74.8 (21.8)	-3.6 (1.54)						
	16	235 (96.7)	76.0 (20.6)	-2.6 (1.55)						
	20	232 (95.5)	75.1 (21.5)	-3.4 (1.60)						
	24	235 (96.7)	75.3 (20.5)	-2.7 (1.50)						
EPTI 100 mg	Basln	229 (100.0)	77.1 (18.7)							
	4	222 (96.9)	80.6 (17.8)	1.72 (1.53)	5.4	1.58	[2.25;8.45]	0.0007	0.3	[0.13;0.50]
	8	223 (97.4)	78.9 (20.4)	-.36 (1.61)	3.1	1.73	[-.26;6.54]	0.0699	0.2	[-.01;0.35]
	12	226 (98.7)	80.8 (17.8)	1.70 (1.56)	5.3	1.63	[2.09;8.51]	0.0012	0.3	[0.12;0.48]
	16	220 (96.1)	81.9 (18.5)	2.60 (1.58)	5.2	1.65	[2.00;8.48]	0.0016	0.3	[0.11;0.48]
	20	215 (93.9)	82.4 (16.3)	2.81 (1.64)	6.2	1.76	[2.75;9.66]	0.0005	0.3	[0.15;0.52]
	24	215 (93.9)	81.1 (17.2)	1.86 (1.54)	4.5	1.57	[1.44;7.61]	0.0041	0.3	[0.09;0.46]
EPTI 300 mg	Basln	243 (100.0)	75.5 (19.9)							
	4	235 (96.7)	79.2 (18.6)	0.79 (1.48)	4.4	1.56	[1.37;7.48]	0.0046	0.3	[0.08;0.44]
	8	235 (96.7)	81.3 (19.4)	2.55 (1.57)	6.1	1.71	[2.71;9.41]	0.0004	0.3	[0.15;0.51]
	12	242 (99.6)	81.6 (18.5)	3.13 (1.51)	6.7	1.61	[3.57;9.88]	<.0001	0.4	[0.20;0.56]
	16	230 (94.7)	82.0 (19.1)	3.21 (1.53)	5.9	1.63	[2.65;9.05]	0.0004	0.3	[0.15;0.52]
	20	230 (94.7)	80.1 (21.1)	1.24 (1.58)	4.6	1.73	[1.24;8.04]	0.0075	0.2	[0.07;0.43]
	24	234 (96.3)	82.8 (17.3)	4.48 (1.47)	7.1	1.54	[4.12;10.2]	<.0001	0.4	[0.25;0.61]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		Hedges' G	
					Diff.	SE	CI	95% CI	SMD 95% CI	G	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

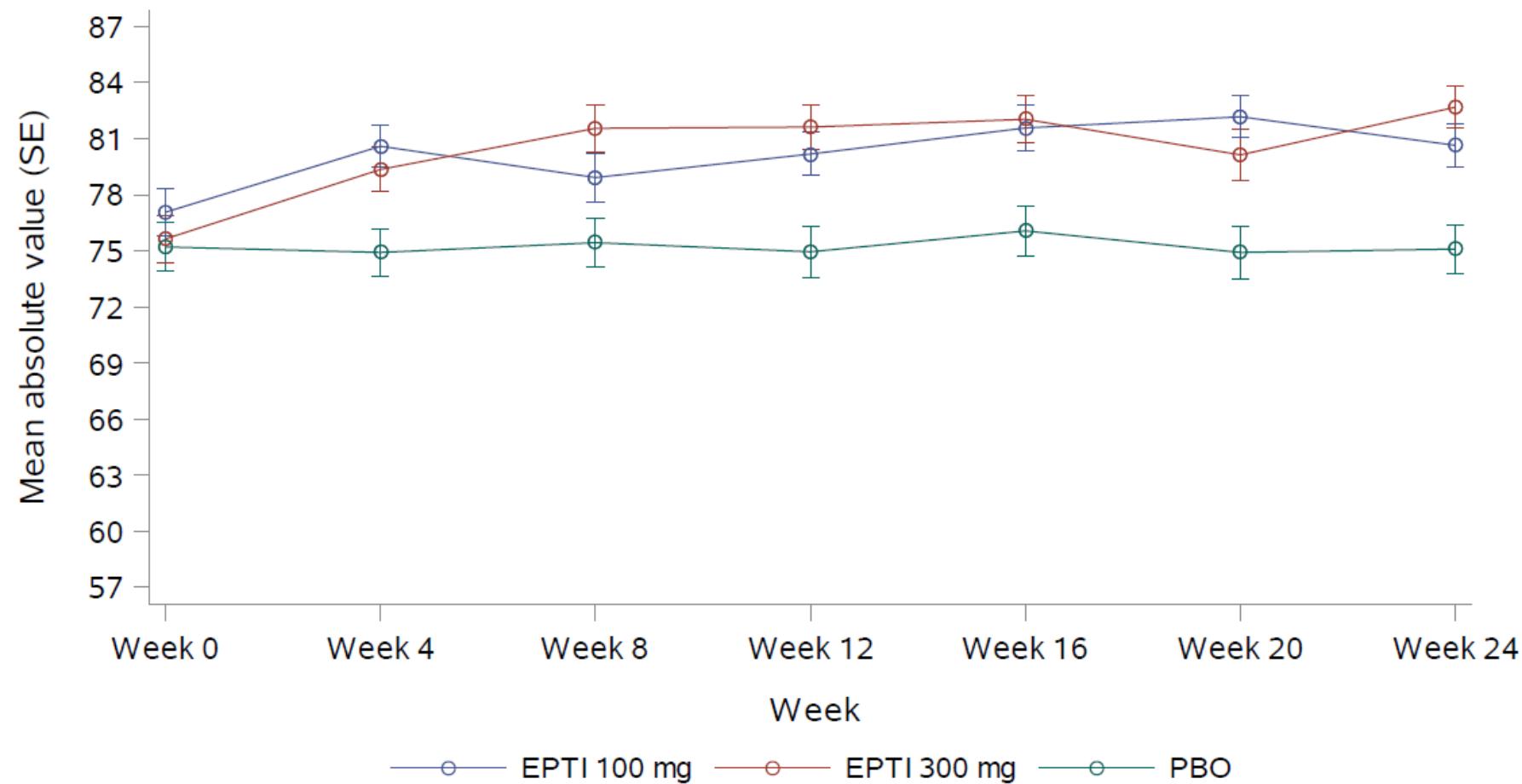
EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) No medication overuse headache at baseline

Tabelle 4G-165: EQ-5D VAS, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	194 (100.0)	75.0 (20.1)							
	4	187 (96.4)	75.1 (18.6)	-2.0 (1.66)						
	8	185 (95.4)	75.5 (20.4)	-2.0 (1.80)						
	12	194 (100.0)	74.0 (22.4)	-3.2 (1.71)						
	16	185 (95.4)	75.5 (20.9)	-2.0 (1.71)						
	20	184 (94.8)	73.8 (21.4)	-3.4 (1.79)						
	24	188 (96.9)	75.2 (20.7)	-1.6 (1.70)						
EPTI 100 mg	Basln	191 (100.0)	77.4 (17.7)							
	4	183 (95.8)	80.3 (17.7)	2.14 (1.67)	4.2	1.71	[0.81;7.53]	0.0151	0.3	[0.05;0.46]
	8	185 (96.9)	78.2 (20.9)	-.43 (1.81)	1.6	1.98	[-2.3;5.48]	0.4173	0.1	[-.12;0.29]
	12	188 (98.4)	81.8 (16.6)	3.50 (1.73)	6.7	1.82	[3.11;10.3]	0.0003	0.4	[0.17;0.58]
	16	183 (95.8)	82.6 (17.2)	4.05 (1.73)	6.1	1.80	[2.53;9.61]	0.0008	0.4	[0.15;0.56]
	20	179 (93.7)	82.8 (15.9)	3.91 (1.81)	7.3	1.96	[3.46;11.1]	0.0002	0.4	[0.19;0.60]
	24	178 (93.2)	80.6 (17.5)	2.24 (1.74)	3.8	1.81	[0.30;7.40]	0.0338	0.2	[0.02;0.43]
EPTI 300 mg	Basln	209 (100.0)	76.3 (20.0)							
	4	199 (95.2)	79.8 (19.2)	1.90 (1.58)	3.9	1.67	[0.64;7.22]	0.0192	0.2	[0.04;0.44]
	8	201 (96.2)	80.5 (20.5)	2.48 (1.72)	4.5	1.93	[0.71;8.31]	0.0200	0.2	[0.04;0.44]
	12	208 (99.5)	81.8 (19.2)	3.82 (1.63)	7.0	1.78	[3.52;10.5]	<.0001	0.4	[0.20;0.59]
	16	197 (94.3)	81.6 (19.8)	3.39 (1.64)	5.4	1.77	[1.93;8.88]	0.0023	0.3	[0.11;0.51]
	20	198 (94.7)	79.4 (22.1)	1.34 (1.71)	4.7	1.91	[0.99;8.48]	0.0132	0.3	[0.05;0.46]
	24	202 (96.7)	82.0 (18.9)	4.33 (1.62)	5.9	1.75	[2.49;9.38]	0.0008	0.3	[0.14;0.54]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					95% CI			SMD 95% CI	
					CFB	LSmeans	Diff.	SE	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

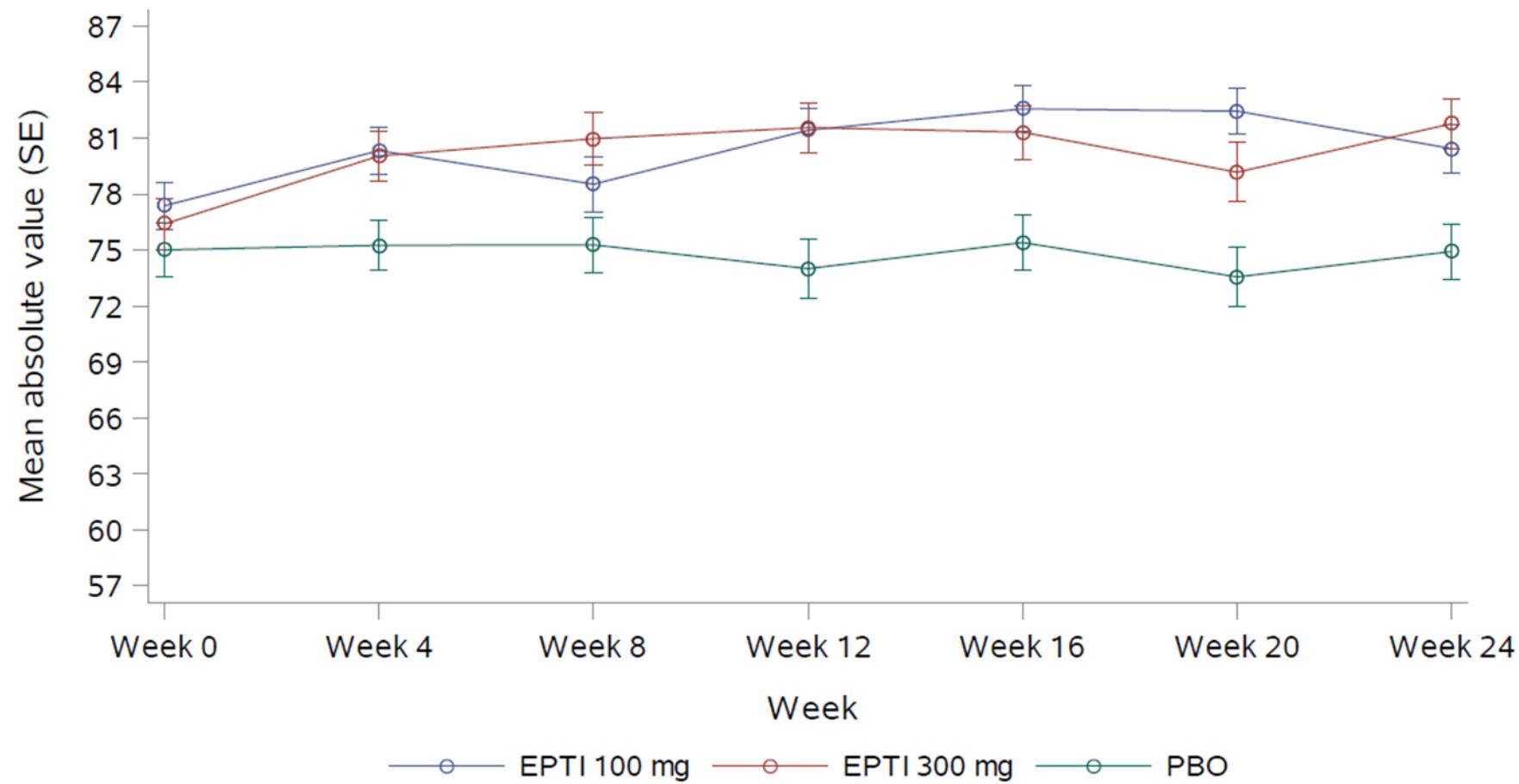
EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : = 2 Previous Failed Treatments

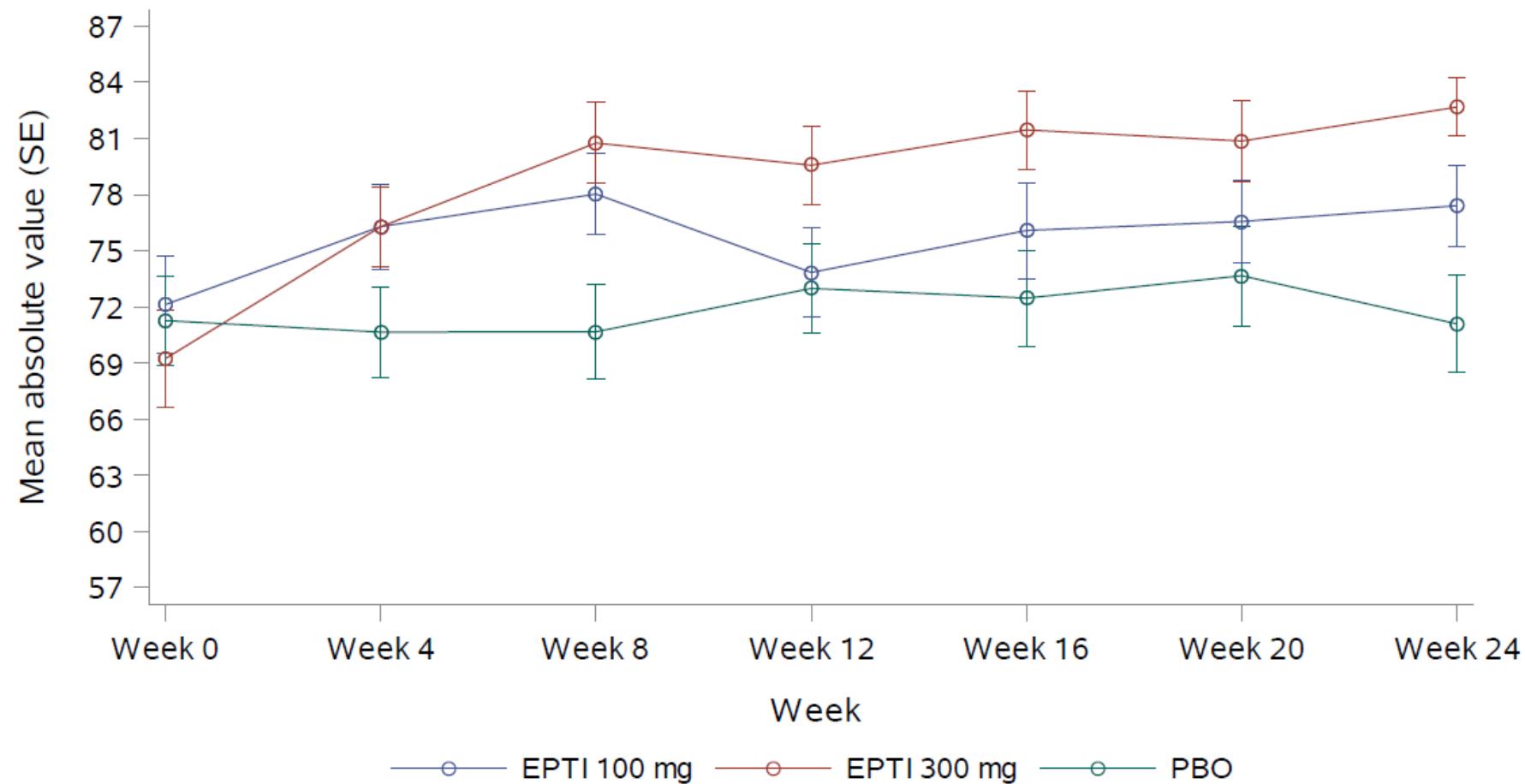
Tabelle 4G-166 :EQ-5D VAS, CFB, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	82 (100.0)	71.3 (21.4)								
	4	79 (96.3)	70.4 (21.7)	-3.2 (2.80)							
	8	81 (98.8)	70.5 (23.1)	-3.0 (2.76)							
	12	82 (100.0)	72.9 (21.7)	-.56 (2.80)							
	16	82 (100.0)	72.3 (23.4)	-1.1 (2.92)							
	20	79 (96.3)	73.7 (24.1)	-.60 (2.89)							
	24	78 (95.1)	70.9 (23.3)	-2.6 (2.70)							
EPTI 100 mg	Basln	71 (100.0)	72.1 (22.0)								
	4	69 (97.2)	75.8 (19.7)	2.30 (2.83)	5.5	3.00	[-.38;11.4]	0.0666	0.3	[-.02;0.63]	
	8	69 (97.2)	78.2 (18.0)	5.26 (2.80)	8.3	2.93	[2.51;14.1]	0.0051	0.5	[0.14;0.79]	
	12	70 (98.6)	73.8 (21.0)	0.85 (2.84)	1.4	3.01	[-4.5;7.34]	0.6389	0.1	[-.24;0.40]	
	16	69 (97.2)	76.2 (22.0)	2.74 (2.99)	3.9	3.27	[-2.6;10.3]	0.2366	0.2	[-.13;0.52]	
	20	67 (94.4)	75.9 (18.9)	2.62 (2.95)	3.2	3.19	[-3.1;9.51]	0.3146	0.2	[-.16;0.49]	
	24	69 (97.2)	77.6 (18.3)	4.38 (2.70)	6.9	2.77	[1.47;12.4]	0.0131	0.4	[0.09;0.74]	
EPTI 300 mg	Basln	67 (100.0)	69.2 (21.4)								
	4	67 (100.0)	76.3 (17.4)	3.79 (2.86)	7.0	3.02	[1.05;13.0]	0.0213	0.4	[0.06;0.71]	
	8	66 (98.5)	80.8 (17.6)	7.73 (2.83)	10.8	2.97	[4.92;16.6]	0.0004	0.6	[0.27;0.93]	
	12	66 (98.5)	79.6 (17.4)	6.92 (2.89)	7.5	3.05	[1.47;13.5]	0.0150	0.4	[0.08;0.73]	
	16	66 (98.5)	81.5 (16.9)	8.29 (3.04)	9.4	3.30	[2.91;15.9]	0.0048	0.5	[0.15;0.80]	
	20	64 (95.5)	80.9 (17.6)	7.17 (2.99)	7.8	3.23	[1.40;14.1]	0.0171	0.4	[0.07;0.74]	
	24	64 (95.5)	82.6 (12.7)	9.56 (2.75)	12.1	2.82	[6.56;17.7]	<.0001	0.7	[0.39;1.06]	

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					95% CI			SMD 95% CI	
					CFB	LSmeans	Diff.	SE	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline EQ-5D-5L VAS Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

EQ-5D-5L VAS Score. Absolute Value: Mean (SE) by Visit (AMNOG) : > 2 Previous Failed Treatments

4.2.12.2 Verbesserung um ≥ 15 PunkteTabelle 4G-167: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Interaktions-p-Werte

Visit	Description	Treatment Group	
		EPTI 100 mg p-value	EPTI 300 mg p-value
Week 12	Interaction test: Age Group	0.4506	0.4964
	Interaction test: EM/CM	0.0117	0.0082
	Interaction test: MOH	0.7906	0.1561
	Interaction test: Number of FPT	0.7944	0.4333
	Interaction test: Sex	0.0102	0.0341
Week 24	Interaction test: Age Group	0.0880	0.7506
	Interaction test: EM/CM	0.7260	0.4588
	Interaction test: MOH	0.5540	0.8572
	Interaction test: Number of FPT	0.4372	0.8374
	Interaction test: Sex	0.8262	0.0946

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-168: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	4	64	5	(7.8)							
	8	64	8	(12.5)							
	12	64	7	(10.9)							
	16	64	10	(15.6)							
	20	64	9	(14.1)							
	24	64	12	(18.8)							

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 100 mg	4	54	13	(24.1)	3.56	[1.05;13.6]	3.34	[1.23;9.07]	16.3	[3.10;29.4]	0.0415
	8	54	18	(33.3)	3.26	[1.17;9.77]	2.81	[1.28;6.16]	20.8	[5.88;35.8]	0.0240
	12	54	14	(25.9)	2.50	[0.82;8.11]	2.50	[1.06;5.88]	15.0	[1.02;29.0]	0.1073
	16	54	18	(33.3)	2.49	[0.92;7.04]	2.27	[1.14;4.53]	17.7	[2.31;33.1]	0.0723
	20	54	14	(25.9)	1.76	[0.62;5.13]	1.95	[0.88;4.33]	11.9	[-2.6;26.3]	0.2875
	24	54	9	(16.7)	0.59	[0.18;1.82]	0.93	[0.42;2.07]	-2.1	[-16;11.7]	0.3656
EPTI 300 mg	4	61	13	(21.3)	4.21	[1.26;16.3]	2.79	[1.04;7.47]	13.5	[1.30;25.7]	0.0191
	8	61	18	(29.5)	3.80	[1.37;11.6]	2.40	[1.11;5.18]	17.0	[2.99;31.0]	0.0098
	12	61	9	(14.8)	1.40	[0.42;4.72]	1.37	[0.54;3.49]	3.82	[-7.9;15.6]	0.5817
	16	61	15	(24.6)	2.05	[0.74;5.91]	1.59	[0.76;3.31]	8.97	[-5.0;23.0]	0.1673
	20	61	13	(21.3)	1.79	[0.64;5.21]	1.55	[0.70;3.40]	7.25	[-6.1;20.6]	0.2716
	24	61	17	(27.9)	2.20	[0.81;6.28]	1.53	[0.80;2.89]	9.12	[-5.6;23.9]	0.1235

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

Tabelle 4G-169 :EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe > 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	4	212	35	(16.5)							
	8	212	48	(22.6)							
	12	212	48	(22.6)							
	16	212	44	(20.8)							
	20	212	51	(24.1)							
	24	212	50	(23.6)							
EPTI 100 mg	4	208	34	(16.3)	1.46	[0.79;2.69]	0.99	[0.64;1.52]	-16	[-7.3;6.92]	0.2245
	8	208	44	(21.2)	1.31	[0.75;2.31]	0.93	[0.65;1.34]	-1.5	[-9.4;6.42]	0.3478

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 300 mg	12	208	45	(21.6)	1.44	[0.80;2.59]	0.96	[0.67;1.37]	-1.0	[-8.9;6.93]	0.2221
	16	208	52	(25.0)	2.10	[1.20;3.73]	1.21	[0.85;1.71]	4.25	[-3.8;12.3]	0.0089
	20	208	48	(23.1)	1.33	[0.78;2.29]	0.96	[0.68;1.35]	-.98	[-9.1;7.14]	0.3008
	24	208	47	(22.6)	1.40	[0.80;2.47]	0.96	[0.68;1.36]	-.99	[-9.0;7.07]	0.2435
	4	214	45	(21.0)	1.64	[0.92;2.97]	1.27	[0.85;1.90]	4.52	[-2.9;11.9]	0.0939
	8	214	57	(26.6)	1.49	[0.87;2.60]	1.18	[0.84;1.64]	3.99	[-4.2;12.2]	0.1490

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

AMNOG: AMNOG population B.

Tabelle 4G-170: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe männlich

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	4	28	1	(3.6)							
	8	28	6	(21.4)							
	12	28	1	(3.6)							
	16	28	7	(25.0)							
	20	28	6	(21.4)							
	24	28	3	(10.7)							
EPTI 100 mg	4	20	5	(25.0)	14.0	[1.69; 316]	9.25	[0.91;94.1]	21.4	[1.24;41.6]	0.0124
	8	20	6	(30.0)	1.83	[0.40;8.67]	1.34	[0.52;3.49]	8.57	[-17;33.8]	0.4351
	12	20	5	(25.0)	15.3	[1.74; 362]	8.72	[0.74; 103]	21.4	[1.24;41.6]	0.0121
	16	20	6	(30.0)	2.09	[0.43;11.0]	1.42	[0.57;3.52]	5.00	[-21;30.7]	0.3608

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 300 mg	20	20	3	(15.0)	0.63	[0.10;3.38]	0.75	[0.16;3.51]	-6.4	[-28;15.4]	0.5978
	24	20	2	(10.0)	1.86	[0.10;31.5]	0.93	[0.14;6.37]	-.71	[-18;16.7]	0.6580
	4	31	7	(22.6)	9.47	[1.35; 197]	5.80	[0.82;40.8]	19.0	[2.76;35.3]	0.0212
	8	31	7	(22.6)	1.02	[0.24;4.34]	1.07	[0.40;2.87]	1.15	[-20;22.3]	0.9736
	12	31	8	(25.8)	13.2	[1.83; 286]	6.56	[0.95;45.5]	22.2	[5.37;39.1]	0.0079
	16	31	8	(25.8)	1.00	[0.21;4.95]	0.98	[0.42;2.29]	0.81	[-21;23.0]	0.9967
	20	31	5	(16.1)	0.60	[0.13;2.61]	0.73	[0.26;2.07]	-5.3	[-25;14.7]	0.4963
	24	31	10	(32.3)	13.2	[1.81; 199]	2.84	[0.88;9.14]	21.5	[1.49;41.6]	0.0086

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

AMNOG: AMNOG population B.

Tabelle 4G-171: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe weiblich

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	4	248	39	(15.7)							
	8	248	50	(20.2)							
	12	248	54	(21.8)							
	16	248	47	(19.0)							
	20	248	54	(21.8)							
	24	248	59	(23.8)							
EPTI 100 mg	4	242	42	(17.4)	1.41	[0.80;2.50]	1.11	[0.74;1.65]	1.63	[-5.0;8.21]	0.2298
	8	242	56	(23.1)	1.53	[0.91;2.59]	1.15	[0.82;1.61]	2.98	[-4.3;10.3]	0.1079
	12	242	54	(22.3)	1.27	[0.75;2.17]	1.03	[0.74;1.43]	0.54	[-6.8;7.88]	0.3701
	16	242	64	(26.4)	2.15	[1.29;3.63]	1.39	[1.00;1.94]	7.49	[0.10;14.9]	0.0031
	20	242	59	(24.4)	1.43	[0.87;2.38]	1.12	[0.81;1.55]	2.61	[-4.9;10.1]	0.1571
	24	242	54	(22.3)	1.06	[0.64;1.77]	0.94	[0.68;1.30]	-1.5	[-8.9;5.98]	0.8104

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 300 mg	4	244	51	(20.9)	1.74	[1.00;3.04]	1.33	[0.91;1.95]	5.18	[-1.6;12.0]	0.0489
	8	244	68	(27.9)	1.99	[1.19;3.34]	1.39	[1.01;1.91]	7.71	[0.19;15.2]	0.0080
	12	244	67	(27.5)	1.74	[1.04;2.95]	1.27	[0.93;1.73]	5.68	[-1.9;13.3]	0.0352
	16	244	66	(27.0)	2.04	[1.22;3.45]	1.43	[1.03;1.99]	8.10	[0.69;15.5]	0.0061
	20	244	68	(27.9)	1.68	[1.03;2.77]	1.28	[0.94;1.75]	6.09	[-1.5;13.7]	0.0385
	24	244	71	(29.1)	1.62	[1.00;2.67]	1.23	[0.92;1.66]	5.31	[-2.5;13.1]	0.0522

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

AMNOG: AMNOG population B.

Tabelle 4G-172: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe EM

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	4	149	18	(12.1)							
	8	149	27	(18.1)							
	12	149	31	(20.8)							
	16	149	29	(19.5)							
	20	149	30	(20.1)							
	24	149	28	(18.8)							
EPTI 100 mg	4	146	24	(16.4)	1.59	[0.71;3.65]	1.36	[0.77;2.40]	4.36	[-3.6;12.3]	0.2618
	8	146	33	(22.6)	1.41	[0.69;2.92]	1.25	[0.79;1.97]	4.48	[-4.7;13.7]	0.3515
	12	146	29	(19.9)	0.83	[0.40;1.68]	0.95	[0.61;1.50]	-.94	[-10;8.24]	0.6005
	16	146	38	(26.0)	1.63	[0.82;3.28]	1.34	[0.87;2.05]	6.56	[-3.0;16.1]	0.1643
	20	146	33	(22.6)	1.14	[0.57;2.26]	1.12	[0.72;1.74]	2.47	[-6.9;11.8]	0.7123
	24	146	29	(19.9)	1.01	[0.50;2.07]	1.06	[0.66;1.69]	1.07	[-7.9;10.1]	0.9688
EPTI 300 mg	4	150	32	(21.3)	2.79	[1.30;6.27]	1.77	[1.04;3.00]	9.25	[0.86;17.6]	0.0078

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
AMNOG population B	EM : Episodic Migraine	8	150	41	(27.3)	2.26	[1.14;4.62]	1.51	[0.98;2.32]	9.21	[-.23;18.7]	0.0192
		12	150	32	(21.3)	1.04	[0.52;2.09]	1.03	[0.66;1.59]	0.53	[-8.7;9.77]	0.9009
		16	150	34	(22.7)	1.34	[0.67;2.73]	1.16	[0.75;1.81]	3.20	[-6.0;12.4]	0.4048
		20	150	39	(26.0)	1.62	[0.84;3.17]	1.29	[0.85;1.96]	5.87	[-3.7;15.4]	0.1509
		24	150	36	(24.0)	1.58	[0.80;3.14]	1.28	[0.82;1.98]	5.21	[-4.1;14.5]	0.1856

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment as factor. CL for RR and RD are based on binomial distribution. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-173: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe CM

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		4	127	22	(17.3)							
		8	127	29	(22.8)							
		12	127	24	(18.9)							
		16	127	25	(19.7)							
		20	127	30	(23.6)							
		24	127	34	(26.8)							
EPTI 100 mg		4	116	23	(19.8)	1.80	[0.86;3.81]	1.14	[0.68;1.94]	2.50	[-7.3;12.3]	0.1177
		8	116	29	(25.0)	1.70	[0.86;3.41]	1.09	[0.70;1.72]	2.17	[-8.6;12.9]	0.1249
		12	116	30	(25.9)	2.79	[1.34;5.98]	1.37	[0.85;2.20]	6.96	[-3.5;17.4]	0.0058
		16	116	32	(27.6)	2.60	[1.30;5.32]	1.40	[0.89;2.22]	7.90	[-2.8;18.6]	0.0065
		20	116	29	(25.0)	1.57	[0.81;3.10]	1.06	[0.68;1.65]	1.38	[-9.4;12.2]	0.1848
		24	116	27	(23.3)	1.18	[0.59;2.37]	0.87	[0.56;1.35]	-3.5	[-14;7.39]	0.6318
EPTI 300 mg		4	125	26	(20.8)	1.39	[0.67;2.91]	1.20	[0.72;2.00]	3.48	[-6.2;13.2]	0.3719
		8	125	34	(27.2)	1.47	[0.75;2.89]	1.19	[0.78;1.83]	4.37	[-6.3;15.0]	0.2640
		12	125	43	(34.4)	3.67	[1.80;7.76]	1.82	[1.18;2.81]	15.5	[4.75;26.3]	0.0003

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		16	125	40	(32.0)	2.61	[1.33;5.27]	1.63	[1.05;2.51]	12.3	[1.61;23.0]	0.0050
		20	125	34	(27.2)	1.37	[0.71;2.67]	1.15	[0.75;1.76]	3.58	[-7.2;14.3]	0.3499
		24	125	45	(36.0)	2.09	[1.09;4.10]	1.34	[0.93;1.95]	9.23	[-2.2;20.6]	0.0263

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment as factor. CL for RR and RD are based on binomial distribution. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-174: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe MOH: ja

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		4	33	6	(18.2)							
		8	33	9	(27.3)							
		12	33	8	(24.2)							
		16	33	7	(21.2)							
		20	33	8	(24.2)							
		24	33	12	(36.4)							
EPTI 100 mg		4	33	6	(18.2)	1.25	[0.30;5.24]	1.08	[0.36;3.22]	0.00	[-19;18.6]	0.7531
		8	33	10	(30.3)	1.32	[0.40;4.44]	1.11	[0.50;2.49]	3.03	[-19;24.9]	0.6429
		12	33	9	(27.3)	1.25	[0.35;4.55]	1.04	[0.45;2.41]	3.03	[-18;24.1]	0.7312
		16	33	12	(36.4)	4.09	[1.02;19.2]	1.79	[0.74;4.34]	15.2	[-6.4;36.7]	0.0460
		20	33	8	(24.2)	1.09	[0.29;4.12]	1.01	[0.38;2.68]	0.00	[-21;20.7]	0.8919
		24	33	9	(27.3)	0.62	[0.17;2.16]	0.71	[0.31;1.61]	-9.1	[-31;13.3]	0.4581
EPTI 300 mg		4	33	12	(36.4)	3.69	[1.05;14.8]	2.11	[0.85;5.23]	18.2	[-2.9;39.2]	0.0417
		8	33	11	(33.3)	1.51	[0.47;5.03]	1.23	[0.57;2.65]	6.06	[-16;28.2]	0.4880
		12	33	14	(42.4)	2.99	[0.91;10.7]	1.68	[0.82;3.46]	18.2	[-4.1;40.5]	0.0717
		16	33	13	(39.4)	4.76	[1.20;22.7]	1.92	[0.82;4.51]	18.2	[-3.6;39.9]	0.0261
		20	33	9	(27.3)	1.28	[0.36;4.73]	1.14	[0.46;2.85]	3.03	[-18;24.1]	0.7004

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
	24	33	13	(39.4)	1.32	[0.40;4.44]	1.09	[0.56;2.12]	3.03	[-20;26.4]	0.6507

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-175: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe MOH: nein

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	4	243	34	(14.0)							
	8	243	47	(19.3)							
	12	243	47	(19.3)							
	16	243	47	(19.3)							
	20	243	52	(21.4)							
	24	243	50	(20.6)							
EPTI 100 mg	4	229	41	(17.9)	1.78	[0.99;3.24]	1.28	[0.85;1.94]	3.91	[-2.7;10.5]	0.0529
	8	229	52	(22.7)	1.59	[0.93;2.75]	1.18	[0.83;1.67]	3.37	[-4.0;10.7]	0.0915
	12	229	50	(21.8)	1.53	[0.88;2.68]	1.13	[0.79;1.61]	2.49	[-4.8;9.79]	0.1328
	16	229	58	(25.3)	1.89	[1.13;3.21]	1.31	[0.93;1.84]	5.99	[-1.5;13.5]	0.0155
	20	229	54	(23.6)	1.38	[0.83;2.32]	1.10	[0.79;1.54]	2.18	[-5.4;9.72]	0.2141
	24	229	47	(20.5)	1.20	[0.70;2.07]	1.00	[0.70;1.42]	-.05	[-7.3;7.24]	0.5139
EPTI 300 mg	4	242	46	(19.0)	1.69	[0.95;3.04]	1.36	[0.90;2.04]	5.02	[-1.6;11.6]	0.0739
	8	242	64	(26.4)	1.86	[1.10;3.18]	1.37	[0.98;1.90]	7.10	[-.35;14.6]	0.0206
	12	242	61	(25.2)	1.74	[1.01;3.03]	1.30	[0.93;1.82]	5.87	[-1.5;13.3]	0.0444
	16	242	61	(25.2)	1.65	[0.98;2.79]	1.30	[0.93;1.82]	5.87	[-1.5;13.3]	0.0577
	20	242	64	(26.4)	1.51	[0.91;2.51]	1.24	[0.90;1.70]	5.05	[-2.5;12.6]	0.1079
	24	242	68	(28.1)	1.91	[1.14;3.23]	1.36	[0.99;1.87]	7.52	[-.09;15.1]	0.0133

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.
AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-176: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe 2 Vortherapien

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO	4	194	29 (14.9)							
	8	194	41 (21.1)							
	12	194	40 (20.6)							
	16	194	37 (19.1)							
	20	194	43 (22.2)							
	24	194	41 (21.1)							
EPTI 100 mg	4	191	30 (15.7)	1.33	[0.71;2.52]	1.06	[0.67;1.70]	0.76	[-6.4;7.96]	0.3778
	8	191	41 (21.5)	1.22	[0.69;2.17]	1.02	[0.69;1.50]	0.33	[-7.8;8.51]	0.4969
	12	191	43 (22.5)	1.51	[0.83;2.75]	1.10	[0.75;1.61]	1.89	[-6.3;10.1]	0.1766
	16	191	49 (25.7)	2.03	[1.15;3.65]	1.34	[0.92;1.96]	6.58	[-1.7;14.9]	0.0145
	20	191	46 (24.1)	1.36	[0.79;2.37]	1.09	[0.76;1.57]	1.92	[-6.5;10.3]	0.2685
	24	191	35 (18.3)	1.00	[0.55;1.81]	0.88	[0.59;1.32]	-2.8	[-11;5.13]	0.9988
EPTI 300 mg	4	208	40 (19.2)	1.60	[0.87;2.97]	1.29	[0.83;1.99]	4.28	[-3.1;11.6]	0.1284
	8	208	50 (24.0)	1.35	[0.77;2.38]	1.14	[0.79;1.64]	2.90	[-5.3;11.1]	0.2901
	12	208	54 (26.0)	1.76	[0.99;3.19]	1.26	[0.88;1.80]	5.34	[-2.9;13.6]	0.0562
	16	208	50 (24.0)	1.64	[0.92;2.94]	1.26	[0.87;1.84]	4.97	[-3.1;13.0]	0.0916
	20	208	50 (24.0)	1.24	[0.72;2.15]	1.09	[0.76;1.55]	1.87	[-6.4;10.1]	0.4428
	24	208	58 (27.9)	1.86	[1.07;3.26]	1.32	[0.94;1.87]	6.75	[-1.6;15.1]	0.0267

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-177: EQ-5D VAS, Verbesserung um ≥ 15 Punkte, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO	4	82	11 (13.4)							
	8	82	15 (18.3)							
	12	82	15 (18.3)							
	16	82	17 (20.7)							
	20	82	17 (20.7)							
	24	82	21 (25.6)							
EPTI 100 mg	4	71	17 (23.9)	3.21	[1.14;9.68]	1.77	[0.89;3.51]	10.5	[-1.8;22.9]	0.0267
	8	71	21 (29.6)	2.93	[1.14;7.96]	1.60	[0.90;2.86]	11.3	[-2.2;24.8]	0.0259
	12	71	16 (22.5)	1.62	[0.61;4.44]	1.24	[0.66;2.32]	4.24	[-8.6;17.1]	0.3351
	16	71	21 (29.6)	2.26	[0.91;5.83]	1.43	[0.81;2.49]	8.85	[-4.9;22.6]	0.0804
	20	71	16 (22.5)	1.28	[0.49;3.34]	1.08	[0.59;1.97]	1.80	[-11;14.9]	0.6168
	24	71	21 (29.6)	1.60	[0.63;4.18]	1.15	[0.69;1.93]	3.97	[-10;18.2]	0.3235
EPTI 300 mg	4	67	18 (26.9)	3.26	[1.18;9.64]	2.01	[1.02;3.96]	13.5	[0.53;26.4]	0.0228
	8	67	25 (37.3)	3.97	[1.57;10.7]	2.04	[1.17;3.56]	19.0	[4.73;33.3]	0.0033
	12	67	21 (31.3)	2.51	[0.98;6.67]	1.71	[0.96;3.05]	13.1	[-.86;27.0]	0.0545
	16	67	24 (35.8)	2.72	[1.11;6.93]	1.73	[1.02;2.93]	15.1	[0.64;29.5]	0.0278
	20	67	23 (34.3)	2.43	[0.99;6.19]	1.65	[0.96;2.85]	13.6	[-.76;28.0]	0.0518
	24	67	23 (34.3)	1.71	[0.68;4.38]	1.34	[0.82;2.21]	8.72	[-6.1;23.5]	0.2545

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in EQ-5D-5L VAS score.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.13 HIT-6 (Beeinträchtigung durch Kopfschmerz)

4.2.13.1 Veränderung gegenüber dem Baseline-Wert

Tabelle 4G-178: HIT-6, CFB, Interaktions-p-Werte Woche 1 – 12

Description	Treatment Group		
	EPTI 100 mg	EPTI 300 mg	p-value
	p-value	p-value	
Interaction test: Age Group	0.4556	0.7380	
Interaction test: EM/CM	0.1159	0.3919	
Interaction test: MOH	0.0223	0.0687	
Interaction test: Number of FPT	0.8480	0.1784	
Interaction test: Sex	0.5419	0.2738	

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-179: HIT-6, CFB, Interaktions-p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.2371	0.9609
Interaction test: EM/CM	0.9242	0.6880
Interaction test: MOH	0.1262	0.2962
Interaction test: Number of FPT	0.4652	0.1662
Interaction test: Sex	0.3138	0.8281

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-180: HIT-6, CFB, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G CI	
					CFB			95% CI	SMD 95% CI
					Diff.	SE	CI	p-value	G
PBO	Basln	64 (100.0)	66.4 (3.76)						
	4	63 (98.4)	63.2 (5.63)						
	8	62 (96.9)	62.2 (7.19)						
	12	64 (100.0)	62.2 (6.83)						
	16	62 (96.9)	62.2 (7.21)						
	20	61 (95.3)	61.4 (8.42)						
	24	63 (98.4)	61.3 (7.28)						
EPTI 100 mg	Basln	55 (100.0)	66.0 (4.71)						
	4	54 (98.2)	58.3 (8.00)		-6.1 (1.14)	-4.7	1.21	[-7.1;-2.3]	0.0002
									-0.7 [-1.1;-.35]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Diff.	SE	CI	p-value	Comparison to PBO	
									95% CI	
									SMD	95% CI
CFB										
			LSmeans						Hedges'	
Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Diff.	SE	CI	p-value	G	CI
	8	53 (96.4)	58.1 (7.57)	-6.2 (1.24)	-3.9	1.37	[-6.6;-1.2]	0.0051	-0.5	[-.90;-.16]
	12	54 (98.2)	58.1 (7.67)	-6.1 (1.21)	-3.9	1.33	[-6.5;-1.2]	0.0042	-0.5	[-.90;-.17]
	16	53 (96.4)	56.7 (8.05)	-7.6 (1.31)	-5.3	1.49	[-8.3;-2.4]	0.0005	-0.7	[-1.0;-.30]
	20	50 (90.9)	56.7 (7.82)	-7.2 (1.32)	-4.1	1.49	[-7.1;-1.2]	0.0062	-0.5	[-.91;-.15]
	24	50 (90.9)	57.9 (7.28)	-6.2 (1.27)	-3.1	1.42	[-5.9;-.25]	0.0328	-0.4	[-.78;-.03]
EPTI 300 mg	Basln	61 (100.0)	66.0 (4.47)							
	4	57 (93.4)	58.9 (7.78)	-5.4 (1.18)	-4.0	1.20	[-6.4;-1.6]	0.0011	-0.6	[-.97;-.24]
	8	57 (93.4)	57.4 (8.87)	-7.1 (1.25)	-4.8	1.35	[-7.5;-2.2]	0.0005	-0.7	[-.10;-.29]
	12	60 (98.4)	57.9 (7.92)	-6.6 (1.22)	-4.3	1.30	[-6.9;-1.7]	0.0012	-0.6	[-.95;-.24]
	16	58 (95.1)	55.2 (9.18)	-9.4 (1.31)	-7.1	1.46	[-10;-4.2]	<.0001	-0.9	[-.13;-.53]
	20	58 (95.1)	55.4 (9.20)	-8.9 (1.31)	-5.9	1.45	[-8.7;-3.0]	<.0001	-0.7	[-.11;-.38]
	24	60 (98.4)	55.1 (9.58)	-9.4 (1.26)	-6.3	1.38	[-9.0;-.35]	<.0001	-0.8	[-.12;-.46]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

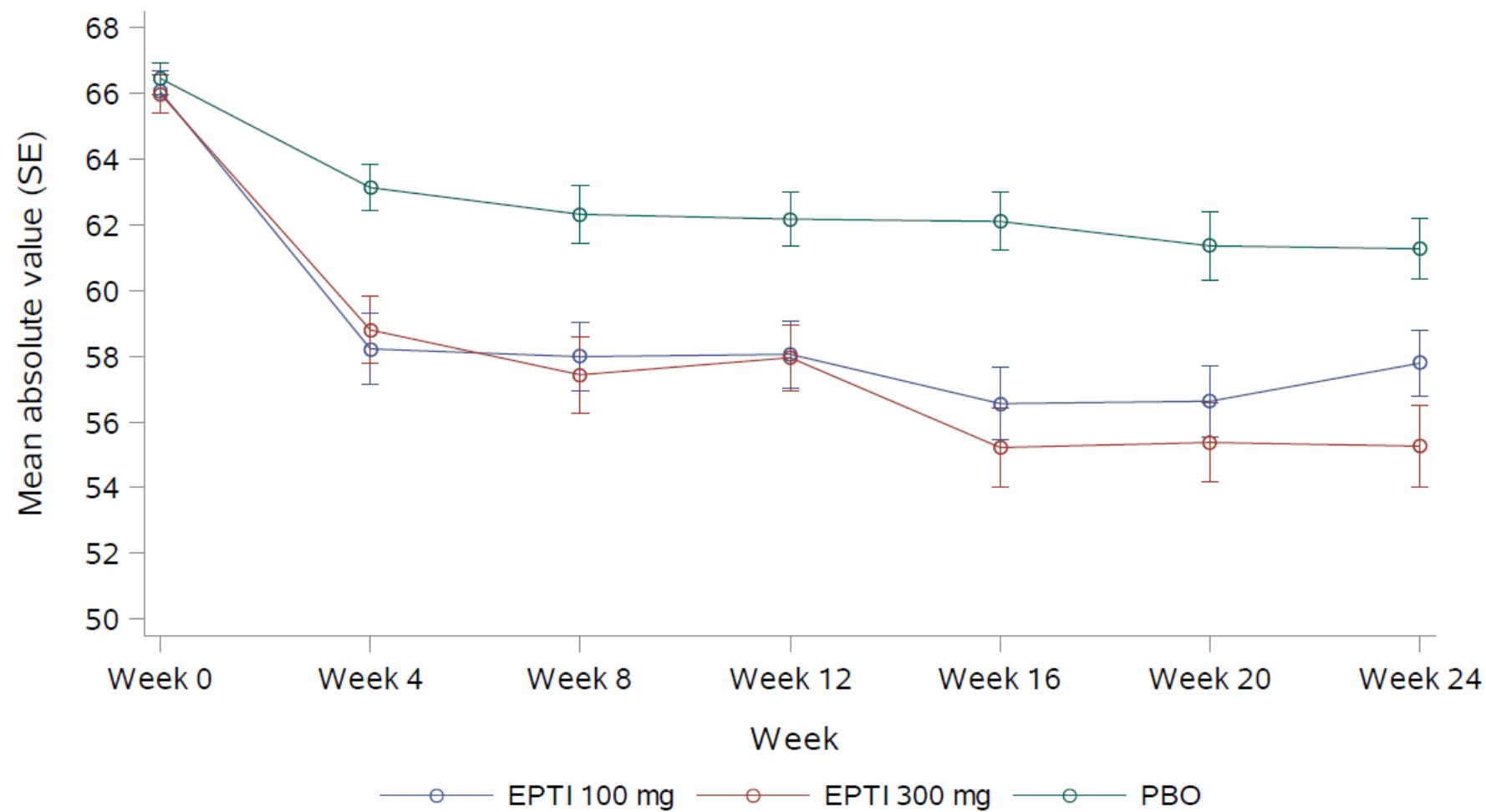
HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Age <= 35 years

Tabelle 4G-181: HIT-6, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB			Comparison to PBO		
					LSmeans			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	213 (100.0)	66.2 (4.55)							
	4	204 (95.8)	63.0 (5.95)	-2.2 (0.73)						
	8	205 (96.2)	62.2 (6.57)	-3.2 (0.78)						
	12	213 (100.0)	61.8 (6.51)	-3.6 (0.76)						
	16	206 (96.7)	60.8 (7.20)	-4.4 (0.78)						
	20	203 (95.3)	60.4 (7.18)	-4.9 (0.78)						
	24	205 (96.2)	60.8 (7.16)	-4.4 (0.77)						
EPTI 100 mg	Basln	212 (100.0)	66.7 (4.70)							
	4	206 (97.2)	58.4 (8.83)	-7.2 (0.73)	-5.0	0.71	[-6.4;-3.7]	<.0001	-0.7	[-.90;-.51]
	8	204 (96.2)	56.9 (9.45)	-8.5 (0.77)	-5.3	0.80	[-6.9;-3.7]	<.0001	-0.7	[-.85;-.46]
	12	210 (99.1)	58.2 (8.59)	-7.4 (0.75)	-3.8	0.76	[-5.3;-2.3]	<.0001	-0.5	[-.68;-.30]
	16	204 (96.2)	55.3 (9.08)	-10 (0.78)	-5.8	0.81	[-7.4;-4.2]	<.0001	-0.7	[-.90;-.51]
	20	200 (94.3)	55.4 (8.82)	-9.9 (0.78)	-5.0	0.81	[-6.6;-3.4]	<.0001	-0.6	[-.81;-.42]
	24	204 (96.2)	55.5 (8.73)	-9.8 (0.77)	-5.5	0.78	[-7.0;-3.9]	<.0001	-0.7	[-.89;-.50]
EPTI 300 mg	Basln	217 (100.0)	66.6 (4.42)							
	4	211 (97.2)	57.9 (8.64)	-7.5 (0.70)	-5.4	0.71	[-6.8;-4.0]	<.0001	-0.7	[-.94;-.55]
	8	211 (97.2)	55.9 (9.53)	-9.6 (0.75)	-6.4	0.80	[-8.0;-4.9]	<.0001	-0.8	[-.98;-.60]
	12	216 (99.5)	56.1 (9.31)	-9.4 (0.73)	-5.9	0.75	[-7.3;-4.4]	<.0001	-0.7	[-.94;-.56]
	16	207 (95.4)	54.0 (9.66)	-11 (0.76)	-6.7	0.81	[-8.3;-5.1]	<.0001	-0.8	[-.10;-.62]
	20	205 (94.5)	54.0 (9.40)	-11 (0.76)	-6.1	0.81	[-7.7;-4.5]	<.0001	-0.7	[-.94;-.55]
	24	209 (96.3)	55.0 (9.00)	-10 (0.74)	-6.0	0.78	[-7.6;-4.5]	<.0001	-0.8	[-.95;-.57]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		
					Diff.	SE	CI	95% CI	SMD	95% CI
									Hedges' G	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

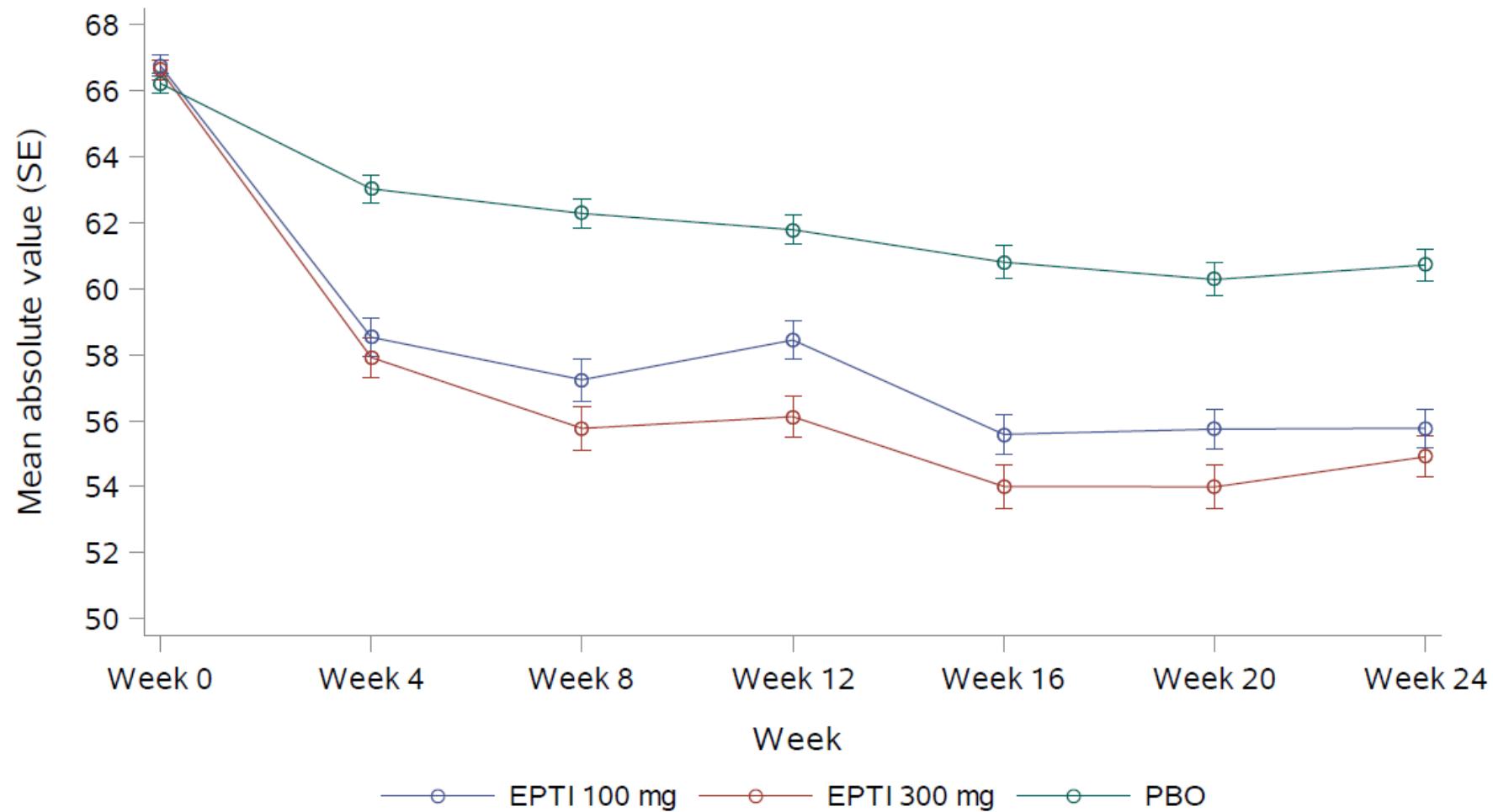
HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Age > 35 years

Tabelle 4G-182: HIT-6, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB			Comparison to PBO		
								95% CI		SMD 95% CI
					LSmeans	Diff.	SE	CI	p-value	Hedges' G
PBO	Basln	28 (100.0)	65.1 (5.60)							
	4	28 (100.0)	62.6 (6.68)	-3.1 (1.66)						
	8	26 (92.9)	61.3 (7.95)	-4.8 (1.80)						
	12	28 (100.0)	61.4 (6.44)	-4.2 (1.67)						
	16	28 (100.0)	60.4 (7.58)	-5.2 (1.86)						
	20	26 (92.9)	59.7 (9.06)	-6.1 (1.82)						
	24	28 (100.0)	61.4 (7.87)	-4.3 (1.74)						
EPTI 100 mg	Basln	20 (100.0)	64.1 (4.48)							
	4	20 (100.0)	57.6 (8.64)	-5.2 (1.81)						
	8	20 (100.0)	56.8 (8.21)	-6.0 (1.97)						
	12	20 (100.0)	56.9 (7.64)	-5.9 (1.82)						
	16	20 (100.0)	53.5 (8.29)	-9.4 (2.07)						
	20	20 (100.0)	55.7 (7.52)	-6.8 (1.99)						
	24	18 (90.0)	55.3 (6.31)	-7.6 (1.95)						
EPTI 300 mg	Basln	31 (100.0)	66.5 (4.30)							
	4	31 (100.0)	59.5 (8.19)	-7.0 (1.53)						
	8	31 (100.0)	58.3 (9.04)	-8.3 (1.65)						
	12	31 (100.0)	59.3 (8.68)	-7.1 (1.54)						
	16	31 (100.0)	54.6 (10.3)	-12 (1.73)						
	20	29 (93.5)	53.9 (9.25)	-12 (1.68)						
	24	31 (100.0)	55.2 (9.35)	-11 (1.60)						

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		
					Diff.	SE	CI	95% CI	SMD	95% CI
									Hedges' G	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

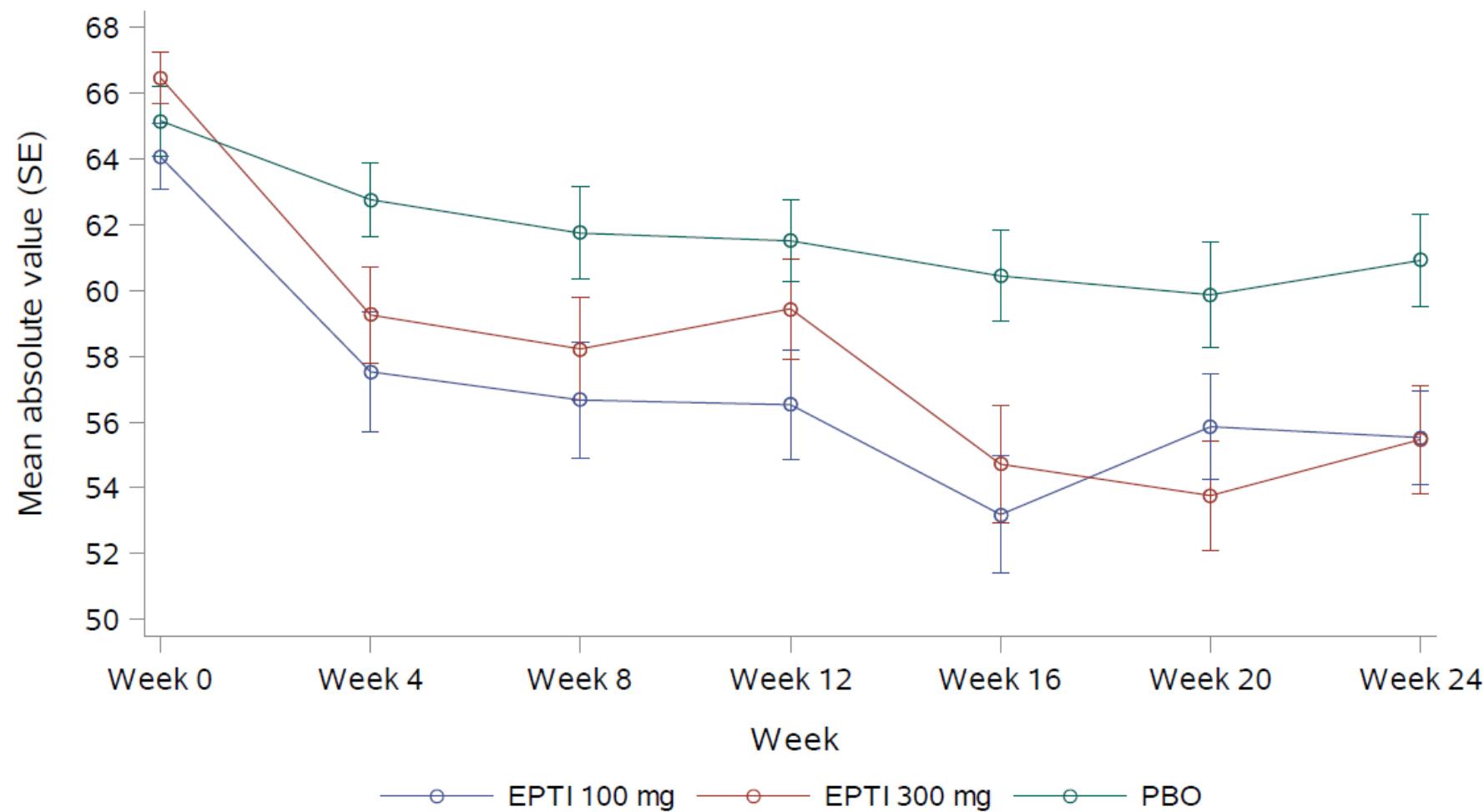
HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Males

Tabelle 4G-183: HIT-6, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								p-value	G	CI
PBO	Basln	249 (100.0)	66.4 (4.21)							
	4	239 (96.0)	63.1 (5.77)	-1.7 (0.67)						
	8	241 (96.8)	62.3 (6.57)	-2.6 (0.72)						
	12	249 (100.0)	61.9 (6.60)	-3.0 (0.70)						
	16	240 (96.4)	61.2 (7.18)	-3.6 (0.72)						
	20	238 (95.6)	60.7 (7.31)	-4.1 (0.72)						
	24	240 (96.4)	60.9 (7.11)	-3.9 (0.71)						
EPTI 100 mg	Basln	247 (100.0)	66.8 (4.67)							
	4	240 (97.2)	58.4 (8.66)	-6.8 (0.67)	-5.1	0.64	[-6.4;-3.9]	<.0001	-0.7	[-.91;-.55]
	8	237 (96.0)	57.2 (9.18)	-7.9 (0.72)	-5.3	0.73	[-6.7;-3.8]	<.0001	-0.7	[-.84;-.48]
	12	244 (98.8)	58.3 (8.46)	-7.0 (0.70)	-3.9	0.69	[-5.3;-2.6]	<.0001	-0.5	[-.69;-.34]
	16	237 (96.0)	55.8 (8.92)	-9.4 (0.73)	-5.8	0.75	[-7.2;-4.3]	<.0001	-0.7	[-.89;-.53]
	20	230 (93.1)	55.7 (8.73)	-9.3 (0.73)	-5.2	0.75	[-6.6;-3.7]	<.0001	-0.6	[-.82;-.46]
	24	236 (95.5)	56.0 (8.66)	-8.9 (0.71)	-5.0	0.72	[-6.5;-3.6]	<.0001	-0.6	[-.82;-.46]
EPTI 300 mg	Basln	247 (100.0)	66.5 (4.45)							
	4	237 (96.0)	58.0 (8.50)	-7.0 (0.65)	-5.3	0.64	[-6.6;-4.0]	<.0001	-0.8	[-.93;-.57]
	8	237 (96.0)	55.9 (9.43)	-9.1 (0.70)	-6.5	0.73	[-7.9;-5.0]	<.0001	-0.8	[-.99;-.63]
	12	245 (99.2)	56.1 (9.04)	-9.0 (0.68)	-5.9	0.69	[-7.3;-4.6]	<.0001	-0.8	[-.95;-.60]
	16	234 (94.7)	54.2 (9.47)	-10 (0.71)	-6.8	0.75	[-8.3;-5.4]	<.0001	-0.8	[-1.0;-.66]
	20	234 (94.7)	54.4 (9.39)	-10 (0.71)	-6.2	0.74	[-7.6;-4.7]	<.0001	-0.8	[-.94;-.58]
	24	238 (96.4)	55.0 (9.10)	-10 (0.69)	-6.1	0.72	[-7.5;-4.6]	<.0001	-0.8	[-.95;-.59]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		
					Diff.	SE	CI	95% CI	SMD	95% CI
									Hedges' G	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

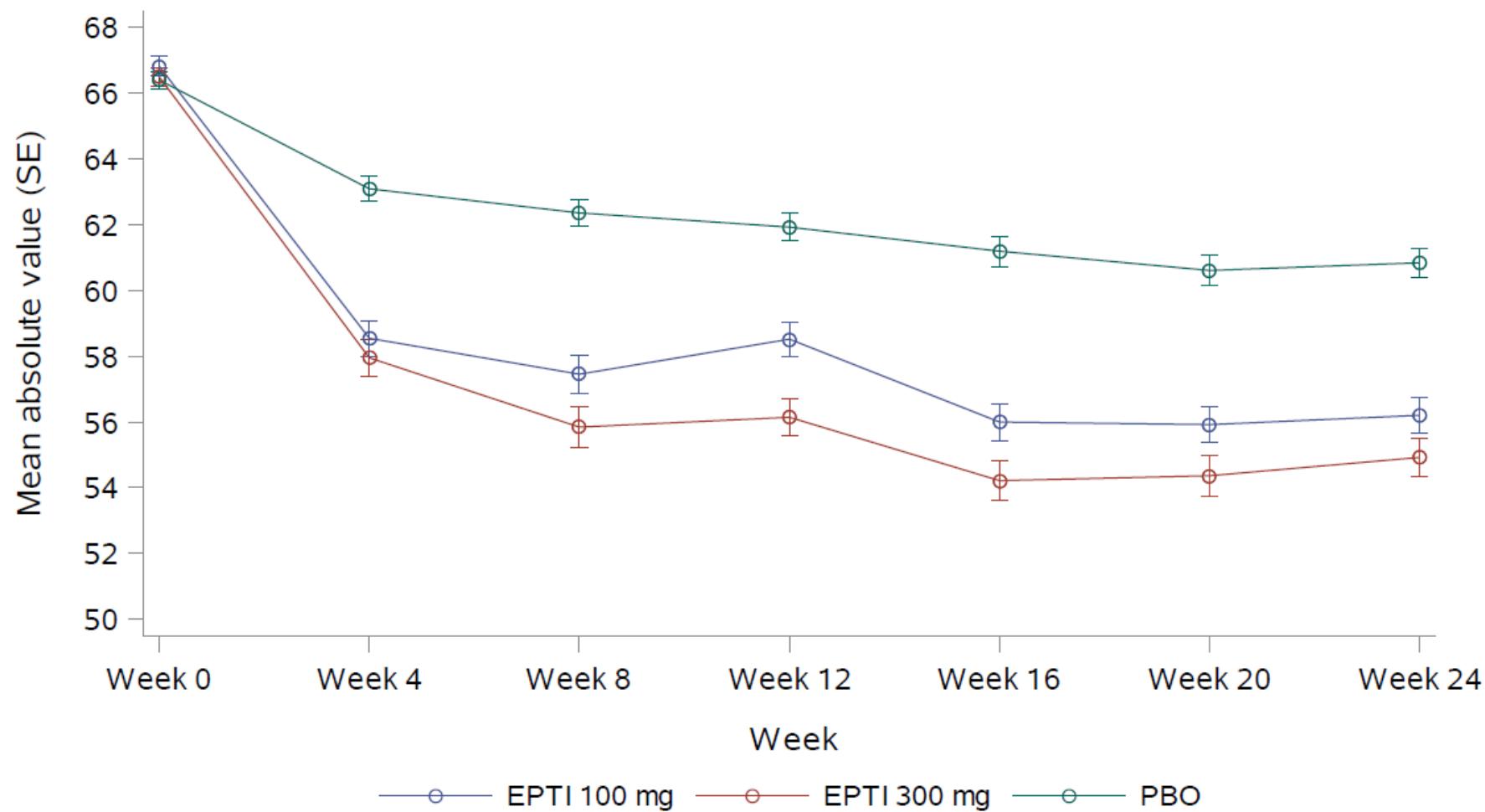
HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Females

Tabelle 4G-184: HIT-6, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO				SMD 95% CI	
					CFB LSmeans			Hedges' G	CI	
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	150 (100.0)	65.7 (4.56)							
	4	144 (96.0)	62.9 (6.04)	-1.8 (0.84)						
	8	146 (97.3)	62.0 (6.92)	-2.6 (0.88)						
	12	150 (100.0)	61.6 (6.96)	-3.1 (0.87)						
	16	148 (98.7)	60.2 (7.78)	-4.5 (0.91)						
	20	145 (96.7)	59.6 (7.49)	-5.2 (0.90)						
	24	147 (98.0)	60.0 (7.53)	-4.9 (0.90)						
EPTI 100 mg	Basln	147 (100.0)	66.2 (4.96)							
	4	144 (98.0)	56.9 (8.86)	-8.2 (0.85)	-6.4	0.83	[-8.0;-4.8]	<.0001	-0.9	[-1.1;-.68]
	8	144 (98.0)	56.5 (9.00)	-8.6 (0.89)	-5.9	0.91	[-7.7;-4.1]	<.0001	-0.8	[-1.0;-.54]
	12	145 (98.6)	57.8 (8.37)	-7.2 (0.88)	-4.1	0.89	[-5.8;-2.3]	<.0001	-0.5	[-.77;-.31]
	16	144 (98.0)	54.6 (8.55)	-10 (0.92)	-5.9	0.97	[-7.8;-4.0]	<.0001	-0.7	[-.95;-.49]
	20	140 (95.2)	54.5 (8.41)	-11 (0.91)	-5.3	0.95	[-7.2;-3.4]	<.0001	-0.7	[-.89;-.43]
	24	138 (93.9)	54.9 (8.17)	-10 (0.91)	-5.1	0.94	[-7.0;-3.3]	<.0001	-0.6	[-.88;-.41]
EPTI 300 mg	Basln	153 (100.0)	66.4 (4.74)							
	4	146 (95.4)	57.3 (9.00)	-7.9 (0.81)	-6.1	0.83	[-7.7;-4.5]	<.0001	-0.9	[-1.1;-.64]
	8	147 (96.1)	55.4 (9.33)	-9.9 (0.85)	-7.3	0.90	[-9.0;-5.5]	<.0001	-0.9	[-1.2;-.71]
	12	152 (99.3)	55.4 (9.24)	-9.9 (0.83)	-6.8	0.88	[-8.5;-5.1]	<.0001	-0.9	[-1.1;-.66]
	16	147 (96.1)	53.0 (9.78)	-12 (0.88)	-7.6	0.96	[-9.5;-5.7]	<.0001	-0.9	[-1.2;-.69]
	20	144 (94.1)	53.2 (9.31)	-12 (0.88)	-6.7	0.94	[-8.6;-4.8]	<.0001	-0.8	[-1.1;-.60]
	24	148 (96.7)	53.8 (9.07)	-11 (0.87)	-6.6	0.93	[-8.4;-4.8]	<.0001	-0.8	[-1.1;-.60]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					CFB		95% CI		
					LSmeans	Diff.	SE		
The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.									
N:	the number of patients with observations in the interval.	Basln:	Baseline.	AMNOG:	AMNOG population	B.	EM : Episodic Migraine.		

HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Episodic Migraine

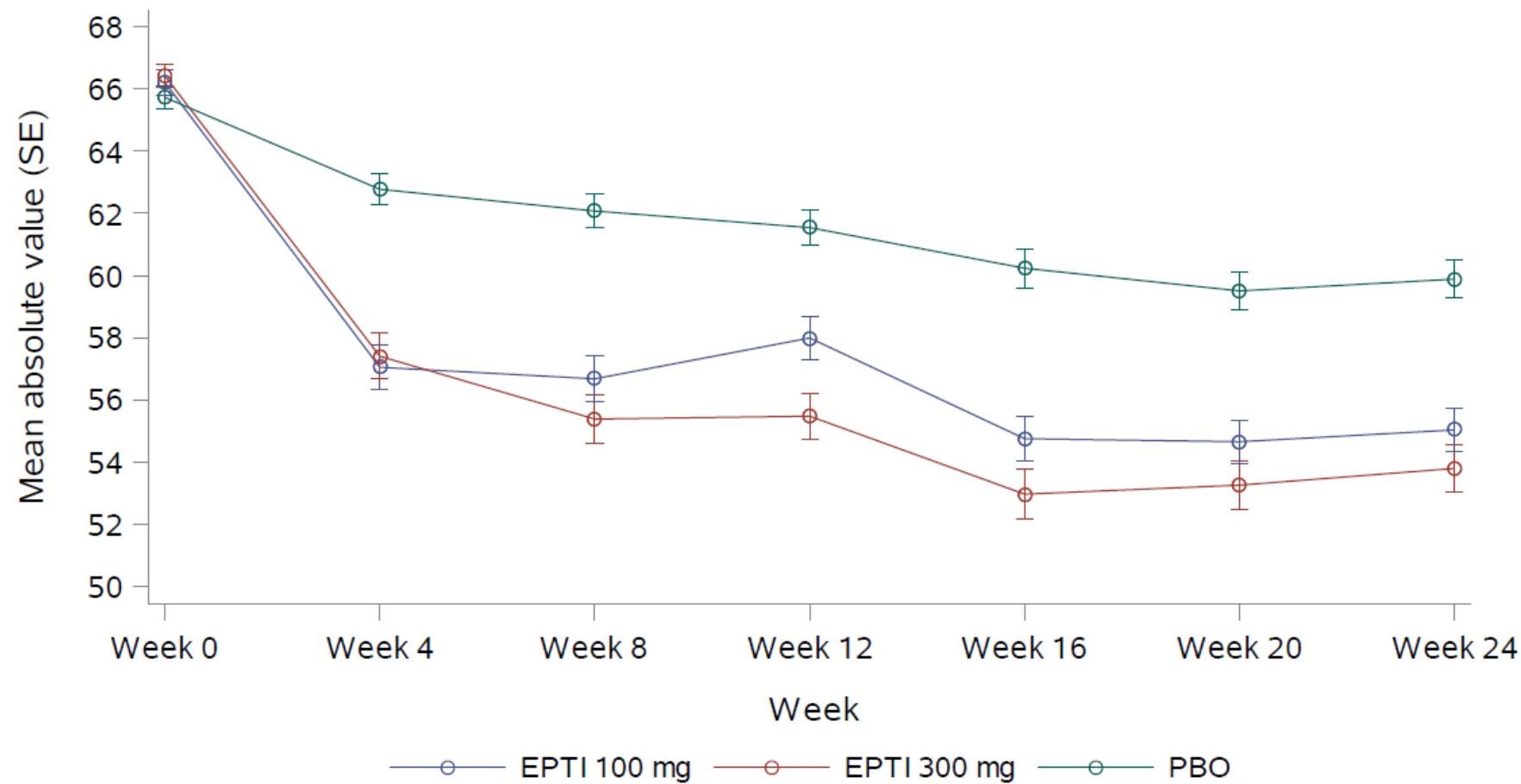


Tabelle 4G-185: HIT-6, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB			Comparison to PBO		
					LSmeans	Diff.	SE	95% CI		SMD 95% CI
								CI	p-value	
PBO	Basln	127 (100.0)	66.9 (4.08)							
	4	123 (96.9)	63.3 (5.67)	-2.0 (1.14)						
	8	121 (95.3)	62.5 (6.45)	-2.3 (1.28)						
	12	127 (100.0)	62.2 (6.11)	-2.3 (1.20)						
	16	120 (94.5)	62.2 (6.31)	-3.3 (1.25)						
	20	119 (93.7)	61.8 (7.32)	-4.0 (1.27)						
	24	121 (95.3)	62.1 (6.57)	-2.7 (1.22)						
EPTI 100 mg	Basln	120 (100.0)	67.1 (4.33)							
	4	116 (96.7)	60.1 (8.06)	-5.4 (1.11)	-3.4	0.90	[-5.1;-1.6]	0.0002	-0.5	[-.74;-.23]
	8	113 (94.2)	58.0 (9.18)	-6.3 (1.26)	-4.1	1.07	[-6.2;-2.0]	0.0002	-0.5	[-.75;-.24]
	12	119 (99.2)	58.6 (8.45)	-6.0 (1.16)	-3.7	0.98	[-5.7;-1.8]	0.0002	-0.5	[-.74;-.23]
	16	113 (94.2)	56.9 (9.16)	-8.9 (1.22)	-5.6	1.05	[-7.7;-3.5]	<.0001	-0.7	[-.95;-.44]
	20	110 (91.7)	57.1 (8.72)	-8.5 (1.24)	-4.6	1.08	[-6.7;-2.5]	<.0001	-0.6	[-.82;-.30]
	24	116 (96.7)	57.2 (8.76)	-7.8 (1.19)	-5.1	1.01	[-7.0;-3.1]	<.0001	-0.6	[-.91;-.39]
EPTI 300 mg	Basln	125 (100.0)	66.5 (4.04)							
	4	122 (97.6)	59.1 (7.69)	-6.0 (1.14)	-4.0	0.88	[-5.7;-2.3]	<.0001	-0.6	[-.83;-.33]
	8	121 (96.8)	57.2 (9.42)	-7.1 (1.29)	-4.8	1.06	[-6.9;-2.7]	<.0001	-0.6	[-.84;-.33]
	12	124 (99.2)	57.8 (8.64)	-6.4 (1.20)	-4.1	0.97	[-6.0;-2.2]	<.0001	-0.5	[-.79;-.29]
	16	118 (94.4)	55.9 (9.04)	-9.2 (1.26)	-5.9	1.04	[-7.9;-3.8]	<.0001	-0.7	[-.99;-.48]
	20	119 (95.2)	55.8 (9.24)	-9.4 (1.28)	-5.4	1.06	[-7.5;-3.3]	<.0001	-0.7	[-.92;-.41]
	24	121 (96.8)	56.5 (8.97)	-8.2 (1.22)	-5.4	0.99	[-7.4;-3.5]	<.0001	-0.7	[-.96;-.45]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			Comparison to PBO		SMD 95% CI	
					Diff.	SE	CI	p-value	G	Hedges' CI	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population. B. CM : Chronic Migraine.

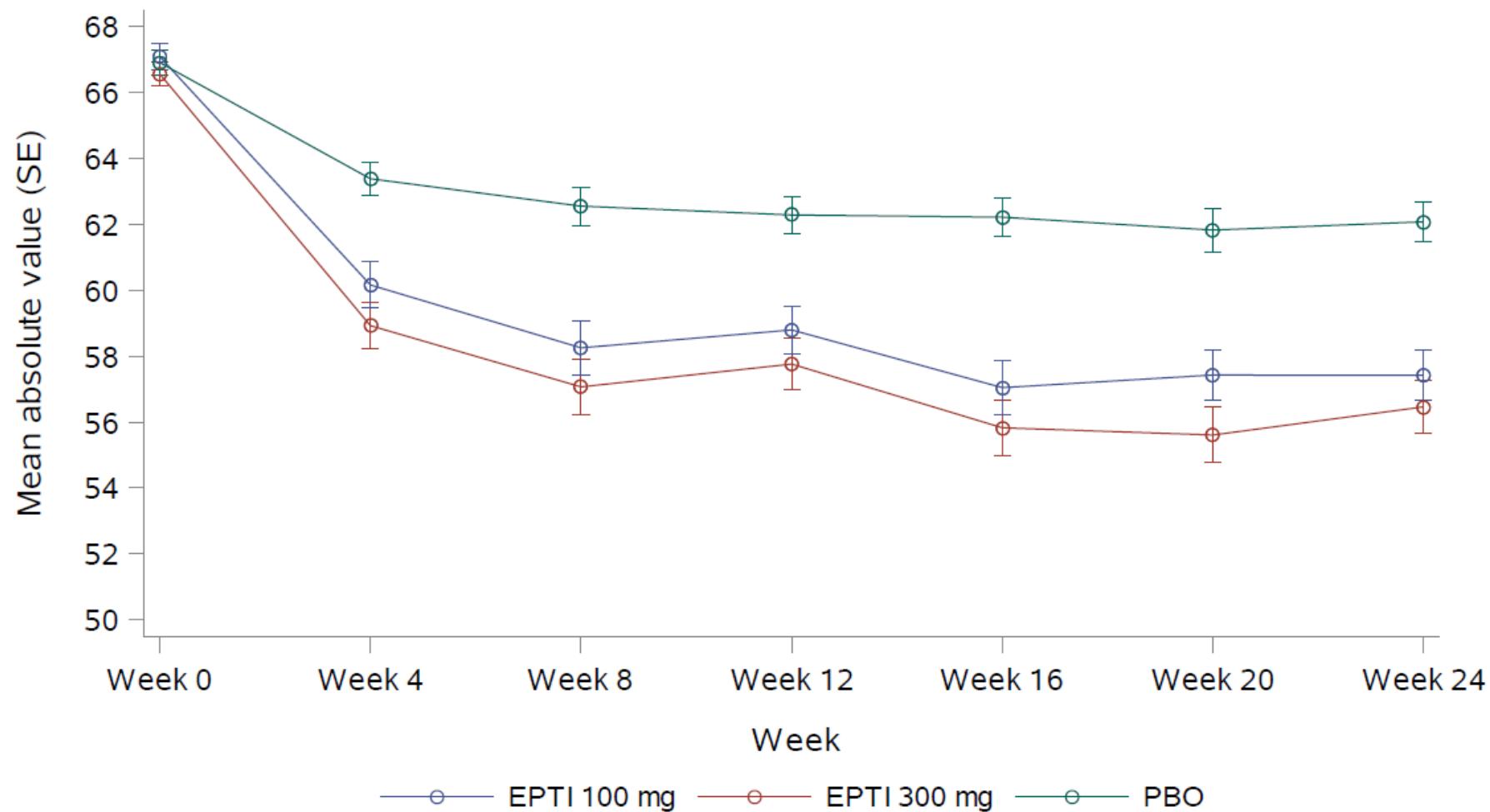
HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Chronic Migraine

Tabelle 4G-186: HIT-6, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	33 (100.0)	67.4 (5.30)							
	4	32 (97.0)	62.6 (6.36)		-6.2 (1.67)					
	8	31 (93.9)	61.1 (7.75)		-7.5 (1.82)					
	12	33 (100.0)	61.6 (6.43)		-6.8 (1.80)					
	16	32 (97.0)	61.0 (7.73)		-8.1 (1.89)					
	20	31 (93.9)	60.4 (8.98)		-8.6 (1.91)					
	24	31 (93.9)	61.2 (6.62)		-7.3 (1.79)					
EPTI 100 mg	Basln	33 (100.0)	66.5 (4.07)							
	4	32 (97.0)	62.0 (6.78)		-4.9 (1.60)					
	8	31 (93.9)	60.0 (7.74)		-6.2 (1.76)					
	12	33 (100.0)	61.1 (7.40)		-5.8 (1.73)					
	16	32 (97.0)	58.7 (8.21)		-8.9 (1.82)					
	20	32 (97.0)	59.1 (7.38)		-8.6 (1.84)					
	24	33 (100.0)	58.1 (6.70)		-9.2 (1.71)					
EPTI 300 mg	Basln	33 (100.0)	67.0 (3.91)							
	4	31 (93.9)	60.3 (8.76)		-7.5 (1.62)					
	8	32 (97.0)	57.8 (8.64)		-9.7 (1.76)					
	12	32 (97.0)	56.0 (9.76)		-11 (1.75)					
	16	33 (100.0)	56.8 (9.04)		-11 (1.82)					
	20	32 (97.0)	57.4 (8.71)		-11 (1.85)					
	24	32 (97.0)	56.2 (8.69)		-12 (1.73)					

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					95% CI			SMD 95% CI	
					CFB	LSmeans	Diff.	SE	CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : Medication overuse headache at baseline

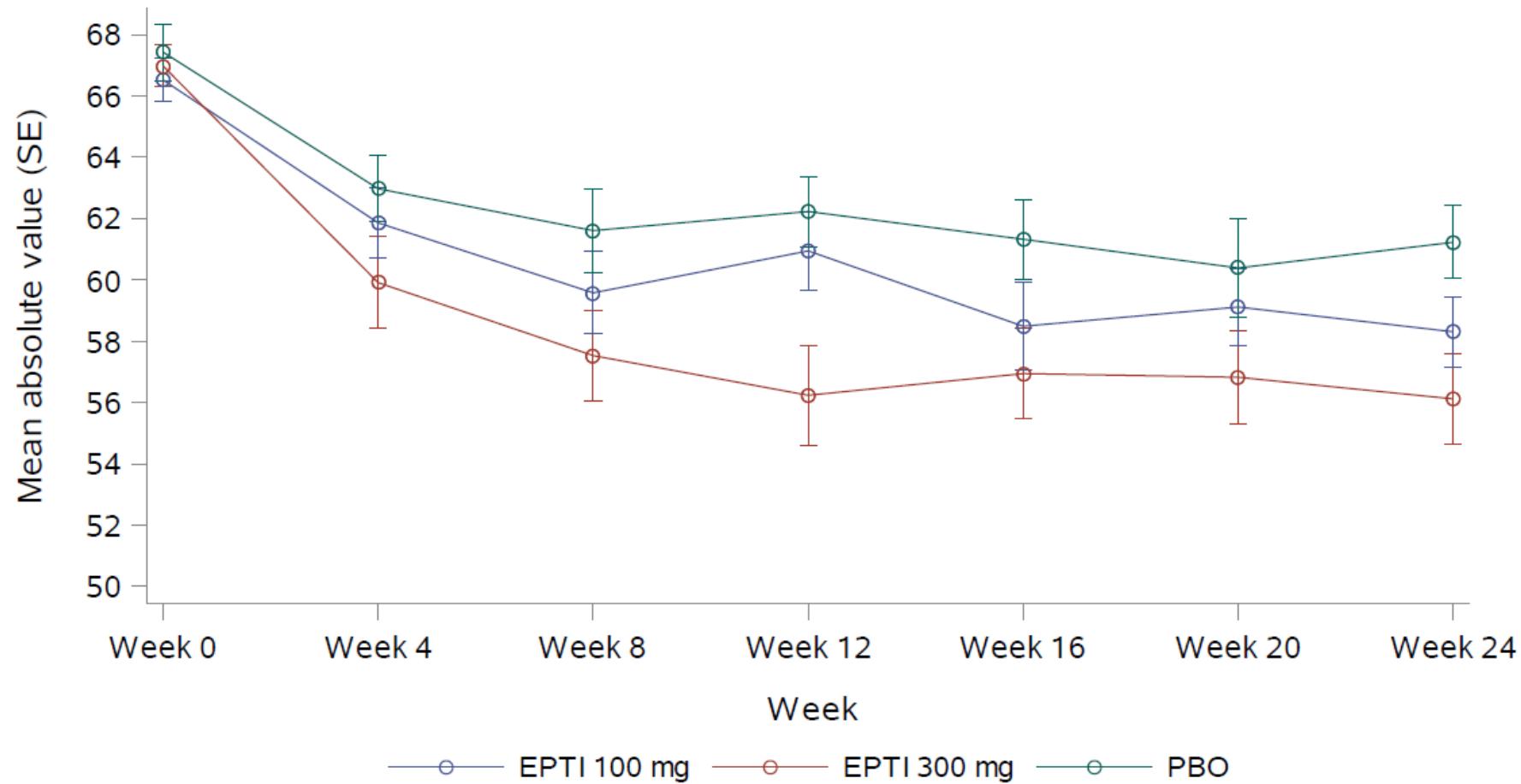


Tabelle 4G-187: HIT-6, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	244 (100.0)	66.1 (4.22)							
	4	235 (96.3)	63.1 (5.80)	-1.7 (0.67)						
	8	236 (96.7)	62.4 (6.56)	-2.5 (0.71)						
	12	244 (100.0)	61.9 (6.61)	-3.1 (0.69)						
	16	236 (96.7)	61.1 (7.16)	-3.7 (0.72)						
	20	233 (95.5)	60.6 (7.28)	-4.2 (0.72)						
	24	237 (97.1)	60.9 (7.26)	-3.9 (0.71)						
EPTI 100 mg	Basln	234 (100.0)	66.6 (4.79)							
	4	228 (97.4)	57.8 (8.77)	-7.4 (0.67)	-5.7	0.65	[-6.9;-4.4]	<.0001	-0.8	[-.99;-.63]
	8	226 (96.6)	56.8 (9.21)	-8.3 (0.72)	-5.7	0.74	[-7.2;-4.3]	<.0001	-0.7	[-.91;-.54]
	12	231 (98.7)	57.7 (8.47)	-7.4 (0.70)	-4.4	0.70	[-5.7;-3.0]	<.0001	-0.6	[-.75;-.39]
	16	225 (96.2)	55.1 (8.90)	-9.9 (0.73)	-6.2	0.76	[-7.7;-4.7]	<.0001	-0.8	[-.94;-.58]
	20	218 (93.2)	55.2 (8.70)	-9.6 (0.73)	-5.4	0.76	[-6.9;-3.9]	<.0001	-0.7	[-.86;-.49]
	24	221 (94.4)	55.7 (8.71)	-9.2 (0.72)	-5.3	0.73	[-6.7;-3.9]	<.0001	-0.7	[-.86;-.49]
EPTI 300 mg	Basln	245 (100.0)	66.4 (4.50)							
	4	237 (96.7)	57.9 (8.40)	-7.1 (0.65)	-5.4	0.64	[-6.7;-4.2]	<.0001	-0.8	[-.96;-.60]
	8	236 (96.3)	56.0 (9.49)	-9.0 (0.69)	-6.5	0.73	[-7.9;-5.0]	<.0001	-0.8	[-.10;-.64]
	12	244 (99.6)	56.5 (8.97)	-8.5 (0.67)	-5.5	0.69	[-6.8;-4.1]	<.0001	-0.7	[-.90;-.54]
	16	232 (94.7)	53.9 (9.59)	-11 (0.71)	-7.1	0.75	[-8.6;-5.6]	<.0001	-0.9	[-.11;-.69]
	20	231 (94.3)	53.9 (9.38)	-11 (0.71)	-6.5	0.75	[-7.9;-5.0]	<.0001	-0.8	[-.98;-.62]
	24	237 (96.7)	54.9 (9.18)	-10 (0.69)	-6.2	0.72	[-7.6;-4.8]	<.0001	-0.8	[-.97;-.61]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI		
					CFB						
					LSmeans	95% CI	Diff.				

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) No medication overuse headache at baseline

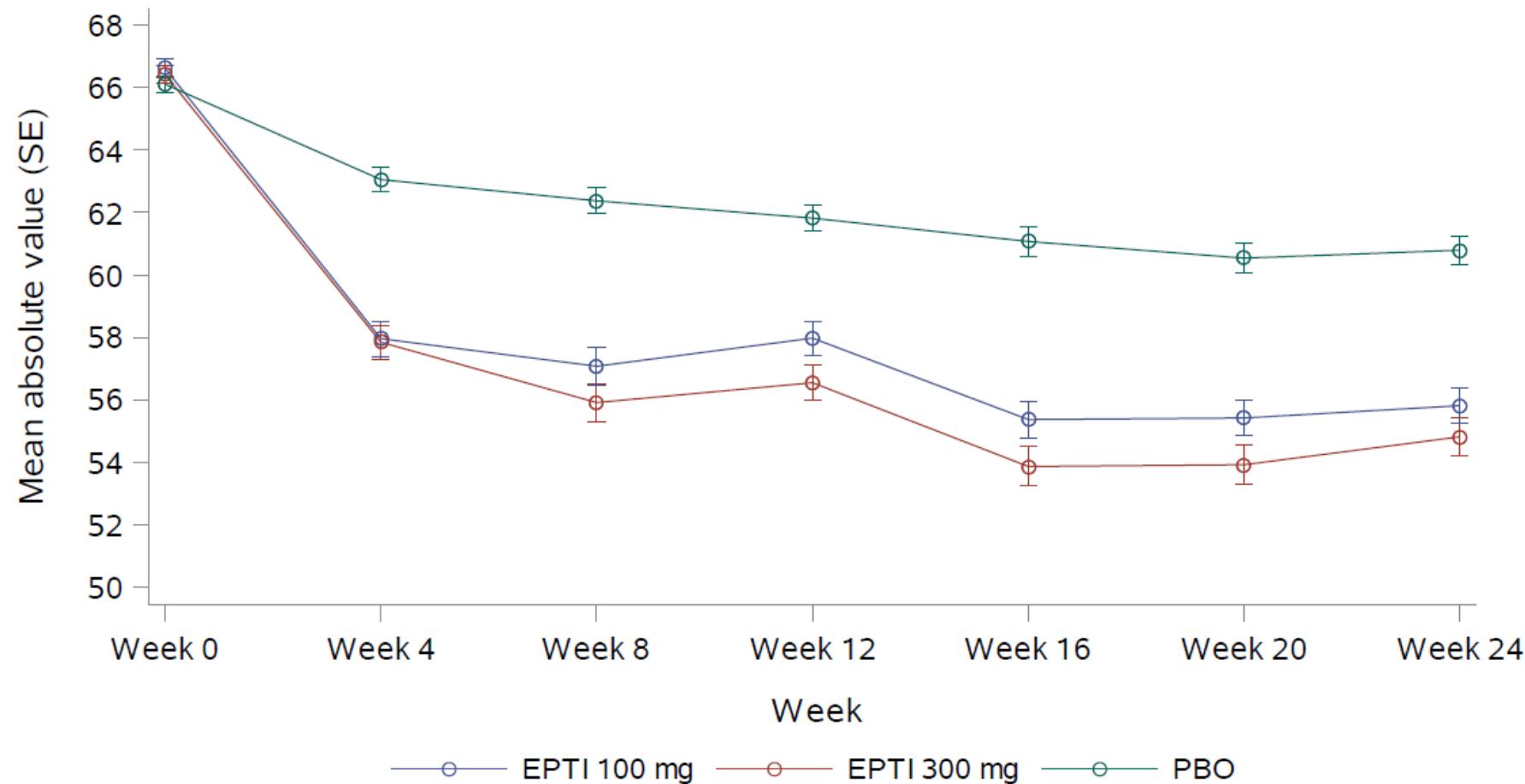


Tabelle 4G-188: HIT-6, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	195 (100.0)	66.2 (4.50)							
	4	188 (96.4)	63.2 (5.90)	-1.9 (0.73)						
	8	186 (95.4)	62.0 (6.81)	-3.3 (0.79)						
	12	195 (100.0)	61.5 (6.79)	-3.6 (0.77)						
	16	186 (95.4)	60.6 (7.59)	-4.4 (0.81)						
	20	185 (94.9)	60.3 (7.40)	-4.8 (0.79)						
	24	190 (97.4)	60.4 (7.56)	-4.5 (0.78)						
EPTI 100 mg	Basln	193 (100.0)	66.5 (4.49)							
	4	189 (97.9)	58.3 (8.20)	-8.2 (0.74)	-4.9	0.71	[-6.3;-3.5]	<.0001	-0.7	[-.91;-.51]
	8	186 (96.4)	56.8 (9.08)	-8.2 (0.80)	-5.0	0.83	[-6.6;-3.3]	<.0001	-0.6	[-.82;-.41]
	12	191 (99.0)	57.8 (8.19)	-7.3 (0.77)	-3.7	0.78	[-5.2;-2.1]	<.0001	-0.5	[-.68;-.28]
	16	185 (95.9)	55.1 (8.73)	-9.9 (0.82)	-5.5	0.86	[-7.2;-3.8]	<.0001	-0.7	[-.87;-.46]
	20	181 (93.8)	55.1 (8.41)	-9.7 (0.81)	-4.9	0.84	[-6.6;-3.3]	<.0001	-0.6	[-.82;-.41]
	24	182 (94.3)	55.7 (8.36)	-9.1 (0.80)	-4.6	0.82	[-6.2;-3.0]	<.0001	-0.6	[-.79;-.38]
EPTI 300 mg	Basln	211 (100.0)	66.5 (4.52)							
	4	201 (95.3)	58.7 (8.50)	-6.4 (0.70)	-4.5	0.70	[-5.9;-3.1]	<.0001	-0.7	[-.85;-.45]
	8	202 (95.7)	56.8 (9.61)	-8.3 (0.75)	-5.0	0.81	[-6.6;-3.4]	<.0001	-0.6	[-.83;-.43]
	12	210 (99.5)	56.6 (9.32)	-8.5 (0.73)	-4.9	0.76	[-6.4;-3.4]	<.0001	-0.6	[-.83;-.44]
	16	199 (94.3)	54.2 (9.88)	-11 (0.77)	-6.2	0.85	[-7.8;-4.5]	<.0001	-0.7	[-.94;-.54]
	20	199 (94.3)	54.4 (9.43)	-10 (0.75)	-5.5	0.82	[-7.1;-3.9]	<.0001	-0.7	[-.89;-.49]
	24	205 (97.2)	55.3 (9.16)	-9.7 (0.74)	-5.2	0.80	[-6.7;-3.6]	<.0001	-0.7	[-.85;-.45]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	CI		
					95% CI		SMD 95% CI				
					CFB	LSmeans					

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : = 2 Previous Failed Treatments

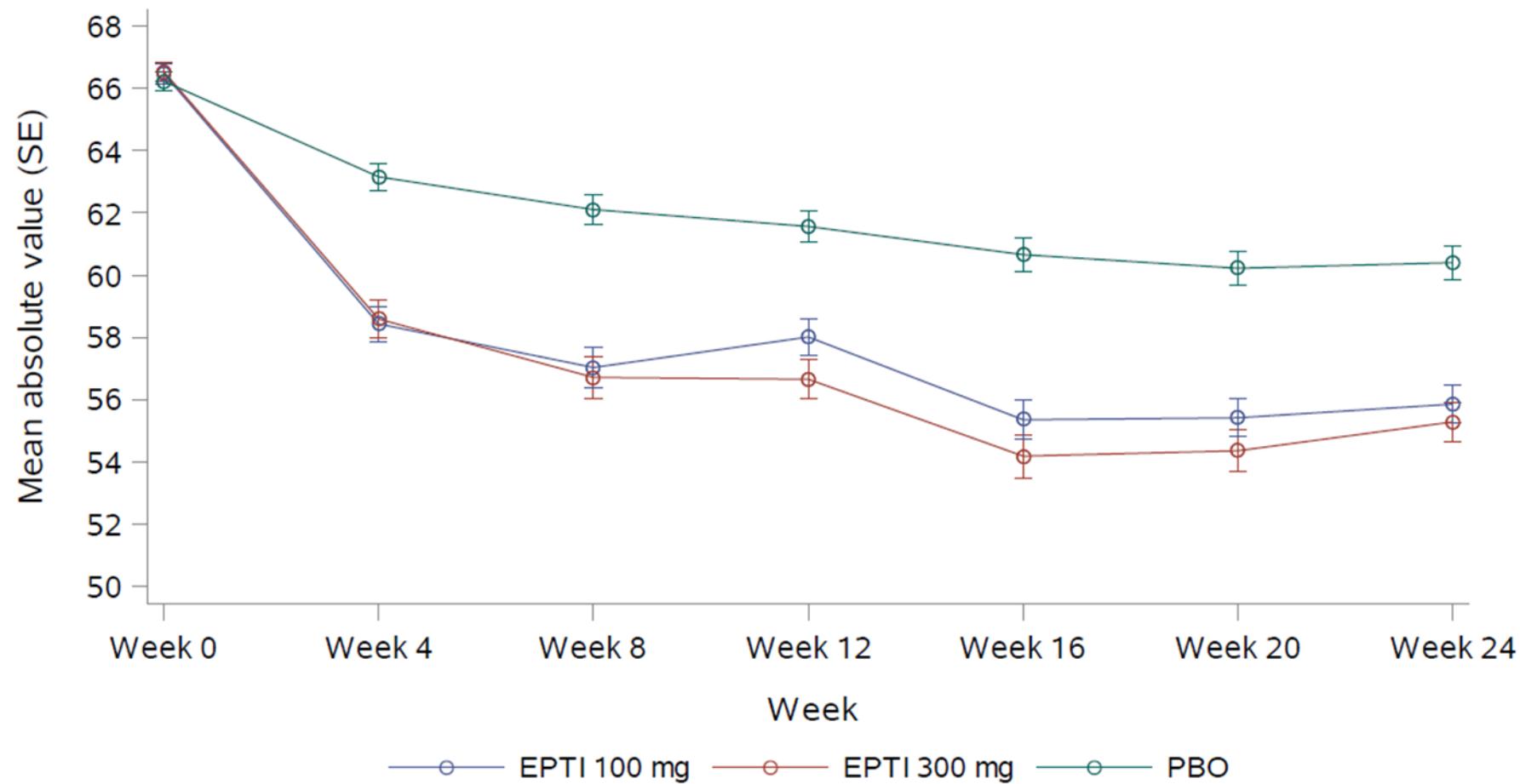


Tabelle 4G-189: HIT-6, CFB, Subgruppe > 2 Vortherapien

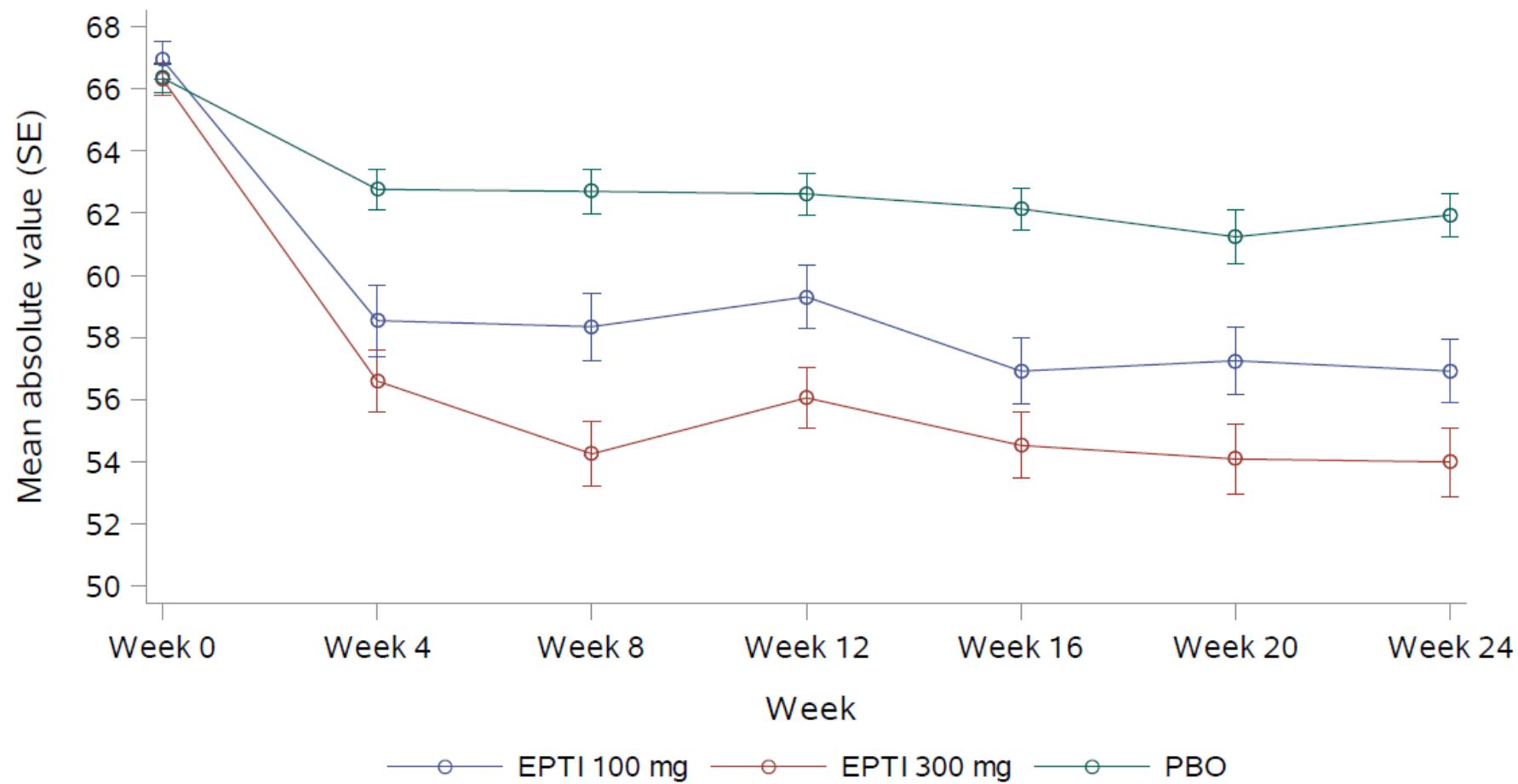
Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' SMD 95% CI		
					CFB			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	82 (100.0)	66.3 (4.10)							
	4	79 (96.3)	62.8 (5.80)	-2.5 (1.25)						
	8	81 (98.8)	62.7 (6.46)	-2.7 (1.26)						
	12	82 (100.0)	62.7 (5.99)	-2.8 (1.24)						
	16	82 (100.0)	62.2 (6.16)	-3.2 (1.25)						
	20	79 (96.3)	61.3 (7.68)	-4.1 (1.30)						
	24	78 (95.1)	62.1 (6.02)	-3.4 (1.25)						
EPTI 100 mg	Basln	74 (100.0)	66.9 (5.23)							
	4	71 (95.9)	58.5 (9.80)	-7.4 (1.25)	-4.9	1.24	[-7.3;-2.5]	0.0001	-0.6	[-.97;-.32]
	8	71 (95.9)	58.1 (9.13)	-7.4 (1.26)	-4.8	1.27	[-7.2;-2.3]	0.0002	-0.6	[-.93;-.29]
	12	73 (98.6)	59.2 (8.90)	-6.6 (1.23)	-3.8	1.22	[-6.2;-1.4]	0.0019	-0.5	[-.82;-.19]
	16	72 (97.3)	56.8 (9.20)	-8.9 (1.24)	-5.7	1.24	[-8.1;-3.3]	<.0001	-0.7	[-.11;-.43]
	20	69 (93.2)	57.1 (9.08)	-8.5 (1.31)	-4.4	1.35	[-7.1;-1.7]	0.0013	-0.5	[-.86;-.21]
	24	72 (97.3)	56.7 (8.87)	-9.0 (1.24)	-5.6	1.24	[-8.1;-3.2]	<.0001	-0.7	[-.11;-.42]
EPTI 300 mg	Basln	67 (100.0)	66.3 (4.15)							
	4	67 (100.0)	56.6 (8.22)	-8.9 (1.26)	-6.4	1.25	[-8.9;-3.9]	<.0001	-0.8	[-.12;-.52]
	8	66 (98.5)	54.3 (8.48)	-11 (1.28)	-8.5	1.29	[-11;-5.9]	<.0001	-1.1	[-.14;-.77]
	12	66 (98.5)	56.0 (8.15)	-9.5 (1.26)	-6.7	1.24	[-9.2;-4.3]	<.0001	-0.9	[-.12;-.57]
	16	66 (98.5)	54.5 (8.57)	-11 (1.27)	-7.6	1.26	[-10;-5.1]	<.0001	-1.0	[-.13;-.67]
	20	64 (95.5)	54.1 (9.19)	-11 (1.33)	-7.0	1.37	[-9.7;-4.3]	<.0001	-0.9	[-.12;-.52]
	24	64 (95.5)	54.0 (8.96)	-11 (1.27)	-8.0	1.26	[-10;-5.5]	<.0001	-1.1	[-.14;-.73]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI
					CFB	LSmeans	95% CI		

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline HIT-6 Total Score as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

HIT-6 Total Score. Absolute Value: Mean (SE) by Visit (AMNOG) : > 2 Previous Failed Treatments



4.2.13.2 Verbesserung um ≥ 5 Punkte

Tabelle 4G-190: HIT-6, Verbesserung um ≥ 5 Punkte, Interaktions-p-Werte

Visit	Description	Treatment Group	
		EPTI 100 mg p-value	EPTI 300 mg p-value
Week 12	Interaction test: Age Group	0.8315	0.1943
	Interaction test: EM/CM	0.9832	0.2077
	Interaction test: MOH	0.0324	0.4332
	Interaction test: Number of FPT	0.3530	0.2532
	Interaction test: Sex	0.6216	0.2863
Week 24	Interaction test: Age Group	0.3631	0.4074
	Interaction test: EM/CM	0.9228	0.6261
	Interaction test: MOH	0.0618	0.4114
	Interaction test: Number of FPT	0.5302	0.9325
	Interaction test: Sex	0.8143	0.4340

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-191: HIT-6, Verbesserung um ≥ 5 Punkte, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n (%)	OR	CL	RR	CL	RD	CL	RD	
PBO	12	64	26 (40.6)								0.0416
	24	64	29 (45.3)								
EPTI 100 mg	12	55	33 (60.0)	2.17	[1.03;4.65]	1.47	[1.01;2.14]	19.4	[1.70;37.1]		0.0553
	24	55	35 (63.6)	2.09	[0.98;4.54]	1.38	[0.98;1.93]	18.3	[0.71;35.9]		

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
EPTI 300 mg	12	60	31	(51.7)	1.60	[0.77;3.33]	1.25	[0.84;1.86]	11.0	[-6.4;28.5]		0.2052
	24	61	39	(63.9)	2.24	[1.07;4.75]	1.39	[1.00;1.94]	18.6	[1.48;35.8]		0.0315

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.

AMNOG: AMNOG population B.

Tabelle 4G-192: HIT-6, Verbesserung um ≥ 5 Punkte, Subgruppe > 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	213	87	(40.8)								
	24	213	101	(47.4)								
EPTI 100 mg	12	212	131	(61.8)	2.30	[1.55;3.43]	1.51	[1.25;1.84]	20.9	[11.7;30.2]		<.0001
	24	212	157	(74.1)	3.18	[2.10;4.87]	1.56	[1.33;1.84]	26.6	[17.7;35.6]		<.0001
EPTI 300 mg	12	216	141	(65.3)	2.73	[1.84;4.07]	1.60	[1.32;1.93]	24.4	[15.3;33.6]		<.0001
	24	216	161	(74.5)	3.32	[2.20;5.08]	1.57	[1.34;1.85]	27.1	[18.2;36.0]		<.0001

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.

AMNOG: AMNOG population B.

Tabelle 4G-193 HIT-6, Verbesserung um ≥ 5 Punkte, Subgruppe männlich

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	12	28	10	(35.7)							
	24	28	14	(50.0)							
EPTI 100 mg	12	20	12	(60.0)	2.64	[0.77;9.64]	1.61	[0.87;2.99]	24.3	[-3.6;52.1]	0.1235
	24	20	15	(75.0)	2.81	[0.80;11.0]	1.46	[0.93;2.31]	25.0	[-1.5;51.5]	0.1065
EPTI 300 mg	12	31	14	(45.2)	1.56	[0.51;4.92]	1.34	[0.73;2.44]	9.45	[-15;34.4]	0.4308
	24	31	21	(67.7)	2.23	[0.75;6.91]	1.39	[0.90;2.14]	17.7	[-7.0;42.5]	0.1476

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.
AMNOG: AMNOG population B.

Tabelle 4G-194: HIT-6, Verbesserung um ≥ 5 Punkte, Subgruppe weiblich

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	12	249	103	(41.4)							
	24	249	116	(46.6)							
EPTI 100 mg	12	247	152	(61.5)	2.24	[1.56;3.24]	1.49	[1.25;1.78]	20.2	[11.6;28.8]	<.0001
	24	247	177	(71.7)	2.94	[2.01;4.33]	1.54	[1.32;1.79]	25.1	[16.7;33.4]	<.0001
EPTI 300 mg	12	245	158	(64.5)	2.64	[1.83;3.83]	1.56	[1.31;1.85]	23.1	[14.6;31.7]	<.0001
	24	246	179	(72.8)	3.23	[2.20;4.79]	1.56	[1.34;1.82]	26.2	[17.9;34.5]	<.0001

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value		
		N	n	(%)	OR	CL	RR	CL	RD	CL				
The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.														
CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.														
Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.														
AMNOG: AMNOG population B.														

Tabelle 4G-195: HIT-6, Verbesserung um \geq 5 Punkte, Subgruppe EM

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	150	63	(42.0)								
	24	150	78	(52.0)								
EPTI 100 mg	12	147	92	(62.6)	2.28	[1.44;3.66]	1.49	[1.19;1.87]	20.6	[9.47;31.7]		0.0005
	24	147	112	(76.2)	2.95	[1.79;4.93]	1.47	[1.23;1.75]	24.2	[13.6;34.7]		<.0001
EPTI 300 mg	12	152	105	(69.1)	3.03	[1.89;4.90]	1.64	[1.33;2.04]	27.1	[16.3;37.9]		<.0001
	24	152	116	(76.3)	2.91	[1.77;4.84]	1.47	[1.23;1.75]	24.3	[13.8;34.8]		<.0001

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-196: HIT-6, Verbesserung um ≥ 5 Punkte, Subgruppe CM

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	12	127	50	(39.4)							
	24	127	52	(40.9)							
EPTI 100 mg	12	120	72	(60.0)	2.45	[1.44;4.22]	1.54	[1.19;2.00]	20.6	[8.42;32.8]	0.0009
	24	120	80	(66.7)	3.09	[1.81;5.35]	1.66	[1.30;2.12]	25.7	[13.7;37.7]	<.0001
EPTI 300 mg	12	124	67	(54.0)	2.06	[1.22;3.52]	1.38	[1.05;1.80]	14.7	[2.45;26.9]	0.0066
	24	125	84	(67.2)	3.37	[1.98;5.81]	1.65	[1.29;2.10]	26.3	[14.4;38.1]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.
AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-197: HIT-6, Verbesserung um ≥ 5 Punkte, Subgruppe MOH: ja

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	12	33	17	(51.5)							
	24	33	18	(54.5)							
EPTI 100 mg	12	33	15	(45.5)	0.88	[0.32;2.45]	0.93	[0.57;1.51]	-6.1	[-30;18.0]	0.8036
	24	33	19	(57.6)	1.36	[0.47;4.00]	1.09	[0.70;1.71]	3.03	[-21;27.0]	0.5668
EPTI 300 mg	12	33	21	(63.6)	1.82	[0.66;5.22]	1.21	[0.78;1.87]	12.1	[-12;35.8]	0.2513
	24	33	23	(69.7)	2.24	[0.77;6.84]	1.29	[0.85;1.95]	15.2	[-8.0;38.3]	0.1393

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value		
		N	n (%)	OR	CL	RR	CL	RD	CL				
The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.													
CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.													
Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.													
AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.													

Tabelle 4G-198: HIT-6, Verbesserung um \geq 5 Punkte, Subgruppe MOH: nein

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n (%)	OR	CL	RR	CL	RD	CL		
PBO	12	244	96 (39.3)								<.0001
	24	244	112 (45.9)								
EPTI 100 mg	12	234	149 (63.7)	2.67	[1.84;3.90]	1.62	[1.35;1.94]	24.3	[15.6;33.0]		<.0001
	24	234	173 (73.9)	3.37	[2.28;5.02]	1.61	[1.38;1.88]	28.0	[19.6;36.4]		
EPTI 300 mg	12	243	151 (62.1)	2.55	[1.77;3.71]	1.58	[1.31;1.90]	22.8	[14.1;31.4]		<.0001
	24	244	177 (72.5)	3.22	[2.19;4.76]	1.58	[1.35;1.85]	26.6	[18.2;35.0]		

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-199: HIT-6, Verbesserung um ≥ 5 Punkte, Subgruppe 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	195	82	(42.1)								
	24	195	92	(47.2)								
EPTI 100 mg	12	193	125	(64.8)	2.52	[1.67;3.83]	1.54	[1.27;1.87]	22.7	[13.0;32.4]	<.0001	
	24	193	140	(72.5)	2.99	[1.94;4.65]	1.53	[1.29;1.81]	25.4	[15.9;34.8]	<.0001	
EPTI 300 mg	12	209	127	(60.8)	2.14	[1.43;3.21]	1.44	[1.18;1.76]	18.7	[9.13;28.3]	0.0002	
	24	210	150	(71.4)	2.89	[1.90;4.44]	1.51	[1.28;1.79]	24.2	[15.0;33.5]	<.0001	

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.
AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-200: HIT-6, Verbesserung um ≥ 5 Punkte, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	82	31	(37.8)								
	24	82	38	(46.3)								
EPTI 100 mg	12	74	39	(52.7)	1.77	[0.92;3.45]	1.39	[0.98;1.97]	14.9	[-.58;30.4]	0.0893	
	24	74	52	(70.3)	2.75	[1.41;5.51]	1.52	[1.15;2.00]	23.9	[8.93;38.9]	0.0030	
EPTI 300 mg	12	67	45	(67.2)	3.62	[1.82;7.40]	1.78	[1.29;2.46]	29.4	[14.0;44.7]	0.0002	
	24	67	50	(74.6)	3.61	[1.79;7.56]	1.61	[1.23;2.12]	28.3	[13.3;43.3]	0.0003	

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		p-value		
		N	n (%)	OR	CL	RR	CL	RD	CL			
The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.												
CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.												
Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.												
AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.												

4.2.13.3 Verbesserung um ≥ 6,3 Punkte

Tabelle 4G-201: HIT-6, Verbesserung um ≥ 6,3 Punkte, Interaktions-p-Werte

Visit	Description	Treatment Group	
		EPTI 100 mg	EPTI 300 mg
Week 12	Interaction test: Age Group	0.8938	0.3174
	Interaction test: EM/CM	0.8287	0.3174
	Interaction test: MOH	0.0745	0.7064
	Interaction test: Number of FPT	0.8206	0.1999
	Interaction test: Sex	0.4437	0.1867
Week 24	Interaction test: Age Group	0.1635	0.7809
	Interaction test: EM/CM	0.7743	0.8375
	Interaction test: MOH	0.0236	0.1658
	Interaction test: Number of FPT	0.7687	0.8137

Visit	Description	Treatment Group		
		EPTI 100 mg	EPTI 300 mg	
		p-value	p-value	
Interaction test: Sex				
0.8506 0.4267				

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-202: HIT-6, Verbesserung um $\geq 6,3$ Punkte, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n (%)	OR	CL	RR	CL	RD	CL	RD	
PBO	12	64	20 (31.3)								0.0537
	24	64	21 (32.8)								
EPTI 100 mg	12	55	27 (49.1)	2.10	[0.99;4.53]	1.57	[0.99;2.49]	17.8	[0.42;35.3]		0.0560
	24	55	28 (50.9)	2.08	[0.98;4.47]	1.53	[0.99;2.37]	18.1	[0.58;35.6]		
EPTI 300 mg	12	60	28 (46.7)	1.97	[0.94;4.19]	1.48	[0.93;2.35]	15.4	[-1.6;32.4]		0.0015
	24	61	37 (60.7)	3.26	[1.56;6.97]	1.82	[1.22;2.73]	27.8	[11.0;44.7]		

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 6.3-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.
AMNOG: AMNOG population B.

Tabelle 4G-203: HIT-6, Verbesserung um $\geq 6,3$ Punkte, Subgruppe > 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	213	66	(31.0)								
	24	213	72	(33.8)								
EPTI 100 mg	12	212	109	(51.4)	2.32	[1.55;3.48]	1.66	[1.31;2.11]	20.4	[11.3;29.6]	<.0001	
	24	212	143	(67.5)	4.10	[2.72;6.22]	2.00	[1.62;2.46]	33.7	[24.7;42.6]	<.0001	
EPTI 300 mg	12	216	127	(58.8)	3.21	[2.15;4.84]	1.90	[1.51;2.39]	27.8	[18.8;36.8]	<.0001	
	24	216	141	(65.3)	3.76	[2.51;5.68]	1.93	[1.56;2.39]	31.5	[22.5;40.5]	<.0001	

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 6.3-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.
AMNOG: AMNOG population B.

Tabelle 4G-204: HIT-6, Verbesserung um $\geq 6,3$ Punkte, Subgruppe männlich

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	28	9	(32.1)								
	24	28	10	(35.7)								
EPTI 100 mg	12	20	12	(60.0)	3.16	[0.89;12.1]	1.75	[0.92;3.29]	27.9	[0.29;55.4]	0.0753	
	24	20	13	(65.0)	3.30	[0.99;11.9]	1.78	[0.99;3.20]	29.3	[1.86;56.7]	0.0517	
EPTI 300 mg	12	31	13	(41.9)	1.68	[0.53;5.56]	1.41	[0.75;2.65]	9.79	[-15;34.3]	0.3776	
	24	31	18	(58.1)	2.54	[0.88;7.73]	1.67	[0.94;2.97]	22.4	[-2.5;47.2]	0.0861	

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value		
		N	n	(%)	OR	CL	RR	CL	RD	CL				
The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.														
CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.														
Response: Patients with a 6.3-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.														
AMNOG: AMNOG population B.														

Tabelle 4G-205: HIT-6, Verbesserung um ≥ 6,3 Punkte, Subgruppe weiblich

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	249	77	(30.9)								
	24	249	83	(33.3)								
EPTI 100 mg	12	247	124	(50.2)	2.22	[1.53;3.24]	1.62	[1.30;2.03]	19.3	[10.8;27.8]	<.0001	
	24	247	158	(64.0)	3.58	[2.46;5.24]	1.92	[1.57;2.34]	30.6	[22.3;39.0]	<.0001	
EPTI 300 mg	12	245	142	(58.0)	3.19	[2.19;4.67]	1.87	[1.51;2.32]	27.0	[18.6;35.5]	<.0001	
	24	246	160	(65.0)	3.87	[2.66;5.69]	1.95	[1.60;2.37]	31.7	[23.4;40.1]	<.0001	

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 6.3-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.

AMNOG: AMNOG population B.

Tabelle 4G-206: HIT-6, Verbesserung um $\geq 6,3$ Punkte, Subgruppe EM

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	12	150	48	(32.0)							
	24	150	55	(36.7)							
EPTI 100 mg	12	147	75	(51.0)	2.18	[1.36;3.52]	1.59	[1.20;2.11]	19.0	[8.02;30.0]	0.0011
	24	147	98	(66.7)	3.45	[2.14;5.63]	1.82	[1.43;2.31]	30.0	[19.2;40.8]	<.0001
EPTI 300 mg	12	152	94	(61.8)	3.38	[2.11;5.48]	1.93	[1.48;2.52]	29.8	[19.1;40.6]	<.0001
	24	152	104	(68.4)	3.68	[2.28;6.01]	1.87	[1.47;2.36]	31.8	[21.1;42.4]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.
AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-207: HIT-6, Verbesserung um $\geq 6,3$ Punkte, Subgruppe CM

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	12	127	38	(29.9)							
	24	127	38	(29.9)							
EPTI 100 mg	12	120	61	(50.8)	2.55	[1.48;4.43]	1.72	[1.25;2.36]	20.9	[8.94;32.9]	0.0007
	24	120	73	(60.8)	3.83	[2.24;6.65]	2.07	[1.53;2.80]	30.9	[19.1;42.7]	<.0001
EPTI 300 mg	12	124	61	(49.2)	2.63	[1.53;4.58]	1.65	[1.19;2.27]	19.3	[7.40;31.1]	0.0004
	24	125	74	(59.2)	3.77	[2.22;6.51]	1.99	[1.46;2.70]	29.3	[17.5;41.0]	<.0001

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value		
		N	n	(%)	OR	CL	RR	CL	RD	CL				
The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.														
CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.														
Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.														
AMNOG: AMNOG population B. CM : Chronic Migraine.														

Tabelle 4G-208: HIT-6, Verbesserung um $\geq 6,3$ Punkte, Subgruppe MOH: ja

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	33	12	(36.4)								
	24	33	15	(45.5)								
EPTI 100 mg	12	33	11	(33.3)	0.95	[0.32;2.80]	0.95	[0.50;1.79]	-3.0	[-26;19.9]		0.9203
	24	33	16	(48.5)	1.40	[0.49;4.14]	1.10	[0.65;1.86]	3.03	[-21;27.1]		0.5378
EPTI 300 mg	12	33	19	(57.6)	2.66	[0.95;7.86]	1.49	[0.87;2.55]	21.2	[-2.3;44.7]		0.0636
	24	33	20	(60.6)	2.25	[0.79;6.75]	1.33	[0.82;2.17]	15.2	[-8.7;39.0]		0.1314

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 6.3-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-209: HIT-6, Verbesserung um $\geq 6,3$ Punkte, Subgruppe MOH: nein

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	12	244	74	(30.3)							
	24	244	78	(32.0)							
EPTI 100 mg	12	234	125	(53.4)	2.59	[1.78;3.80]	1.76	[1.41;2.21]	23.1	[14.5;31.7]	<.0001
	24	234	155	(66.2)	4.18	[2.85;6.19]	2.07	[1.69;2.54]	34.3	[25.8;42.7]	<.0001
EPTI 300 mg	12	243	136	(56.0)	2.95	[2.03;4.32]	1.85	[1.48;2.30]	25.6	[17.1;34.1]	<.0001
	24	244	158	(64.8)	3.99	[2.73;5.87]	2.03	[1.65;2.49]	32.8	[24.4;41.2]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 6.3-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.
AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-210: HIT-6, Verbesserung um $\geq 6,3$ Punkte, Subgruppe 2 Vortherapien

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL	
PBO	12	195	64	(32.8)							
	24	195	66	(33.8)							
EPTI 100 mg	12	193	101	(52.3)	2.24	[1.48;3.41]	1.59	[1.25;2.03]	19.5	[9.86;29.2]	0.0001
	24	193	124	(64.2)	3.55	[2.33;5.46]	1.89	[1.51;2.36]	30.4	[20.9;39.9]	<.0001
EPTI 300 mg	12	209	115	(55.0)	2.53	[1.68;3.83]	1.67	[1.32;2.12]	22.2	[12.8;31.6]	<.0001
	24	210	133	(63.3)	3.46	[2.29;5.27]	1.87	[1.50;2.33]	29.5	[20.2;38.8]	<.0001

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value		
		N	n	(%)	OR	CL	RR	CL	RD	CL				
The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.														
CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.														
Response: Patients with a 6.3-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.														
AMNOG: AMNOG population B. EM : Episodic Migraine.														

Tabelle 4G-211: HIT-6, Verbesserung um ≥ 6,3 Punkte, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n	(%)	OR	CL	RR	CL	RD	CL		
PBO	12	82	22	(26.8)								
	24	82	27	(32.9)								
EPTI 100 mg	12	74	35	(47.3)	2.38	[1.21;4.77]	1.76	[1.14;2.71]	20.5	[5.59;35.3]		0.0118
	24	74	47	(63.5)	3.55	[1.82;7.07]	1.92	[1.35;2.74]	30.6	[15.6;45.5]		0.0002
EPTI 300 mg	12	67	40	(59.7)	4.26	[2.13;8.77]	2.23	[1.48;3.35]	32.9	[17.7;48.0]		<.0001
	24	67	45	(67.2)	4.39	[2.21;9.01]	2.05	[1.44;2.91]	34.2	[19.1;49.4]		<.0001

The OR and p-values are based on logistic regression model. The model includes baseline HIT-6 Total Score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors.

CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. LOCF is used to impute potentially missing values at Week 12 or Week 24. Baseline values will not be carried forward.

Response: Patients with a 6.3-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.14 MSQ (Migraine Specific Quality of Life Questionnaire), Einschränkung der Rollenfunktion

4.2.14.1 Veränderung gegenüber dem Baseline-Wert

Tabelle 4G-212: MSQ, Einschränkung der Rollenfunktion, CFB, Interaktions-p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.9751	0.5951
Interaction test: EM/CM	0.3508	0.5402
Interaction test: MOH	0.4387	0.3034
Interaction test: Number of FPT	0.9932	0.3510
Interaction test: Sex	0.7138	0.6826

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-213: MSQ, Einschränkung der Rollenfunktion, CFB, Interaktions-p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.8896	0.8699
Interaction test: EM/CM	0.1836	0.5055
Interaction test: MOH	0.2531	0.6413
Interaction test: Number of FPT	0.9377	0.1311

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Sex	0.6929	0.9350

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-214: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe ≤ 35 Jahre

Treatment	Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G		
						CFB	95% CI	SMD 95% CI	95% CI		
									Diff.	SE	p-value
PBO		Basln	64 (100.0)	34.2 (16.7)							
		12	64 (100.0)	49.0 (23.8)		9.52 (3.60)					
		24	63 (98.4)	50.3 (22.9)		10.8 (3.59)					
EPTI 100 mg		Basln	53 (100.0)	36.0 (17.2)							
		12	53 (100.0)	61.7 (23.3)		21.5 (3.73)	11.9	3.99	[4.06;19.8]	0.0032	0.6 [0.19;0.92]
		24	49 (92.5)	65.8 (20.1)		25.9 (3.74)	15.1	3.98	[7.22;22.9]	0.0002	0.7 [0.35;1.10]
EPTI 300 mg		Basln	61 (100.0)	37.9 (16.0)							
		12	60 (98.4)	64.2 (21.4)		23.6 (3.76)	14.1	3.91	[6.32;21.8]	0.0004	0.6 [0.29;1.00]
		24	59 (96.7)	68.2 (23.9)		27.8 (3.72)	16.9	3.87	[9.28;24.6]	<.0001	0.8 [0.44;1.15]

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	
					CFB	LSmeans	95% CI	SMD	95% CI

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

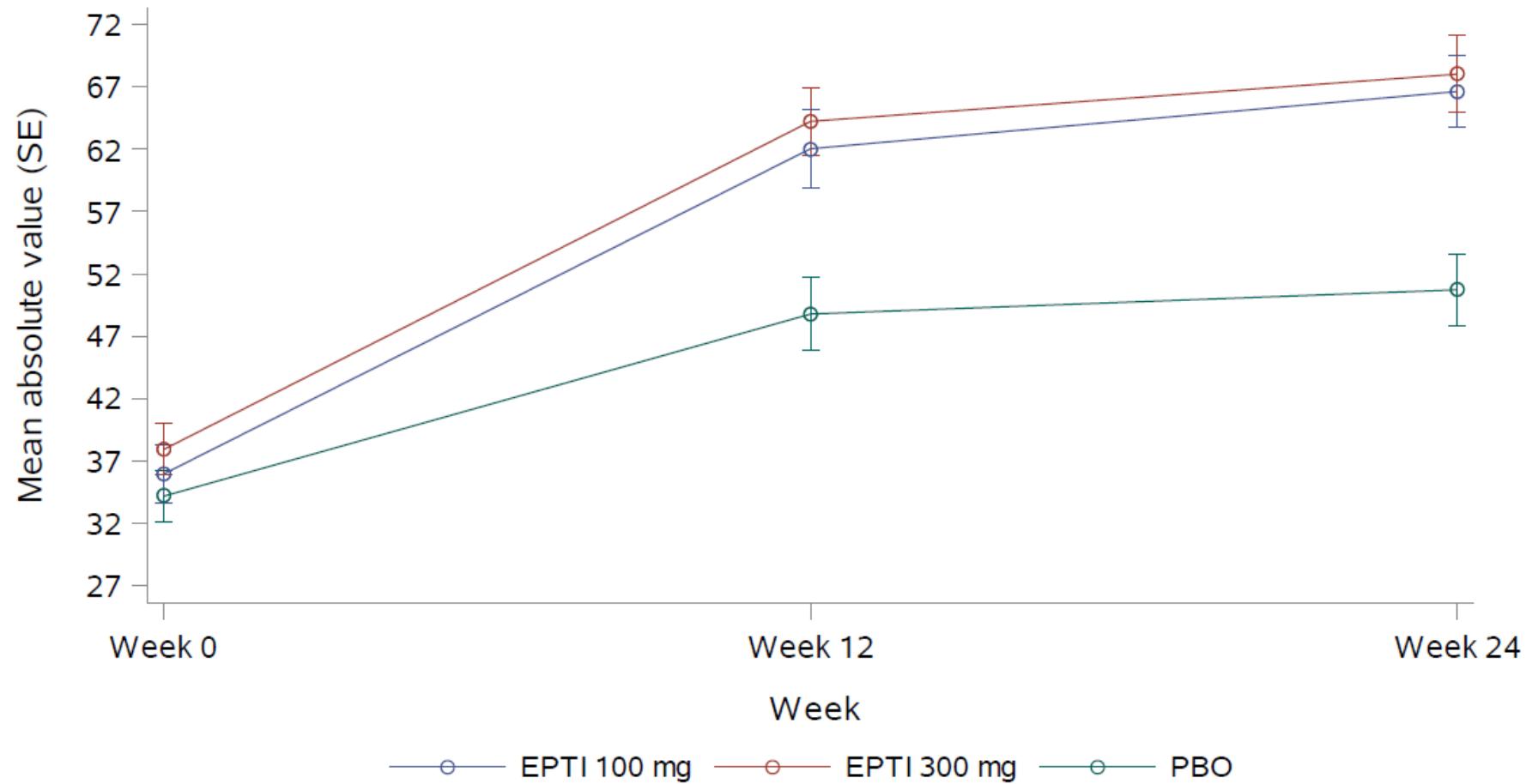
MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) : Age <= 35 years

Tabelle 4G-215: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	213 (100.0)	35.3 (17.1)								
	12	213 (100.0)	52.5 (20.0)	15.8 (2.11)							
	24	205 (96.2)	54.1 (21.5)	17.2 (2.13)							
EPTI 100 mg	Basln	205 (100.0)	35.6 (17.7)								
	12	205 (100.0)	63.7 (22.6)	27.1 (2.11)	11.3	1.99	[7.36;15.2]	<.0001	0.6	[0.36;0.75]	
	24	198 (96.6)	69.4 (21.0)	32.5 (2.15)	15.2	2.03	[11.2;19.2]	<.0001	0.7	[0.55;0.94]	
EPTI 300 mg	Basln	216 (100.0)	35.0 (16.9)								
	12	216 (100.0)	67.8 (21.8)	31.4 (2.03)	15.6	1.98	[11.7;19.4]	<.0001	0.8	[0.57;0.95]	
	24	209 (96.8)	68.7 (22.6)	32.1 (2.06)	14.8	2.01	[10.9;18.8]	<.0001	0.7	[0.53;0.92]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

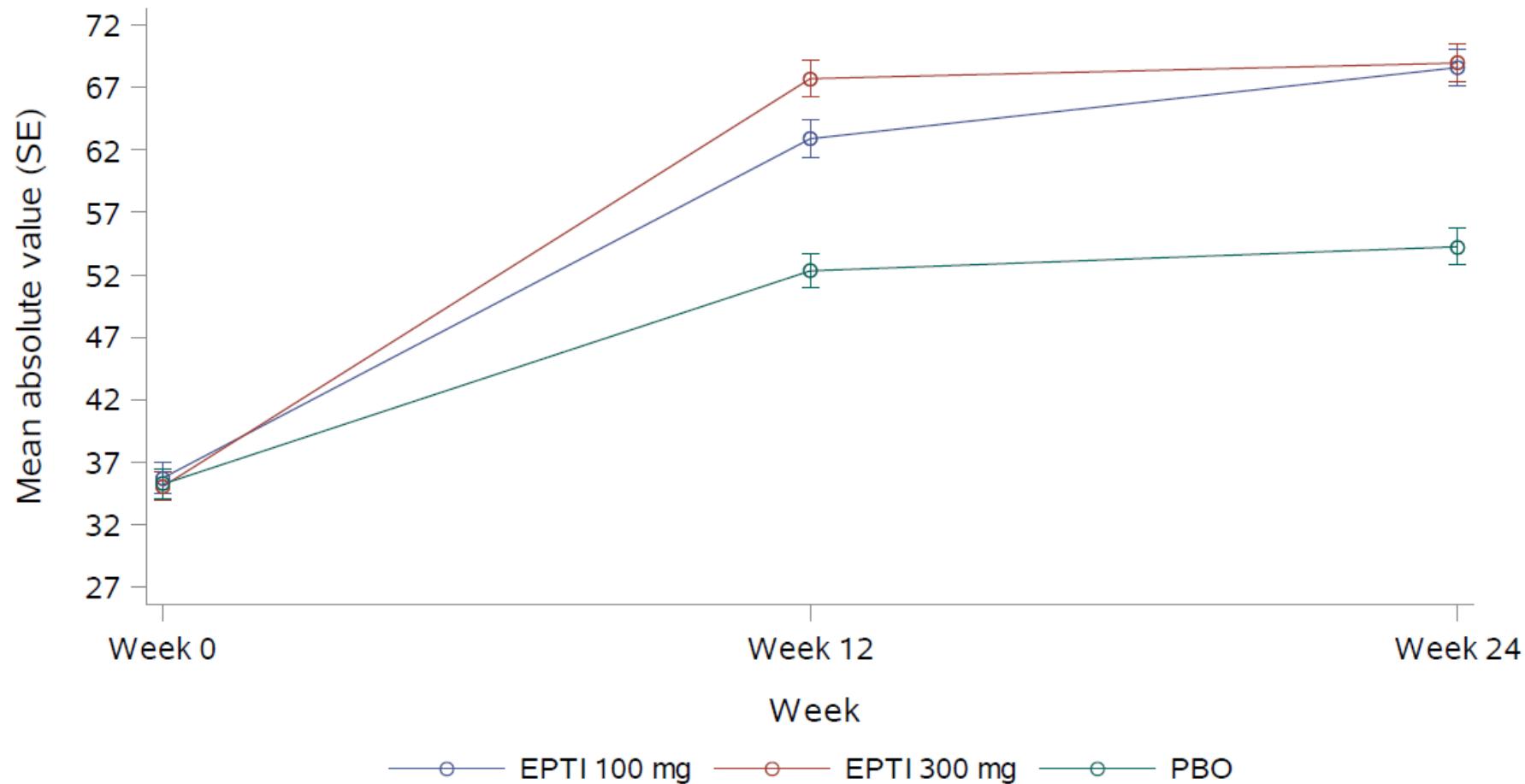
MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) : Age > 35 years

Tabelle 4G-216: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	28 (100.0)	38.9 (19.0)	11.8 (4.56)	9.9	6.01	[-2.2;21.9]	0.1060	0.5	[-.10;1.06]	
	12	28 (100.0)	49.5 (20.9)								
	24	28 (100.0)	50.3 (25.7)								
EPTI 100 mg	Basln	20 (100.0)	38.9 (18.4)	21.7 (4.90)	12.1	6.69	[-1.3;25.4]	0.0755	0.5	[-.06;1.15]	
	12	20 (100.0)	65.1 (25.8)								
	24	18 (90.0)	67.8 (19.0)								
EPTI 300 mg	Basln	31 (100.0)	34.7 (16.7)	26.3 (4.19)	14.5	5.00	[4.48;24.5]	0.0052	0.8	[0.23;1.28]	
	12	31 (100.0)	60.2 (26.9)								
	24	31 (100.0)	64.1 (25.5)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

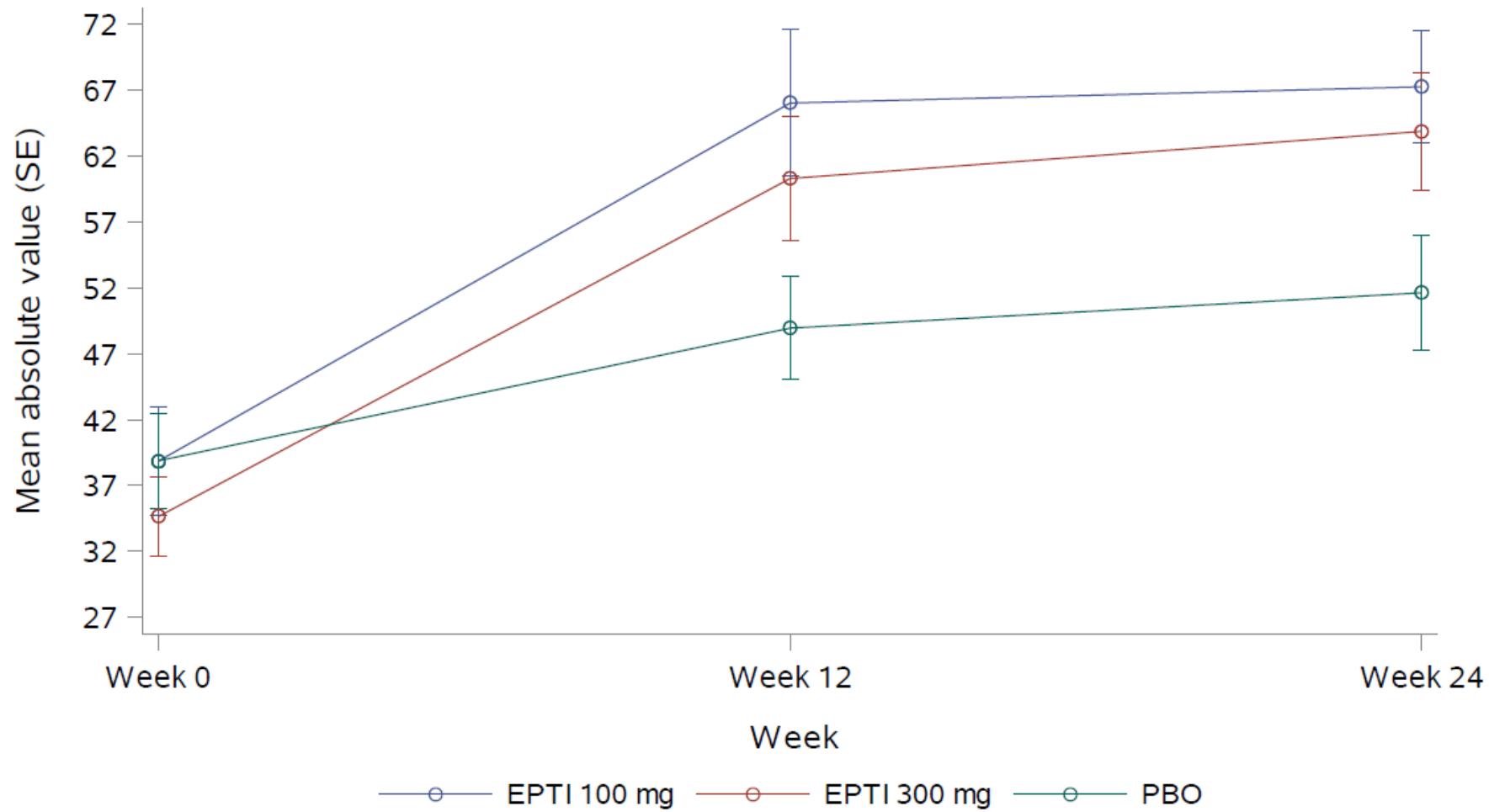
MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) : Males

Tabelle 4G-217: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	249 (100.0)	34.6 (16.7)		13.7 (1.98)	1.86	[7.44;14.7]	<.0001	0.5	[0.36;0.72]	
	12	249 (100.0)	51.9 (21.0)								
	24	240 (96.4)	53.5 (21.4)								
EPTI 100 mg	Basln	238 (100.0)	35.4 (17.5)		24.8 (2.00)	1.87	[11.3;18.7]	<.0001	0.7	[0.56;0.92]	
	12	238 (100.0)	63.1 (22.5)								
	24	229 (96.2)	68.8 (21.0)								
EPTI 300 mg	Basln	246 (100.0)	35.7 (16.8)		29.5 (1.92)	1.85	[12.2;19.4]	<.0001	0.8	[0.59;0.95]	
	12	245 (99.6)	67.9 (20.9)								
	24	237 (96.3)	69.2 (22.5)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

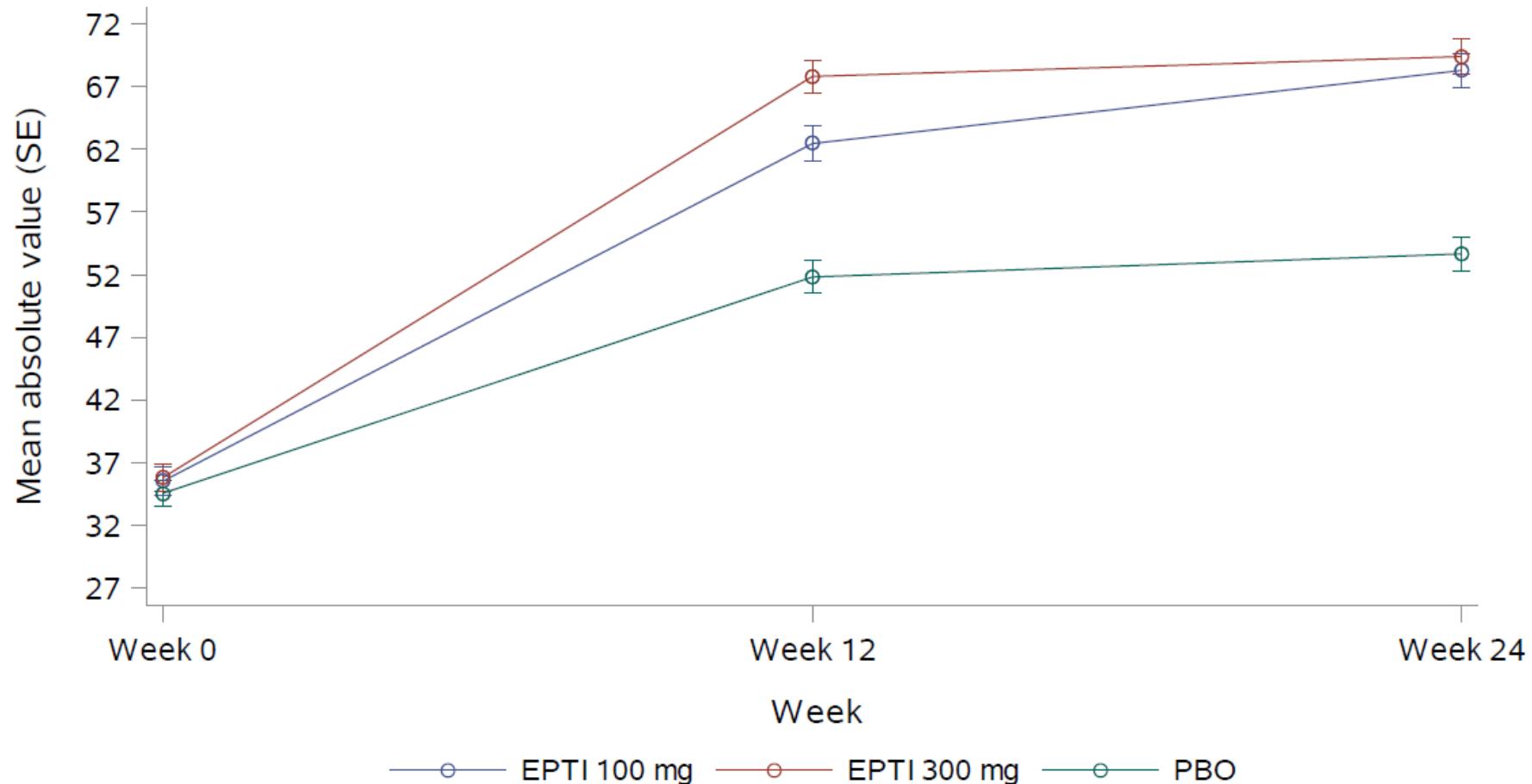
MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) : Females

Tabelle 4G-218: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	150 (100.0)	37.4 (18.7)	17.3 (2.46)	9.6	2.31	[5.02;14.1]	<.0001	0.5	[0.25;0.71]
	12	150 (100.0)	55.9 (20.9)							
	24	147 (98.0)	58.2 (22.2)							
EPTI 100 mg	Basln	144 (100.0)	37.4 (17.9)	26.8 (2.52)	13.2	2.44	[8.42;18.0]	<.0001	0.6	[0.41;0.88]
	12	144 (100.0)	65.3 (21.5)							
	24	136 (94.4)	71.3 (20.0)							
EPTI 300 mg	Basln	152 (100.0)	37.0 (17.0)	32.9 (2.38)	15.7	2.29	[11.2;20.2]	<.0001	0.8	[0.56;1.01]
	12	152 (100.0)	71.2 (20.2)							
	24	148 (97.4)	72.1 (22.2)							

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. EM : Episodic Migraine.

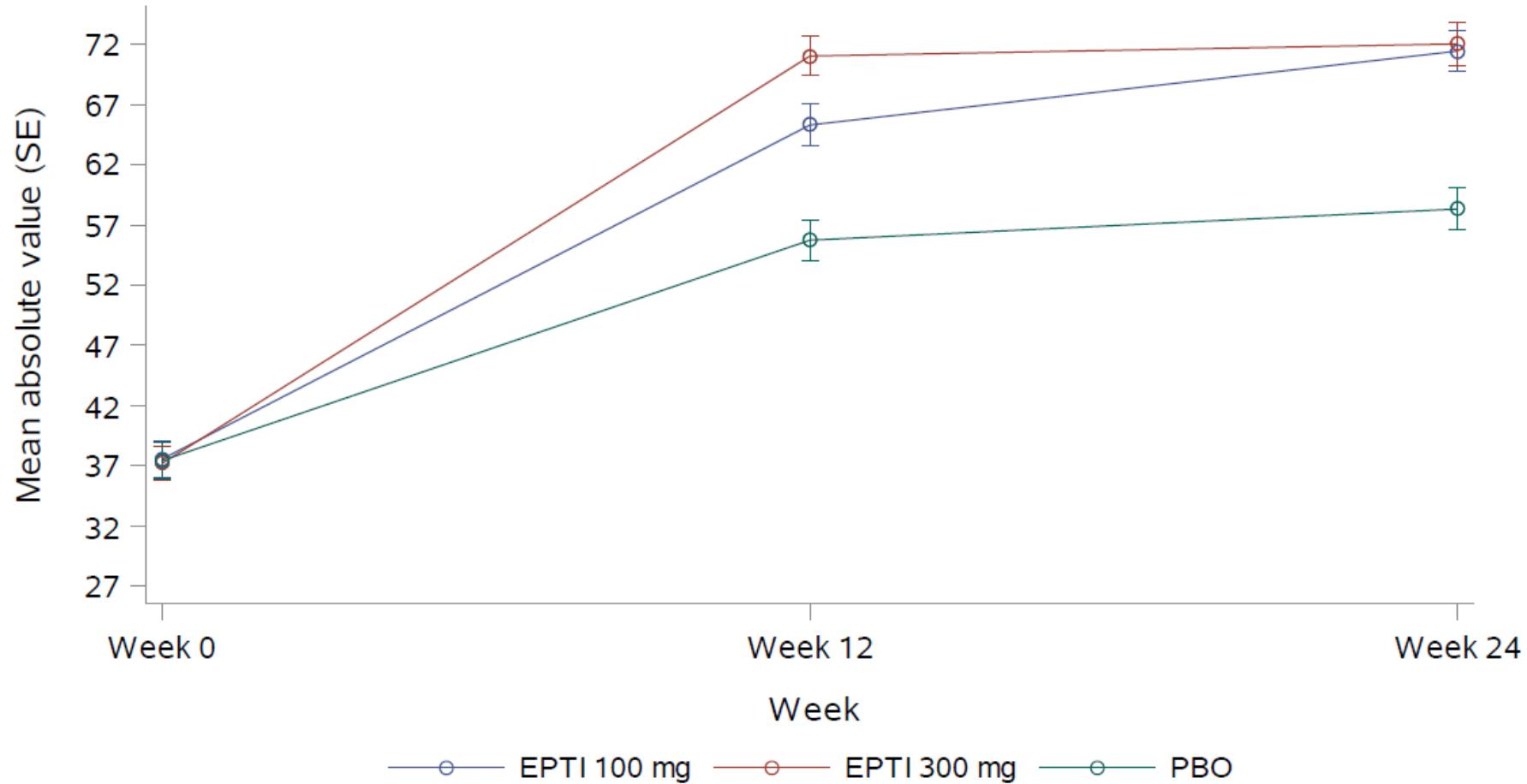
**MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) :
Episodic Migraine**

Tabelle 4G-219: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		Hedges' G	
					Diff.	SE	CI	95% CI		SMD 95% CI	
								p-value	G	CI	
PBO	Basln	127 (100.0)	32.1 (14.2)		14.2	2.79	[8.74;19.7]	<.0001	0.7	[0.40;0.91]	
	12	127 (100.0)	46.6 (20.0)								
	24	121 (95.3)	47.1 (20.0)								
EPTI 100 mg	Basln	114 (100.0)	33.5 (17.0)		14.2	2.79	[8.74;19.7]	<.0001	0.7	[0.40;0.91]	
	12	114 (100.0)	60.8 (24.1)								
	24	111 (97.4)	65.5 (21.5)								
EPTI 300 mg	Basln	125 (100.0)	33.9 (16.2)		14.7	2.71	[9.32;20.0]	<.0001	0.7	[0.43;0.93]	
	12	124 (99.2)	61.9 (22.6)								
	24	120 (96.0)	64.3 (23.0)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. CM : Chronic Migraine.

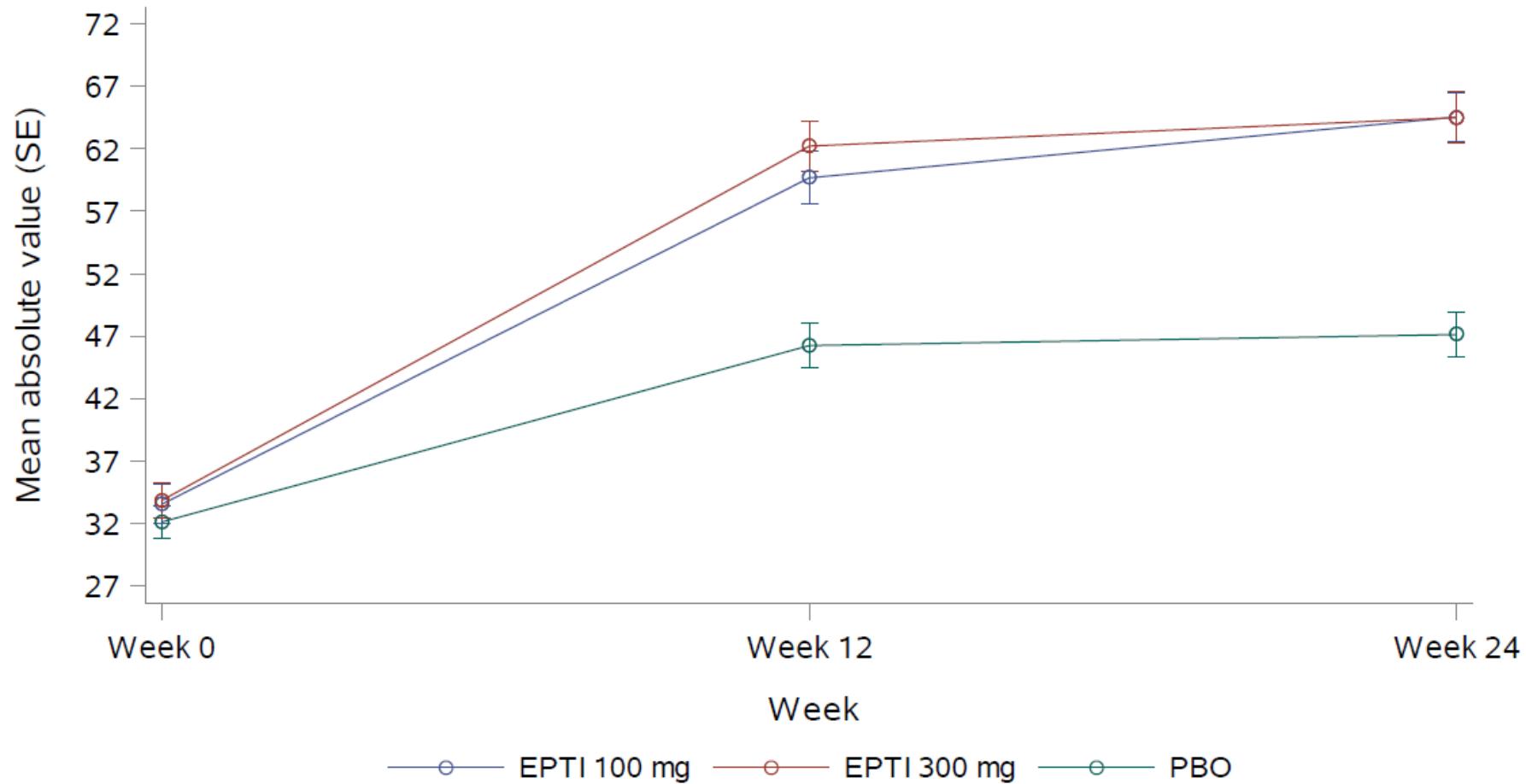
MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) : Chronic Migraine

Tabelle 4G-220: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	33 (100.0)	31.9 (15.7)		20.8 (4.79)	5.6	5.08	[-4.5;15.7]	0.2713	0.3 [-.22;0.77]
	12	33 (100.0)	45.9 (21.5)							
	24	31 (93.9)	50.9 (21.8)							
EPTI 100 mg	Basln	32 (100.0)	33.5 (16.4)		32.1 (4.69)	6.4	5.36	[-4.3;17.0]	0.2383	0.3 [-.20;0.80]
	12	32 (100.0)	55.4 (20.1)							
	24	32 (100.0)	60.9 (18.4)							
EPTI 300 mg	Basln	32 (100.0)	30.6 (14.9)		36.0 (4.80)	16.5	4.97	[6.60;26.4]	0.0014	0.8 [0.33;1.32]
	12	32 (100.0)	63.4 (25.0)							
	24	32 (100.0)	62.1 (23.5)							

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

**MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) :
Medication overuse headache at baseline**

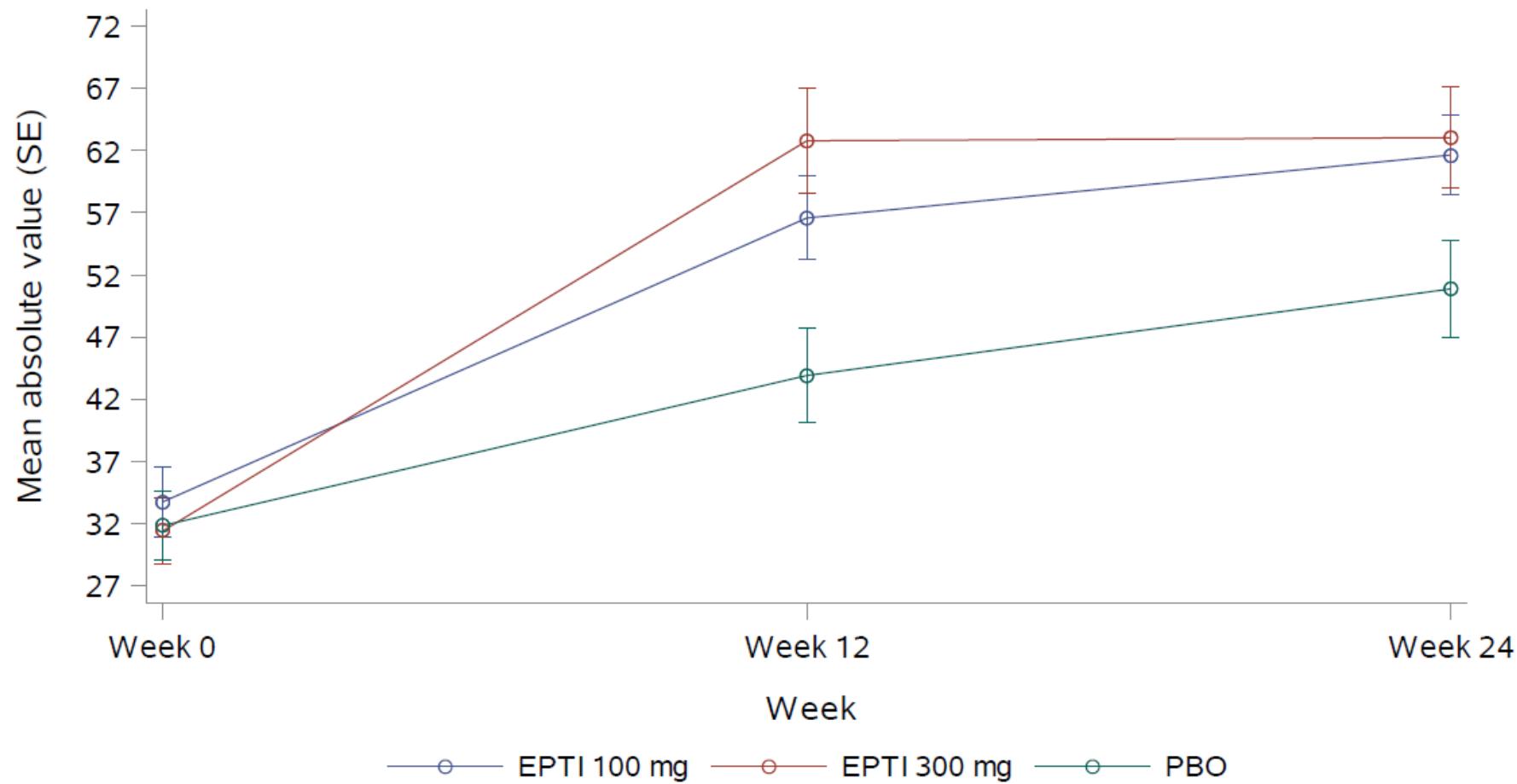


Tabelle 4G-221: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	244 (100.0)	35.4 (17.1)							
	12	244 (100.0)	52.4 (20.8)	13.7 (1.97)						
	24	237 (97.1)	53.5 (21.9)	14.5 (1.99)						
EPTI 100 mg	Basln	226 (100.0)	36.0 (17.8)							
	12	226 (100.0)	64.4 (22.9)	25.3 (2.00)	11.6	1.89	[7.92;15.3]	<.0001	0.6	[0.39;0.75]
	24	215 (95.1)	69.9 (20.9)	30.4 (2.03)	15.9	1.92	[12.1;19.6]	<.0001	0.8	[0.59;0.96]
EPTI 300 mg	Basln	245 (100.0)	36.3 (16.9)							
	12	244 (99.6)	67.5 (21.3)	28.1 (1.93)	14.5	1.85	[10.9;18.1]	<.0001	0.7	[0.53;0.89]
	24	236 (96.3)	69.5 (22.7)	29.9 (1.94)	15.4	1.88	[11.7;19.1]	<.0001	0.8	[0.57;0.93]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

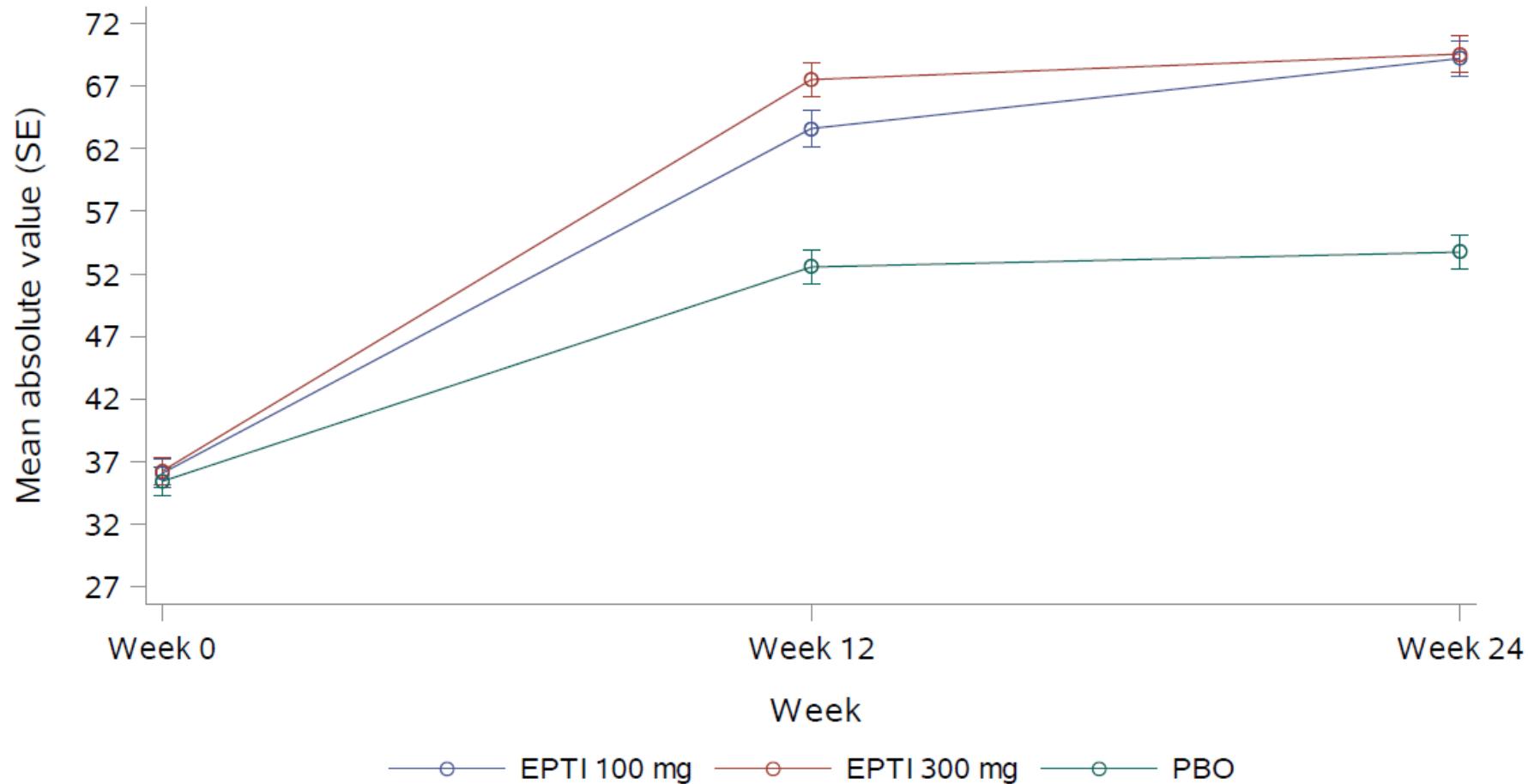
MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) No medication overuse headache at baseline

Tabelle 4G-222: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	195 (100.0)	35.8 (17.3)		15.0 (2.18)	2.10	[6.90;15.2]	<.0001	0.5	[0.34;0.74]	
	12	195 (100.0)	53.8 (21.1)								
	24	190 (97.4)	54.2 (22.6)								
EPTI 100 mg	Basln	188 (100.0)	35.8 (17.5)		26.0 (2.21)	1.10	[10.8;19.1]	<.0001	0.7	[0.53;0.94]	
	12	188 (100.0)	65.5 (22.0)								
	24	178 (94.7)	69.7 (20.4)								
EPTI 300 mg	Basln	211 (100.0)	35.8 (16.7)		28.4 (2.07)	1.35	[9.45;17.5]	<.0001	0.7	[0.46;0.85]	
	12	210 (99.5)	67.7 (22.0)								
	24	204 (96.7)	68.0 (23.2)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

**MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) : = 2
Previous Failed Treatments**

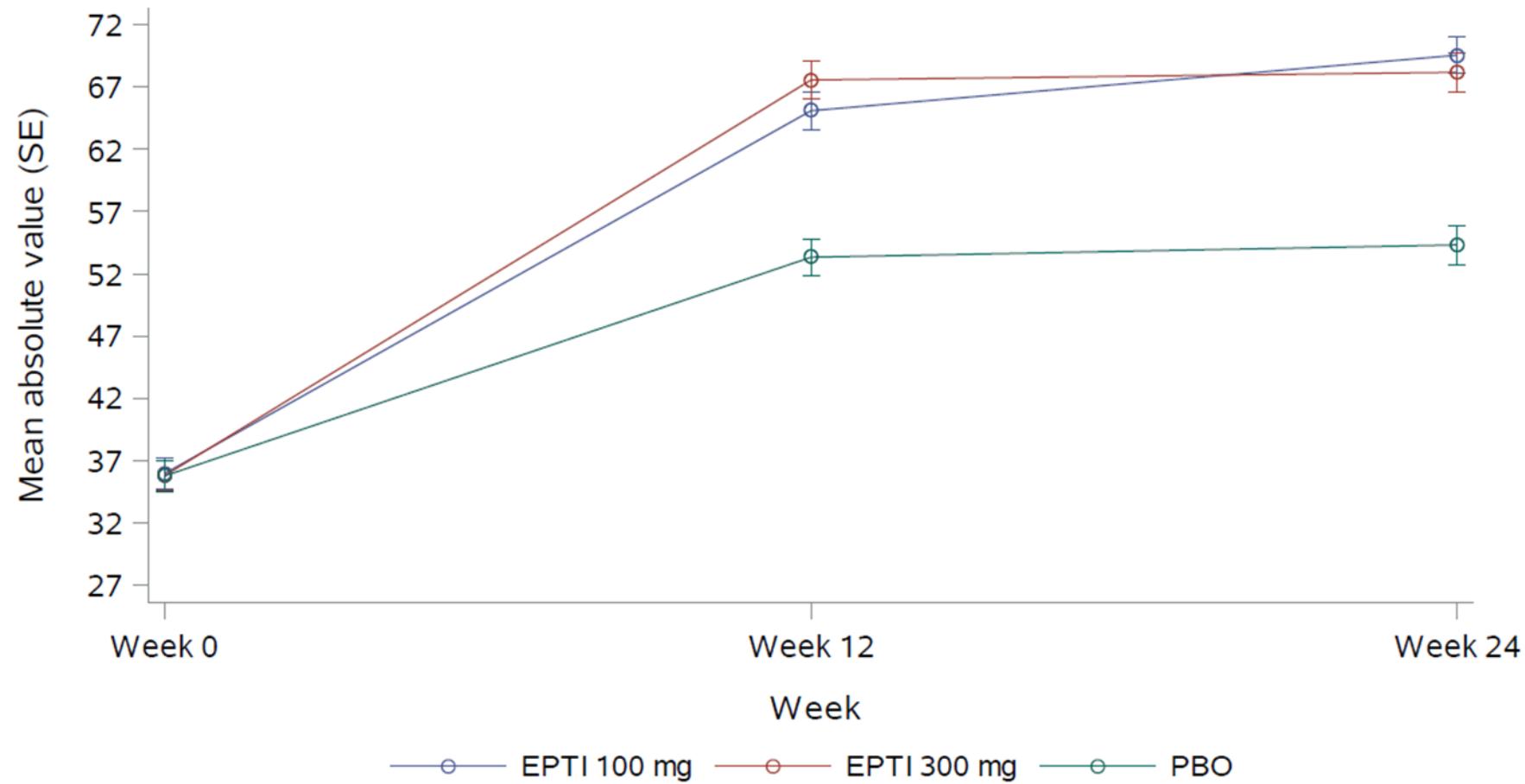
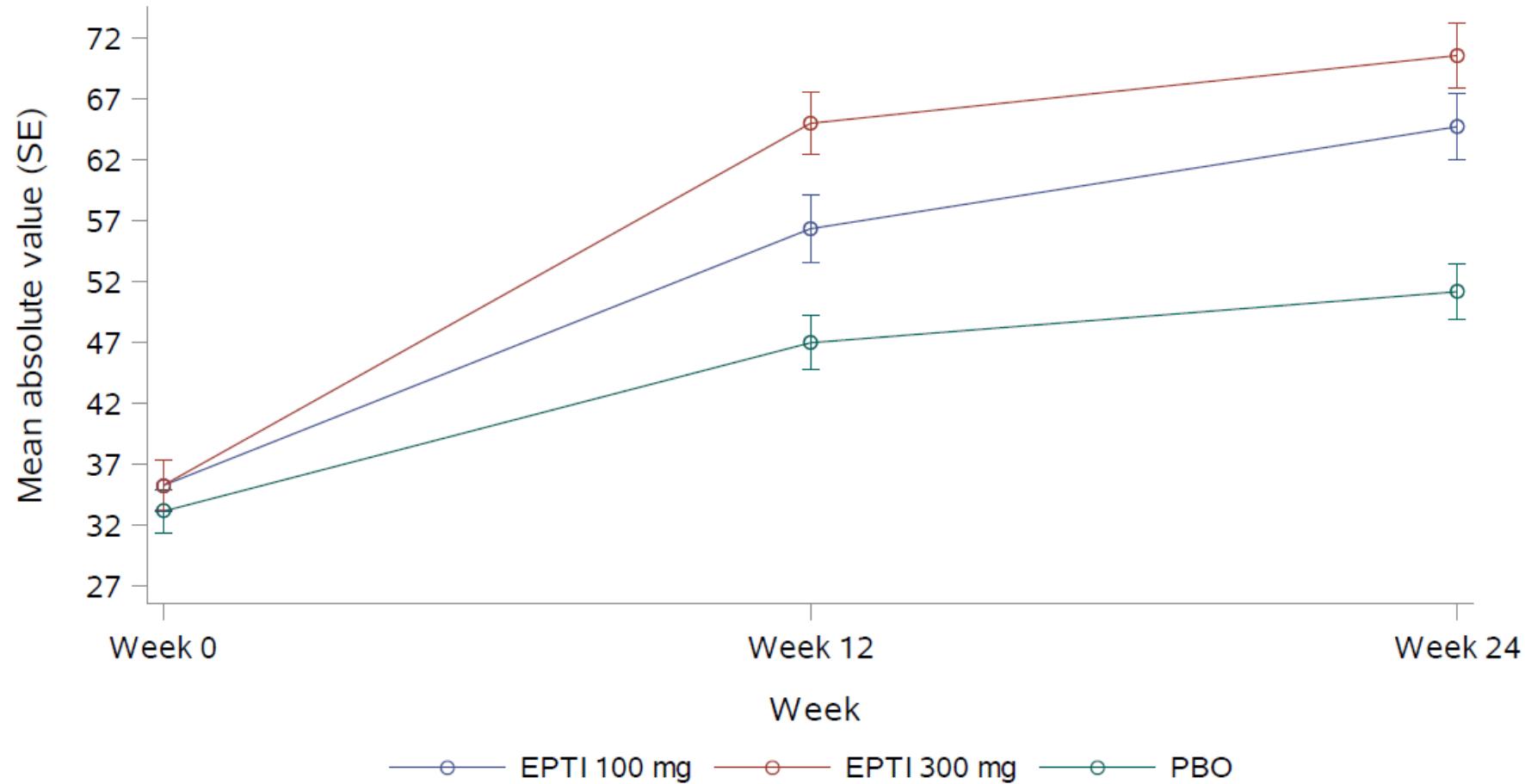


Tabelle 4G-223: MSQ, Einschränkung der Rollenfunktion, CFB, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	82 (100.0)	33.2 (16.2)		12.0 (3.43)	3.33	[4.33;17.4]	0.0012	0.5	[0.21;0.85]	
	12	82 (100.0)	46.6 (20.0)								
	24	78 (95.1)	50.8 (20.1)								
EPTI 100 mg	Basln	70 (100.0)	35.3 (18.0)		22.9 (3.45)	15.2	[8.51;21.8]	<.0001	0.7	[0.42;1.07]	
	12	70 (100.0)	57.5 (23.9)								
	24	69 (98.6)	66.0 (21.9)								
EPTI 300 mg	Basln	66 (100.0)	35.0 (16.8)		29.7 (3.51)	3.37	[11.0;24.3]	<.0001	0.9	[0.54;1.19]	
	12	66 (100.0)	65.0 (20.9)								
	24	64 (97.0)	70.5 (21.9)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

MSQ role function restrictive. Absolute Value: Mean (SE) by Visit (AMNOG) : > 2 Previous Failed Treatments

4.2.14.2 Verbesserung um ≥ 15 Punkte

Tabelle 4G-224: MSQ, Einschränkung der Rollenfunktion, Responder, Interaktions-p-Werte

Visit	Description	Treatment Group	
		EPTI 100 mg p-value	EPTI 300 mg p-value
Week 12	Interaction test: Age Group	0.7637	0.8638
	Interaction test: EM/CM	0.8905	0.3988
	Interaction test: MOH	0.4014	0.7434
	Interaction test: Number of FPT	0.7765	0.7974
	Interaction test: Sex	0.2693	0.6209
Week 24	Interaction test: Age Group	0.2967	0.6169
	Interaction test: EM/CM	0.2782	0.7813
	Interaction test: MOH	0.3045	0.4976
	Interaction test: Number of FPT	0.8801	0.6954
	Interaction test: Sex	0.9807	0.5770

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-225: MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	64	31 (48.4)							
	24	64	31 (48.4)							
EPTI 100 mg	12	53	33 (62.3)	1.74	[0.81;3.82]	1.26	[0.90;1.75]	13.8	[-4.1;31.7]	0.1583
	24	53	33 (62.3)	1.73	[0.81;3.75]	1.27	[0.92;1.76]	13.8	[-4.1;31.7]	0.1593

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 300 mg	12	61	41	(67.2)	2.46	[1.16;5.34]	1.37	[1.01;1.87]	18.8	[1.78;35.8]	0.0187
	24	61	41	(67.2)	2.37	[1.13;5.09]	1.37	[1.01;1.85]	18.8	[1.78;35.8]	0.0223

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.

AMNOG: AMNOG population B.

Tabelle 4G-226: MSQ, Einschränkung der Rollenfunktion, Responder, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	213	109	(51.2)							
	24	213	104	(48.8)							
EPTI 100 mg	12	205	138	(67.3)	2.13	[1.41;3.24]	1.32	[1.12;1.55]	16.1	[6.85;25.4]	0.0003
	24	205	147	(71.7)	2.84	[1.88;4.35]	1.47	[1.25;1.73]	22.9	[13.8;32.0]	<.0001
EPTI 300 mg	12	215	156	(72.6)	2.74	[1.80;4.20]	1.42	[1.22;1.65]	21.4	[12.4;30.4]	<.0001
	24	215	157	(73.0)	3.00	[1.99;4.58]	1.50	[1.28;1.75]	24.2	[15.2;33.2]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.

AMNOG: AMNOG population B.

Tabelle 4G-227: MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe männlich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	28	12	(42.9)							
		24	28	10	(35.7)							
EPTI 100 mg		12	20	15	(75.0)	3.60	[1.00;14.5]	1.64	[1.02;2.66]	32.1	[5.76;58.5]	0.0499
		24	20	12	(60.0)	2.40	[0.69;8.74]	1.59	[0.88;2.87]	24.3	[-3.6;52.1]	0.1687
EPTI 300 mg		12	31	19	(61.3)	2.48	[0.82;7.95]	1.51	[0.93;2.45]	18.4	[-6.7;43.5]	0.1065
		24	31	21	(67.7)	4.51	[1.44;15.5]	2.01	[1.18;3.40]	32.0	[7.82;56.2]	0.0092

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.

AMNOG: AMNOG population B.

Tabelle 4G-228: MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe weiblich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	249	128	(51.4)							
		24	249	125	(50.2)							
EPTI 100 mg		12	238	156	(65.5)	1.96	[1.34;2.89]	1.27	[1.09;1.48]	14.1	[5.48;22.8]	0.0005
		24	238	168	(70.6)	2.54	[1.73;3.74]	1.40	[1.21;1.63]	20.4	[11.9;28.9]	<.0001
EPTI 300 mg		12	245	178	(72.7)	2.86	[1.93;4.27]	1.41	[1.22;1.63]	21.2	[12.9;29.6]	<.0001
		24	245	177	(72.2)	2.78	[1.90;4.11]	1.44	[1.24;1.66]	22.0	[13.7;30.4]	<.0001

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.
AMNOG: AMNOG population B.

Tabelle 4G-229: MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe EM

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	150	81	(54.0)							
	24	150	81	(54.0)							
EPTI 100 mg	12	144	101	(70.1)	2.13	[1.29;3.54]	1.30	[1.08;1.56]	16.1	[5.21;27.1]	0.0030
	24	144	102	(70.8)	2.15	[1.31;3.55]	1.31	[1.09;1.57]	16.8	[5.94;27.7]	0.0022
EPTI 300 mg	12	151	117	(77.5)	3.15	[1.88;5.35]	1.43	[1.21;1.70]	23.5	[13.1;33.9]	<.0001
	24	151	114	(75.5)	2.72	[1.65;4.54]	1.40	[1.18;1.66]	21.5	[11.0;32.0]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment as factor. CL for RR and RD are based on binomial distribution. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.
AMNOG: AMNOG population B. EM : Episodic Migraine.

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Tabelle 4G-230: MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe CM

		Responders			Odds Ratio		Relative Risk		Risk Difference				
Treatment		Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	127	59	(46.5)									
	24	127	54	(42.5)									
EPTI 100 mg	12	114	70	(61.4)	1.99	[1.18;3.41]	1.32	[1.04;1.67]	14.9	[2.49;27.4]	0.0104		
	24	114	78	(68.4)	3.14	[1.84;5.44]	1.61	[1.27;2.04]	25.9	[13.8;38.0]	<.0001		
EPTI 300 mg	12	125	80	(64.0)	2.28	[1.36;3.88]	1.38	[1.10;1.73]	17.5	[5.46;29.6]	0.0018		
	24	125	84	(67.2)	2.99	[1.78;5.09]	1.58	[1.25;2.00]	24.7	[12.8;36.6]	<.0001		

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment as factor. CL for RR and RD are based on binomial distribution. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.

AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-231: MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe MOH: ja

		Responders			Odds Ratio		Relative Risk		Risk Difference				
Treatment		Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	33	16	(48.5)									
	24	33	18	(54.5)									
EPTI 100 mg	12	32	18	(56.3)	1.36	[0.49;3.86]	1.13	[0.72;1.79]	7.77	[-16;32.0]	0.5585		
	24	32	21	(65.6)	1.49	[0.53;4.33]	1.16	[0.78;1.74]	11.1	[-13;34.7]	0.4527		
EPTI 300 mg	12	32	22	(68.8)	2.26	[0.80;6.66]	1.38	[0.91;2.09]	20.3	[-3.2;43.7]	0.1231		
	24	32	23	(71.9)	1.98	[0.69;5.91]	1.28	[0.87;1.87]	17.3	[-5.7;40.4]	0.2046		

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-232: MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe MOH: nein

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	244	124	(50.8)							
	24	244	117	(48.0)							
EPTI 100 mg	12	226	153	(67.7)	2.19	[1.48;3.26]	1.33	[1.14;1.55]	16.9	[8.13;25.6]	<.0001
	24	226	159	(70.4)	2.74	[1.86;4.08]	1.47	[1.26;1.71]	22.4	[13.8;31.0]	<.0001
EPTI 300 mg	12	244	175	(71.7)	2.75	[1.86;4.10]	1.41	[1.22;1.63]	20.9	[12.5;29.3]	<.0001
	24	244	175	(71.7)	2.99	[2.04;4.43]	1.50	[1.29;1.74]	23.8	[15.3;32.2]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-233: MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	195	102	(52.3)							
	24	195	94	(48.2)							
EPTI 100 mg	12	188	130	(69.1)	2.12	[1.37;3.29]	1.32	[1.12;1.55]	16.8	[7.21;26.5]	0.0007
	24	188	131	(69.7)	2.50	[1.64;3.85]	1.44	[1.21;1.71]	21.5	[11.9;31.1]	<.0001
EPTI 300 mg	12	210	152	(72.4)	2.57	[1.67;3.97]	1.38	[1.18;1.62]	20.1	[10.8;29.3]	<.0001
	24	210	152	(72.4)	2.92	[1.92;4.47]	1.50	[1.27;1.77]	24.2	[14.9;33.4]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-234 :MSQ, Einschränkung der Rollenfunktion, Responder, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	82	38	(46.3)							
	24	82	41	(50.0)							
EPTI 100 mg	12	70	41	(58.6)	1.90	[0.97;3.78]	1.27	[0.94;1.73]	12.2	[-3.6;28.0]	0.0628
	24	70	49	(70.0)	2.98	[1.46;6.28]	1.41	[1.08;1.84]	20.0	[4.76;35.2]	0.0025
EPTI 300 mg	12	66	45	(68.2)	2.93	[1.45;6.09]	1.47	[1.11;1.95]	21.8	[6.26;37.4]	0.0026
	24	66	46	(69.7)	2.87	[1.39;6.13]	1.39	[1.06;1.82]	19.7	[4.20;35.2]	0.0041

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		p-value
		N	n (%)	OR	CL	RR	CL	RD	CL	

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function restrictive score.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.15 MSQ (Migraine Specific Quality of Life Questionnaire), Verhinderung der Rollenfunktion

4.2.15.1 Veränderung gegenüber dem Baseline-Wert

Tabelle 4G-235: MSQ, Verhinderung der Rollenfunktion, CFB, Interaktions-p-Werte, Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.6133	0.8886
Interaction test: EM/CM	0.2468	0.4876
Interaction test: MOH	0.2945	0.6189
Interaction test: Number of FPT	0.8969	0.3553
Interaction test: Sex	0.7742	0.8564

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-236: MSQ, Verhinderung der Rollenfunktion, CFB, Interaktions-p-Werte, Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.5906	0.8284
Interaction test: EM/CM	0.1387	0.2286
Interaction test: MOH	0.1516	0.3515
Interaction test: Number of FPT	0.9031	0.2363
Interaction test: Sex	0.7495	0.9404

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-237: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	CFB LSmeans			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									G	CI	
PBO	Basln	64 (100.0)	52.0 (21.7)		6.37 (3.32)	3.73	[5.76;20.5]	0.0006	0.7	[0.29;1.02]	
	12	64 (100.0)	61.8 (25.5)	6.37 (3.32)							
	24	63 (98.4)	65.8 (24.5)	10.4 (3.29)							
EPTI 100 mg	Basln	53 (100.0)	50.2 (21.4)		19.5 (3.44)	3.73	[4.42;19.0]	0.0018	0.6	[0.23;0.98]	
	12	53 (100.0)	73.4 (20.7)	19.5 (3.44)							
	24	49 (92.5)	76.1 (18.8)	22.1 (3.43)							
EPTI 300 mg	Basln	61 (100.0)	53.4 (19.8)		21.4 (3.47)	3.64	[7.86;22.2]	<.0001	0.7	[0.39;1.10]	
	12	60 (98.4)	76.6 (18.8)	21.4 (3.47)							

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI		
					CFB						
					LSmeans	95% CI	p-value				
	24	59 (96.7)	78.6 (19.8)	23.7 (3.41)	13.3	3.56 [6.23;20.3]	0.0003	0.7 [0.32;1.03]			

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

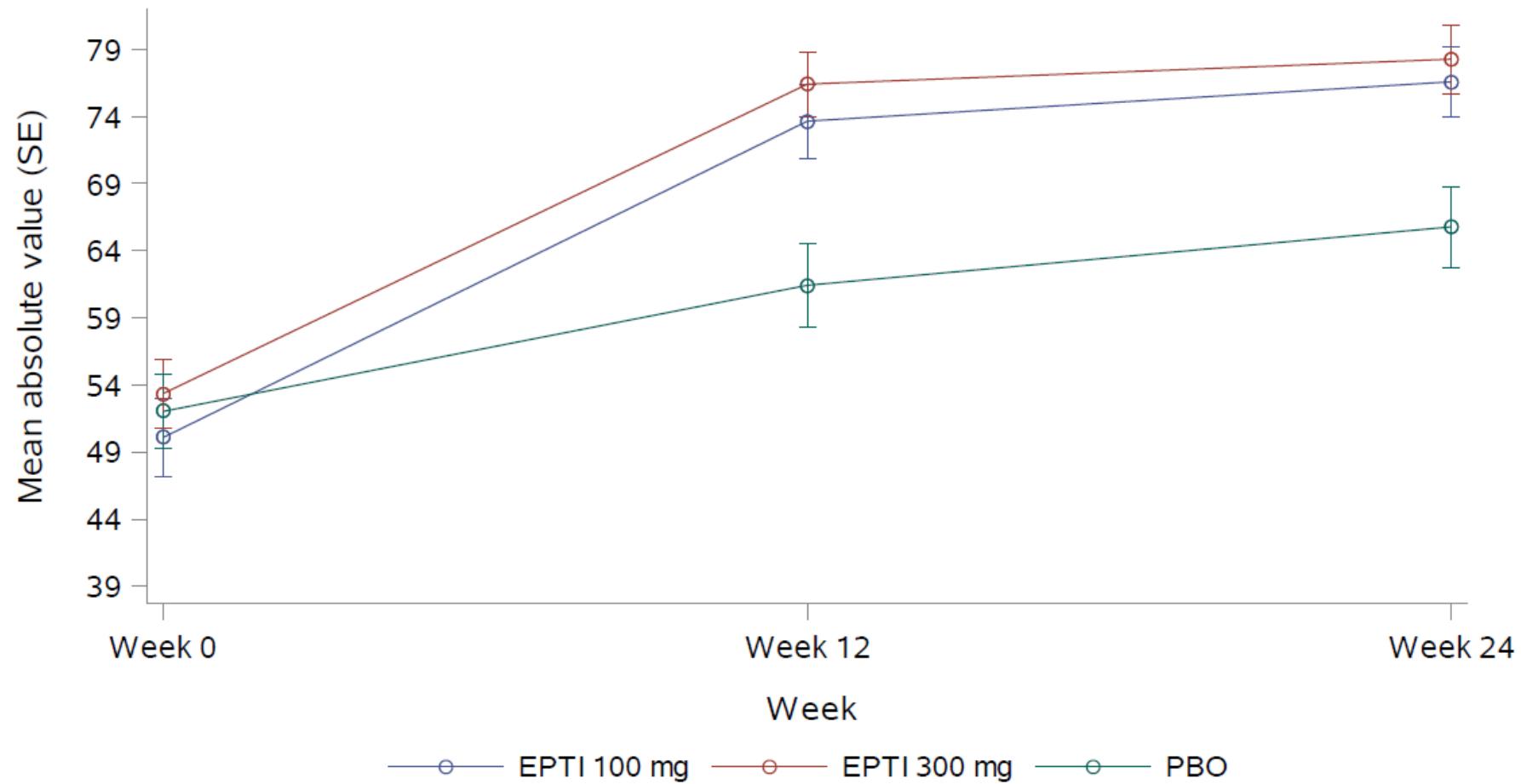
MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) : Age <= 35 years

Tabelle 4G-238: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	213 (100.0)	50.0 (22.1)							
	12	213 (100.0)	65.3 (21.3)	14.0 (1.96)						
	24	205 (96.2)	66.2 (22.3)	14.9 (1.97)						
EPTI 100 mg	Basln	205 (100.0)	50.2 (21.7)							
	12	205 (100.0)	76.2 (20.6)	25.0 (1.97)	10.9	1.87	[7.25;14.6]	<.0001	0.6	[0.38;0.76]
	24	198 (96.6)	79.6 (19.2)	28.3 (1.99)	13.4	1.88	[9.72;17.1]	<.0001	0.7	[0.51;0.91]
EPTI 300 mg	Basln	216 (100.0)	50.4 (22.0)							
	12	216 (100.0)	79.0 (20.9)	27.4 (1.89)	13.4	1.85	[9.73;17.0]	<.0001	0.7	[0.51;0.89]
	24	209 (96.8)	80.1 (20.2)	28.4 (1.91)	13.5	1.86	[9.83;17.2]	<.0001	0.7	[0.52;0.90]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

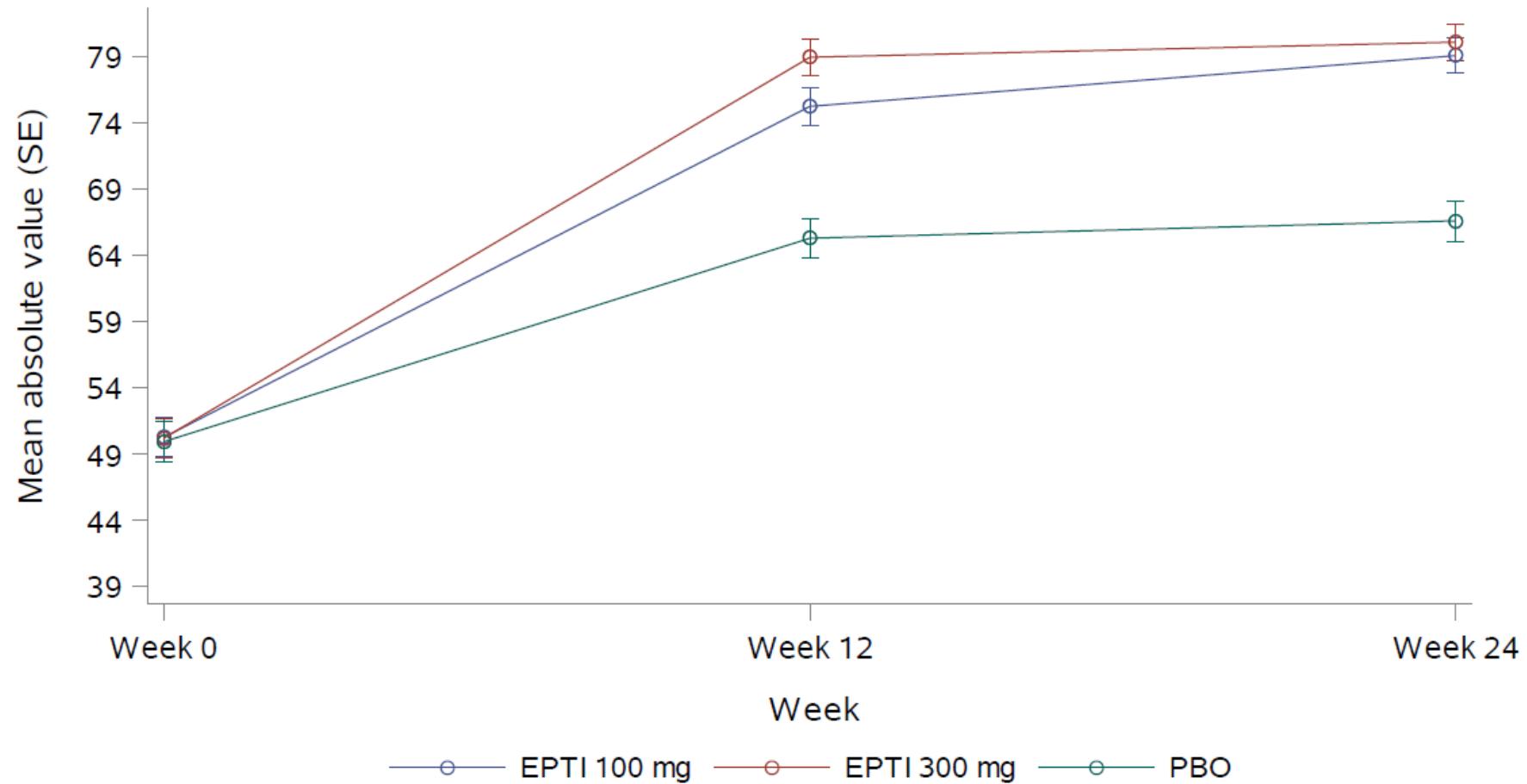
MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) : Age > 35 years

Tabelle 4G-239: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	28 (100.0)	57.1 (23.2)								
	12	28 (100.0)	63.0 (23.7)	8.02 (4.31)							
	24	28 (100.0)	64.1 (25.7)	9.20 (4.39)							
EPTI 100 mg	Basln	20 (100.0)	59.8 (16.1)								
	12	20 (100.0)	78.5 (20.5)	18.1 (4.67)	10.0	5.73	[-1.4;21.5]	0.0848	0.5	[-.07;1.10]	
	24	18 (90.0)	79.4 (16.3)	19.3 (4.99)	10.1	5.97	[-1.8;22.0]	0.0950	0.5	[-.09;1.11]	
EPTI 300 mg	Basln	31 (100.0)	50.2 (23.8)								
	12	31 (100.0)	72.6 (22.5)	22.1 (3.96)	14.0	4.83	[4.38;23.7]	0.0051	0.8	[0.24;1.28]	
	24	31 (100.0)	75.5 (20.5)	24.6 (4.04)	15.4	4.96	[5.46;25.3]	0.0029	0.8	[0.29;1.33]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

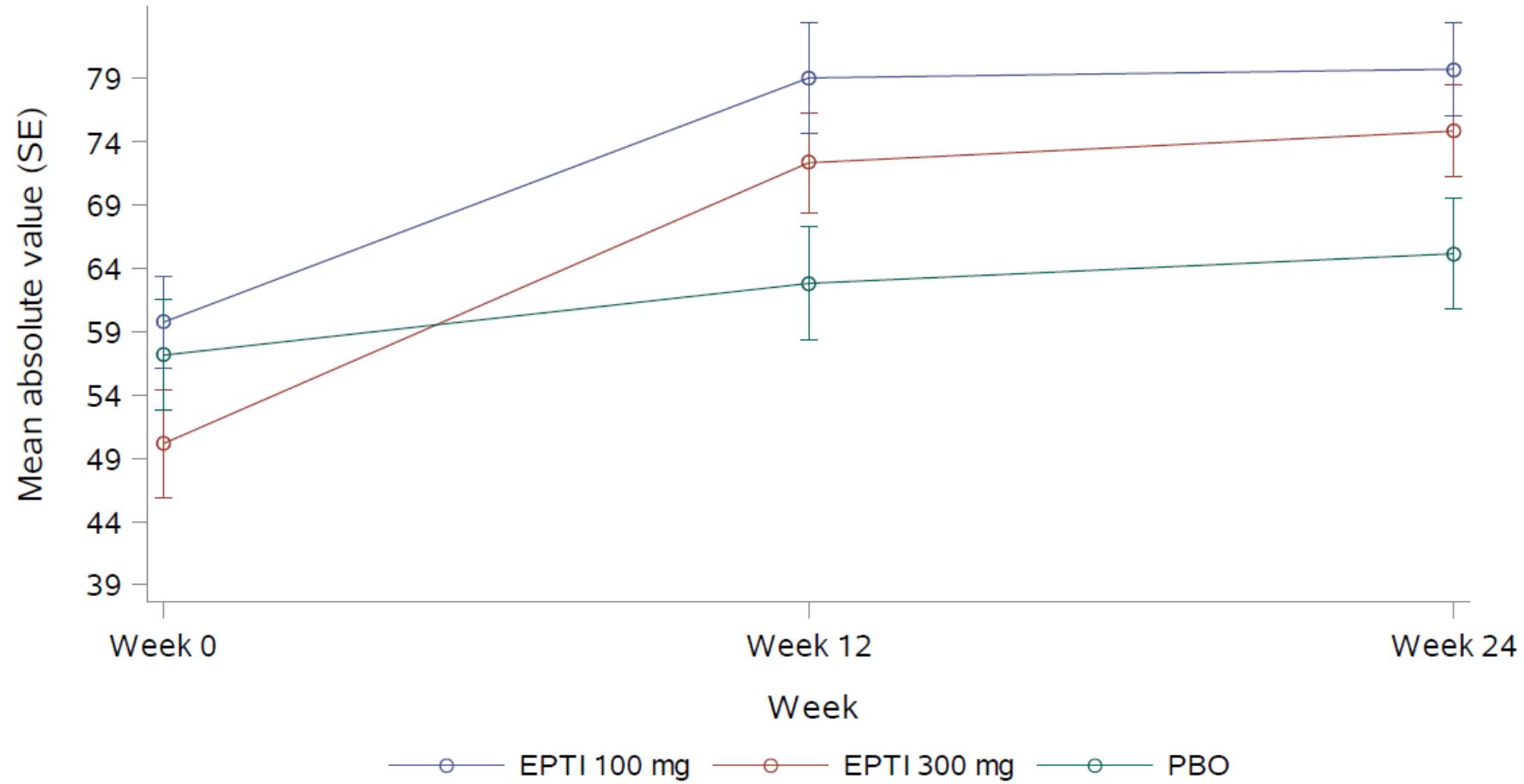
**MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) :
Males**

Tabelle 4G-240: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' SMD 95% CI		
					CFB			95% CI		
					Diff.	SE	CI	p-value	G	CI
PBO	Basln	249 (100.0)	49.7 (21.8)	11.7 (1.85)	11.0	1.75	[7.55;14.4]	<.0001	0.6	[0.39;0.75]
	12	249 (100.0)	64.6 (22.2)							
	24	240 (96.4)	66.4 (22.5)							
EPTI 100 mg	Basln	238 (100.0)	49.4 (21.8)	22.7 (1.86)	12.8	1.74	[9.33;16.2]	<.0001	0.7	[0.49;0.86]
	12	238 (100.0)	75.4 (20.6)							
	24	229 (96.2)	78.9 (19.4)							
EPTI 300 mg	Basln	246 (100.0)	51.2 (21.3)	25.8 (1.80)	14.1	1.74	[10.7;17.6]	<.0001	0.7	[0.56;0.91]
	12	245 (99.6)	79.2 (20.1)							
	24	237 (96.3)	80.4 (20.0)							

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

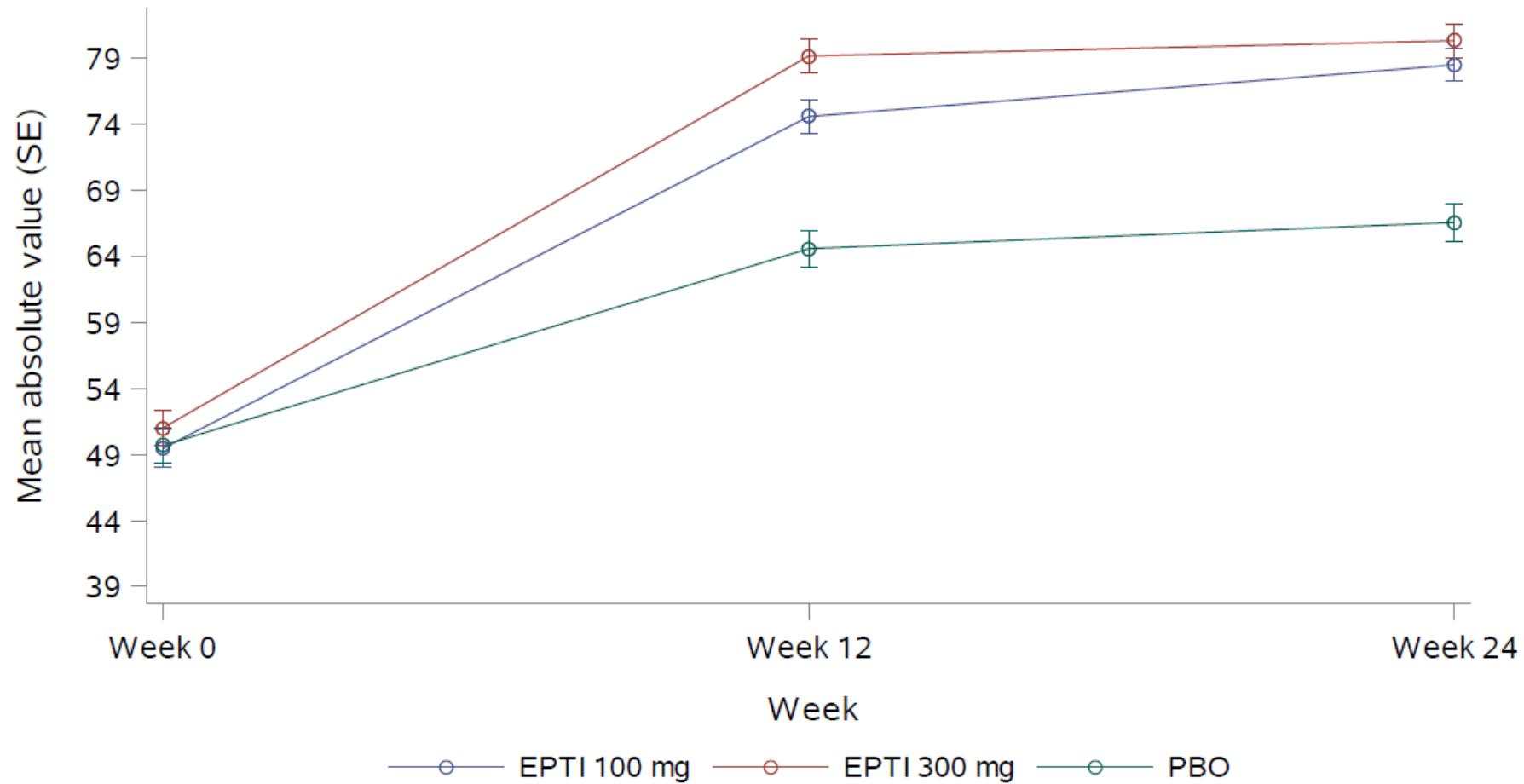
MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) : Females

Tabelle 4G-241: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		Hedges' G	
					Diff.	SE	CI	95% CI		SMD 95% CI	
								p-value	G	CI	
PBO	Basln	150 (100.0)	53.0 (23.9)								
	12	150 (100.0)	68.6 (22.8)	14.4 (2.35)							
	24	147 (98.0)	70.9 (23.2)	16.8 (2.37)							
EPTI 100 mg	Basln	144 (100.0)	51.3 (22.1)								
	12	144 (100.0)	77.0 (19.4)	23.7 (2.40)	9.2	2.22	[4.87;13.6]	<.0001	0.5	[0.26;0.71]	
	24	136 (94.4)	80.8 (19.1)	27.4 (2.44)	10.5	2.29	[6.02;15.0]	<.0001	0.5	[0.31;0.78]	
EPTI 300 mg	Basln	152 (100.0)	53.3 (22.1)								
	12	152 (100.0)	81.8 (19.7)	27.9 (2.28)	13.4	2.20	[9.10;17.7]	<.0001	0.7	[0.48;0.93]	
	24	148 (97.4)	82.6 (20.3)	28.6 (2.33)	11.8	2.25	[7.40;16.2]	<.0001	0.6	[0.38;0.84]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. EM : Episodic Migraine.

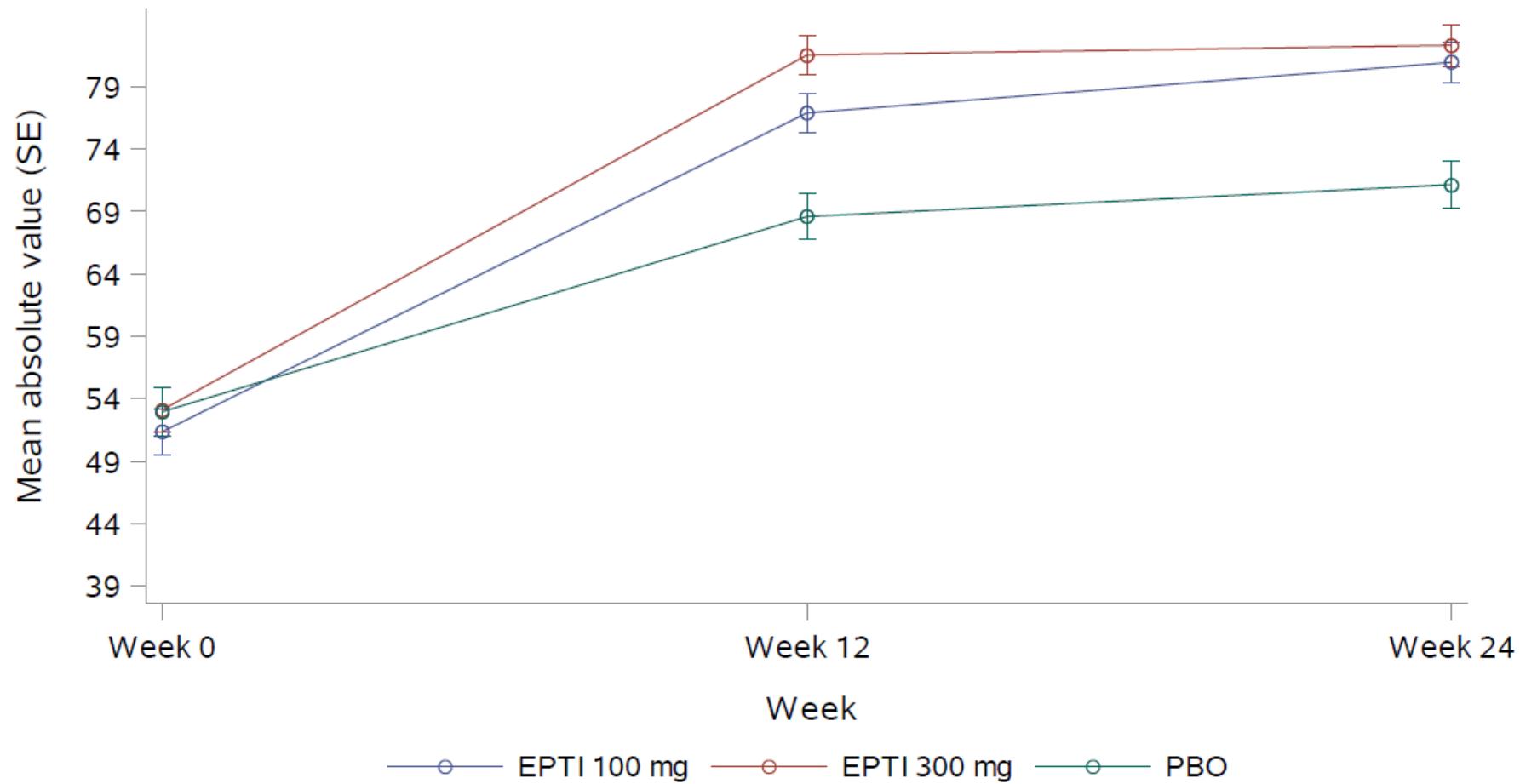
**MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) :
Episodic Migraine**

Tabelle 4G-242: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' SMD 95% CI	
					CFB			95% CI	
					Diff.	SE	CI	p-value	G
PBO	Basln	127 (100.0)	47.4 (19.2)	6.84 (3.23)	14.2	2.55	[9.24;19.3]	<.0001	0.7 [0.47;0.98]
	12	127 (100.0)	59.6 (20.9)						
	24	121 (95.3)	60.4 (21.0)						
EPTI 100 mg	Basln	114 (100.0)	48.8 (21.0)	21.1 (3.16)	16.4	2.39	[11.7;21.1]	<.0001	0.9 [0.64;1.16]
	12	114 (100.0)	73.9 (22.0)						
	24	111 (97.4)	76.7 (19.1)						
EPTI 300 mg	Basln	125 (100.0)	48.4 (20.6)	21.2 (3.22)	14.4	2.47	[9.52;19.2]	<.0001	0.7 [0.49;0.98]
	12	124 (99.2)	74.4 (20.7)						
	24	120 (96.0)	76.4 (19.4)						

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. CM : Chronic Migraine.

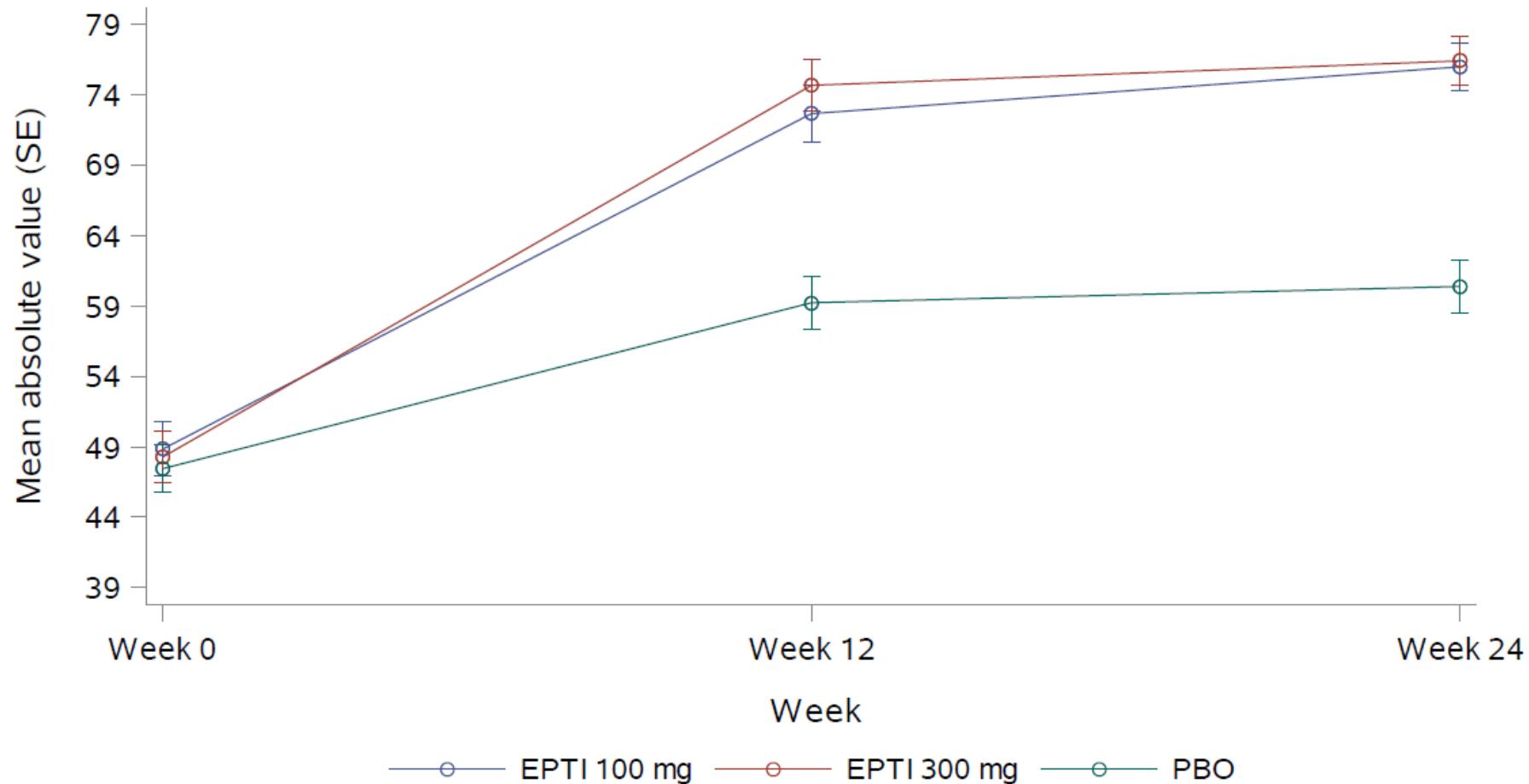
MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) : Chronic Migraine

Tabelle 4G-243: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	33 (100.0)	45.0 (19.6)								
	12	33 (100.0)	60.9 (23.7)	17.6 (4.83)							
	24	31 (93.9)	64.8 (20.1)	22.6 (4.72)							
EPTI 100 mg	Basln	32 (100.0)	49.8 (22.2)								
	12	32 (100.0)	69.4 (19.5)	22.2 (4.62)	4.6	5.20	[-5.7;15.0]	0.3784	0.2	[-.27;0.71]	
	24	32 (100.0)	73.1 (17.1)	27.7 (4.47)	5.1	5.00	[-4.9;15.0]	0.3141	0.3	[-.25;0.76]	
EPTI 300 mg	Basln	32 (100.0)	44.7 (23.1)								
	12	32 (100.0)	72.5 (26.0)	28.8 (4.70)	11.2	5.09	[1.08;21.3]	0.0305	0.5	[0.05;1.04]	
	24	32 (100.0)	73.3 (20.7)	30.3 (4.55)	7.7	4.88	[-2.0;17.4]	0.1190	0.4	[-10;0.90]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

**MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) :
Medication overuse headache at baseline**

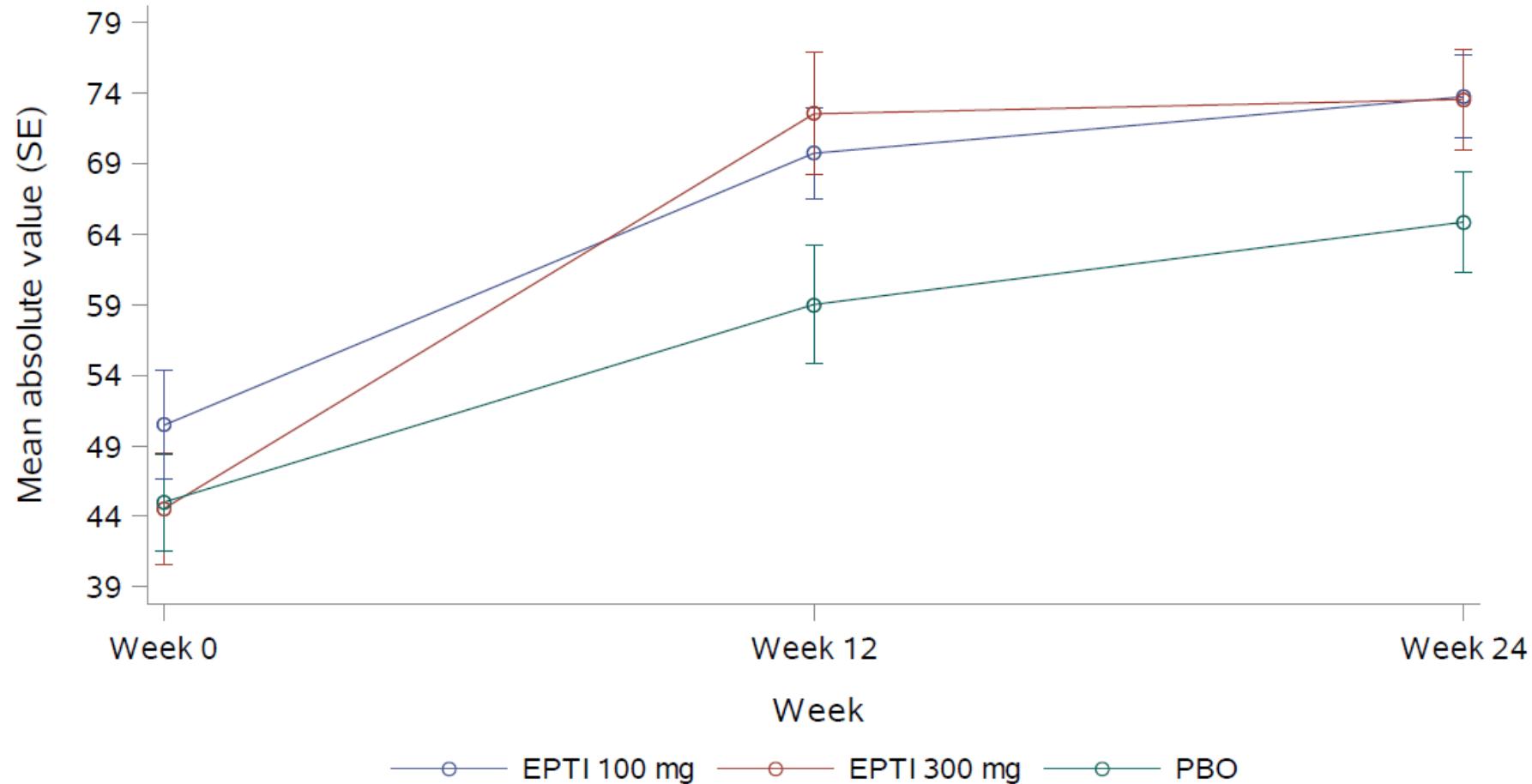


Tabelle 4G-244: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			Comparison to PBO		
					Diff.	SE	CI	95% CI		SMD 95% CI
								Hedges' G	CI	
PBO	Basln	244 (100.0)	51.2 (22.2)							
	12	244 (100.0)	65.0 (22.2)	11.2 (1.83)						
	24	237 (97.1)	66.3 (23.2)	12.5 (1.84)						
EPTI 100 mg	Basln	226 (100.0)	50.2 (21.6)							
	12	226 (100.0)	76.5 (20.6)	23.1 (1.85)	11.8	1.76	[8.38;15.3]	<.0001	0.6	[0.44;0.80]
	24	215 (95.1)	79.8 (19.3)	26.3 (1.88)	13.7	1.78	[10.2;17.2]	<.0001	0.7	[0.54;0.91]
EPTI 300 mg	Basln	245 (100.0)	51.9 (21.2)							
	12	244 (99.6)	79.2 (19.5)	25.0 (1.78)	13.7	1.72	[10.4;17.1]	<.0001	0.7	[0.54;0.90]
	24	236 (96.3)	80.7 (19.9)	26.3 (1.80)	13.8	1.74	[10.3;17.2]	<.0001	0.7	[0.55;0.91]

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

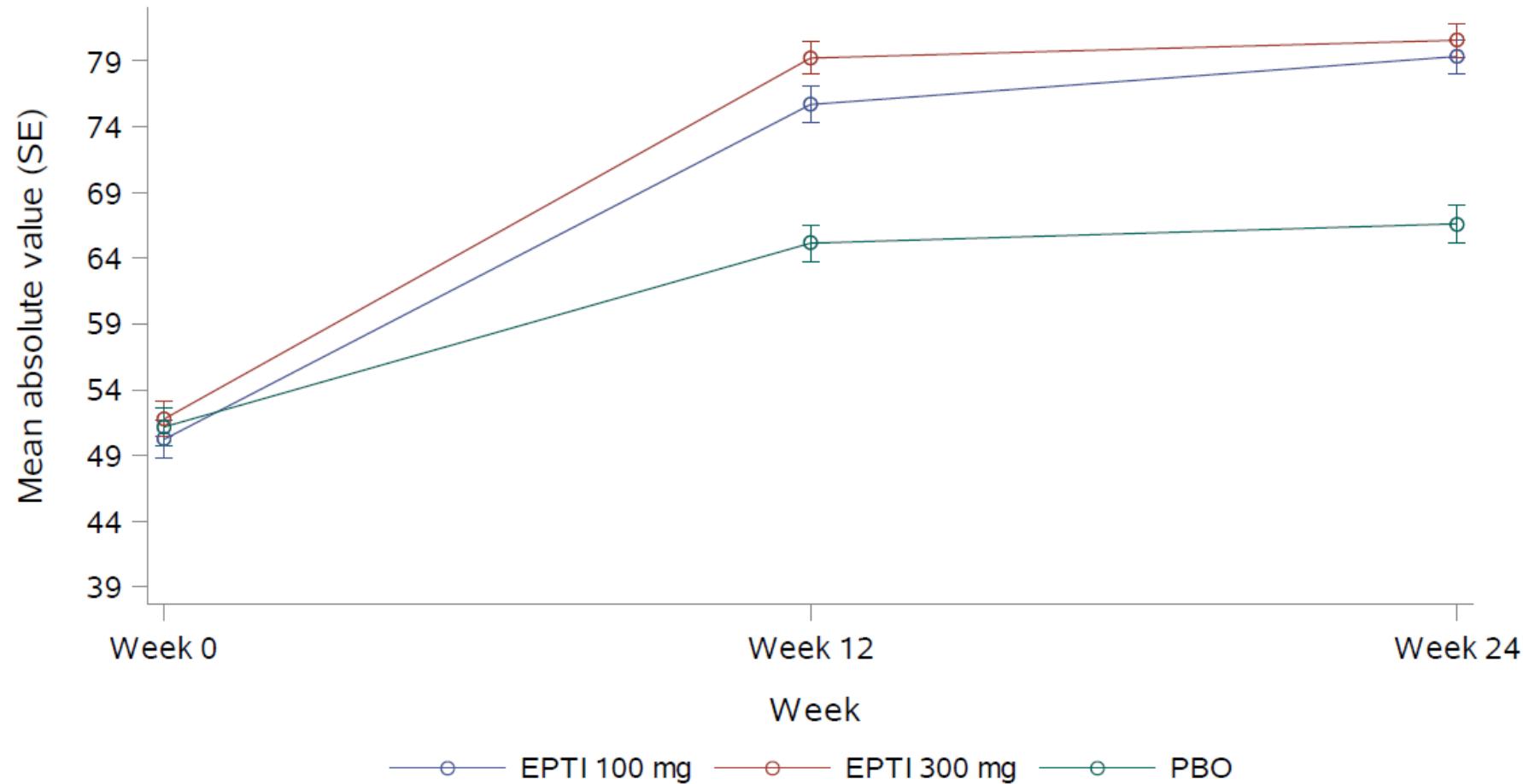
MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) No medication overuse headache at baseline

Tabelle 4G-245: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	195 (100.0)	51.2 (22.8)								
	12	195 (100.0)	66.5 (21.4)	12.1 (1.96)							
	24	190 (97.4)	67.4 (22.9)	12.7 (1.97)							
EPTI 100 mg	Basln	188 (100.0)	50.3 (21.7)								
	12	188 (100.0)	77.0 (20.0)	22.4 (1.98)	10.3	1.90	[6.57;14.0]	<.0001	0.6	[0.35;0.75]	
	24	178 (94.7)	79.9 (18.1)	25.1 (2.02)	12.4	1.93	[8.56;16.2]	<.0001	0.7	[0.46;0.87]	
EPTI 300 mg	Basln	211 (100.0)	51.4 (21.3)								
	12	210 (99.5)	79.0 (19.8)	24.1 (1.86)	12.0	1.85	[8.37;15.6]	<.0001	0.6	[0.45;0.84]	
	24	204 (96.7)	79.9 (20.2)	24.8 (1.87)	12.1	1.87	[8.42;15.8]	<.0001	0.7	[0.45;0.85]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

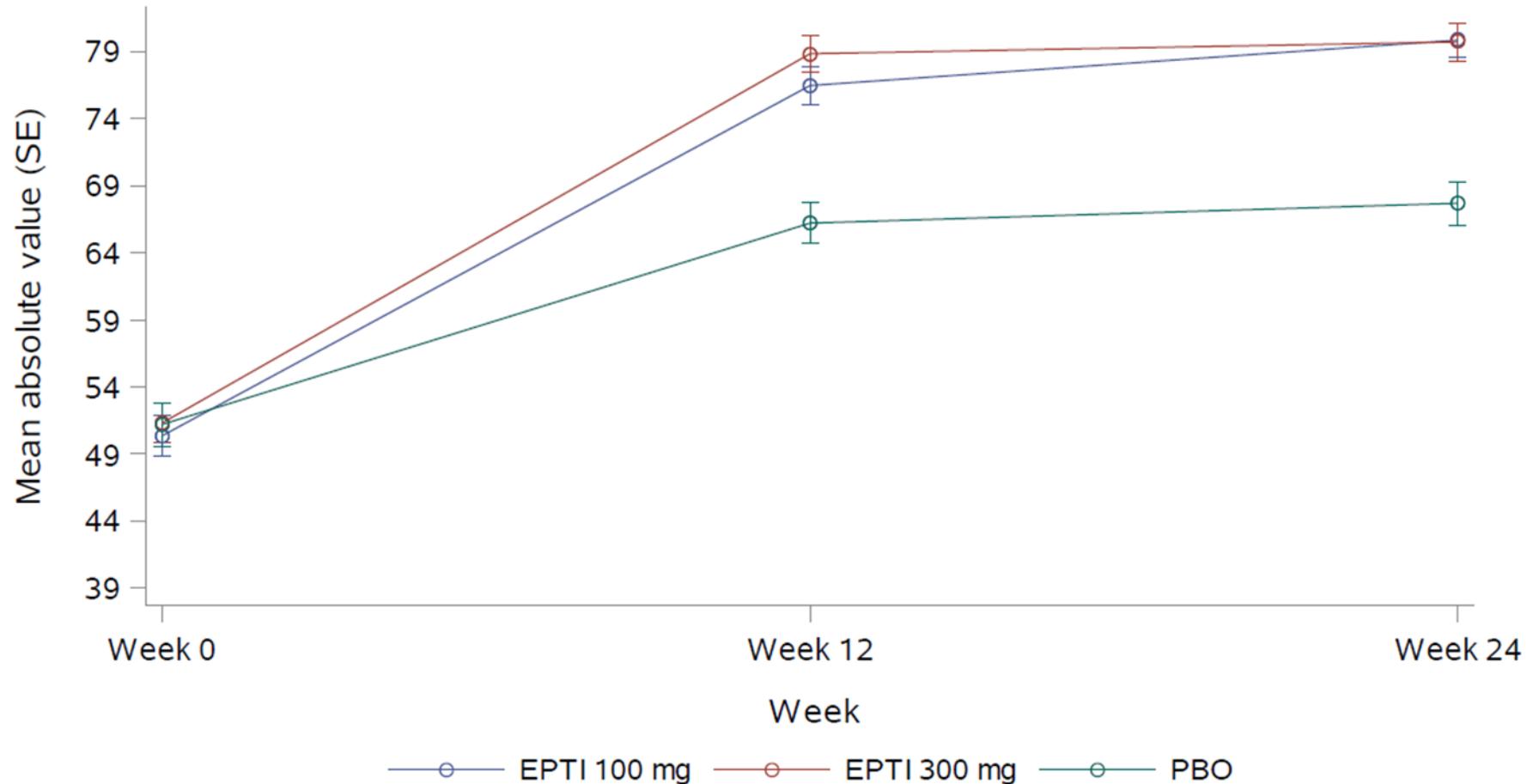
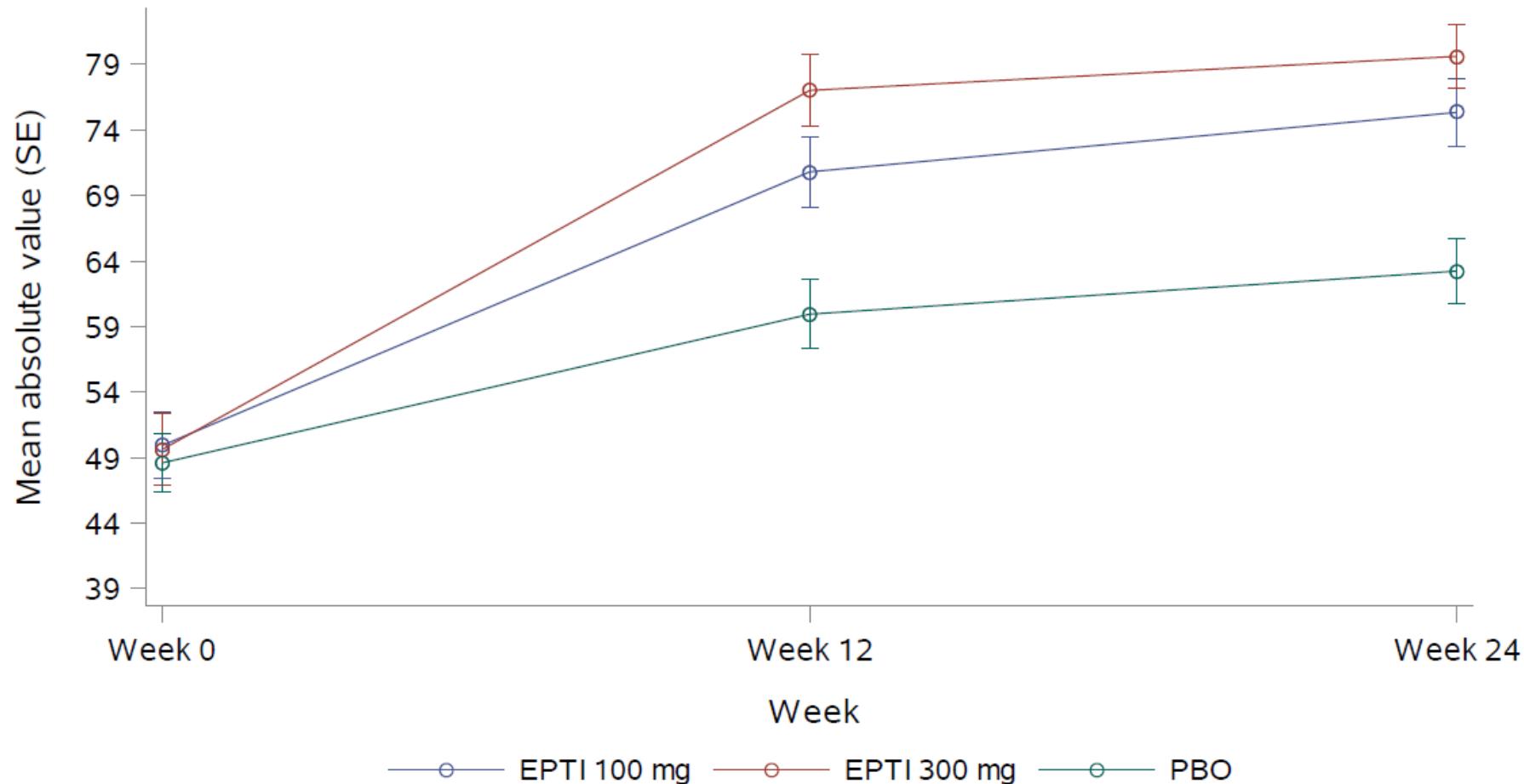
**MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) : = 2
Previous Failed Treatments**

Tabelle 4G-246: MSQ, Verhinderung der Rollenfunktion, CFB, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	82 (100.0)	48.6 (19.9)	10.4 (3.45)	12.4	3.39	[5.71;19.1]	<.0001	0.6	[0.27;0.92]	
	12	82 (100.0)	59.6 (24.0)								
	24	78 (95.1)	63.0 (22.4)								
EPTI 100 mg	Basln	70 (100.0)	50.0 (21.6)	22.8 (3.47)	13.2	3.28	[6.78;19.7]	<.0001	0.7	[0.34;0.99]	
	12	70 (100.0)	71.9 (21.9)								
	24	69 (98.6)	76.4 (21.5)								
EPTI 300 mg	Basln	66 (100.0)	49.8 (22.3)	27.2 (3.53)	16.8	3.44	[10.0;23.6]	<.0001	0.8	[0.48;1.13]	
	12	66 (100.0)	76.7 (22.5)								
	24	64 (97.0)	79.6 (20.0)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

MSQ role function preventive. Absolute Value: Mean (SE) by Visit (AMNOG) : > 2 Previous Failed Treatments

4.2.15.2 Verbesserung um ≥ 15 Punkte

Tabelle 4G-247: MSQ, Verhinderung der Rollenfunktion, Responder, Interaktions-p-Werte

Visit	Description	Treatment Group	
		EPTI 100 mg p-value	EPTI 300 mg p-value
Week 12	Interaction test: Age Group	0.4276	0.6414
	Interaction test: EM/CM	0.1396	0.6880
	Interaction test: MOH	0.2839	0.0964
	Interaction test: Number of FPT	0.6768	0.7156
	Interaction test: Sex	0.7659	0.3905
Week 24	Interaction test: Age Group	0.1715	0.7212
	Interaction test: EM/CM	0.0517	0.2123
	Interaction test: MOH	0.6598	0.2700
	Interaction test: Number of FPT	0.0898	0.5381
	Interaction test: Sex	0.3706	0.5720

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-248: MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference			p-value
		N	n (%)	OR	CL	RR	CL	RD	CL	RD	
PBO	12	64	26 (40.6)								
	24	64	27 (42.2)								
EPTI 100 mg	12	53	37 (69.8)	3.65	[1.61;8.62]	1.73	[1.22;2.45]	29.2	[11.9;46.4]	0.0018	
	24	53	32 (60.4)	2.02	[0.93;4.47]	1.43	[1.00;2.05]	18.2	[0.31;36.1]	0.0771	

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 300 mg	12	61	40	(65.6)	3.40	[1.56;7.70]	1.61	[1.13;2.29]	24.9	[8.01;41.9]	0.0019
	24	61	41	(67.2)	3.17	[1.48;6.99]	1.58	[1.13;2.20]	25.0	[8.14;41.9]	0.0027

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B.

Tabelle 4G-249: MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe > 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	213	109	(51.2)							
	24	213	95	(44.6)							
EPTI 100 mg	12	205	143	(69.8)	2.63	[1.69;4.12]	1.36	[1.16;1.60]	18.6	[9.38;27.8]	<.0001
	24	205	148	(72.2)	4.14	[2.64;6.57]	1.62	[1.36;1.92]	27.6	[18.5;36.7]	<.0001
EPTI 300 mg	12	215	153	(71.2)	2.89	[1.86;4.53]	1.39	[1.19;1.63]	20.0	[10.9;29.0]	<.0001
	24	215	155	(72.1)	4.18	[2.68;6.61]	1.62	[1.36;1.92]	27.5	[18.5;36.5]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B.

Tabelle 4G-250: MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe männlich

		Responders			Odds Ratio		Relative Risk		Risk Difference				
Treatment		Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	28	12	(42.9)									
	24	28	8	(28.6)									
EPTI 100 mg	12	20	12	(60.0)	2.10	[0.61;7.57]	1.35	[0.77;2.38]	17.1	[-11;45.4]	0.2407		
	24	20	13	(65.0)	5.38	[1.45;22.5]	2.14	[1.13;4.06]	36.4	[9.65;63.2]	0.0114		
EPTI 300 mg	12	31	19	(61.3)	1.91	[0.63;5.94]	1.45	[0.87;2.42]	18.4	[-6.7;43.5]	0.2537		
	24	31	21	(67.7)	5.78	[1.78;20.9]	2.51	[1.35;4.68]	39.2	[15.7;62.6]	0.0031		

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B.

Tabelle 4G-251 MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe weiblich

		Responders			Odds Ratio		Relative Risk		Risk Difference				
Treatment		Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	249	123	(49.4)									
	24	249	114	(45.8)									
EPTI 100 mg	12	238	168	(70.6)	2.93	[1.94;4.46]	1.43	[1.23;1.66]	21.2	[12.7;29.7]	<.0001		
	24	238	167	(70.2)	3.31	[2.21;5.02]	1.53	[1.31;1.79]	24.4	[15.9;32.9]	<.0001		
EPTI 300 mg	12	245	174	(71.0)	3.27	[2.17;4.97]	1.44	[1.24;1.67]	21.6	[13.2;30.0]	<.0001		
	24	245	175	(71.4)	3.84	[2.55;5.83]	1.56	[1.33;1.82]	25.6	[17.3;34.0]	<.0001		

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B.

Tabelle 4G-252: MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe EM

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	150	79 (52.7)							
	24	150	75 (50.0)							
EPTI 100 mg	12	144	100 (69.4)	2.21	[1.30;3.82]	1.32	[1.09;1.59]	16.8	[5.80;27.8]	0.0035
	24	144	100 (69.4)	2.47	[1.47;4.22]	1.39	[1.14;1.68]	19.4	[8.46;30.4]	0.0007
EPTI 300 mg	12	151	109 (72.2)	2.88	[1.69;5.00]	1.37	[1.14;1.64]	19.5	[8.80;30.2]	<.0001
	24	151	109 (72.2)	3.16	[1.87;5.42]	1.44	[1.20;1.74]	22.2	[11.5;32.9]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment as factor. CL for RR and RD are based on binomial distribution. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-253: MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe CM

		Responders			Odds Ratio		Relative Risk		Risk Difference		
Treatment Group		Weeks	N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	127	56 (44.1)							
		24	127	47 (37.0)							
EPTI 100 mg		12	114	80 (70.2)	3.73	[2.11;6.74]	1.59	[1.27;2.00]	26.1	[14.0;38.1]	<.0001
		24	114	80 (70.2)	5.21	[2.92;9.54]	1.90	[1.47;2.45]	33.2	[21.3;45.0]	<.0001
EPTI 300 mg		12	125	84 (67.2)	3.15	[1.82;5.55]	1.52	[1.21;1.92]	23.1	[11.2;35.0]	<.0001
		24	125	87 (69.6)	4.99	[2.84;8.98]	1.88	[1.46;2.43]	32.6	[21.0;44.2]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment as factor. CL for RR and RD are based on binomial distribution. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B. CM : Chronic Migraine.

Tabelle 4G-254: MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe MOH: ja

		Responders			Odds Ratio		Relative Risk		Risk Difference		
Treatment Group		Weeks	N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	33	19 (57.6)							
		24	33	16 (48.5)							
EPTI 100 mg		12	32	20 (62.5)	1.62	[0.55;4.91]	1.12	[0.75;1.67]	4.92	[-19;28.7]	0.3812
		24	32	21 (65.6)	3.14	[1.03;10.3]	1.38	[0.90;2.12]	17.1	[-6.6;40.8]	0.0433
EPTI 300 mg		12	32	20 (62.5)	1.29	[0.44;3.82]	1.10	[0.74;1.64]	4.92	[-19;28.7]	0.6443
		24	32	21 (65.6)	2.37	[0.79;7.49]	1.37	[0.89;2.10]	17.1	[-6.6;40.8]	0.1226

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

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Tabelle 4G-255 MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe MOH: nein

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	244	116	(47.5)							
	24	244	106	(43.4)							
EPTI 100 mg	12	226	160	(70.8)	3.12	[2.05;4.79]	1.49	[1.27;1.74]	23.3	[14.6;31.9]	<.0001
	24	226	159	(70.4)	3.59	[2.38;5.49]	1.62	[1.37;1.91]	26.9	[18.3;35.5]	<.0001
EPTI 300 mg	12	244	173	(70.9)	3.44	[2.27;5.25]	1.49	[1.28;1.74]	23.4	[14.9;31.8]	<.0001
	24	244	175	(71.7)	4.21	[2.79;6.42]	1.65	[1.40;1.94]	28.3	[19.9;36.7]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-256: MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe 2 Vortherapien

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	195	95	(48.7)							
		24	195	83	(42.6)							
EPTI 100 mg		12	188	134	(71.3)	3.07	[1.92;4.97]	1.46	[1.23;1.73]	22.6	[13.0;32.1]	<.0001
		24	188	137	(72.9)	4.33	[2.71;7.00]	1.71	[1.42;2.05]	30.3	[20.9;39.7]	<.0001
EPTI 300 mg		12	210	146	(69.5)	2.98	[1.89;4.75]	1.43	[1.20;1.69]	20.8	[11.4;30.2]	<.0001
		24	210	150	(71.4)	4.23	[2.70;6.73]	1.68	[1.40;2.02]	28.9	[19.6;38.1]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-257: MSQ, Verhinderung der Rollenfunktion, Responder, Subgruppe > 2 Vortherapien

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	82	40	(48.8)							
		24	82	39	(47.6)							
EPTI 100 mg		12	70	46	(65.7)	2.29	[1.15;4.67]	1.34	[1.01;1.78]	16.9	[1.42;32.4]	0.0186
		24	70	43	(61.4)	2.06	[1.03;4.23]	1.29	[0.96;1.74]	13.9	[-1.8;29.6]	0.0418
EPTI 300 mg		12	66	47	(71.2)	3.07	[1.50;6.51]	1.46	[1.12;1.91]	22.4	[7.06;37.8]	0.0021
		24	66	46	(69.7)	3.19	[1.54;6.86]	1.46	[1.11;1.93]	22.1	[6.65;37.6]	0.0017

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		p-value
		N	n (%)	OR	CL	RR	CL	RD	CL	

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ role function preventive score.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.16 MSQ (Migraine Specific Quality of Life Questionnaire), Emotionale Funktion

4.2.16.1 Veränderung gegenüber dem Baseline-Wert

Tabelle 4G-258: MSQ, Emotionale Funktion, CFB, Interaktions p-Werte Woche 1 – 12

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.9026	0.4391
Interaction test: EM/CM	0.2946	0.3851
Interaction test: MOH	0.7799	0.8594
Interaction test: Number of FPT	0.9894	0.4350
Interaction test: Sex	0.8352	0.7324

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-259: MSQ, Emotionale Funktion, CFB, Interaktions p-Werte Woche 13 – 24

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
	p-value	p-value
Interaction test: Age Group	0.9849	0.5031
Interaction test: EM/CM	0.6295	0.1359
Interaction test: MOH	0.8157	0.6051
Interaction test: Number of FPT	0.9739	0.2586
Interaction test: Sex	0.6447	0.9093

The assumption of equal treatment effect across subgroups is tested by adding the three-way interaction term subgroup-by-treatment-by-week to the model.

The test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model is performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-260: MSQ, Emotionale Funktion, CFB, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO				Hedges' G CI	
					Diff.	SE	CI	p-value	95% CI	
									SMD	95% CI
PBO	Basln	64 (100.0)	42.1 (28.8)	4.09 (4.10)	11.0	4.44	[2.23;19.8]	0.0143	0.5	[0.09;0.83]
	12	64 (100.0)	55.7 (31.9)							
	24	63 (98.4)	55.4 (31.4)							
EPTI 100 mg	Basln	53 (100.0)	49.8 (20.3)	15.1 (4.19)	15.9	4.73	[6.56;25.2]	0.0010	0.6	[0.26;1.02]
	12	53 (100.0)	69.9 (24.3)							
	24	49 (92.5)	72.9 (22.7)							
EPTI 300 mg	Basln	61 (100.0)	52.7 (24.2)	17.2 (4.23)	13.1	4.38	[4.42;21.7]	0.0033	0.5	[0.18;0.89]
	12	60 (98.4)	73.0 (22.8)							

Treatment Group	Weeks	N (%)	Mean (SD)	(SE)	Comparison to PBO			Hedges' G	SMD 95% CI		
					CFB						
					LSmeans	Diff.	SE				
	24	59 (96.7)	75.8 (25.5)	20.7 (4.34)		18.1	4.61	[9.04;27.3]	0.0001	0.7 [0.36;1.07]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

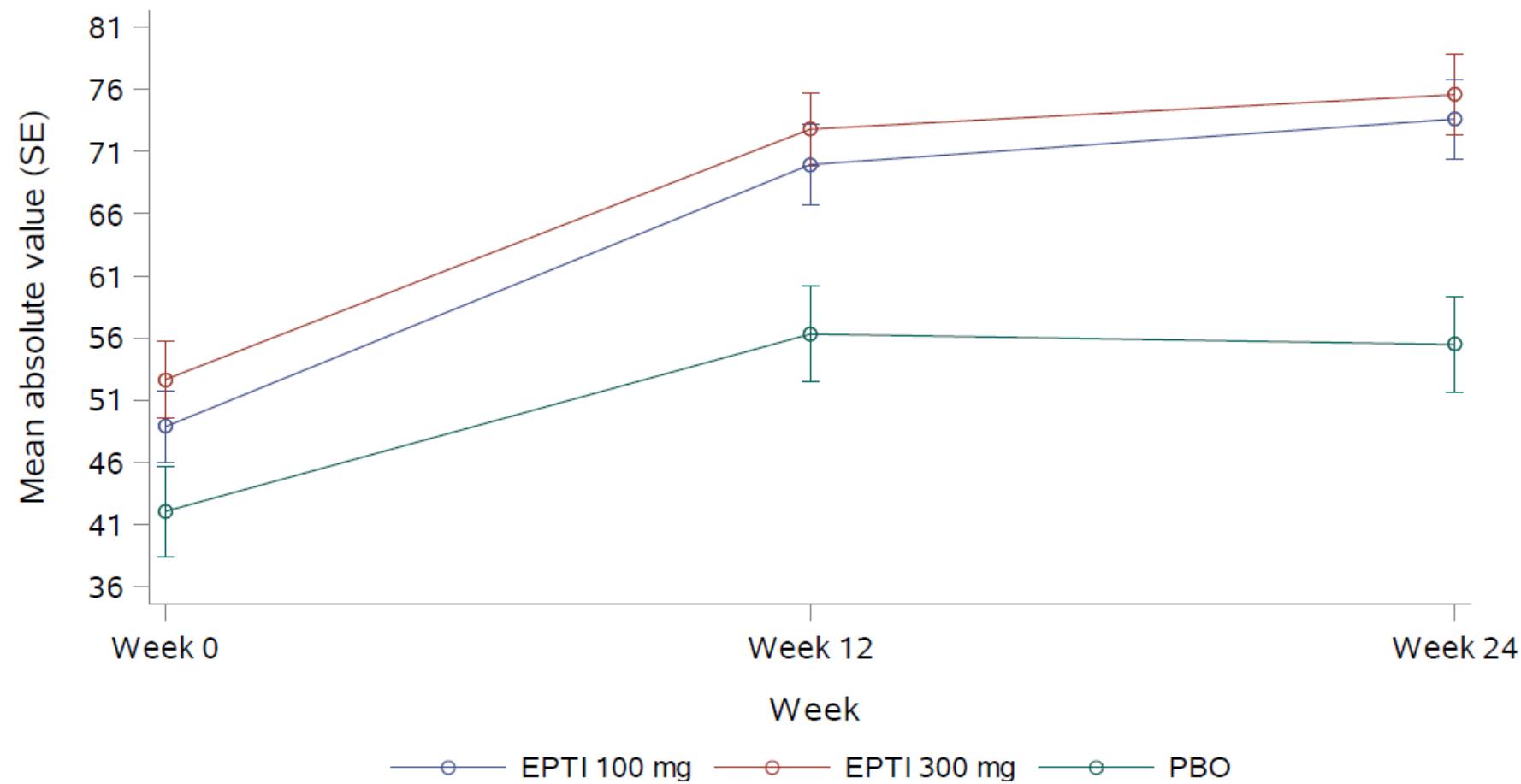
MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) : Age <= 35 years

Tabelle 4G-261: MSQ, Emotionale Funktion, CFB, Subgruppe > 35 Jahre

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	213 (100.0)	50.5 (25.8)								
	12	213 (100.0)	64.3 (24.4)	12.4 (2.14)							
	24	205 (96.2)	66.0 (25.1)	13.8 (2.13)							
EPTI 100 mg	Basln	205 (100.0)	50.2 (25.5)								
	12	205 (100.0)	75.3 (24.6)	23.7 (2.14)	11.3	2.06	[7.25;15.3]	<.0001	0.5	[0.34;0.73]	
	24	198 (96.6)	79.7 (21.1)	27.3 (2.15)	13.5	2.03	[9.49;17.5]	<.0001	0.7	[0.47;0.86]	
EPTI 300 mg	Basln	216 (100.0)	47.4 (23.6)								
	12	216 (100.0)	76.9 (22.3)	26.4 (2.07)	14.0	2.04	[10.0;18.0]	<.0001	0.7	[0.47;0.85]	
	24	209 (96.8)	78.1 (22.2)	27.1 (2.06)	13.2	2.01	[9.27;17.2]	<.0001	0.6	[0.45;0.84]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

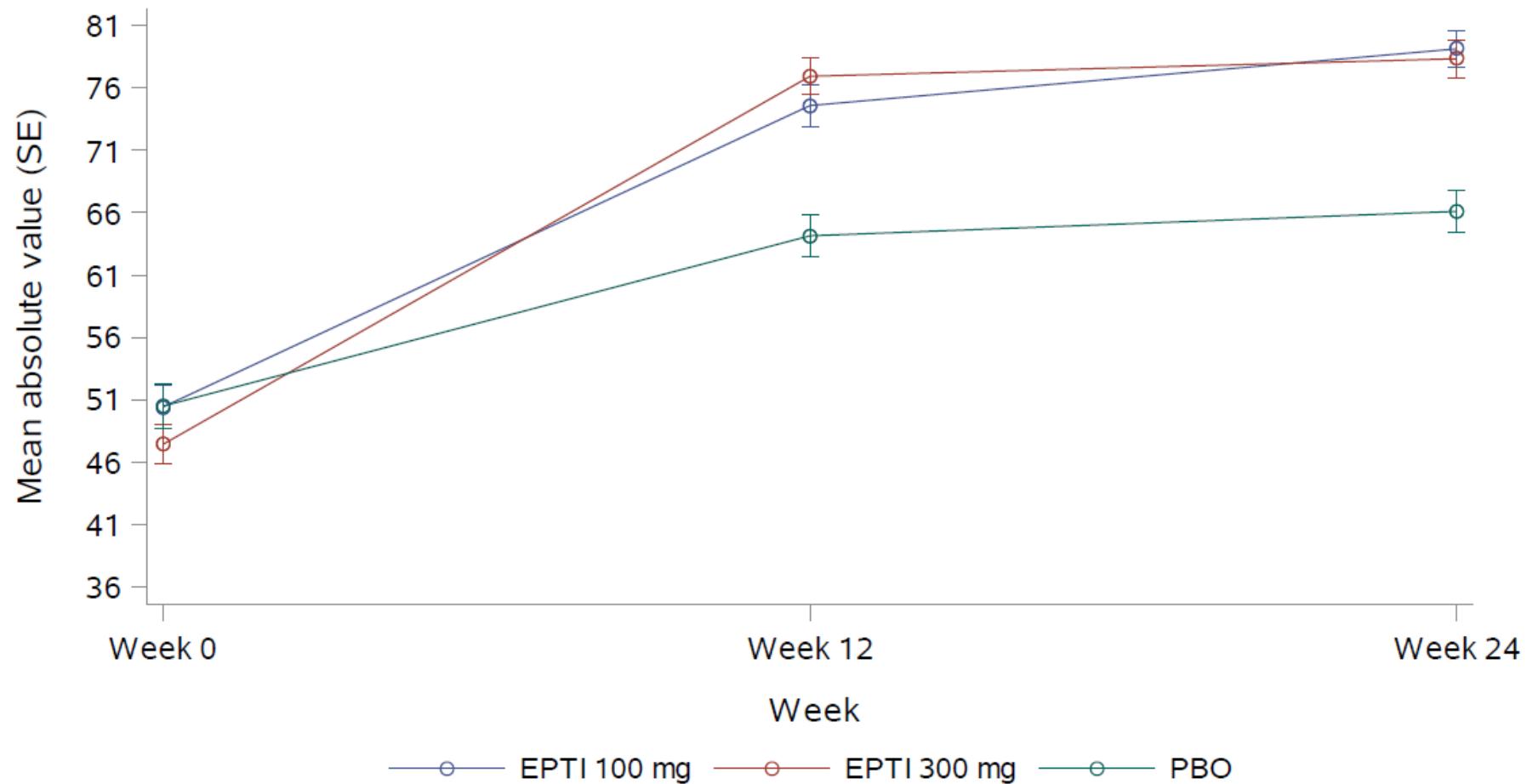
MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) : Age > 35 years

Tabelle 4G-262: MSQ, Emotionale Funktion, CFB, Subgruppe männlich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	28 (100.0)	54.0 (29.9)		7.09 (4.98)	6.58	[-5.0;21.3]	0.2208	0.4	[-.22;0.95]	
	12	28 (100.0)	61.0 (27.9)								
	24	28 (100.0)	60.0 (29.3)								
EPTI 100 mg	Basln	20 (100.0)	59.7 (19.9)		15.2 (5.35)	8.1	[-4.6;25.2]	0.1714	0.4	[-.19;1.02]	
	12	20 (100.0)	77.3 (26.1)								
	24	18 (90.0)	77.8 (21.3)								
EPTI 300 mg	Basln	31 (100.0)	51.6 (24.6)		19.4 (4.60)	12.3	[1.37;23.3]	0.0281	0.6	[0.06;1.11]	
	12	31 (100.0)	72.3 (24.5)								
	24	31 (100.0)	75.3 (25.4)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

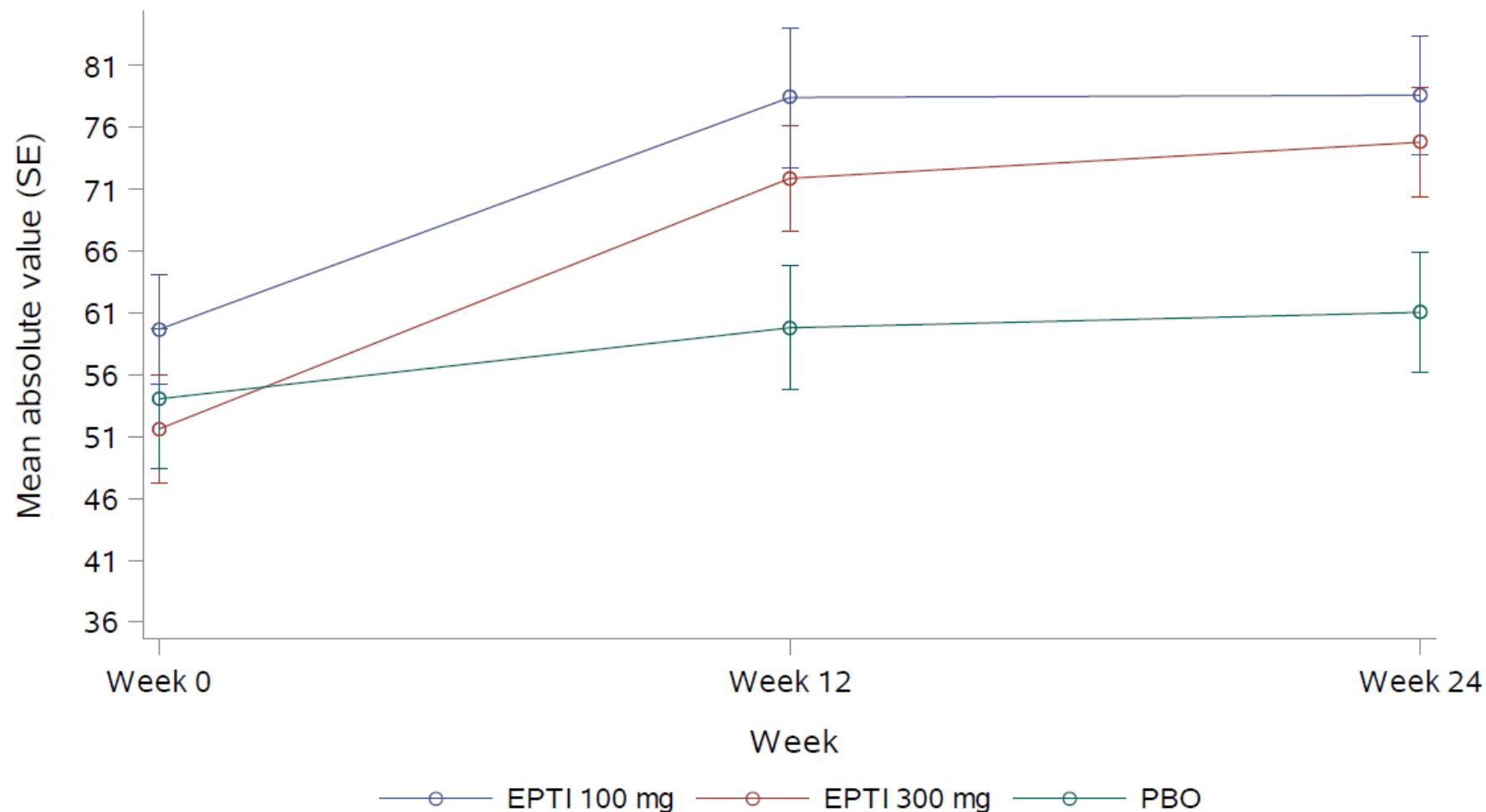
MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) : Males

Tabelle 4G-263: MSQ, Emotionale Funktion, CFB, Subgruppe weiblich

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	249 (100.0)	48.0 (26.3)		10.1 (2.08)	1.96	[7.22;14.9]	<.0001	0.5	[0.33;0.69]	
	12	249 (100.0)	62.5 (26.4)								
	24	240 (96.4)	64.0 (26.8)								
EPTI 100 mg	Basln	238 (100.0)	49.3 (24.7)		21.2 (2.10)	1.96	[7.22;14.9]	<.0001	0.5	[0.33;0.69]	
	12	238 (100.0)	73.9 (24.5)								
	24	229 (96.2)	78.4 (21.6)								
EPTI 300 mg	Basln	246 (100.0)	48.2 (23.7)		24.5 (2.02)	1.95	[10.5;18.1]	<.0001	0.7	[0.48;0.84]	
	12	245 (99.6)	76.6 (22.1)								
	24	237 (96.3)	77.9 (22.6)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B.

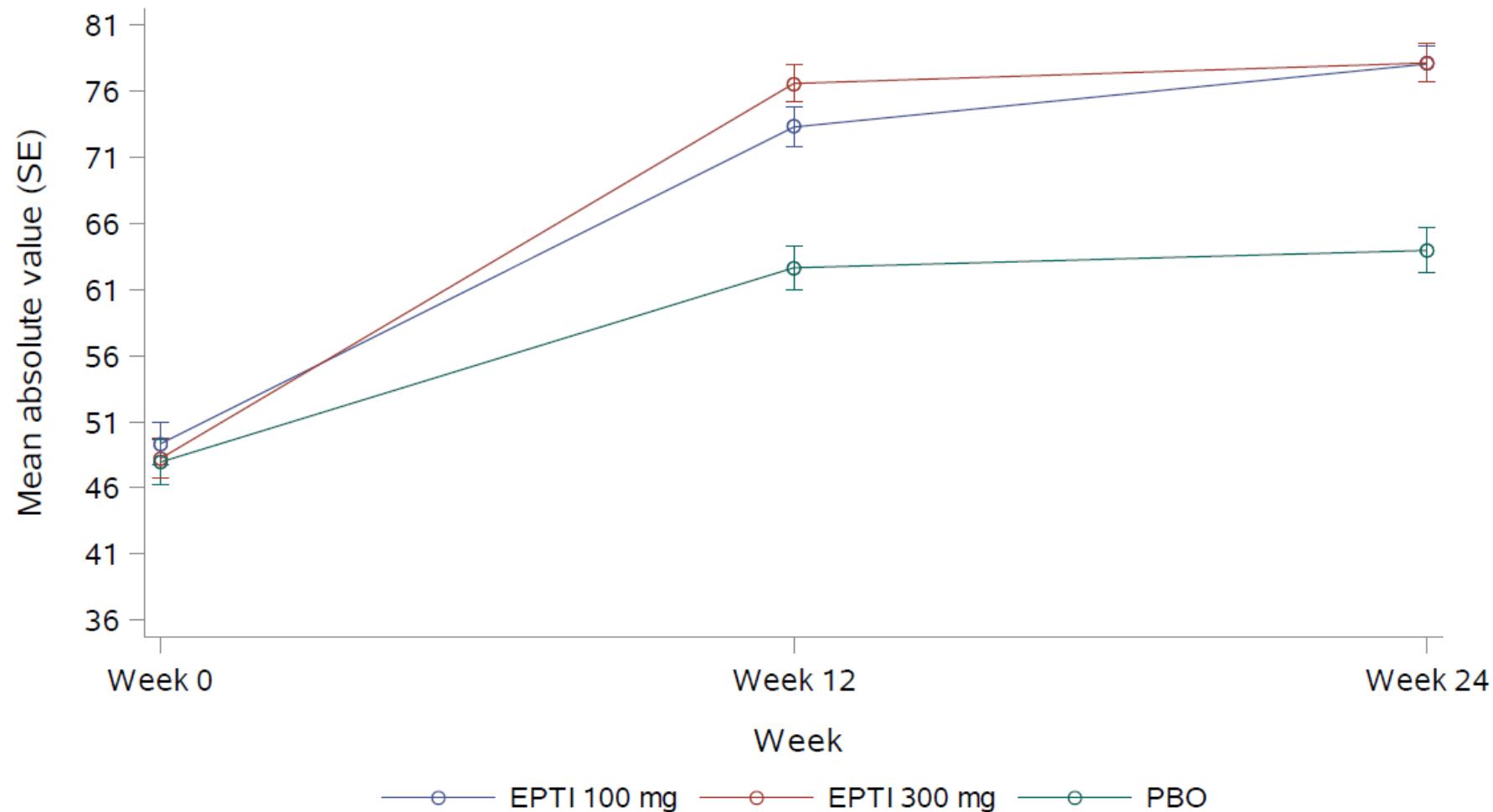
MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) : Females

Tabelle 4G-264: MSQ, Emotionale Funktion, CFB, Subgruppe EM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	150 (100.0)	53.1 (26.5)								
	12	150 (100.0)	67.8 (24.4)	12.0 (2.52)							
	24	147 (98.0)	69.6 (25.3)	13.9 (2.51)							
EPTI 100 mg	Basln	144 (100.0)	54.1 (24.1)								
	12	144 (100.0)	76.8 (23.3)	20.8 (2.58)	8.8	2.41	[4.04;13.5]	0.0003	0.4	[0.20;0.65]	
	24	136 (94.4)	83.3 (18.2)	27.2 (2.58)	13.3	2.41	[8.57;18.1]	<.0001	0.7	[0.42;0.89]	
EPTI 300 mg	Basln	152 (100.0)	52.7 (24.3)								
	12	152 (100.0)	79.3 (22.0)	24.1 (2.44)	12.1	2.39	[7.44;16.8]	<.0001	0.6	[0.36;0.81]	
	24	148 (97.4)	81.0 (21.9)	25.7 (2.46)	11.8	2.37	[7.11;16.4]	<.0001	0.6	[0.35;0.81]	

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. EM : Episodic Migraine.

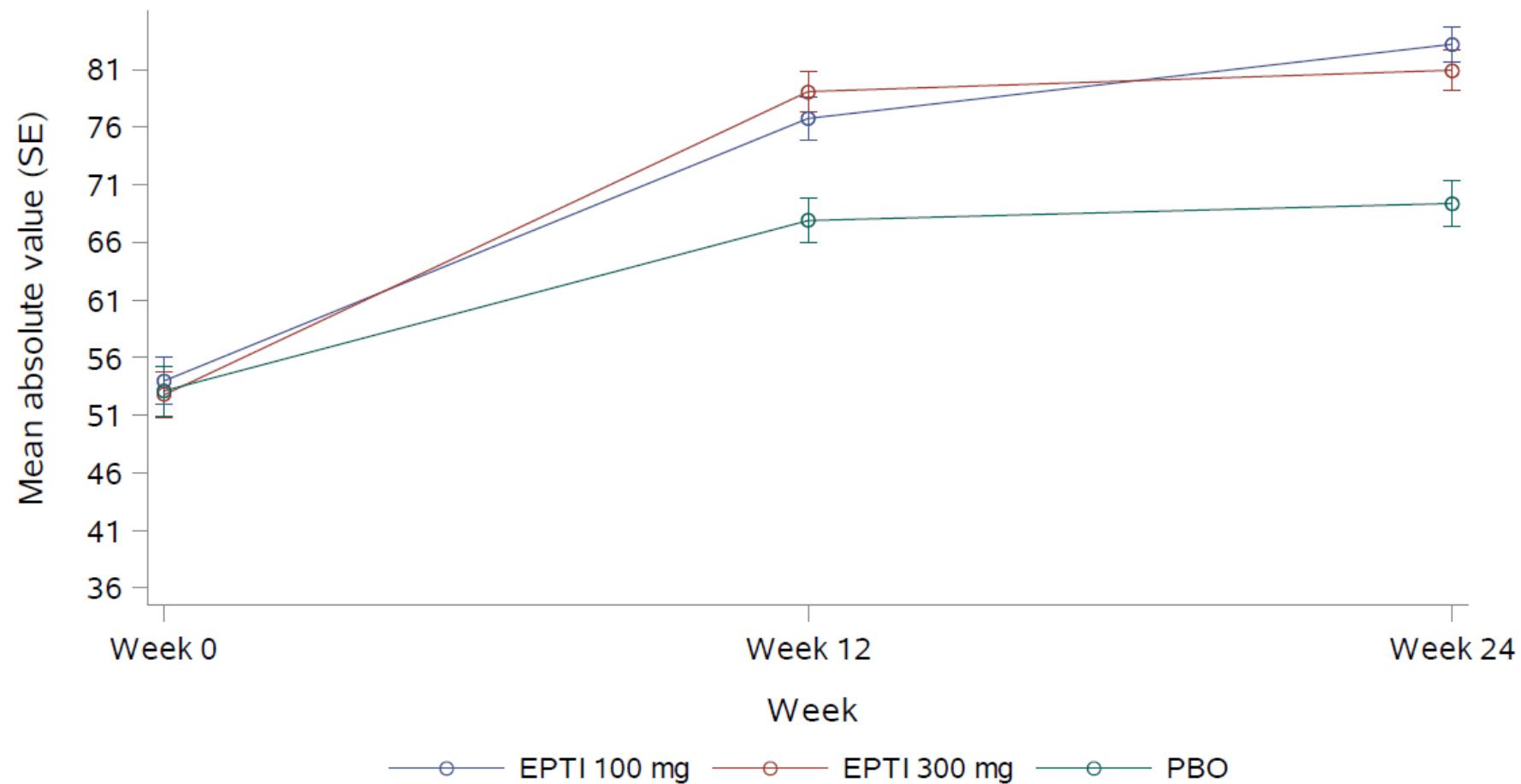
MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) : Episodic Migraine

Tabelle 4G-265: MSQ, Emotionale Funktion, CFB, Subgruppe CM

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	127 (100.0)	43.2 (26.1)		14.7	2.98	[8.83;20.6]	<.0001	0.6	[0.38;0.89]	
	12	127 (100.0)	55.8 (27.5)								
	24	121 (95.3)	56.2 (27.3)								
EPTI 100 mg	Basln	114 (100.0)	45.1 (24.1)		15.2	2.94	[9.41;21.0]	<.0001	0.7	[0.42;0.94]	
	12	114 (100.0)	70.9 (26.0)								
	24	111 (97.4)	72.2 (23.8)								
EPTI 300 mg	Basln	125 (100.0)	43.6 (22.2)		16.1	2.89	[10.4;21.8]	<.0001	0.7	[0.46;0.95]	
	12	124 (99.2)	72.1 (22.4)								
	24	120 (96.0)	73.3 (23.5)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. CM : Chronic Migraine.

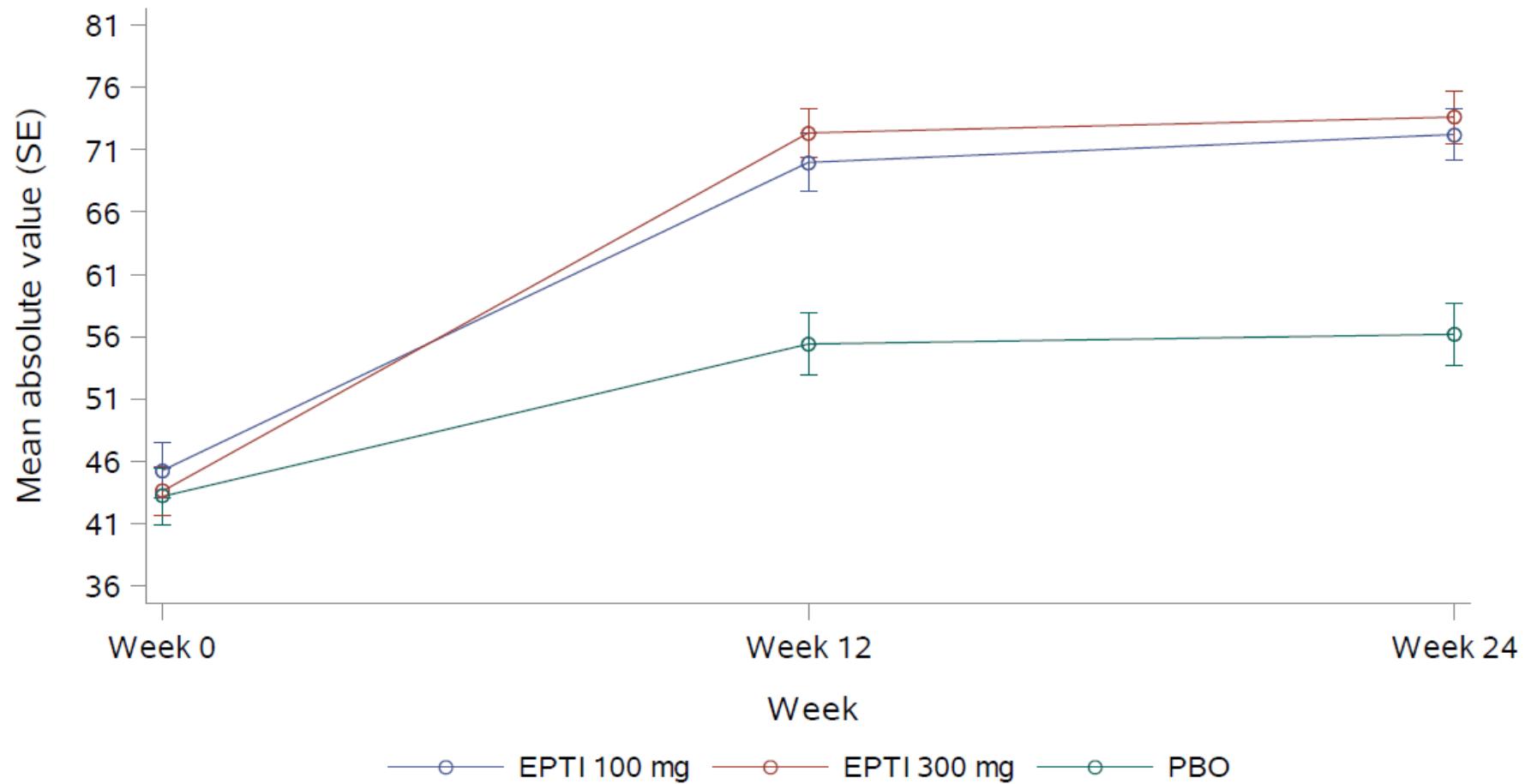
MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) : Chronic Migraine

Tabelle 4G-266: MSQ, Emotionale Funktion, CFB, Subgruppe MOH: ja

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	Comparison to PBO			Hedges' G	
					95% CI			SMD 95% CI	
					CFB				
PBO	Basln	33 (100.0)	43.4 (26.1)	16.4 (5.62)	7.7	6.05	[-4.3;19.7]	0.2065	0.3
	12	33 (100.0)	58.0 (29.9)						
	24	31 (93.9)	59.4 (28.0)						
EPTI 100 mg	Basln	32 (100.0)	40.8 (22.4)	31.1 (5.26)	11.8	5.92	[0.05;23.6]	0.0490	0.5
	12	32 (100.0)	64.8 (26.2)						
	24	32 (100.0)	71.3 (20.5)						
EPTI 300 mg	Basln	32 (100.0)	43.1 (24.7)	33.5 (5.36)	14.3	5.78	[2.76;25.7]	0.0157	0.6
	12	32 (100.0)	74.0 (21.8)						
	24	32 (100.0)	74.6 (24.5)						

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

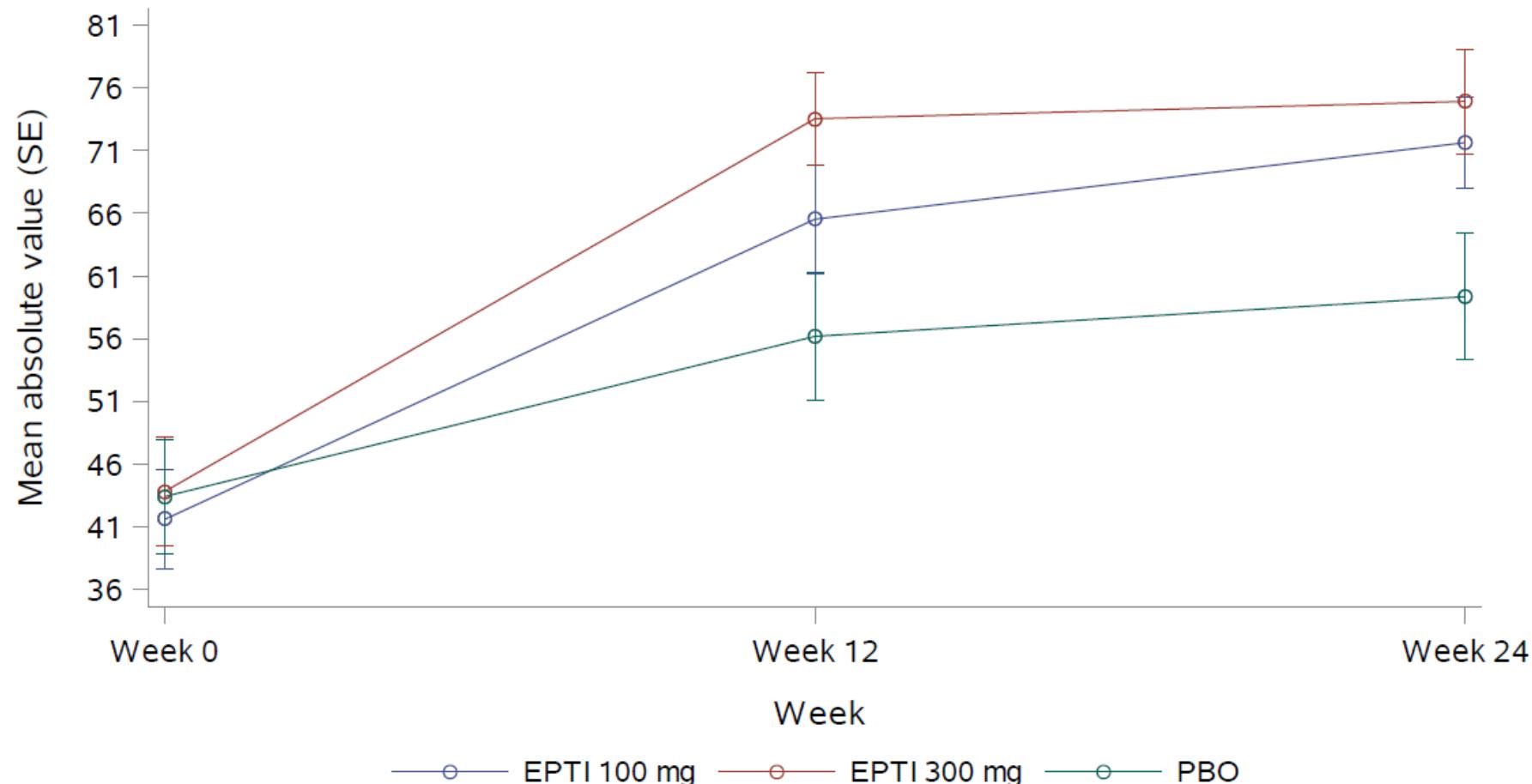
**MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) :
Medication overuse headache at baseline**

Tabelle 4G-267: MSQ, Emotionale Funktion, CFB, Subgruppe MOH: nein

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI		
									G	CI	
PBO	Basln	244 (100.0)	49.3 (26.8)		9.07 (2.05)	1.98	[7.75;15.5]	<.0001	0.5	[0.36;0.72]	
	12	244 (100.0)	62.9 (26.0)								
	24	237 (97.1)	64.1 (26.9)								
EPTI 100 mg	Basln	226 (100.0)	51.4 (24.6)		20.7 (2.08)	1.99	[10.1;18.0]	<.0001	0.7	[0.48;0.85]	
	12	226 (100.0)	75.5 (24.1)								
	24	215 (95.1)	79.4 (21.6)								
EPTI 300 mg	Basln	245 (100.0)	49.3 (23.6)		22.4 (2.00)	1.94	[9.50;17.1]	<.0001	0.6	[0.44;0.80]	
	12	244 (99.6)	76.4 (22.5)								
	24	236 (96.3)	78.0 (22.7)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

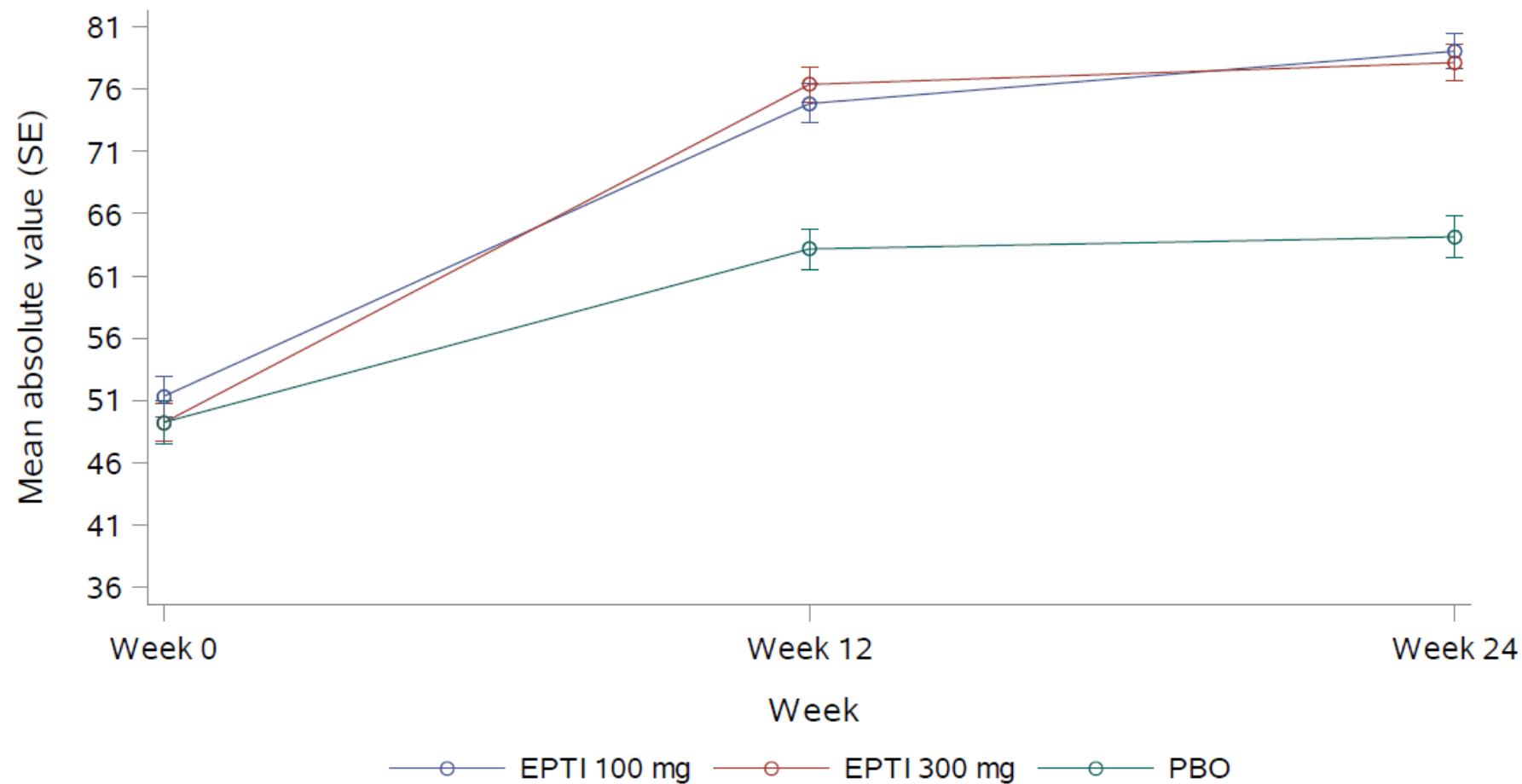
MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) No medication overuse headache at baseline

Tabelle 4G-268: MSQ, Emotionale Funktion, CFB, Subgruppe 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	195 (100.0)	49.1 (26.3)		10.3 (2.25)	2.17	[6.55;15.1]	<.0001	0.5	[0.31;0.71]	
	12	195 (100.0)	63.8 (26.4)								
	24	190 (97.4)	64.0 (27.8)								
EPTI 100 mg	Basln	188 (100.0)	49.8 (24.6)		21.1 (2.28)	13.8	[9.34;18.3]	<.0001	0.6	[0.43;0.84]	
	12	188 (100.0)	75.5 (23.5)								
	24	178 (94.7)	78.9 (21.6)								
EPTI 300 mg	Basln	211 (100.0)	48.6 (23.6)		22.6 (2.14)	2.11	[8.12;16.4]	<.0001	0.6	[0.38;0.77]	
	12	210 (99.5)	76.3 (22.6)								
	24	204 (96.7)	76.9 (24.1)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) : = 2
Previous Failed Treatments

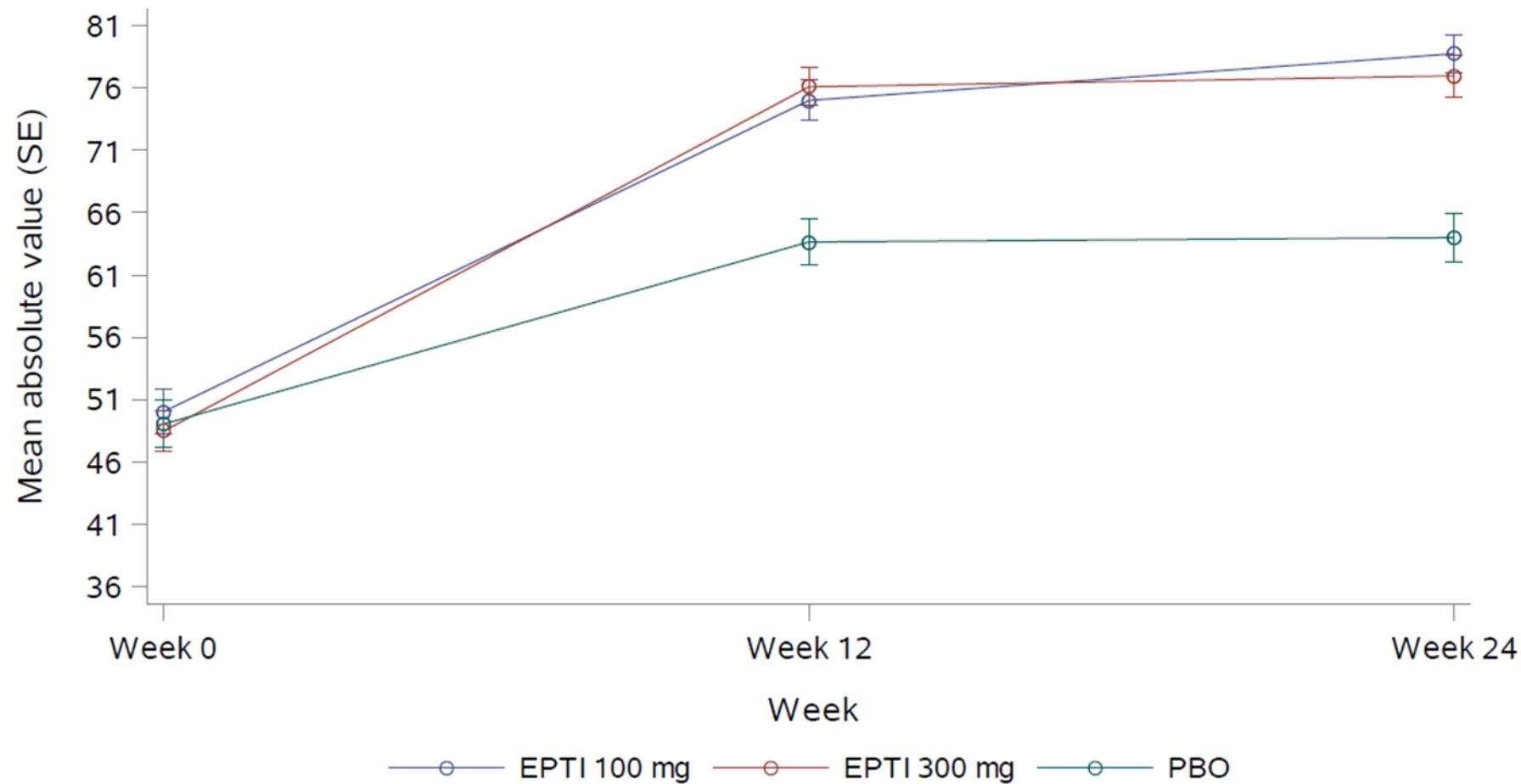


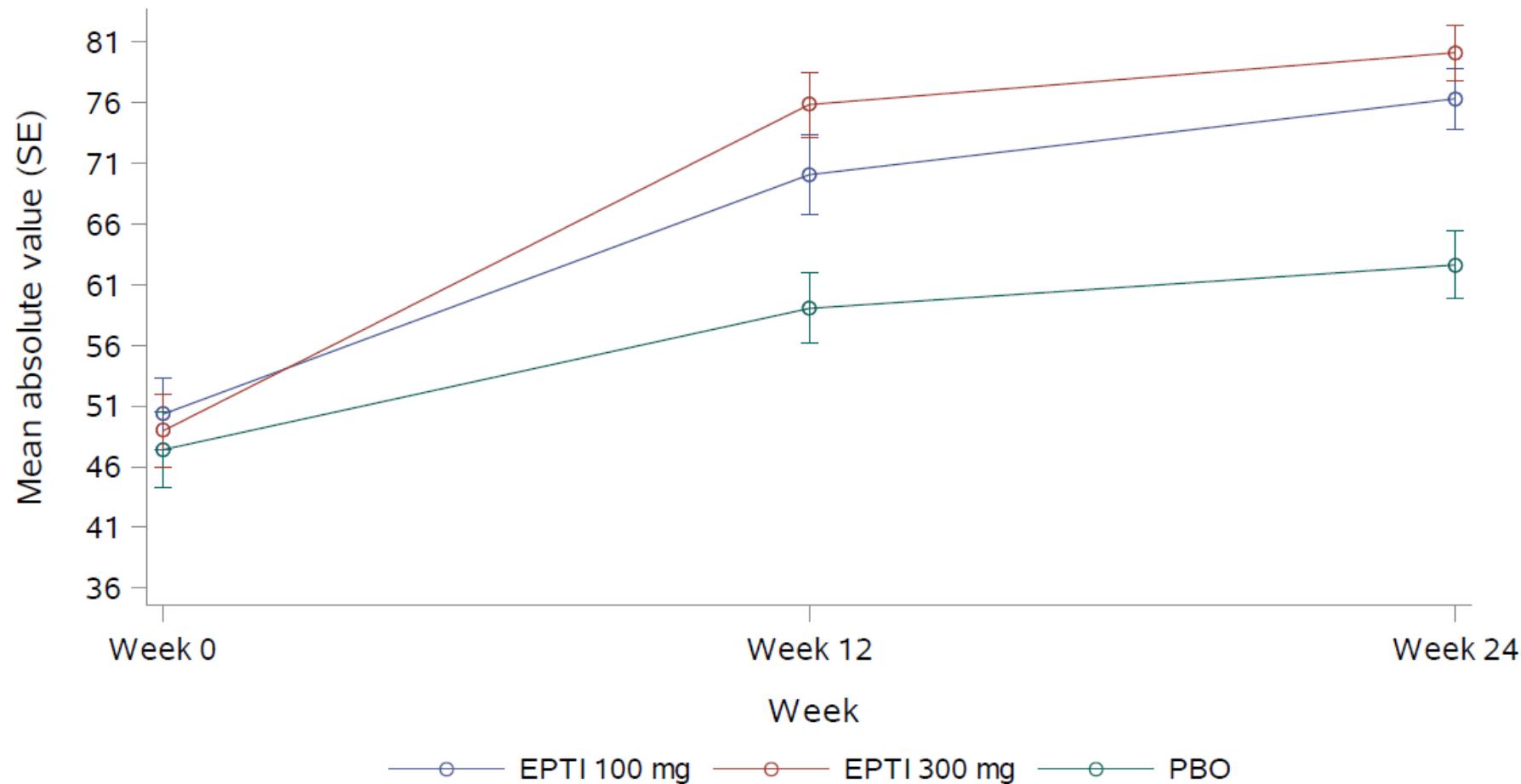
Tabelle 4G-269: MSQ, Emotionale Funktion, CFB, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	N (%)	Mean (SD)	LSmeans (SE)	CFB			p-value	Comparison to PBO		
					Diff.	SE	CI		95% CI	SMD 95% CI	
									Hedges' G	CI	
PBO	Basln	82 (100.0)	47.4 (27.7)	9.86 (3.69)	10.9	3.73	[3.56;18.3]	<.0001	0.5 [0.15;0.80]	0.7 [0.36;1.01]	
	12	82 (100.0)	58.7 (26.4)								
	24	78 (95.1)	62.4 (25.0)								
EPTI 100 mg	Basln	70 (100.0)	51.0 (24.5)	26.8 (3.48)	13.7	3.30	[7.18;20.2]	<.0001	0.7 [0.36;1.01]	0.9 [0.53;1.20]	
	12	70 (100.0)	70.8 (27.3)								
	24	69 (98.6)	76.8 (21.6)								
EPTI 300 mg	Basln	66 (100.0)	48.7 (24.6)	30.3 (3.55)	17.1	3.35	[10.5;23.7]	<.0001	0.7 [0.39;1.05]	0.9 [0.53;1.20]	
	12	66 (100.0)	75.6 (22.0)								
	24	64 (97.0)	79.9 (18.5)								

The model includes the following fixed effects: visit, country, stratification factor (MHDs at baseline: <=14/>14) and treatment as factors, baseline MSQ v2.1 sub-scores as a continuous covariate, baseline score-by-visit interaction, treatment-by-visit interaction, and stratum-by-visit interaction.

N: the number of patients with observations in the interval. Basln: Baseline. AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

**MSQ emotional function. Absolute Value: Mean (SE) by Visit (AMNOG) : > 2
Previous Failed Treatments**



4.2.16.2 Verbesserung um ≥ 15 Punkte

Tabelle 4G-270: MSQ, Emotionale Funktion, Responder, CFB, Interaktions-p-Werte

Visit	Description	Treatment Group	
		EPTI 100 mg p-value	EPTI 300 mg p-value
Week 12	Interaction test: Age Group	0.2609	0.5410
	Interaction test: EM/CM	0.7373	0.4191
	Interaction test: MOH	0.2963	0.2132
	Interaction test: Number of FPT	0.9591	0.4946
	Interaction test: Sex	0.3669	0.2340
Week 24	Interaction test: Age Group	0.2723	0.8786
	Interaction test: EM/CM	0.4736	0.1286
	Interaction test: MOH	0.7055	0.8969
	Interaction test: Number of FPT	0.4328	0.0786
	Interaction test: Sex	0.8981	0.4403

The assumption of equal treatment effect across subgroups is tested by adding the two-way interaction term subgroup-by-treatment to the model.

The test for whether the subgroup-by-treatment term can be removed from the model is performed by comparing the model without the subgroup-by-treatment interaction term to the model with the interaction term.

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-271: MSQ, Emotionale Funktion, Responder, Subgruppe ≤ 35 Jahre

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	64	22 (34.4)							
	24	64	26 (40.6)							
EPTI 100 mg	12	53	31 (58.5)	3.89	[1.73;9.17]	1.74	[1.14;2.66]	24.1	[6.47;41.8]	0.0009
	24	53	24 (45.3)	1.43	[0.66;3.14]	1.11	[0.73;1.69]	4.66	[-13;22.7]	0.3684

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
EPTI 300 mg	12	61	32	(52.5)	3.28	[1.49;7.58]	1.54	[1.02;2.34]	18.1	[0.98;35.2]	0.0030
	24	61	32	(52.5)	2.17	[1.02;4.75]	1.28	[0.88;1.88]	11.8	[-5.5;29.2]	0.0444

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B.

Tabelle 4G-272: MSQ, Emotionale Funktion, Responder, Subgruppe > 35 Jahre

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	213	82	(38.5)							
	24	213	88	(41.3)							
EPTI 100 mg	12	205	119	(58.0)	2.69	[1.73;4.22]	1.51	[1.23;1.85]	19.6	[10.2;28.9]	<.0001
	24	205	127	(62.0)	2.79	[1.80;4.36]	1.50	[1.24;1.82]	20.6	[11.3;30.0]	<.0001
EPTI 300 mg	12	215	135	(62.8)	3.03	[1.96;4.73]	1.63	[1.34;1.99]	24.3	[15.1;33.5]	<.0001
	24	215	139	(64.7)	2.84	[1.85;4.40]	1.56	[1.30;1.89]	23.3	[14.1;32.5]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B.

Tabelle 4G-273: MSQ, Emotionale Funktion, Responder, Subgruppe männlich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	28	10	(35.7)							
		24	28	6	(21.4)							
EPTI 100 mg		12	20	13	(65.0)	4.91	[1.29;21.2]	1.81	[0.97;3.39]	29.3	[1.86;56.7]	0.0187
		24	20	6	(30.0)	2.23	[0.50;10.8]	1.34	[0.52;3.49]	8.57	[-17;33.8]	0.2958
EPTI 300 mg		12	31	14	(45.2)	1.76	[0.54;6.13]	1.28	[0.69;2.39]	9.45	[-15;34.4]	0.3512
		24	31	15	(48.4)	5.50	[1.49;24.6]	2.37	[1.08;5.19]	27.0	[3.71;50.2]	0.0094

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B.

Tabelle 4G-274: MSQ, Emotionale Funktion, Responder, Subgruppe weiblich

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	249	94	(37.8)							
		24	249	108	(43.4)							
EPTI 100 mg		12	238	137	(57.6)	2.81	[1.88;4.25]	1.53	[1.26;1.85]	19.8	[11.1;28.5]	<.0001
		24	238	145	(60.9)	2.40	[1.62;3.59]	1.40	[1.18;1.67]	17.6	[8.81;26.3]	<.0001
EPTI 300 mg		12	245	153	(62.4)	3.43	[2.29;5.18]	1.66	[1.38;2.00]	24.7	[16.2;33.2]	<.0001
		24	245	156	(63.7)	2.63	[1.78;3.92]	1.47	[1.24;1.74]	20.3	[11.7;28.9]	<.0001

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B.

Tabelle 4G-275: MSQ, Emotionale Funktion, Responder, Subgruppe EM

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	150	57 (38.0)							
	24	150	67 (44.7)							
EPTI 100 mg	12	144	83 (57.6)	2.88	[1.70;4.95]	1.52	[1.18;1.94]	19.6	[8.44;30.8]	<.0001
	24	144	86 (59.7)	2.21	[1.32;3.73]	1.34	[1.07;1.67]	15.1	[3.77;26.3]	0.0025
EPTI 300 mg	12	151	88 (58.3)	2.82	[1.67;4.80]	1.53	[1.20;1.96]	20.3	[9.22;31.3]	<.0001
	24	151	91 (60.3)	2.15	[1.29;3.61]	1.35	[1.08;1.68]	15.6	[4.45;26.7]	0.0031

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment as factor. CL for RR and RD are based on binomial distribution. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B. EM : Episodic Migraine.

Tabelle 4G-276: MSQ, Emotionale Funktion, Responder, Subgruppe CM

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	127	47	(37.0)							
		24	127	47	(37.0)							
EPTI 100 mg		12	114	67	(58.8)	3.05	[1.73;5.47]	1.59	[1.21;2.09]	21.8	[9.43;34.1]	<.0001
		24	114	65	(57.0)	2.70	[1.55;4.78]	1.54	[1.17;2.03]	20.0	[7.64;32.4]	0.0004
EPTI 300 mg		12	125	79	(63.2)	3.58	[2.05;6.34]	1.71	[1.31;2.22]	26.2	[14.3;38.1]	<.0001
		24	125	80	(64.0)	3.57	[2.07;6.28]	1.73	[1.33;2.25]	27.0	[15.1;38.9]	<.0001
The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment as factor. CL for RR and RD are based on binomial distribution. Non-response imputation is used to impute potentially missing values at a visit. Response: Patients with a 15-point increase from baseline in MSQ emotional function score. AMNOG: AMNOG population B. CM : Chronic Migraine.												

Tabelle 4G-277: MSQ, Emotionale Funktion, Responder, Subgruppe MOH: ja

		Responders			Odds Ratio		Relative Risk		Risk Difference			
Treatment	Group	Weeks	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO		12	33	15	(45.5)							
		24	33	12	(36.4)							
EPTI 100 mg		12	32	19	(59.4)	1.85	[0.64;5.51]	1.42	[0.88;2.30]	13.9	[-10;38.0]	0.2604
		24	32	20	(62.5)	3.51	[1.12;11.8]	1.79	[1.02;3.13]	26.1	[2.67;49.6]	0.0305
EPTI 300 mg		12	32	18	(56.3)	1.70	[0.59;5.07]	1.26	[0.75;2.12]	10.8	[-13;35.0]	0.3281
		24	32	19	(59.4)	3.39	[1.08;11.6]	1.69	[0.98;2.92]	23.0	[-63;46.7]	0.0365

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-278: MSQ, Emotionale Funktion, Responder, Subgruppe MOH: nein

Treatment Group	Weeks	Responders		Odds Ratio		Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	244	89 (36.5)							
	24	244	102 (41.8)							
EPTI 100 mg	12	226	131 (58.0)	3.24	[2.14;4.96]	1.59	[1.30;1.94]	21.5	[12.7;30.3]	<.0001
	24	226	131 (58.0)	2.33	[1.56;3.50]	1.39	[1.15;1.67]	16.2	[7.23;25.1]	<.0001
EPTI 300 mg	12	244	149 (61.1)	3.48	[2.31;5.28]	1.67	[1.38;2.03]	24.6	[16.0;33.2]	<.0001
	24	244	152 (62.3)	2.67	[1.80;4.00]	1.49	[1.25;1.78]	20.5	[11.8;29.2]	<.0001

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B. MOH: Medication overuse headache at baseline.

Tabelle 4G-279: MSQ, Emotionale Funktion, Responder, Subgruppe 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	195	75	(38.5)							
	24	195	83	(42.6)							
EPTI 100 mg	12	188	113	(60.1)	3.01	[1.90;4.82]	1.56	[1.26;1.94]	21.6	[11.9;31.4]	<.0001
	24	188	111	(59.0)	2.16	[1.39;3.37]	1.38	[1.13;1.69]	16.5	[6.60;26.4]	0.0005
EPTI 300 mg	12	210	127	(60.5)	2.95	[1.89;4.65]	1.57	[1.28;1.94]	22.0	[12.5;31.5]	<.0001
	24	210	126	(60.0)	2.20	[1.44;3.39]	1.41	[1.16;1.72]	17.4	[7.84;27.0]	0.0003

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-280: MSQ, Emotionale Funktion, Responder, Subgruppe > 2 Vortherapien

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
PBO	12	82	29	(35.4)							
	24	82	31	(37.8)							
EPTI 100 mg	12	70	37	(52.9)	2.63	[1.29;5.50]	1.48	[1.02;2.14]	17.5	[1.88;33.1]	0.0075
	24	70	40	(57.1)	3.49	[1.64;7.69]	1.51	[1.06;2.14]	19.3	[3.70;35.0]	0.0010
EPTI 300 mg	12	66	40	(60.6)	3.56	[1.73;7.58]	1.72	[1.21;2.44]	25.2	[9.55;40.9]	0.0005
	24	66	45	(68.2)	5.73	[2.59;13.5]	1.80	[1.30;2.49]	30.4	[15.0;45.8]	<.0001

Treatment Group	Weeks	Responders			Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value

The OR and p-values are based on logistic regression model. The model includes baseline score as a continuous covariate, and treatment and stratification factor (MHD at baseline:<=14/>14) as factors. CL for RR and RD are based on binomial distribution. RR are adjusted by stratification factor. Non-response imputation is used to impute potentially missing values at a visit.

Response: Patients with a 15-point increase from baseline in MSQ emotional function score.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

4.2.17 Unerwünschte Ereignisse

Tabelle 4G-281: UE, Interaktions-p-Werte

Description	Treatment Group	
	EPTI 100 mg	EPTI 300 mg
Interaction test: Age Group	0.0689	0.1175
Interaction test: EM/CM	0.8241	0.8559
Interaction test: MOH	0.6181	0.7030
Interaction test: Number of FPT	0.9770	0.8171
Interaction test: Sex	0.2283	0.7762

Both models are fitted using (maximum likelihood) ML and compared via a likelihood ratio test.

AMNOG: AMNOG population B. FPT: Failed Previous Treatments by AMNOG population B.

Tabelle 4G-282: UE, Subgruppenanalysen nach Alter (≤ 35 Jahre/ > 35 Jahre)

Pooled Group 1	Age Treatment Group				Odds Ratio		Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
<= 35 years	PBO	67	32	47.8							
	EPTI 100 mg	57	20	35.1	0.6	[0.3; 1.2]	0.7	[0.5; 1.1]	-12.7	[-29.9; 4.5]	0.1338
	EPTI 300 mg	62	23	37.1	0.6	[0.3; 1.3]	0.8	[0.5; 1.2]	-10.7	[-27.6; 6.3]	0.2257
> 35 years	PBO	220	80	36.4							

Pooled Group 1	Age Treatment Group	Odds Ratio				Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL
		EPTI 100 mg	227	95	41.9	1.3	[0.9; 1.8]	1.1	[0.9; 1.5]	5.5
		EPTI 300 mg	224	92	41.1	1.2	[0.8; 1.8]	1.1	[0.9; 1.4]	4.7

CL for RR and RD are based on binomial distribution. The common OR is estimated using Mantel-Haenszel method. The p-values are calculated using CMH test.
OR, RR and p-values are adjusted by stratification factor.

Tabelle 4G-283: UE, Subgruppenanalysen nach Geschlecht (männlich/weiblich)

Sex	Treatment Group	Odds Ratio				Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL
F	PBO	254	99	39.0						
	EPTI 100 mg	263	103	39.2	1.0	[0.7; 1.4]	1.0	[0.8; 1.2]	0.2	[-8.2; 8.6]
	EPTI 300 mg	254	101	39.8	1.0	[0.7; 1.5]	1.0	[0.8; 1.3]	0.8	[-7.7; 9.3]
M	PBO	33	13	39.4						
	EPTI 100 mg	21	12	57.1	2.0	[0.6; 6.1]	1.4	[0.8; 2.5]	17.7	[-9.2; 44.7]
	EPTI 300 mg	32	14	43.8	1.3	[0.5; 3.4]	1.1	[0.6; 2.0]	4.4	[-19.6; 28.3]

CL for RR and RD are based on binomial distribution. The common OR is estimated using Mantel-Haenszel method. The p-values are calculated using CMH test.
OR, RR and p-values are adjusted by stratification factor.

Tabelle 4G-284: UE, Subgruppenanalysen nach Migränesubtyp (EM/CM)

Migraine Type Group	Treatment Group	Odds Ratio				Relative Risk		Risk Difference		
		N	n	(%)	OR	CL	RR	CL	RD	CL
		CM	PBO	128	52	40.6				
CM	EPTI 100 mg	130	56	43.1	1.1	[0.7; 1.8]	1.0	[0.8; 1.4]	2.5	[-9.6; 14.5]
										0.7800

						Odds Ratio		Relative Risk		Risk Difference				
Migraine Type		Treatment	Group	Group	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
		EPTI 300 mg			130	53	40.8	1.0	[0.6; 1.6]	1.0	[0.7; 1.3]	0.1	[-11.8; 12.1]	0.9775
EM	PBO				159	60	37.7							
	EPTI 100 mg				154	59	38.3	1.0	[0.6; 1.6]	1.0	[0.8; 1.3]	0.6	[-10.2; 11.3]	0.9166
	EPTI 300 mg				155	61	39.4	1.1	[0.7; 1.7]	1.0	[0.8; 1.4]	1.6	[-9.1; 12.4]	0.7686

CL for RR and RD are based on binomial distribution. The common OR is estimated using Mantel-Haenszel method. The p-values are calculated using CMH test. OR, RR and p-values are adjusted by stratification factor.

Tabelle 4G-285: UE, Subgruppenanalysen nach Vorliegen einer MOH-Diagnose (ja/nein)

						Odds Ratio		Relative Risk		Risk Difference				
MOH		Treatment	Group	Group	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
		EPTI-3												
No	PBO				252	97	38.5							
	EPTI 100 mg				248	101	40.7	1.1	[0.8; 1.6]	1.1	[0.9; 1.3]	2.2	[-6.3; 10.8]	0.6147
	EPTI 300 mg				251	101	40.2	1.1	[0.8; 1.5]	1.0	[0.8; 1.3]	1.7	[-6.8; 10.3]	0.6914
Yes	PBO				35	15	42.9							
	EPTI 100 mg				36	14	38.9	0.8	[0.3; 2.0]	0.9	[0.5; 1.5]	-4.0	[-26.8; 18.9]	0.5973
	EPTI 300 mg				35	14	40.0	0.8	[0.3; 2.1]	0.9	[0.5; 1.5]	-2.9	[-25.9; 20.2]	0.6665

			Odds Ratio		Relative Risk		Risk Difference				
MOH											
Diagnosis per Treatment		ICHD-3	Group	N	n (%)	OR	CL	RR	CL	RD	CL p-value
CL for RR and RD are based on binomial distribution. The common OR is estimated using Mantel-Haenszel method. The p-values are calculated using CMH test. OR, RR and p-values are adjusted by stratification factor.											

Tabelle 4G-286: UE, Subgruppenanalysen nach Anzahl der versagten Vortherapien (2> 2)

			Odds Ratio		Relative Risk		Risk Difference				
Previous Treatment Failures			Treatment Group	N	n (%)	OR	CL	RR	CL	RD	CL p-value
2	PBO	204	81	39.7							
	EPTI 100 mg	207	85	41.1	1.1	[0.7; 1.6]	1.0	[0.8; 1.3]	1.4	[-8.1; 10.8]	0.7681
	EPTI 300 mg	218	90	41.3	1.1	[0.7; 1.6]	1.0	[0.8; 1.3]	1.6	[-7.8; 10.9]	0.7445
>2	PBO	83	31	37.3							
	EPTI 100 mg	77	30	39.0	1.1	[0.6; 2.1]	1.1	[0.7; 1.6]	1.6	[-13.5; 16.7]	0.7980
	EPTI 300 mg	68	25	36.8	1.0	[0.5; 1.9]	1.0	[0.6; 1.5]	-0.6	[-16.1; 14.9]	0.9392
CL for RR and RD are based on binomial distribution. The common OR is estimated using Mantel-Haenszel method. The p-values are calculated using CMH test. OR, RR and p-values are adjusted by stratification factor.											

4.2.18 Schwerwiegende unerwünschte Ereignisse

Keine Subgruppenanalysen durchgeführt. Nicht ausreichend Ereignisse für eine aussagekräftige Subgruppenanalyse.

4.2.19 Unerwünschte Ereignisse, die zum Therapieabbruch führten

Keine Subgruppenanalysen durchgeführt

4.2.20 Unerwünschte Ereignisse von besonderem Interesse

Tabelle 4G-287: AESI, Interaktions-p-Werte

GRPVAR_LBL	trt01a	pval
Age Group	EPTI 100 mg	0.9431242
EM/CM	EPTI 100 mg	0.3125408
MOH	EPTI 100 mg	0.0808747
Number of FPT	EPTI 100 mg	0.869024
Sex	EPTI 100 mg	0.136862
Age Group	EPTI 300 mg	0.5238408
EM/CM	EPTI 300 mg	0.0511613
MOH	EPTI 300 mg	0.1903754
Number of FPT	EPTI 300 mg	0.2495799
Sex	EPTI 300 mg	0.1932928

Fitting a logistic regression with TRT01A*&grpvar &grpvar TRT01A STRATAR and testing if TRT01A*&grpvar can be dropped. In the case of the EM/CM subgroup analysis (i.e., &grpvar = MIGTYPGR), the STRATAR term will be dropped.

Tabelle 4G-288: AESI, Subgruppenanalysen nach Alter ($\leq 35/ > 35$)

Pooled Group 1	AgeTreatment				Odds Ratio		Relative Risk		Risk Difference		
		Group	N	n	(%)	OR	CL	RR	CL	RD	CL
<= 35 years	PBO	67	5	7.5							
	EPTI 100 mg	57	5	8.8	1.2	[0.3; 4.3]	1.2	[0.4; 3.8]	1.3	[-8.4; 11.0]	0.8124
	EPTI 300 mg	62	4	6.5	0.9	[0.2; 3.3]	0.9	[0.2; 3.1]	-1.0	[-9.8; 7.8]	0.8258
> 35 years	PBO	220	12	5.5							
	EPTI 100 mg	227	14	6.2	1.1	[0.5; 2.5]	1.1	[0.5; 2.4]	0.7	[-3.6; 5.0]	0.7566
	EPTI 300 mg	224	17	7.6	1.4	[0.7; 3.0]	1.4	[0.7; 2.8]	2.1	[-2.5; 6.7]	0.3656

Pooled Group 1	Age Group	Odds Ratio			Relative Risk		Risk Difference			
		N	n (%)	OR	CL	RR	CL	RD	CL	
CL for RR and RD are based on binomial distribution. The common OR is estimated using Mantel-Haenszel method.										
The p-values are calculated using CMH test.										
values are adjusted by stratification factor.										
For OR, RR and RD, each 2-by-2 table (AE or not AE vs PBO or active treatment, with active treatment = EPTI 100 mg or EPTI 300 mg) which contains a cell with zero has been adjusted by adding 0.5 to every cell.										
For RD, the analysis is not stratification adjusted so stratification is not taken into account when performing the 0.5 adjustment. I.e., the analysis is based on a single 2-by-2 table where, if any cell in the table contains a zero, 0.5 is added to every cell.										
For OR, RR and p-values, the 0.5 adjustment is done on comparison-by-stratum level, i.e., only strata which contain zeros are adjusted.										

Tabelle 4G-289: AESI, Subgruppenanalysen nach Geschlecht (männlich/weiblich)

Sex	Treatment Group	Odds Ratio			Relative Risk		Risk Difference		
		N	n (%)	OR	CL	RR	CL	RD	CL
F	PBO	254	16	6.3					
	EPTI 100 mg	263	16	6.1	1.0	[0.5; 2.0]	1.0	[0.5; 1.9]	-0.2
	EPTI 300 mg	254	21	8.3	1.3	[0.7; 2.6]	1.3	[0.7; 2.5]	2.0
M	PBO	33	1	3.0					
	EPTI 100 mg	21	3	14.3	3.4	[0.6; 18.4]	3.1	[0.7; 14.7]	11.7
	EPTI 300 mg	32	0	0.0	0.5	[0.0; 6.4]	0.5	[0.0; 6.1]	-2.8

Sex	Treatment Group	N	n	(%)	Odds Ratio		Relative Risk		Risk Difference	
					OR	CL	RR	CL	RD	CL
CL for RR and RD are based on binomial distribution. The common OR is estimated using Mantel-Haenszel method. The p-values are calculated using CMH test. OR, RR and p-values are adjusted by stratification factor. For OR, RR and RD, each 2-by-2 table (AE or not AE vs PBO or active treatment, with active treatment = EPTI 100 mg or EPTI 300 mg) which contains a cell with zero has been adjusted by adding 0.5 to every cell. For RD, the analysis is not stratification adjusted so stratification is not taken into account when performing the 0.5 adjustment. I.e., the analysis is based on a single 2-by-2 table where, if any cell in the table contains a zero, 0.5 is added to every cell. For OR, RR and p-values, the 0.5 adjustment is done on comparison-by-stratum level, i.e., only strata which contain zeros are adjusted.										

Tabelle 4G-290: AESI, Subgruppenanalysen nach Migränesubtyp (EM/CM)

Migraine Type	Treatment	Group	Group	Odds Ratio		Relative Risk		Risk Difference		CL	p-value	
				N	n	(%)	OR	CL	RR	CL		
CM	PBO	CM	128	6	4.7							
	EPTI 100 mg		130	10	7.7	1.7	[0.6; 4.5]	1.6	[0.6; 4.1]	2.9	[-3.2; 9.1]	0.3224
	EPTI 300 mg		130	14	10.8	2.3	[0.9; 6.1]	2.2	[0.9; 5.3]	6.0	[-0.7; 12.6]	0.0803
EM	PBO	EM	159	11	6.9							
	EPTI 100 mg		154	9	5.8	0.8	[0.3; 2.1]	0.8	[0.4; 2.0]	-1.1	[-6.6; 4.4]	0.6982
	EPTI 300 mg		155	7	4.5	0.6	[0.2; 1.7]	0.7	[0.3; 1.6]	-2.4	[-7.6; 2.8]	0.3607

					Odds Ratio		Relative Risk		Risk Difference				
Migraine TypeTreatment		Group	Group	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
CL for RR and RD are based on binomial distribution.													
The common OR is estimated using Mantel-Haenszel method.													
The p-values are calculated using CMH test.													
OR, RR and p-values are adjusted by stratification factor.													
For OR, RR and p-values, the 0.5 adjustment is done on comparison-by-stratum level, i.e., only strata which contain zeros are adjusted.													

Tabelle 4G-291: AESI, Subgruppenanalysen nach MOH (ja/nein)

					Odds Ratio		Relative Risk		Risk Difference					
MOH		Diagnosis	perTreatment	Group	N	n	(%)	OR	CL	RR	CL	RD	CL	p-value
No	PBO	252	16	6.3										
	EPTI 100 mg	248	14	5.6	0.9	[0.4; 1.9]		0.9	[0.4; 1.8]		-0.7	[-4.9; 3.5]		0.7415
	EPTI 300 mg	251	17	6.8	1.1	[0.5; 2.2]		1.1	[0.5; 2.1]		0.4	[-3.9; 4.8]		0.8568
Yes	PBO	35	1	2.9										
	EPTI 100 mg	36	5	13.9	4.0	[0.6; 25.5]		3.5	[0.6; 19.6]		10.4	[-3.3; 24.1]		0.1216
	EPTI 300 mg	35	4	11.4	3.2	[0.5; 21.5]		2.9	[0.5; 17.1]		8.1	[-5.1; 21.3]		0.2176

					Odds Ratio	Relative Risk		Risk Difference			
MOH	Diagnosis per Treatment	ICHD-3	Group	N	n (%)	OR	CL	RR	CL	RD	CL p-value
CL for RR and RD are based on binomial distribution.											
The common OR is estimated using Mantel-Haenszel method.											
The p-values are calculated using CMH test.											
OR, RR and p-values are adjusted by stratification factor.											
For OR, RR and RD, each 2-by-2 table (AE or not AE vs PBO or active treatment, with active treatment = EPTI 100 mg or EPTI 300 mg) which contains a cell with zero has been adjusted by adding 0.5 to every cell.											
For RD, the analysis is not stratification adjusted so stratification is not taken into account when performing the 0.5 adjustment. I.e., the analysis is based on a single 2-by-2 table where, if any cell in the table contains a zero, 0.5 is added to every cell.											
For OR, RR and p-values, the 0.5 adjustment is done on comparison-by-stratum level, i.e., only strata which contain zeros are adjusted.											

Tabelle 4G-292: AESI, Subgruppenanalysen nach Anzahl der versagten Vortherapien (2> 2)

					Odds Ratio	Relative Risk		Risk Difference			
Previous Treatment	Treatment	Failures	Group	N	n (%)	OR	CL	RR	CL	RD	CL p-value
2	PBO	2	204	9	4.4	1.2	[0.5; 3.0]	1.2	[0.5; 2.8]	0.9	[-3.3; 5.1]
	EPTI 100 mg		207	11	5.3						
	EPTI 300 mg		218	16	7.3						
>2	PBO	>2	83	8	9.6	1.1	[0.4; 3.0]	1.1	[0.4; 2.8]	0.8	[-8.6; 10.1]
	EPTI 100 mg		77	8	10.4						
	EPTI 300 mg		68	5	7.4						

					Odds Ratio	Relative Risk		Risk Difference			
Previous	Treatment	Treatment	N	n (%)	OR	CL	RR	CL	RD	CL	p-value
Failures	Group										

CL for RR and RD are based on binomial distribution.

The common OR is estimated using Mantel-Haenszel method.

The p-values are calculated using CMH test.

OR, RR and p-values are adjusted by stratification factor.

For OR, RR and RD, each 2-by-2 table (AE or not AE vs PBO or active treatment, with active treatment = EPTI 100 mg or EPTI 300 mg) which contains a cell with zero has been adjusted by adding 0.5 to every cell.

For RD, the analysis is not stratification adjusted so stratification is not taken into account when performing the 0.5 adjustment. I.e., the analysis is based on a single 2-by-2 table where, if any cell in the table contains a zero, 0.5 is added to every cell.

For OR, RR and p-values, the 0.5 adjustment is done on comparison-by-stratum level, i.e., only strata which contain zeros are adjusted.