

Eigene Vorlage

**Dossier zur Nutzenbewertung
gemäß § 35a SGB V**

Cannabidiol (Epidyolex®)

**Separater Anhang 4-G
zu Modul 4A**

Subgruppenanalysen

Stand: 30.11.2023

Inhaltsverzeichnis

- 1. Subgruppenanalysen der In-Label Population – Studie GWEP1424**
 - 1.1 Endpunkt Morbidität: Veränderung der Gesamt-Krampfanfallshäufigkeit (Negativ-binomial Modell, Responderanalysen)**
 - 1.2 Endpunkt Morbidität: Veränderung der Häufigkeit konvulsiver Krampfanfälle (Negativ-binomial Modell, Responderanalysen)**
 - 1.3 Endpunkt Morbidität: Veränderung der Häufigkeit nicht-konvulsiver Krampfanfälle (Negativ-binomial Modell, Responderanalysen)**
 - 1.4 Endpunkt Morbidität: Epileptische Krampfanfälle – Längste Anzahl von konsekutiven Tagen ohne jegliche Krampfanfälle (Negativ-binomial Modell)**
 - 1.5 Endpunkt Morbidität: Globaler Patienten-Eindruck der Veränderung (mittels CGIC, Responderanalysen)**
 - 1.6 Endpunkt Verträglichkeit: Unerwünschte Ereignisse**
- 2. Subgruppenanalysen der In-Label Population – Studie GWEP1332B**
 - 2.1 Endpunkt Morbidität: Veränderung der Gesamt-Krampfanfallshäufigkeit (Negativ-binomial Modell, Responderanalysen)**
 - 2.2 Endpunkt Morbidität: Veränderung der Häufigkeit konvulsiver Krampfanfälle (Negativ-binomial Modell, Responderanalysen)**
 - 2.3 Endpunkt Morbidität: Veränderung der Häufigkeit nicht-konvulsiver Krampfanfälle (Negativ-binomial Modell, Responderanalysen)**
 - 2.4 Endpunkt Morbidität: Epileptische Krampfanfälle – Längste Anzahl von konsekutiven Tagen ohne jegliche Krampfanfälle (Negativ-binomial Modell)**
 - 2.5 Endpunkt Morbidität: Globaler Patienten-Eindruck der Veränderung (mittels CGIC, Responderanalysen)**
 - 2.6 Endpunkt Verträglichkeit: Unerwünschte Ereignisse**
- 3. Subgruppenanalysen der ASM-Population – Studie GWEP1424**
 - 3.1 Endpunkt Morbidität: Veränderung der Gesamt-Krampfanfallshäufigkeit (Negativ-binomial Modell, Responderanalysen)**
 - 3.2 Endpunkt Morbidität: Veränderung der Häufigkeit konvulsiver Krampfanfälle (Negativ-binomial Modell, Responderanalysen)**
 - 3.3 Endpunkt Morbidität: Veränderung der Häufigkeit nicht-konvulsiver Krampfanfälle (Negativ-binomial Modell, Responderanalysen)**

- 3.4 Endpunkt Morbidität: Epileptische Krampfanfälle – Längste Anzahl von konsekutiven Tagen ohne jegliche Krampfanfälle (Negativ-binomial Modell)**
- 3.5 Endpunkt Morbidität: Globaler Patienten-Eindruck der Veränderung (mittels CGIC, Responderanalysen)**
- 3.6 Endpunkt Verträglichkeit: Unerwünschte Ereignisse**
- 4. Subgruppenanalysen der ASM-Population – Studie GWEP1332B**
 - 4.1 Endpunkt Morbidität: Veränderung der Gesamt-Krampfanfallshäufigkeit (Negativ-binomial Modell, Responderanalysen)**
 - 4.2 Endpunkt Morbidität: Veränderung der Häufigkeit konvulsiver Krampfanfälle (Negativ-binomial Modell, Responderanalysen)**
 - 4.3 Endpunkt Morbidität: Veränderung der Häufigkeit nicht-konvulsiver Krampfanfälle (Negativ-binomial Modell, Responderanalysen)**
 - 4.4 Endpunkt Morbidität: Epileptische Krampfanfälle – Längste Anzahl von konsekutiven Tagen ohne jegliche Krampfanfälle (Negativ-binomial Modell)**
 - 4.5 Endpunkt Morbidität: Globaler Patienten-Eindruck der Veränderung (mittels CGIC, Responderanalysen)**
 - 4.6 Endpunkt Verträglichkeit: Unerwünschte Ereignisse**

Hinweis: In den nachstehenden Tabellen entspricht der Komparator, der mit „Placebo“ gekennzeichnet ist, der „patientenindividuellen anfallssuppressiven Therapie (PIAT) + Placebo“.

Adhoc Table: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data	10 mg/kg			45 / 41	0.340 [66.0%] / 0.593 [40.7%]	0.574 [42.6%]	(0.420, 0.783)	0.0006
	20 mg/kg			40 / 41	0.423 [57.7%] / 0.593 [40.7%]	0.714 [28.6%]	(0.518, 0.984)	0.0399
Age Group	10 mg/kg	0.7968	2-5 years	13 / 13	0.280 [72.0%] / 0.416 [58.4%]	0.672 [32.8%]	(0.375, 1.205)	0.1806
			6-12 years	23 / 16	0.342 [65.8%] / 0.655 [34.5%]	0.522 [47.8%]	(0.327, 0.832)	0.0068
			13-18 years	9 / 12	0.436 [56.4%] / 0.738 [26.2%]	0.591 [40.9%]	(0.310, 1.129)	0.1104
	20 mg/kg	0.6429	2-5 years	10 / 13	0.377 [62.3%] / 0.416 [58.4%]	0.906 [9.4%]	(0.489, 1.677)	0.7507
			6-12 years	22 / 16	0.438 [56.2%] / 0.655 [34.5%]	0.668 [33.2%]	(0.415, 1.075)	0.0956
			13-18 years	8 / 12	0.448 [55.2%] / 0.738 [26.2%]	0.607 [39.3%]	(0.308, 1.196)	0.1473
Sex	10 mg/kg	0.8849	Female	22 / 22	0.372 [62.8%] / 0.633 [36.7%]	0.588 [41.2%]	(0.380, 0.911)	0.0179
			Male	23 / 19	0.309 [69.1%] / 0.551 [44.9%]	0.562 [43.8%]	(0.357, 0.883)	0.0129
	20 mg/kg	0.8490	Female	17 / 22	0.443 [55.7%] / 0.633 [36.7%]	0.700 [30.0%]	(0.434, 1.130)	0.1433
			Male	23 / 19	0.411 [58.9%] / 0.551 [44.9%]	0.746 [25.4%]	(0.477, 1.168)	0.1978
Region	10 mg/kg	0.1818	USA	22 / 23	0.258 [74.2%] / 0.574 [42.6%]	0.449 [55.1%]	(0.291, 0.693)	0.0004
			Rest of the World	23 / 18	0.430 [57.0%] / 0.622 [37.8%]	0.690 [31.0%]	(0.435, 1.096)	0.1149
	20 mg/kg	0.7059	USA	21 / 23	0.386 [61.4%] / 0.574 [42.6%]	0.673 [32.7%]	(0.437, 1.036)	0.0714
			Rest of the World	19 / 18	0.474 [52.6%] / 0.622 [37.8%]	0.762 [23.8%]	(0.466, 1.247)	0.2769

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Adhoc Table: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Valproic Acid Use	10 mg/kg	0.1949	Not Currently Taking	15 / 12	0.485 [51.5%] / 0.631 [36.9%]	0.769 [23.1%]	(0.444, 1.330)	0.3441
			Currently Taking	30 / 29	0.286 [71.4%] / 0.576 [42.4%]	0.496 [50.4%]	(0.341, 0.723)	0.0003
	20 mg/kg	0.8427	Not Currently Taking	10 / 12	0.480 [52.0%] / 0.631 [36.9%]	0.759 [24.1%]	(0.417, 1.381)	0.3642
			Currently Taking	30 / 29	0.407 [59.3%] / 0.576 [42.4%]	0.707 [29.3%]	(0.484, 1.033)	0.0726
Stiripentol Use	10 mg/kg	0.0159	Not Currently Taking	28 / 24	0.241 [75.9%] / 0.561 [43.9%]	0.430 [57.0%]	(0.293, 0.630)	<.0001
			Currently Taking	17 / 17	0.601 [39.9%] / 0.651 [34.9%]	0.923 [7.7%]	(0.568, 1.499)	0.7430
	20 mg/kg	0.5554	Not Currently Taking	22 / 24	0.432 [56.8%] / 0.561 [43.9%]	0.769 [23.1%]	(0.514, 1.151)	0.1991
			Currently Taking	18 / 17	0.415 [58.5%] / 0.651 [34.9%]	0.637 [36.3%]	(0.392, 1.034)	0.0677
Levetiracetam Use	10 mg/kg	0.2875	Not Currently Taking	34 / 33	0.341 [65.9%] / 0.545 [45.5%]	0.625 [37.5%]	(0.439, 0.892)	0.0099
			Currently Taking	11 / 8	0.335 [66.5%] / 0.809 [19.1%]	0.414 [58.6%]	(0.211, 0.814)	0.0110
	20 mg/kg	0.5794	Not Currently Taking	31 / 33	0.407 [59.3%] / 0.545 [45.5%]	0.746 [25.4%]	(0.518, 1.076)	0.1154
			Currently Taking	9 / 8	0.484 [51.6%] / 0.809 [19.1%]	0.598 [40.2%]	(0.297, 1.203)	0.1478
Topiramate Use	10 mg/kg	0.2511	Not Currently Taking	37 / 30	0.303 [69.7%] / 0.572 [42.8%]	0.530 [47.0%]	(0.371, 0.757)	0.0006
			Currently Taking	8 / 11	0.543 [45.7%] / 0.658 [34.2%]	0.825 [17.5%]	(0.422, 1.611)	0.5698
	20 mg/kg	0.4309	Not Currently Taking	30 / 30	0.440 [56.0%] / 0.572 [42.8%]	0.769 [23.1%]	(0.529, 1.119)	0.1683
			Currently Taking	10 / 11	0.377 [62.3%] / 0.658 [34.2%]	0.572 [42.8%]	(0.302, 1.084)	0.0862

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Adhoc Table: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Baseline Convulsive Seizure Frequency	10 mg/kg	0.8658	<=7	16 / 13	0.338 [66.2%] / 0.545 [45.5%]	0.621 [37.9%]	(0.348, 1.109)	0.1061
			>7 to <=21	16 / 13	0.313 [68.7%] / 0.500 [50.0%]	0.627 [37.3%]	(0.363, 1.083)	0.0937
			>21	13 / 15	0.376 [62.4%] / 0.720 [28.0%]	0.522 [47.8%]	(0.309, 0.883)	0.0158
	20 mg/kg	0.2222	<=7	12 / 13	0.362 [63.8%] / 0.545 [45.5%]	0.664 [33.6%]	(0.352, 1.250)	0.2026
			>7 to <=21	18 / 13	0.506 [49.4%] / 0.500 [50.0%]	1.012 [-1.2%]	(0.596, 1.720)	0.9645
			>21	10 / 15	0.371 [62.9%] / 0.720 [28.0%]	0.515 [48.5%]	(0.293, 0.908)	0.0221
Number of concurrent AEDs	10 mg/kg	0.3905	<3	12 / 10	0.292 [70.8%] / 0.638 [36.2%]	0.458 [54.2%]	(0.250, 0.841)	0.0123
			>=3	33 / 31	0.360 [64.0%] / 0.577 [42.3%]	0.623 [37.7%]	(0.434, 0.895)	0.0108
	20 mg/kg	0.3211	<3	8 / 10	0.619 [38.1%] / 0.638 [36.2%]	0.970 [3.0%]	(0.506, 1.859)	0.9271
			>=3	32 / 31	0.384 [61.6%] / 0.577 [42.3%]	0.666 [33.4%]	(0.460, 0.964)	0.0313
Number of prior AEDs	10 mg/kg	0.3054	<4	17 / 17	0.274 [72.6%] / 0.598 [40.2%]	0.459 [54.1%]	(0.275, 0.766)	0.0032
			>=4	28 / 24	0.379 [62.1%] / 0.591 [40.9%]	0.641 [35.9%]	(0.433, 0.949)	0.0267
	20 mg/kg	0.1953	<4	14 / 17	0.322 [67.8%] / 0.598 [40.2%]	0.539 [46.1%]	(0.317, 0.916)	0.0228
			>=4	26 / 24	0.494 [50.6%] / 0.591 [40.9%]	0.836 [16.4%]	(0.558, 1.253)	0.3823
Number of prior and concurrent AEDs	10 mg/kg	0.1151	<8	23 / 22	0.290 [71.0%] / 0.651 [34.9%]	0.446 [55.4%]	(0.287, 0.692)	0.0004
			>=8	22 / 19	0.392 [60.8%] / 0.533 [46.7%]	0.736 [26.4%]	(0.472, 1.150)	0.1764
	20 mg/kg	0.6628	<8	20 / 22	0.436 [56.4%] / 0.651 [34.9%]	0.669 [33.1%]	(0.426, 1.052)	0.0811
			>=8	20 / 19	0.411 [58.9%] / 0.533 [46.7%]	0.772 [22.8%]	(0.486, 1.225)	0.2690

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Total Seizure Responder (subgroups) (ITT Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			Odds Ratio		Risk Difference				
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	p-value (vs. Placebo)	Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Total Seizures <=25pct	Age Group	10 mg/kg	0.7407	2-5 years	13	11	13	10	1.1000	0.7543	1.6042	1.0000	1.6500	0.2270	11.9934	0.0769	-0.2246	0.3785
				6-12 years	23	19	16	9	1.4686	0.9169	2.3522	0.1461	3.6944	0.8561	15.9439	0.2636	-0.0246	0.5518
				13-18 years	9	5	12	5	1.3333	0.5483	3.2423	0.6699	1.7500	0.3056	10.0223	0.1389	-0.2891	0.5669
Sex	10 mg/kg	0.3969	F		22	18	22	12	1.5000	0.9764	2.3043	0.1040	3.7500	0.9525	14.7637	0.2727	0.0095	0.5359
				M	23	17	19	12	1.1703	0.7685	1.7822	0.5159	1.6528	0.4427	6.1700	0.1076	-0.1740	0.3891
Region	10 mg/kg	0.4215	REST OF THE WORLD		23	16	18	10	1.2522	0.7642	2.0517	0.5149	1.8286	0.5055	6.6148	0.1401	-0.1566	0.4368
				USA	22	19	23	14	1.4188	0.9826	2.0486	0.0909	4.0714	0.9289	17.8462	0.2549	0.0093	0.5006
Valproate Use	10 mg/kg	0.1526	N		15	9	12	7	1.0286	0.5467	1.9351	1.0000	1.0714	0.2288	5.0181	0.0167	-0.3565	0.3899
				Y	30	26	29	17	1.4784	1.0560	2.0698	0.0204	4.5882	1.2679	16.6042	0.2805	0.0638	0.4971
Stiripentol Use	10 mg/kg	0.0533	N		28	26	24	15	1.4857	1.0719	2.0593	0.0147	7.8000	1.4850	40.9708	0.3036	0.0877	0.5195
				Y	17	9	17	9	1.0000	0.5306	1.8848	1.0000	1.0000	0.2601	3.8453	0.0000	-0.3355	0.3355
Levetiracetam Use	10 mg/kg	0.9364	N		34	28	33	21	1.2941	0.9575	1.7490	0.1036	2.6667	0.8601	8.2682	0.1872	-0.0211	0.3954
				Y	11	7	8	3	1.6970	0.6243	4.6125	0.3698	2.9167	0.4423	19.2341	0.2614	-0.1784	0.7011
Topiramate Use	10 mg/kg	0.0755	N		37	31	30	17	1.4785	1.0487	2.0846	0.0277	3.9510	1.2714	12.2781	0.2712	0.0577	0.4846
				Y	8	4	11	7	0.7857	0.3445	1.7919	0.6577	0.5714	0.0897	3.6414	-0.1364	-0.5845	0.3118
Baseline Convulsive Seizure Frequency	10 mg/kg	0.4250	<=7		16	12	13	8	1.2188	0.7286	2.0387	0.6882	1.8750	0.3823	9.1970	0.1346	-0.2044	0.4737
				>7 to <=21	16	12	13	9	1.0833	0.6841	1.7156	1.0000	1.3333	0.2604	6.8277	0.0577	-0.2709	0.3863
				>21	13	11	15	7	1.8132	1.0065	3.2663	0.0546	6.2857	1.0222	38.6509	0.3795	0.0598	0.6992
Current AEDs	10 mg/kg	0.3063	<3		12	11	10	6	1.5278	0.8956	2.6061	0.1353	7.3333	0.6609	81.3646	0.3167	-0.0249	0.6582
				>=3	33	24	31	18	1.2525	0.8696	1.8041	0.2938	1.9259	0.6761	5.4861	0.1466	-0.0842	0.3774
Prior AEDs	10 mg/kg	0.5682	<4		17	13	17	11	1.1818	0.7618	1.8333	0.7080	1.7727	0.3962	7.9324	0.1176	-0.1861	0.4214
				>=4	28	22	24	13	1.4505	0.9571	2.1983	0.0799	3.1026	0.9269	10.3850	0.2440	-0.0066	0.4947
Prior + Current AEDs	10 mg/kg	0.5847	<8		23	19	22	13	1.3980	0.9418	2.0752	0.1075	3.2885	0.8332	12.9789	0.2352	-0.0221	0.4925
				>=8	22	16	19	11	1.2562	0.7922	1.9919	0.3458	1.9394	0.5246	7.1703	0.1483	-0.1414	0.4380
Age Group	20 mg/kg	0.5173	2-5 years		10	8	13	10	1.0400	0.6767	1.5983	1.0000	1.2000	0.1598	9.0128	0.0308	-0.3067	0.3683
				6-12 years	22	19	16	9	1.5354	0.9664	2.4393	0.0623	4.9259	1.0270	23.6273	0.3011	0.0189	0.5834
				13-18 years	8	6	12	5	1.8000	0.8252	3.9262	0.1968	4.2000	0.5861	30.0950	0.3333	-0.0764	0.7430
Sex	20 mg/kg	0.7323	F		17	13	22	12	1.4020	0.8817	2.2291	0.1935	2.7083	0.6678	10.9833	0.2193	-0.0705	0.5090
				M	23	20	19	12	1.3768	0.9433	2.0096	0.1435	3.8889	0.8419	17.9629	0.2380	-0.0189	0.4949
Region	20 mg/kg	0.6722	REST OF THE WORLD		19	16	18	10	1.5158	0.9600	2.3934	0.0789	4.2667	0.9108	19.9883	0.2865	0.0045	0.5686
				USA	21	17	23	14	1.3299	0.9024	1.9600	0.1936	2.7321	0.6916	10.7938	0.2008	-0.0599	0.4616
Valproate Use	20 mg/kg	0.1094	N		10	6	12	7	1.0286	0.5127	2.0635	1.0000	1.0714	0.1941	5.9128	0.0167	-0.3956	0.4290
				Y	30	27	29	17	1.5353	1.1057	2.1318	0.0074	6.3529	1.5617	25.8439	0.3138	0.1049	0.5227
Stiripentol Use	20 mg/kg	0.0690	N		22	16	24	15	1.1636	0.7785	1.7392	0.5386	1.6000	0.4583	5.5862	0.1023	-0.1663	0.3709
				Y	18	17	17	9	1.7840	1.1240	2.8315	0.0072	15.1111	1.6243	140.5798	0.4150	0.1552	0.6748
Levetiracetam Use	20 mg/kg	0.5864	N		31	26	33	21	1.3180	0.9758	1.7801	0.0914	2.9714	0.9028	9.7796	0.2023	-0.0067	0.4114
				Y	9	7	8	3	2.0741	0.7939	5.4187	0.1534	5.8333	0.6963	48.8725	0.4028	-0.0289	0.8344
Topiramate Use	20 mg/kg	0.6623	N		30	25	30	17	1.4706	1.0348	2.0899	0.0470	3.8235	1.1500	12.7126	0.2667	0.0448	0.4885
				Y	10	8	11	7	1.2571	0.7299	2.1652	0.6351	2.2857	0.3164	16.5116	0.1636	-0.2136	0.5408

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Baseline Convulsive Seizure Frequency	20 mg/kg	0.3996 <=7	12	10	13	8	1.3542	0.8224	2.2298	0.3783	3.1250	0.4745	20.5830	0.2179	-0.1203	0.5562
		>7 to <=21	18	14	13	9	1.1235	0.7246	1.7418	0.6894	1.5556	0.3081	7.8544	0.0855	-0.2305	0.4014
		>21	10	9	15	7	1.9286	1.0808	3.4414	0.0405	10.2857	1.0296	102.7534	0.4333	0.1198	0.7469
Current AEDs	20 mg/kg	0.0433 <3	8	4	10	6	0.8333	0.3533	1.9655	1.0000	0.6667	0.1021	4.3538	-0.1000	-0.5607	0.3607
		>=3	32	29	31	18	1.5608	1.1342	2.1477	0.0038	6.9815	1.7453	27.9264	0.3256	0.1247	0.5265
Prior AEDs	20 mg/kg	0.1071 <4	14	14	17	11	1.5455	1.0879	2.1955	0.0209	-	-	-	0.3529	0.1258	0.5801
		>=4	26	19	24	13	1.3491	0.8726	2.0859	0.2395	2.2967	0.7047	7.4847	0.1891	-0.0732	0.4514
Prior + Current AEDs	20 mg/kg	0.7055 <8	20	16	22	13	1.3538	0.8976	2.0420	0.1900	2.7692	0.6921	11.0808	0.2091	-0.0610	0.4792
		>=8	20	17	19	11	1.4682	0.9595	2.2465	0.0824	4.1212	0.8939	19.0011	0.2711	-0.0006	0.5427
Total Seizures <=50pct																
Age Group	10 mg/kg	0.8079 2-5 years	13	10	13	8	1.2500	0.7411	2.1085	0.6728	2.0833	0.3780	11.4817	0.1538	-0.1960	0.5037
		6-12 years	23	15	16	5	2.0870	0.9513	4.5785	0.0536	4.1250	1.0571	16.0966	0.3397	0.0406	0.6388
		13-18 years	9	5	12	4	1.6667	0.6188	4.4890	0.3964	2.5000	0.4215	14.8280	0.2222	-0.1979	0.6424
Sex	10 mg/kg	0.8352 F	22	14	22	8	1.7500	0.9258	3.3078	0.1308	3.0625	0.8965	10.4615	0.2727	-0.0115	0.5570
		M	23	16	19	9	1.4686	0.8510	2.5344	0.2092	2.5397	0.7169	8.9970	0.2220	-0.0709	0.5148
Region	10 mg/kg	0.4007 REST OF THE WORLD	23	13	18	7	1.4534	0.7355	2.8719	0.3499	2.0429	0.5818	7.1735	0.1763	-0.1266	0.4793
		USA	22	17	23	10	1.7773	1.0586	2.9839	0.0331	4.4200	1.2121	16.1180	0.3379	0.0702	0.6057
Valproate Use	10 mg/kg	0.6874 N	15	8	12	4	1.6000	0.6315	4.0540	0.4408	2.2857	0.4748	11.0028	0.2000	-0.1673	0.5673
		Y	30	22	29	13	1.6359	1.0350	2.5857	0.0352	3.3846	1.1368	10.0773	0.2851	0.0446	0.5255
Stiripentol Use	10 mg/kg	0.1279 N	28	23	24	11	1.7922	1.1224	2.8617	0.0088	5.4364	1.5467	19.1079	0.3631	0.1184	0.6078
		Y	17	7	17	6	1.1667	0.4944	2.7530	1.0000	1.2833	0.3208	5.1344	0.0588	-0.2673	0.3849
Levetiracetam Use	10 mg/kg	0.3614 N	34	24	33	16	1.4559	0.9631	2.2008	0.0837	2.5500	0.9333	6.9672	0.2210	-0.0082	0.4502
		Y	11	6	8	1	4.3636	0.6455	29.5004	0.1473	8.4000	0.7559	93.3444	0.4205	0.0475	0.7934
Topiramate Use	10 mg/kg	0.5964 N	37	26	30	13	1.6216	1.0240	2.5681	0.0454	3.0909	1.1267	8.4794	0.2694	0.0389	0.4999
		Y	8	4	11	4	1.3750	0.4837	3.9084	0.6577	1.7500	0.2746	11.1519	0.1364	-0.3118	0.5845
Baseline Convulsive Seizure Frequency	10 mg/kg	0.2625 <=7	16	11	13	5	1.7875	0.8336	3.8330	0.1436	3.5200	0.7560	16.3895	0.3029	-0.0457	0.6515
		>7 to <=21	16	10	13	8	1.0156	0.5724	1.8019	1.0000	1.0417	0.2307	4.7040	0.0096	-0.3456	0.3649
		>21	13	9	15	4	2.5962	1.0407	6.4763	0.0557	6.1875	1.1976	31.9675	0.4256	0.0894	0.7618
Current AEDs	10 mg/kg	0.2694 <3	12	9	10	3	2.5000	0.9183	6.8061	0.0836	7.0000	1.0675	45.9011	0.4500	0.0749	0.8251
		>=3	33	21	31	14	1.4091	0.8844	2.2451	0.2089	2.1250	0.7804	5.7862	0.1848	-0.0553	0.4248
Prior AEDs	10 mg/kg	0.9092 <4	17	12	17	8	1.5000	0.8313	2.7066	0.2960	2.7000	0.6575	11.0878	0.2353	-0.0860	0.5566
		>=4	28	18	24	9	1.7143	0.9544	3.0791	0.0940	3.0000	0.9676	9.3017	0.2679	0.0052	0.5306
Prior + Current AEDs	10 mg/kg	0.4220 <8	23	16	22	8	1.9130	1.0339	3.5397	0.0377	4.0000	1.1548	13.8550	0.3320	0.0568	0.6073
		>=8	22	14	19	9	1.3434	0.7601	2.3746	0.3550	1.9444	0.5564	6.7951	0.1627	-0.1387	0.4640
Age Group	20 mg/kg	0.2511 2-5 years	10	6	13	8	0.9750	0.5020	1.8938	1.0000	0.9375	0.1733	5.0702	-0.0154	-0.4180	0.3873
		6-12 years	22	16	16	5	2.3273	1.0770	5.0289	0.0201	5.8667	1.4274	24.1127	0.4148	0.1211	0.7084
		13-18 years	8	5	12	4	1.8750	0.7154	4.9142	0.3618	3.3333	0.5148	21.5839	0.2917	-0.1369	0.7202
Sex	20 mg/kg	0.8054 F	17	10	22	8	1.6176	0.8187	3.1962	0.2057	2.5000	0.6820	9.1644	0.2246	-0.0838	0.5330
		M	23	17	19	9	1.5604	0.9161	2.6577	0.1133	3.1481	0.8622	11.4946	0.2654	-0.0220	0.5529
Region	20 mg/kg	0.8405 REST OF THE WORLD	19	12	18	7	1.6241	0.8283	3.1842	0.1939	2.6939	0.7130	10.1780	0.2427	-0.0700	0.5554
		USA	21	15	23	10	1.6429	0.9585	2.8158	0.0759	3.2500	0.9261	11.4048	0.2795	-0.0005	0.5595
Valproate Use	20 mg/kg	0.6131 N	10	5	12	4	1.5000	0.5452	4.1271	0.6656	2.0000	0.3562	11.2299	0.1667	-0.2422	0.5755
		Y	30	22	29	13	1.6359	1.0350	2.5857	0.0352	3.3846	1.1368	10.0773	0.2851	0.0446	0.5255

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Stiripentol Use	20 mg/kg	0.6939 N	22	15	24	11	1.4876	0.8842	2.5028	0.1490	2.5325	0.7597	8.4417	0.2235	-0.0551	0.5021
		Y	18	12	17	6	1.8889	0.9178	3.8876	0.0943	3.6667	0.9075	14.8151	0.3137	-0.0010	0.6284
Levetiracetam Use	20 mg/kg	0.3662 N	31	22	33	16	1.4637	0.9641	2.2223	0.0800	2.5972	0.9243	7.2983	0.2248	-0.0089	0.4585
		Y	9	5	8	1	4.4444	0.6488	30.4445	0.1312	8.7500	0.7374	103.8236	0.4306	0.0332	0.8279
Topiramate Use	20 mg/kg	0.6782 N	30	20	30	13	1.5385	0.9509	2.4890	0.1188	2.6154	0.9173	7.4567	0.2333	-0.0114	0.4781
		Y	10	7	11	4	1.9250	0.7978	4.6446	0.1984	4.0833	0.6569	25.3821	0.3364	-0.0655	0.7382
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4236 <=7	12	9	13	5	1.9500	0.9108	4.1749	0.1107	4.8000	0.8602	26.7854	0.3654	0.0049	0.7259
		>7 to <=21	18	12	13	8	1.0833	0.6314	1.8587	1.0000	1.2500	0.2828	5.5254	0.0513	-0.2913	0.3939
		>21	10	6	15	4	2.2500	0.8445	5.9949	0.1221	4.1250	0.7491	22.7143	0.3333	-0.0439	0.7105
Current AEDs	20 mg/kg	0.7995 <3	8	4	10	3	1.6667	0.5156	5.3875	0.6305	2.3333	0.3365	16.1802	0.2000	-0.2480	0.6480
		>=3	32	23	31	14	1.5915	1.0205	2.4819	0.0420	3.1032	1.0902	8.8328	0.2671	0.0327	0.5016
Prior AEDs	20 mg/kg	0.3067 <4	14	12	17	8	1.8214	1.0533	3.1497	0.0570	6.7500	1.1449	39.7959	0.3866	0.0867	0.6864
		>=4	26	15	24	9	1.5385	0.8339	2.8384	0.1713	2.2727	0.7305	7.0709	0.2019	-0.0693	0.4732
Prior + Current AEDs	20 mg/kg	0.8080 <8	20	13	22	8	1.7875	0.9430	3.3884	0.1215	3.2500	0.9178	11.5088	0.2864	-0.0036	0.5764
		>=8	20	14	19	9	1.4778	0.8492	2.5717	0.2003	2.5926	0.6970	9.6435	0.2263	-0.0749	0.5275
Total Seizures <=75pct Age Group	10 mg/kg	0.2729 2-5 years	13	5	13	2	2.5000	0.5873	10.6414	0.3783	3.4375	0.5268	22.4321	0.2308	-0.0985	0.5600
		6-12 years	23	8	16	0	-	-	-	0.0125	-	-	-	0.3478	0.1532	0.5425
		13-18 years	9	2	12	0	-	-	-	0.1714	-	-	-	0.2222	-0.0494	0.4938
Sex	10 mg/kg	0.1206 F	22	6	22	2	3.0000	0.6780	13.2740	0.2404	3.7500	0.6648	21.1539	0.1818	-0.0397	0.4033
		M	23	9	19	0	-	-	-	0.0020	-	-	-	0.3913	0.1919	0.5908
Region	10 mg/kg	0.0334 REST OF THE WORLD	23	5	18	2	1.9565	0.4282	8.9403	0.4376	2.2222	0.3775	13.0818	0.1063	-0.1162	0.3288
		USA	22	10	23	0	-	-	-	0.0002	-	-	-	0.4545	0.2465	0.6626
Valproate Use	10 mg/kg	0.4604 N	15	4	12	0	-	-	-	0.1060	-	-	-	0.2667	0.0429	0.4905
		Y	30	11	29	2	5.3167	1.2883	21.9418	0.0102	7.8158	1.5515	39.3722	0.2977	0.1021	0.4933
Stiripentol Use	10 mg/kg	0.0065 N	28	13	24	0	-	-	-	<.0001	-	-	-	0.4643	0.2796	0.6490
		Y	17	2	17	2	1.0000	0.1586	6.3033	1.0000	1.0000	0.1241	8.0570	0.0000	-0.2166	0.2166
Levetiracetam Use	10 mg/kg	0.4462 N	34	11	33	2	5.3382	1.2794	22.2730	0.0115	7.4130	1.4963	36.7273	0.2629	0.0859	0.4400
		Y	11	4	8	0	-	-	-	0.1032	-	-	-	0.3636	0.0794	0.6479
Topiramate Use	10 mg/kg	0.6708 N	37	14	30	2	5.6757	1.3980	23.0427	0.0035	8.5217	1.7536	41.4111	0.3117	0.1317	0.4917
		Y	8	1	11	0	-	-	-	0.4211	-	-	-	0.1250	-0.1042	0.3542
Baseline Convulsive Seizure Frequency	10 mg/kg	0.0925 <=7	16	4	13	2	1.6250	0.3513	7.5158	0.6628	1.8333	0.2786	12.0661	0.0962	-0.1928	0.3851
		>7 to <=21	16	7	13	0	-	-	-	0.0084	-	-	-	0.4375	0.1944	0.6806
		>21	13	4	15	0	-	-	-	0.0349	-	-	-	0.3077	0.0568	0.5586
Current AEDs	10 mg/kg	0.3214 <3	12	5	10	0	-	-	-	0.0396	-	-	-	0.4167	0.1377	0.6956
		>=3	33	10	31	2	4.6970	1.1163	19.7622	0.0231	6.3043	1.2554	31.6596	0.2385	0.0594	0.4176
Prior AEDs	10 mg/kg	0.9013 <4	17	7	17	1	7.0000	0.9621	50.9287	0.0391	11.2000	1.1932	105.1320	0.3529	0.0936	0.6123
		>=4	28	8	24	1	6.8571	0.9224	50.9772	0.0281	9.2000	1.0573	80.0542	0.2440	0.0586	0.4295
Prior + Current AEDs	10 mg/kg	0.6604 <8	23	9	22	1	8.6087	1.1867	62.4491	0.0098	13.5000	1.5355	118.6924	0.3458	0.1282	0.5635
		>=8	22	6	19	1	5.1818	0.6832	39.2996	0.0994	6.7500	0.7320	62.2448	0.2201	0.0086	0.4316
Age Group	20 mg/kg	0.1785 2-5 years	10	2	13	2	1.3000	0.2196	7.6946	1.0000	1.3750	0.1584	11.9373	0.0462	-0.2700	0.3623
		6-12 years	22	5	16	0	-	-	-	0.0612	-	-	-	0.2273	0.0522	0.4024
		13-18 years	8	2	12	0	-	-	-	0.1474	-	-	-	0.2500	-0.0501	0.5501

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Sex	20 mg/kg	0.2274 F	17	4	22	2	2.5882	0.5358	12.5027	0.3741	3.0769	0.4909	19.2849	0.1444	-0.0903	0.3791
		M	23	5	19	0	-	-	-	0.0532	-	-	-	0.2174	0.0488	0.3860
Region	20 mg/kg	0.0627 REST OF THE WORLD	19	3	18	2	1.4211	0.2678	7.5415	1.0000	1.5000	0.2202	10.2181	0.0468	-0.1722	0.2658
		USA	21	6	23	0	-	-	-	0.0077	-	-	-	0.2857	0.0925	0.4789
Valproate Use	20 mg/kg	0.1563 N	10	4	12	0	-	-	-	0.0287	-	-	-	0.4000	0.0964	0.7036
		Y	30	5	29	2	2.4167	0.5087	11.4817	0.4238	2.7000	0.4798	15.1948	0.0977	-0.0644	0.2598
Stiripentol Use	20 mg/kg	0.0243 N	22	7	24	0	-	-	-	0.0032	-	-	-	0.3182	0.1236	0.5128
		Y	18	2	17	2	0.9444	0.1493	5.9734	1.0000	0.9375	0.1168	7.5245	-0.0065	-0.2176	0.2045
Levetiracetam Use	20 mg/kg	0.3390 N	31	6	33	2	3.1935	0.6961	14.6509	0.1423	3.7200	0.6900	20.0559	0.1329	-0.0282	0.2941
		Y	9	3	8	0	-	-	-	0.2059	-	-	-	0.3333	0.0254	0.6413
Topiramate Use	20 mg/kg	0.1751 N	30	5	30	2	2.5000	0.5255	11.8945	0.4238	2.8000	0.4983	15.7344	0.1000	-0.0605	0.2605
		Y	10	4	11	0	-	-	-	0.0351	-	-	-	0.4000	0.0964	0.7036
Baseline Convulsive Seizure Frequency	20 mg/kg	0.2307 <=7	12	3	13	2	1.6250	0.3255	8.1132	0.6447	1.8333	0.2495	13.4697	0.0962	-0.2177	0.4100
		>7 to <=21	18	3	13	0	-	-	-	0.2452	-	-	-	0.1667	-0.0055	0.3388
		>21	10	3	15	0	-	-	-	0.0522	-	-	-	0.3000	0.0160	0.5840
Current AEDs	20 mg/kg	0.5951 <3	8	1	10	0	-	-	-	0.4444	-	-	-	0.1250	-0.1042	0.3542
		>=3	32	8	31	2	3.8750	0.8922	16.8306	0.0816	4.8333	0.9365	24.9458	0.1855	0.0123	0.3587
Prior AEDs	20 mg/kg	0.9244 <4	14	4	17	1	4.8571	0.6105	38.6462	0.1484	6.4000	0.6231	65.7388	0.2269	-0.0349	0.4886
		>=4	26	5	24	1	4.6154	0.5800	36.7268	0.1919	5.4762	0.5906	50.7772	0.1506	-0.0206	0.3219
Prior + Current AEDs	20 mg/kg	0.7869 <8	20	5	22	1	5.5000	0.7011	43.1472	0.0866	7.0000	0.7400	66.2118	0.2045	-0.0042	0.4133
		>=8	20	4	19	1	3.8000	0.4656	31.0135	0.3416	4.5000	0.4546	44.5462	0.1474	-0.0547	0.3494

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc Table: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data	10 mg/kg			45 / 41	0.390 [61.0%] / 0.622 [37.8%]	0.627 [37.3%]	(0.449, 0.875)	0.0064
	20 mg/kg			40 / 41	0.430 [57.0%] / 0.622 [37.8%]	0.691 [30.9%]	(0.488, 0.977)	0.0369
Age Group	10 mg/kg	0.3300	2-5 years	13 / 13	0.348 [65.2%] / 0.442 [55.8%]	0.787 [21.3%]	(0.420, 1.475)	0.4519
			6-12 years	23 / 16	0.450 [55.0%] / 0.675 [32.5%]	0.666 [33.4%]	(0.404, 1.098)	0.1101
			13-18 years	9 / 12	0.319 [68.1%] / 0.794 [20.6%]	0.402 [59.8%]	(0.204, 0.794)	0.0091
	20 mg/kg	0.7786	2-5 years	10 / 13	0.372 [62.8%] / 0.442 [55.8%]	0.841 [15.9%]	(0.432, 1.640)	0.6092
			6-12 years	22 / 16	0.432 [56.8%] / 0.675 [32.5%]	0.640 [36.0%]	(0.383, 1.070)	0.0880
			13-18 years	8 / 12	0.497 [50.3%] / 0.794 [20.6%]	0.626 [37.4%]	(0.307, 1.279)	0.1967
Sex	10 mg/kg	0.3732	Female	22 / 22	0.479 [52.1%] / 0.659 [34.1%]	0.727 [27.3%]	(0.458, 1.153)	0.1739
			Male	23 / 19	0.313 [68.7%] / 0.583 [41.7%]	0.538 [46.2%]	(0.331, 0.873)	0.0126
	20 mg/kg	0.8901	Female	17 / 22	0.449 [55.1%] / 0.659 [34.1%]	0.682 [31.8%]	(0.409, 1.138)	0.1419
			Male	23 / 19	0.418 [58.2%] / 0.583 [41.7%]	0.717 [28.3%]	(0.443, 1.160)	0.1733
Region	10 mg/kg	0.0078	USA	22 / 23	0.229 [77.1%] / 0.614 [38.6%]	0.373 [62.7%]	(0.237, 0.588)	<.0001
			Rest of the World	23 / 18	0.590 [41.0%] / 0.639 [36.1%]	0.923 [7.7%]	(0.570, 1.496)	0.7440
	20 mg/kg	0.4537	USA	21 / 23	0.376 [62.4%] / 0.614 [38.6%]	0.613 [38.7%]	(0.389, 0.966)	0.0351
			Rest of the World	19 / 18	0.509 [49.1%] / 0.639 [36.1%]	0.796 [20.4%]	(0.475, 1.335)	0.3845

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Adhoc Table: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Valproic Acid Use	10 mg/kg	0.5460	Not Currently Taking	15 / 12	0.421 [57.9%] / 0.582 [41.8%]	0.725 [27.5%]	(0.402, 1.307)	0.2816
			Currently Taking	30 / 29	0.376 [62.4%] / 0.647 [35.3%]	0.582 [41.8%]	(0.386, 0.877)	0.0101
	20 mg/kg	0.7329	Not Currently Taking	10 / 12	0.438 [56.2%] / 0.582 [41.8%]	0.754 [24.6%]	(0.395, 1.439)	0.3888
			Currently Taking	30 / 29	0.427 [57.3%] / 0.647 [35.3%]	0.660 [34.0%]	(0.435, 1.003)	0.0514
Stiripentol Use	10 mg/kg	0.0020	Not Currently Taking	28 / 24	0.251 [74.9%] / 0.610 [39.0%]	0.411 [58.9%]	(0.274, 0.616)	<.0001
			Currently Taking	17 / 17	0.763 [23.7%] / 0.652 [34.8%]	1.170 [-17.0%]	(0.698, 1.962)	0.5481
	20 mg/kg	0.7878	Not Currently Taking	22 / 24	0.437 [56.3%] / 0.610 [39.0%]	0.716 [28.4%]	(0.464, 1.106)	0.1313
			Currently Taking	18 / 17	0.426 [57.4%] / 0.652 [34.8%]	0.654 [34.6%]	(0.392, 1.090)	0.1025
Levetiracetam Use	10 mg/kg	0.7113	Not Currently Taking	34 / 33	0.378 [62.2%] / 0.582 [41.8%]	0.650 [35.0%]	(0.444, 0.951)	0.0269
			Currently Taking	11 / 8	0.434 [56.6%] / 0.779 [22.1%]	0.558 [44.2%]	(0.271, 1.148)	0.1120
	20 mg/kg	0.9775	Not Currently Taking	31 / 33	0.400 [60.0%] / 0.582 [41.8%]	0.687 [31.3%]	(0.461, 1.023)	0.0644
			Currently Taking	9 / 8	0.541 [45.9%] / 0.779 [22.1%]	0.695 [30.5%]	(0.333, 1.452)	0.3302
Topiramate Use	10 mg/kg	0.3570	Not Currently Taking	37 / 30	0.359 [64.1%] / 0.618 [38.2%]	0.581 [41.9%]	(0.395, 0.855)	0.0063
			Currently Taking	8 / 11	0.537 [46.3%] / 0.633 [36.7%]	0.848 [15.2%]	(0.416, 1.730)	0.6481
	20 mg/kg	0.6841	Not Currently Taking	30 / 30	0.444 [55.6%] / 0.618 [38.2%]	0.719 [28.1%]	(0.478, 1.081)	0.1119
			Currently Taking	10 / 11	0.385 [61.5%] / 0.633 [36.7%]	0.609 [39.1%]	(0.304, 1.222)	0.1611

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Adhoc Table: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Baseline Convulsive Seizure Frequency	10 mg/kg	0.1757	<=7	16 / 13	0.522 [47.8%] / 0.529 [47.1%]	0.986 [1.4%]	(0.514, 1.893)	0.9667
			>7 to <=21	16 / 13	0.417 [58.3%] / 0.587 [41.3%]	0.711 [28.9%]	(0.403, 1.253)	0.2355
			>21	13 / 15	0.348 [65.2%] / 0.767 [23.3%]	0.453 [54.7%]	(0.267, 0.768)	0.0036
	20 mg/kg	0.1165	<=7	12 / 13	0.263 [73.7%] / 0.529 [47.1%]	0.496 [50.4%]	(0.238, 1.036)	0.0617
			>7 to <=21	18 / 13	0.641 [35.9%] / 0.587 [41.3%]	1.090 [-9.0%]	(0.625, 1.902)	0.7585
			>21	10 / 15	0.401 [59.9%] / 0.767 [23.3%]	0.523 [47.7%]	(0.297, 0.922)	0.0253
Number of concurrent AEDs	10 mg/kg	0.0269	<3 ≥3	12 / 10 33 / 31	0.236 [76.4%] / 0.702 [29.8%] 0.466 [53.4%] / 0.595 [40.5%]	0.336 [66.4%] 0.782 [21.8%]	(0.177, 0.637) (0.532, 1.151)	0.0010 0.2102
	20 mg/kg	0.8089	<3 ≥3	8 / 10 32 / 31	0.534 [46.6%] / 0.702 [29.8%] 0.409 [59.1%] / 0.595 [40.5%]	0.760 [24.0%] 0.688 [31.2%]	(0.372, 1.554) (0.465, 1.019)	0.4494 0.0616
Number of prior AEDs	10 mg/kg	0.7554	<4 ≥4	17 / 17 28 / 24	0.341 [65.9%] / 0.589 [41.1%] 0.418 [58.2%] / 0.647 [35.3%]	0.580 [42.0%] 0.647 [35.3%]	(0.336, 1.001) (0.422, 0.991)	0.0505 0.0454
	20 mg/kg	0.7330	<4 ≥4	14 / 17 26 / 24	0.372 [62.8%] / 0.589 [41.1%] 0.463 [53.7%] / 0.647 [35.3%]	0.632 [36.8%] 0.717 [28.3%]	(0.354, 1.128) (0.461, 1.113)	0.1194 0.1367
Number of prior and concurrent AEDs	10 mg/kg	0.8646	<8 ≥8	23 / 22 22 / 19	0.405 [59.5%] / 0.626 [37.4%] 0.377 [62.3%] / 0.618 [38.2%]	0.647 [35.3%] 0.610 [39.0%]	(0.403, 1.037) (0.375, 0.993)	0.0699 0.0467
	20 mg/kg	0.9954	<8 ≥8	20 / 22 20 / 19	0.432 [56.8%] / 0.626 [37.4%] 0.427 [57.3%] / 0.618 [38.2%]	0.690 [31.0%] 0.692 [30.8%]	(0.421, 1.132) (0.418, 1.144)	0.1403 0.1493

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Convulsive Seizure Responder (subgroups) (ITT Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI	
Convulsive Seizures <=25pct	Age Group	10 mg/kg	0.2528	2-5 years	13	9	13	11	0.8182	0.5321	1.2580	0.6447	0.4091	0.0604	2.7692	-0.1538	-0.4723	0.1646
				6-12 years	23	16	16	8	1.3913	0.7950	2.4348	0.3178	2.2857	0.6090	8.5786	0.1957	-0.1132	0.5045
				13-18 years	9	6	12	5	1.6000	0.7094	3.6088	0.3870	2.8000	0.4631	16.9287	0.2500	-0.1655	0.6655
Sex	10 mg/kg	0.8908	F	22	14	22	12	1.1667	0.7110	1.9144	0.7597	1.4583	0.4358	4.8799	0.0909	-0.1984	0.3802	
			M	23	17	19	12	1.1703	0.7685	1.7822	0.5159	1.6528	0.4427	6.1700	0.1076	-0.1740	0.3891	
Region	10 mg/kg	0.2490	REST OF THE WORLD	23	12	18	9	1.0435	0.5696	1.9116	1.0000	1.0909	0.3176	3.7476	0.0217	-0.2865	0.3300	
			USA	22	19	23	15	1.3242	0.9411	1.8634	0.1653	3.3778	0.7616	14.9817	0.2115	-0.0303	0.4532	
Valproate Use	10 mg/kg	0.2634	N	15	9	12	8	0.9000	0.5064	1.5997	1.0000	0.7500	0.1539	3.6542	-0.0667	-0.4308	0.2975	
			Y	30	22	29	16	1.3292	0.8975	1.9684	0.1799	2.2344	0.7504	6.6526	0.1816	-0.0588	0.4220	
Stiripentol Use	10 mg/kg	0.0580	N	28	25	24	16	1.3393	0.9817	1.8272	0.0862	4.1667	0.9601	18.0819	0.2262	0.0055	0.4469	
			Y	17	6	17	8	0.7500	0.3311	1.6988	0.7283	0.6136	0.1548	2.4321	-0.1176	-0.4461	0.2108	
Levetiracetam Use	10 mg/kg	0.5405	N	34	23	33	20	1.1162	0.7786	1.6001	0.6154	1.3591	0.4990	3.7014	0.0704	-0.1588	0.2996	
			Y	11	8	8	4	1.4545	0.6656	3.1786	0.3765	2.6667	0.3915	18.1655	0.2273	-0.2078	0.6624	
Topiramate Use	10 mg/kg	0.0902	N	37	27	30	16	1.3682	0.9283	2.0167	0.1263	2.3625	0.8517	6.5533	0.1964	-0.0324	0.4252	
			Y	8	4	11	8	0.6875	0.3146	1.5024	0.3765	0.3750	0.0550	2.5545	-0.2273	-0.6624	0.2078	
Baseline Convulsive Seizure Frequency	10 mg/kg	0.4672	<=7	16	10	13	9	0.9028	0.5342	1.5258	1.0000	0.7407	0.1568	3.5002	-0.0673	-0.4126	0.2780	
			>7 to <=21	16	11	13	7	1.2768	0.6993	2.3311	0.4657	1.8857	0.4130	8.6110	0.1490	-0.2045	0.5026	
			>21	13	10	15	8	1.4423	0.8245	2.5231	0.2543	2.9167	0.5651	15.0542	0.2359	-0.1050	0.5768	
Current AEDs	10 mg/kg	0.3875	<3	12	10	10	6	1.3889	0.7888	2.4456	0.3476	3.3333	0.4620	24.0516	0.2333	-0.1363	0.6030	
			>=3	33	21	31	18	1.0960	0.7383	1.6268	0.7983	1.2639	0.4622	3.4562	0.0557	-0.1833	0.2947	
Prior AEDs	10 mg/kg	0.4290	<4	17	12	17	12	1.0000	0.6479	1.5433	1.0000	1.0000	0.2287	4.3728	0.0000	-0.3063	0.3063	
			>=4	28	19	24	12	1.3571	0.8445	2.1810	0.2594	2.1111	0.6843	6.5132	0.1786	-0.0859	0.4430	
Prior + Current AEDs	10 mg/kg	0.3787	<8	23	16	22	15	1.0203	0.6886	1.5117	1.0000	1.0667	0.3018	3.7696	0.0138	-0.2568	0.2845	
			>=8	22	15	19	9	1.4394	0.8277	2.5031	0.2159	2.3810	0.6679	8.4881	0.2081	-0.0890	0.5053	
Age Group	20 mg/kg	0.1490	2-5 years	10	8	13	11	0.9455	0.6421	1.3922	1.0000	0.7273	0.0838	6.3140	-0.0462	-0.3623	0.2700	
			6-12 years	22	20	16	8	1.8182	1.0945	3.0202	0.0082	10.0000	1.7325	57.7215	0.4091	0.1362	0.6820	
			13-18 years	8	6	12	5	1.8000	0.8252	3.9262	0.1968	4.2000	0.5861	30.0950	0.3333	-0.0764	0.7430	
Sex	20 mg/kg	1.0000	F	17	14	22	12	1.5098	0.9720	2.3452	0.0933	3.8889	0.8651	17.4819	0.2781	0.0022	0.5540	
			M	23	20	19	12	1.3768	0.9433	2.0096	0.1435	3.8889	0.8419	17.9629	0.2380	-0.0189	0.4949	
Region	20 mg/kg	0.6403	REST OF THE WORLD	19	16	18	9	1.6842	1.0202	2.7805	0.0382	5.3333	1.1424	24.8991	0.3421	0.0588	0.6254	
			USA	21	18	23	15	1.3143	0.9301	1.8572	0.1685	3.2000	0.7188	14.2468	0.2050	-0.0406	0.4505	
Valproate Use	20 mg/kg	0.1085	N	10	7	12	8	1.0500	0.5939	1.8563	1.0000	1.1667	0.1913	7.1165	0.0333	-0.3563	0.4230	
			Y	30	27	29	16	1.6313	1.1506	2.3127	0.0034	7.3125	1.8043	29.6362	0.3483	0.1378	0.5587	
Stiripentol Use	20 mg/kg	0.0520	N	22	17	24	16	1.1591	0.8067	1.6655	0.5207	1.7000	0.4590	6.2967	0.1061	-0.1513	0.3634	
			Y	18	17	17	8	2.0069	1.1974	3.3639	0.0027	19.1250	2.0558	177.9213	0.4739	0.2141	0.7337	
Levetiracetam Use	20 mg/kg	0.8561	N	31	27	33	20	1.4371	1.0576	1.9528	0.0234	4.3875	1.2432	15.4838	0.2649	0.0607	0.4692	
			Y	9	7	8	4	1.5556	0.7160	3.3798	0.3348	3.5000	0.4306	28.4473	0.2778	-0.1625	0.7180	
Topiramate Use	20 mg/kg	0.8521	N	30	25	30	16	1.5625	1.0782	2.2644	0.0251	4.3750	1.3197	14.5039	0.3000	0.0772	0.5228	
			Y	10	9	11	8	1.2375	0.8158	1.8772	0.5865	3.3750	0.2897	39.3222	0.1727	-0.1495	0.4950	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Baseline Convulsive Seizure Frequency	20 mg/kg	0.3214 <=7	12	12	13	9	1.4444	1.0053	2.0753	0.0957	-	-	-	0.3077	0.0568	0.5586
		>7 to <=21	18	13	13	7	1.3413	0.7516	2.3934	0.4491	2.2286	0.4968	9.9971	0.1838	-0.1572	0.5247
		>21	10	9	15	8	1.6875	1.0068	2.8285	0.0875	7.8750	0.7883	78.6705	0.3667	0.0531	0.6802
Current AEDs	20 mg/kg	0.1202 <3	8	5	10	6	1.0417	0.4981	2.1783	1.0000	1.1111	0.1645	7.5060	0.0250	-0.4275	0.4775
		>=3	32	29	31	18	1.5608	1.1342	2.1477	0.0038	6.9815	1.7453	27.9264	0.3256	0.1247	0.5265
Prior AEDs	20 mg/kg	0.8479 <4	14	13	17	12	1.3155	0.9368	1.8473	0.1848	5.4167	0.5508	53.2707	0.2227	-0.0325	0.4779
		>=4	26	21	24	12	1.6154	1.0384	2.5129	0.0359	4.2000	1.1895	14.8295	0.3077	0.0568	0.5586
Prior + Current AEDs	20 mg/kg	0.4275 <8	20	17	22	15	1.2467	0.8876	1.7509	0.2842	2.6444	0.5782	12.0947	0.1682	-0.0816	0.4179
		>=8	20	17	19	9	1.7944	1.0792	2.9837	0.0187	6.2963	1.3739	28.8547	0.3763	0.1026	0.6500
Convulsive Seizures <=50pct Age Group	10 mg/kg	0.9465 2-5 years	13	9	13	7	1.2857	0.6915	2.3905	0.6882	1.9286	0.3874	9.6007	0.1538	-0.2155	0.5231
		6-12 years	23	11	16	4	1.9130	0.7399	4.9465	0.1923	2.7500	0.6806	11.1113	0.2283	-0.0662	0.5227
		13-18 years	9	5	12	4	1.6667	0.6188	4.4890	0.3964	2.5000	0.4215	14.8280	0.2222	-0.1979	0.6424
Sex	10 mg/kg	0.6813 F	22	10	22	7	1.4286	0.6654	3.0669	0.5365	1.7857	0.5227	6.1000	0.1364	-0.1485	0.4213
		M	23	15	19	8	1.5489	0.8451	2.8389	0.2133	2.5781	0.7377	9.0100	0.2311	-0.0641	0.5264
Region	10 mg/kg	0.0918 REST OF THE WORLD	23	7	18	5	1.0957	0.4163	2.8839	1.0000	1.1375	0.2916	4.4369	0.0266	-0.2530	0.3062
		USA	22	18	23	10	1.8818	1.1347	3.1209	0.0134	5.8500	1.4994	22.8248	0.3834	0.1245	0.6423
Valproate Use	10 mg/kg	0.7253 N	15	7	12	4	1.4000	0.5329	3.6779	0.6960	1.7500	0.3635	8.4240	0.1333	-0.2339	0.5006
		Y	30	18	29	11	1.5818	0.9129	2.7408	0.1205	2.4545	0.8615	6.9931	0.2207	-0.0281	0.4695
Stiripentol Use	10 mg/kg	0.0222 N	28	22	24	10	1.8857	1.1308	3.1446	0.0100	5.1333	1.5249	17.2807	0.3690	0.1200	0.6181
		Y	17	3	17	5	0.6000	0.1696	2.1230	0.6880	0.5143	0.1012	2.6139	-0.1176	-0.4001	0.1648
Levetiracetam Use	10 mg/kg	0.2162 N	34	19	33	14	1.3172	0.8012	2.1656	0.3319	1.7190	0.6537	4.5206	0.1346	-0.1027	0.3718
		Y	11	6	8	1	4.3636	0.6455	29.5004	0.1473	8.4000	0.7559	93.3444	0.4205	0.0475	0.7934
Topiramate Use	10 mg/kg	0.8089 N	37	21	30	11	1.5479	0.8949	2.6775	0.1409	2.2670	0.8448	6.0837	0.2009	-0.0341	0.4359
		Y	8	4	11	4	1.3750	0.4837	3.9084	0.6577	1.7500	0.2746	11.1519	0.1364	-0.3118	0.5845
Baseline Convulsive Seizure Frequency	10 mg/kg	0.5178 <=7	16	7	13	5	1.1375	0.4699	2.7534	1.0000	1.2444	0.2801	5.5291	0.0529	-0.3063	0.4121
		>7 to <=21	16	10	13	6	1.3542	0.6730	2.7246	0.4667	1.9444	0.4392	8.6083	0.1635	-0.1967	0.5236
		>21	13	8	15	4	2.3077	0.8989	5.9245	0.1248	4.4000	0.8889	21.7801	0.3487	0.0023	0.6952
Current AEDs	10 mg/kg	0.3300 <3	12	8	10	3	2.2222	0.7951	6.2110	0.1984	4.6667	0.7650	28.4659	0.3667	-0.0230	0.7563
		>=3	33	17	31	12	1.3308	0.7655	2.3135	0.3275	1.6823	0.6225	4.5463	0.1281	-0.1138	0.3699
Prior AEDs	10 mg/kg	0.4422 <4	17	11	17	6	1.8333	0.8807	3.8164	0.1694	3.3611	0.8233	13.7222	0.2941	-0.0271	0.6154
		>=4	28	14	24	9	1.3333	0.7062	2.5175	0.4121	1.6667	0.5494	5.0564	0.1250	-0.1430	0.3930
Prior + Current AEDs	10 mg/kg	0.5543 <8	23	13	22	7	1.7764	0.8743	3.6095	0.1362	2.7857	0.8237	9.4207	0.2470	-0.0339	0.5280
		>=8	22	12	19	8	1.2955	0.6758	2.4834	0.5359	1.6500	0.4782	5.6927	0.1244	-0.1799	0.4287
Age Group	20 mg/kg	0.7939 2-5 years	10	7	13	7	1.3000	0.6811	2.4814	0.6693	2.0000	0.3520	11.3642	0.1615	-0.2310	0.5541
		6-12 years	22	13	16	4	2.3636	0.9446	5.9142	0.0516	4.3333	1.0525	17.8418	0.3409	0.0456	0.6363
		13-18 years	8	5	12	4	1.8750	0.7154	4.9142	0.3618	3.3333	0.5148	21.5839	0.2917	-0.1369	0.7202
Sex	20 mg/kg	0.8531 F	17	10	22	7	1.8487	0.8913	3.8348	0.1146	3.0612	0.8192	11.4395	0.2701	-0.0343	0.5744
		M	23	15	19	8	1.5489	0.8451	2.8389	0.2133	2.5781	0.7377	9.0100	0.2311	-0.0641	0.5264
Region	20 mg/kg	0.9011 REST OF THE WORLD	19	10	18	5	1.8947	0.8031	4.4704	0.1837	2.8889	0.7347	11.3599	0.2485	-0.0568	0.5539
		USA	21	15	23	10	1.6429	0.9585	2.8158	0.0759	3.2500	0.9261	11.4048	0.2795	-0.0005	0.5595
Valproate Use	20 mg/kg	0.9543 N	10	6	12	4	1.8000	0.6984	4.6392	0.3913	3.0000	0.5245	17.1587	0.2667	-0.1375	0.6708
		Y	30	19	29	11	1.6697	0.9737	2.8633	0.0698	2.8264	0.9837	8.1214	0.2540	0.0072	0.5008
Stiripentol Use	20 mg/kg	0.6464 N	22	14	24	10	1.5273	0.8645	2.6982	0.1547	2.4500	0.7463	8.0432	0.2197	-0.0619	0.5013

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		Y	18	11	17	5	2.0778	0.9119	4.7341	0.0922	3.7714	0.9213	15.4384	0.3170	0.0045	0.6295
Levetiracetam Use	20 mg/kg	0.3439 N	31	20	33	14	1.5207	0.9452	2.4467	0.0869	2.4675	0.8997	6.7674	0.2209	-0.0174	0.4593
		Y	9	5	8	1	4.4444	0.6488	30.4445	0.1312	8.7500	0.7374	103.8236	0.4306	0.0332	0.8279
Topiramate Use	20 mg/kg	0.9027 N	30	19	30	11	1.7273	1.0031	2.9742	0.0698	2.9835	1.0439	8.5270	0.2667	0.0228	0.5105
		Y	10	6	11	4	1.6500	0.6502	4.1872	0.3949	2.6250	0.4501	15.3104	0.2364	-0.1796	0.6523
Baseline Convulsive Seizure Frequency	20 mg/kg	0.2350 <=7	12	10	13	5	2.1667	1.0413	4.5081	0.0414	8.0000	1.2146	52.6926	0.4487	0.1105	0.7870
		>7 to <=21	18	9	13	6	1.0833	0.5132	2.2868	1.0000	1.1667	0.2794	4.8714	0.0385	-0.3176	0.3945
		>21	10	6	15	4	2.2500	0.8445	5.9949	0.1221	4.1250	0.7491	22.7143	0.3333	-0.0439	0.7105
Current AEDs	20 mg/kg	0.7315 <3	8	5	10	3	2.0833	0.7016	6.1860	0.3416	3.8889	0.5427	27.8658	0.3250	-0.1146	0.7646
		>=3	32	20	31	12	1.6146	0.9619	2.7101	0.0793	2.6389	0.9543	7.2970	0.2379	-0.0020	0.4778
Prior AEDs	20 mg/kg	0.4693 <4	14	10	17	6	2.0238	0.9813	4.1740	0.0732	4.5833	0.9947	21.1188	0.3613	0.0333	0.6894
		>=4	26	15	24	9	1.5385	0.8339	2.8384	0.1713	2.2727	0.7305	7.0709	0.2019	-0.0693	0.4732
Prior + Current AEDs	20 mg/kg	0.4763 <8	20	13	22	7	2.0429	1.0235	4.0773	0.0623	3.9796	1.1018	14.3733	0.3318	0.0462	0.6174
		>=8	20	12	19	8	1.4250	0.7535	2.6950	0.3431	2.0625	0.5754	7.3929	0.1789	-0.1299	0.4878
Convulsive Seizures <=75pct Age Group	10 mg/kg	0.8138 2-5 years	13	5	13	2	2.5000	0.5873	10.6414	0.3783	3.4375	0.5268	22.4321	0.2308	-0.0985	0.5600
		6-12 years	23	7	16	1	4.8696	0.6618	35.8299	0.1091	6.5625	0.7195	59.8534	0.2418	0.0195	0.4642
		13-18 years	9	4	12	1	5.3333	0.7120	39.9508	0.1194	8.8000	0.7724	100.2554	0.3611	0.0008	0.7214
Sex	10 mg/kg	0.1779 F	22	6	22	3	2.0000	0.5710	7.0058	0.4566	2.3750	0.5106	11.0475	0.1364	-0.0986	0.3713
		M	23	10	19	1	8.2609	1.1592	58.8683	0.0059	13.8462	1.5716	121.9854	0.3822	0.1560	0.6083
Region	10 mg/kg	0.0032 REST OF THE WORLD	23	3	18	3	0.7826	0.1787	3.4265	1.0000	0.7500	0.1323	4.2504	-0.0362	-0.2567	0.1842
		USA	22	13	23	1	13.5909	1.9372	95.3506	<.0001	31.7778	3.6038	280.2138	0.5474	0.3257	0.7691
Valproate Use	10 mg/kg	0.3588 N	15	5	12	2	2.0000	0.4675	8.5565	0.4082	2.5000	0.3894	16.0495	0.1667	-0.1517	0.4851
		Y	30	11	29	2	5.3167	1.2883	21.9418	0.0102	7.8158	1.5515	39.3722	0.2977	0.1021	0.4933
Stiripentol Use	10 mg/kg	0.0004 N	28	14	24	0	-	-	-	<.0001	-	-	-	0.5000	0.3148	0.6852
		Y	17	2	17	4	0.5000	0.1052	2.3760	0.6562	0.4333	0.0679	2.7635	-0.1176	-0.3709	0.1356
Levetiracetam Use	10 mg/kg	0.8275 N	34	12	33	3	3.8824	1.2038	12.5213	0.0174	5.4545	1.3728	21.6724	0.2620	0.0738	0.4502
		Y	11	4	8	1	2.9091	0.3964	21.3475	0.3378	4.0000	0.3525	45.3840	0.2386	-0.1265	0.6038
Topiramate Use	10 mg/kg	0.3579 N	37	15	30	3	4.0541	1.2937	12.7045	0.0059	6.1364	1.5727	23.9425	0.3054	0.1142	0.4966
		Y	8	1	11	1	1.3750	0.1003	18.8474	1.0000	1.4286	0.0759	26.8953	0.0341	-0.2512	0.3194
Baseline Convulsive Seizure Frequency	10 mg/kg	0.1458 <=7	16	5	13	3	1.3542	0.3958	4.6335	0.6968	1.5152	0.2858	8.0325	0.0817	-0.2408	0.4043
		>7 to <=21	16	6	13	1	4.8750	0.6687	35.5380	0.0927	7.2000	0.7385	70.2004	0.2981	0.0201	0.5760
		>21	13	5	15	0	-	-	-	0.0131	-	-	-	0.3846	0.1202	0.6491
Current AEDs	10 mg/kg	0.1162 <3	12	6	10	0	-	-	-	0.0152	-	-	-	0.5000	0.2171	0.7829
		>=3	33	10	31	4	2.3485	0.8212	6.7165	0.1322	2.9348	0.8111	10.6189	0.1740	-0.0222	0.3702
Prior AEDs	10 mg/kg	0.9951 <4	17	7	17	2	3.5000	0.8456	14.4859	0.1175	5.2500	0.9001	30.6207	0.2941	0.0145	0.5737
		>=4	28	9	24	2	3.8571	0.9213	16.1483	0.0463	5.2105	1.0001	27.1463	0.2381	0.0328	0.4434
Prior + Current AEDs	10 mg/kg	0.9391 <8	23	8	22	2	3.8261	0.9110	16.0685	0.0706	5.3333	0.9862	28.8439	0.2569	0.0282	0.4856
		>=8	22	8	19	2	3.4545	0.8327	14.3307	0.0752	4.8571	0.8844	26.6759	0.2584	0.0146	0.5022
Age Group	20 mg/kg	0.8472 2-5 years	10	4	13	2	2.6000	0.5897	11.4643	0.3413	3.6667	0.5127	26.2235	0.2462	-0.1153	0.6076
		6-12 years	22	5	16	1	3.6364	0.4690	28.1956	0.3696	4.4118	0.4620	42.1308	0.1648	-0.0467	0.3763
		13-18 years	8	1	12	1	1.5000	0.1088	20.6753	1.0000	1.5714	0.0840	29.4092	0.0417	-0.2358	0.3191
Sex	20 mg/kg	0.6466 F	17	5	22	3	2.1569	0.5974	7.7872	0.2610	2.6389	0.5309	13.1158	0.1578	-0.1020	0.4175
		M	23	5	19	1	4.1304	0.5268	32.3833	0.1973	5.0000	0.5300	47.1659	0.1648	-0.0314	0.3610

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Region	20 mg/kg	0.1661 REST OF THE WORLD	19	4	18	3	1.2632	0.3271	4.8775	1.0000	1.3333	0.2537	7.0070	0.0439	-0.2076	0.2953
		USA	21	6	23	1	6.5714	0.8608	50.1693	0.0420	8.8000	0.9592	80.7330	0.2422	0.0318	0.4527
Valproate Use	20 mg/kg	0.6258 N	10	3	12	2	1.8000	0.3707	8.7404	0.6241	2.1429	0.2805	16.3692	0.1333	-0.2204	0.4871
		Y	30	7	29	2	3.3833	0.7654	14.9563	0.1455	4.1087	0.7758	21.7602	0.1644	-0.0129	0.3416
Stiripentol Use	20 mg/kg	0.0023 N	22	8	24	0	-	-	-	0.0012	-	-	-	0.3636	0.1626	0.5646
		Y	18	2	17	4	0.4722	0.0990	2.2531	0.4018	0.4063	0.0640	2.5796	-0.1242	-0.3727	0.1243
Levetiracetam Use	20 mg/kg	0.3367 N	31	9	33	3	3.1935	0.9512	10.7223	0.0566	4.0909	0.9911	16.8863	0.1994	0.0119	0.3869
		Y	9	1	8	1	0.8889	0.0658	12.0044	1.0000	0.8750	0.0457	16.7443	-0.0139	-0.3216	0.2938
Topiramate Use	20 mg/kg	0.4478 N	30	6	30	3	2.0000	0.5504	7.2671	0.4716	2.2500	0.5066	9.9934	0.1000	-0.0789	0.2789
		Y	10	4	11	1	4.4000	0.5854	33.0706	0.1486	6.6667	0.5965	74.5056	0.3091	-0.0388	0.6570
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4745 <=7	12	6	13	3	2.1667	0.6913	6.7910	0.2262	3.3333	0.5992	18.5433	0.2692	-0.0948	0.6332
		>7 to <=21	18	2	13	1	1.4444	0.1460	14.2924	1.0000	1.5000	0.1214	18.5395	0.0342	-0.1709	0.2393
		>21	10	2	15	0	-	-	-	0.1500	-	-	-	0.2000	-0.0479	0.4479
Current AEDs	20 mg/kg	0.1354 <3	8	3	10	0	-	-	-	0.0686	-	-	-	0.3750	0.0395	0.7105
		>=3	32	7	31	4	1.6953	0.5505	5.2209	0.5092	1.8900	0.4931	7.2435	0.0897	-0.0959	0.2753
Prior AEDs	20 mg/kg	0.9413 <4	14	4	17	2	2.4286	0.5191	11.3619	0.3697	3.0000	0.4594	19.5923	0.1681	-0.1138	0.4499
		>=4	26	6	24	2	2.7692	0.6172	12.4239	0.2503	3.3000	0.5962	18.2646	0.1474	-0.0487	0.3435
Prior + Current AEDs	20 mg/kg	0.3235 <8	20	7	22	2	3.8500	0.9030	16.4148	0.0622	5.3846	0.9646	30.0590	0.2591	0.0180	0.5002
		>=8	20	3	19	2	1.4250	0.2668	7.6108	1.0000	1.5000	0.2218	10.1430	0.0447	-0.1639	0.2534

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc Table: GWEPl424 - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value	
All Data	10 mg/kg			45 / 41	0.257 [74.3%] / 0.479 [52.1%]	0.537 [46.3%]	(0.331, 0.870)	0.0119	
	20 mg/kg			40 / 41	0.395 [60.5%] / 0.479 [52.1%]	0.825 [17.5%]	(0.498, 1.366)	0.4511	
Age Group	10 mg/kg	0.5224	2-5 years	13 / 13	0.206 [79.4%] / 0.327 [67.3%]	0.631 [36.9%]	(0.257, 1.549)	0.3116	
			6-12 years	23 / 16	0.236 [76.4%] / 0.543 [45.7%]	0.434 [56.6%]	(0.217, 0.871)	0.0192	
			13-18 years	9 / 12	0.535 [46.5%] / 0.591 [40.9%]	0.905 [9.5%]	(0.294, 2.783)	0.8600	
	20 mg/kg	0.9129	2-5 years	10 / 13	0.321 [67.9%] / 0.327 [67.3%]	0.983 [1.7%]	(0.373, 2.590)	0.9717	
			6-12 years	22 / 16	0.416 [58.4%] / 0.543 [45.7%]	0.766 [23.4%]	(0.377, 1.556)	0.4574	
			13-18 years	8 / 12	0.457 [54.3%] / 0.591 [40.9%]	0.773 [22.7%]	(0.228, 2.619)	0.6766	
Sex	10 mg/kg	0.2439	Female	22 / 22	0.315 [68.5%] / 0.460 [54.0%]	0.685 [31.5%]	(0.348, 1.348)	0.2704	
			Male	23 / 19	0.191 [80.9%] / 0.499 [50.1%]	0.382 [61.8%]	(0.187, 0.783)	0.0090	
	20 mg/kg	0.6900	Female	17 / 22	0.427 [57.3%] / 0.460 [54.0%]	0.927 [7.3%]	(0.435, 1.972)	0.8423	
			Male	23 / 19	0.375 [62.5%] / 0.499 [50.1%]	0.753 [24.7%]	(0.374, 1.517)	0.4236	
	Region	10 mg/kg	0.3845	USA	22 / 23	0.282 [71.8%] / 0.432 [56.8%]	0.654 [34.6%]	(0.332, 1.288)	0.2172
				Rest of the World	23 / 18	0.237 [76.3%] / 0.562 [43.8%]	0.423 [57.7%]	(0.206, 0.869)	0.0196
20 mg/kg		0.7797	USA	21 / 23	0.375 [62.5%] / 0.432 [56.8%]	0.869 [13.1%]	(0.444, 1.702)	0.6803	
			Rest of the World	19 / 18	0.422 [57.8%] / 0.562 [43.8%]	0.750 [25.0%]	(0.340, 1.654)	0.4734	

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Adhoc Table: GWEPl424 - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Valproic Acid Use	10 mg/kg	0.5187	Not Currently Taking	15 / 12	0.441 [55.9%] / 0.668 [33.2%]	0.661 [33.9%]	(0.269, 1.624)	0.3632
			Currently Taking	30 / 29	0.199 [80.1%] / 0.427 [57.3%]	0.466 [53.4%]	(0.261, 0.831)	0.0101
	20 mg/kg	0.9854	Not Currently Taking	10 / 12	0.539 [46.1%] / 0.668 [33.2%]	0.807 [19.3%]	(0.315, 2.068)	0.6532
			Currently Taking	30 / 29	0.349 [65.1%] / 0.427 [57.3%]	0.816 [18.4%]	(0.445, 1.495)	0.5070
Stiripentol Use	10 mg/kg	0.7165	Not Currently Taking	28 / 24	0.227 [77.3%] / 0.451 [54.9%]	0.504 [49.6%]	(0.271, 0.939)	0.0313
			Currently Taking	17 / 17	0.321 [67.9%] / 0.529 [47.1%]	0.607 [39.3%]	(0.275, 1.342)	0.2153
	20 mg/kg	0.3694	Not Currently Taking	22 / 24	0.437 [56.3%] / 0.451 [54.9%]	0.968 [3.2%]	(0.515, 1.819)	0.9193
			Currently Taking	18 / 17	0.311 [68.9%] / 0.529 [47.1%]	0.588 [41.2%]	(0.240, 1.440)	0.2427
Levetiracetam Use	10 mg/kg	0.5594	Not Currently Taking	34 / 33	0.254 [74.6%] / 0.448 [55.2%]	0.567 [43.3%]	(0.327, 0.984)	0.0436
			Currently Taking	11 / 8	0.264 [73.6%] / 0.672 [32.8%]	0.392 [60.8%]	(0.129, 1.198)	0.0997
	20 mg/kg	0.7988	Not Currently Taking	31 / 33	0.369 [63.1%] / 0.448 [55.2%]	0.825 [17.5%]	(0.459, 1.483)	0.5172
			Currently Taking	9 / 8	0.471 [52.9%] / 0.672 [32.8%]	0.701 [29.9%]	(0.228, 2.150)	0.5309
Topiramate Use	10 mg/kg	0.8355	Not Currently Taking	37 / 30	0.237 [76.3%] / 0.443 [55.7%]	0.535 [46.5%]	(0.309, 0.928)	0.0262
			Currently Taking	8 / 11	0.387 [61.3%] / 0.635 [36.5%]	0.610 [39.0%]	(0.202, 1.844)	0.3777
	20 mg/kg	0.3173	Not Currently Taking	30 / 30	0.427 [57.3%] / 0.443 [55.7%]	0.964 [3.6%]	(0.522, 1.780)	0.9067
			Currently Taking	10 / 11	0.342 [65.8%] / 0.635 [36.5%]	0.539 [46.1%]	(0.204, 1.422)	0.2095

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Adhoc Table: GWEPl424 - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Baseline Convulsive Seizure Frequency	10 mg/kg	0.2479	<=7	16 / 13	0.154 [84.6%] / 0.504 [49.6%]	0.304 [69.6%]	(0.124, 0.749)	0.0101
			>7 to <=21	16 / 13	0.315 [68.5%] / 0.361 [63.9%]	0.872 [12.8%]	(0.372, 2.047)	0.7515
			>21	13 / 15	0.326 [67.4%] / 0.613 [38.7%]	0.533 [46.7%]	(0.231, 1.229)	0.1384
	20 mg/kg	0.2742	<=7	12 / 13	0.525 [47.5%] / 0.504 [49.6%]	1.042 [-4.2%]	(0.403, 2.694)	0.9322
			>7 to <=21	18 / 13	0.411 [58.9%] / 0.361 [63.9%]	1.139 [-13.9%]	(0.498, 2.603)	0.7565
			>21	10 / 15	0.265 [73.5%] / 0.613 [38.7%]	0.433 [56.7%]	(0.166, 1.126)	0.0855
Number of concurrent AEDs	10 mg/kg	0.8369	<3 ≥3	12 / 10 33 / 31	0.254 [74.6%] / 0.514 [48.6%] 0.258 [74.2%] / 0.466 [53.4%]	0.494 [50.6%] 0.555 [44.5%]	(0.186, 1.311) (0.318, 0.969)	0.1552 0.0386
	20 mg/kg	0.2572	<3 ≥3	8 / 10 32 / 31	0.688 [31.2%] / 0.514 [48.6%] 0.327 [67.3%] / 0.466 [53.4%]	1.339 [-33.9%] 0.701 [29.9%]	(0.517, 3.466) (0.384, 1.279)	0.5445 0.2447
Number of prior AEDs	10 mg/kg	0.0964	<4 ≥4	17 / 17 28 / 24	0.185 [81.5%] / 0.619 [38.1%] 0.296 [70.4%] / 0.412 [58.8%]	0.299 [70.1%] 0.717 [28.3%]	(0.128, 0.695) (0.394, 1.304)	0.0054 0.2730
	20 mg/kg	0.0496	<4 ≥4	14 / 17 26 / 24	0.272 [72.8%] / 0.619 [38.1%] 0.517 [48.3%] / 0.412 [58.8%]	0.439 [56.1%] 1.254 [-25.4%]	(0.193, 1.000) (0.656, 2.397)	0.0501 0.4903
Number of prior and concurrent AEDs	10 mg/kg	0.0429	<8 ≥8	23 / 22 22 / 19	0.211 [78.9%] / 0.665 [33.5%] 0.302 [69.8%] / 0.348 [65.2%]	0.317 [68.3%] 0.870 [13.0%]	(0.155, 0.648) (0.447, 1.692)	0.0019 0.6792
	20 mg/kg	0.3947	<8 ≥8	20 / 22 20 / 19	0.431 [56.9%] / 0.665 [33.5%] 0.351 [64.9%] / 0.348 [65.2%]	0.649 [35.1%] 1.009 [-0.9%]	(0.324, 1.300) (0.476, 2.138)	0.2202 0.9815

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Non-Convulsive Seizure Responder (subgroups) (ITT Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio	Odds Ratio		Risk Difference		
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI			95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Non-Convulsive Seizures <=25pct	Age Group	10 mg/kg	0.4548	2-5 years	11	9	11	9	1.0000	0.6744	1.4829	1.0000	1.0000	0.1145	8.7305	0.0000	-0.3223	0.3223
				6-12 years	17	15	14	9	1.3725	0.8953	2.1042	0.1975	4.1667	0.6642	26.1383	0.2395	-0.0545	0.5335
				13-18 years	6	4	7	5	0.9333	0.4477	1.9457	1.0000	0.8000	0.0755	8.4737	-0.0476	-0.5519	0.4566
	Sex	10 mg/kg	0.4830	F	19	15	16	12	1.0526	0.7300	1.5178	1.0000	1.2500	0.2574	6.0697	0.0395	-0.2409	0.3199
				M	15	13	16	11	1.2606	0.8574	1.8533	0.3944	2.9545	0.4759	18.3421	0.1792	-0.1057	0.4641
	Region	10 mg/kg	0.2394	REST OF THE WORLD	19	16	15	9	1.4035	0.8889	2.2161	0.1392	3.5556	0.7117	17.7632	0.2421	-0.0551	0.5393
				USA	15	12	17	14	0.9714	0.6947	1.3584	1.0000	0.8571	0.1451	5.0643	-0.0235	-0.2952	0.2482
	Valproate Use	10 mg/kg	0.0751	N	11	7	6	5	0.7636	0.4308	1.3535	0.6000	0.3500	0.0295	4.1529	-0.1970	-0.6090	0.2150
				Y	23	21	26	18	1.3188	0.9912	1.7548	0.0796	4.6667	0.8763	24.8521	0.2207	0.0092	0.4322
	Stiripentol Use	10 mg/kg	0.5566	N	22	19	18	13	1.1958	0.8587	1.6652	0.4295	2.4359	0.4939	12.0141	0.1414	-0.1103	0.3932
				Y	12	9	14	10	1.0500	0.6594	1.6720	1.0000	1.2000	0.2092	6.8845	0.0357	-0.3049	0.3763
	Levetiracetam Use	10 mg/kg	0.7061	N	25	21	28	20	1.1760	0.8799	1.5718	0.3370	2.1000	0.5458	8.0797	0.1257	-0.0949	0.3463
				Y	9	7	4	3	1.0370	0.5334	2.0163	1.0000	1.1667	0.0742	18.3460	0.0278	-0.4760	0.5316
	Topiramate Use	10 mg/kg	0.3188	N	29	25	25	18	1.1973	0.9008	1.5914	0.3104	2.4306	0.6178	9.5627	0.1421	-0.0741	0.3582
				Y	5	3	7	5	0.8400	0.3571	1.9759	1.0000	0.6000	0.0530	6.7948	-0.1143	-0.6587	0.4301
	Baseline Convulsive Seizure Frequency	10 mg/kg	0.4822	<=7	12	11	11	9	1.1204	0.8082	1.5532	0.5901	2.4444	0.1895	31.5261	0.0985	-0.1779	0.3749
				>7 to <=21	10	7	12	9	0.9333	0.5544	1.5713	1.0000	0.7778	0.1186	5.1001	-0.0500	-0.4251	0.3251
				>21	12	10	9	5	1.5000	0.7935	2.8356	0.3310	4.0000	0.5368	29.8045	0.2778	-0.1093	0.6649
	Current AEDs	10 mg/kg	0.8342	<3	9	8	7	6	1.0370	0.7088	1.5173	1.0000	1.3333	0.0686	25.9125	0.0317	-0.2989	0.3624
				>=3	25	20	25	17	1.1765	0.8435	1.6409	0.5202	1.8824	0.5177	6.8446	0.1200	-0.1209	0.3609
Prior AEDs	10 mg/kg	0.3707	<4	11	10	13	9	1.3131	0.8734	1.9742	0.3271	4.4444	0.4158	47.5028	0.2168	-0.0862	0.5198	
			>=4	23	18	19	14	1.0621	0.7527	1.4988	1.0000	1.2857	0.3099	5.3341	0.0458	-0.2143	0.3058	
Prior + Current AEDs	10 mg/kg	0.2237	<8	15	13	16	10	1.3867	0.9036	2.1281	0.2200	3.9000	0.6446	23.5977	0.2417	-0.0514	0.5347	
			>=8	19	15	16	13	0.9717	0.6981	1.3524	1.0000	0.8654	0.1627	4.6019	-0.0230	-0.2879	0.2419	
Age Group	20 mg/kg	0.6498	2-5 years	8	6	11	9	0.9167	0.5630	1.4926	1.0000	0.6667	0.0727	6.1108	-0.0682	-0.4450	0.3086	
			6-12 years	16	13	14	9	1.2639	0.8012	1.9939	0.4171	2.4074	0.4556	12.7205	0.1696	-0.1459	0.4852	
			13-18 years	4	3	7	5	1.0500	0.5037	2.1889	1.0000	1.2000	0.0734	19.6314	0.0357	-0.5047	0.5761	
Sex	20 mg/kg	0.3384	F	14	10	16	12	0.9524	0.6160	1.4723	1.0000	0.8333	0.1649	4.2117	-0.0357	-0.3535	0.2821	
			M	14	12	16	11	1.2468	0.8412	1.8479	0.3992	2.7273	0.4364	17.0455	0.1696	-0.1222	0.4615	
Region	20 mg/kg	0.1892	REST OF THE WORLD	12	10	15	9	1.3889	0.8555	2.2547	0.2357	3.3333	0.5314	20.9107	0.2333	-0.0921	0.5588	
			USA	16	12	17	14	0.9107	0.6364	1.3033	0.6880	0.6429	0.1194	3.4626	-0.0735	-0.3526	0.2055	
Valproate Use	20 mg/kg	0.0432	N	8	4	6	5	0.6000	0.2751	1.3087	0.3007	0.2000	0.0155	2.5755	-0.3333	-0.7905	0.1238	
			Y	20	18	26	18	1.3000	0.9679	1.7460	0.1501	4.0000	0.7443	21.4963	0.2077	-0.0131	0.4285	
Stiripentol Use	20 mg/kg	0.1139	N	20	14	18	13	0.9692	0.6462	1.4538	1.0000	0.8974	0.2199	3.6632	-0.0222	-0.3106	0.2661	
			Y	8	8	14	10	1.4000	1.0052	1.9499	0.2536	-	-	-	0.2857	0.0491	0.5224	
Levetiracetam Use	20 mg/kg	0.7652	N	20	16	28	20	1.1200	0.8127	1.5436	0.7365	1.6000	0.4072	6.2869	0.0857	-0.1566	0.3281	
			Y	8	6	4	3	1.0000	0.5001	1.9996	1.0000	1.0000	0.0625	15.9875	0.0000	-0.5197	0.5197	
Topiramate Use	20 mg/kg	0.9761	N	19	15	25	18	1.0965	0.7827	1.5361	0.7315	1.4583	0.3572	5.9533	0.0695	-0.1847	0.3236	
			Y	9	7	7	5	1.0889	0.6070	1.9533	1.0000	1.4000	0.1445	13.5680	0.0635	-0.3675	0.4945	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Baseline Convulsive Seizure Frequency	20 mg/kg	0.3608 <=7	7	5	11	9	0.8730	0.5062	1.5057	1.0000	0.5556	0.0589	5.2407	-0.1039	-0.5088	0.3010
		>7 to <=21	13	10	12	9	1.0256	0.6592	1.5957	1.0000	1.1111	0.1771	6.9702	0.0192	-0.3161	0.3546
		>21	8	7	9	5	1.5750	0.8302	2.9880	0.2941	5.6000	0.4720	66.4471	0.3194	-0.0779	0.7168
Current AEDs	20 mg/kg	0.0267 <3	8	4	7	6	0.5833	0.2739	1.2424	0.2821	0.1667	0.0133	2.0929	-0.3571	-0.7899	0.0756
		>=3	20	18	25	17	1.3235	0.9746	1.7974	0.1474	4.2353	0.7852	22.8459	0.2200	-0.0052	0.4452
Prior AEDs	20 mg/kg	0.0413 <4	11	11	13	9	1.4444	1.0053	2.0753	0.0983	-	-	-	0.3077	0.0568	0.5586
		>=4	17	11	19	14	0.8782	0.5644	1.3664	0.7206	0.6548	0.1574	2.7239	-0.0898	-0.3911	0.2116
Prior + Current AEDs	20 mg/kg	0.7257 <8	16	12	16	10	1.2000	0.7475	1.9265	0.7043	1.8000	0.3944	8.2151	0.1250	-0.1933	0.4433
		>=8	12	10	16	13	1.0256	0.7260	1.4490	1.0000	1.1538	0.1609	8.2738	0.0208	-0.2638	0.3055
Non-Convulsive Seizures <=50pct																
Age Group	10 mg/kg	0.2163 2-5 years	11	7	11	8	0.8750	0.4924	1.5548	1.0000	0.6563	0.1076	4.0030	-0.0909	-0.4783	0.2965
		6-12 years	17	13	14	6	1.7843	0.9224	3.4517	0.0751	4.3333	0.9276	20.2440	0.3361	0.0077	0.6645
		13-18 years	6	3	7	4	0.8750	0.3138	2.4401	1.0000	0.7500	0.0838	6.7102	-0.0714	-0.6141	0.4712
Sex	10 mg/kg	0.3433 F	19	12	16	10	1.0105	0.6057	1.6859	1.0000	1.0286	0.2598	4.0720	0.0066	-0.3148	0.3280
		M	15	11	16	8	1.4667	0.8234	2.6123	0.2734	2.7500	0.6095	12.4067	0.2333	-0.0985	0.5652
Region	10 mg/kg	0.4269 REST OF THE WORLD	19	13	15	7	1.4662	0.7877	2.7290	0.2960	2.4762	0.6096	10.0583	0.2175	-0.1102	0.5453
		USA	15	10	17	11	1.0303	0.6241	1.7009	1.0000	1.0909	0.2525	4.7140	0.0196	-0.3098	0.3490
Valproate Use	10 mg/kg	0.0978 N	11	5	6	4	0.6818	0.2886	1.6109	0.6199	0.4167	0.0525	3.3058	-0.2121	-0.6905	0.2663
		Y	23	18	26	14	1.4534	0.9588	2.2032	0.1317	3.0857	0.8792	10.8293	0.2441	-0.0111	0.4994
Stiripentol Use	10 mg/kg	0.4962 N	22	16	18	10	1.3091	0.8052	2.1284	0.3267	2.1333	0.5694	7.9928	0.1717	-0.1238	0.4672
		Y	12	7	14	8	1.0208	0.5281	1.9734	1.0000	1.0500	0.2204	5.0030	0.0119	-0.3689	0.3927
Levetiracetam Use	10 mg/kg	0.2368 N	25	18	28	15	1.3440	0.8807	2.0510	0.2565	2.2286	0.7083	7.0116	0.1843	-0.0709	0.4394
		Y	9	5	4	3	0.7407	0.3284	1.6708	1.0000	0.4167	0.0304	5.7082	-0.1944	-0.7287	0.3398
Topiramate Use	10 mg/kg	0.7386 N	29	20	25	14	1.2315	0.8054	1.8831	0.4017	1.7460	0.5727	5.3229	0.1297	-0.1277	0.3870
		Y	5	3	7	4	1.0500	0.4016	2.7454	1.0000	1.1250	0.1091	11.5954	0.0286	-0.5360	0.5932
Baseline Convulsive Seizure Frequency	10 mg/kg	0.2209 <=7	12	10	11	6	1.5278	0.8419	2.7723	0.1930	4.1667	0.6066	28.6209	0.2879	-0.0741	0.6499
		>7 to <=21	10	5	12	8	0.7500	0.3587	1.5683	0.6656	0.5000	0.0890	2.8075	-0.1667	-0.5755	0.2422
		>21	12	8	9	4	1.5000	0.6522	3.4497	0.3964	2.5000	0.4215	14.8280	0.2222	-0.1979	0.6424
Current AEDs	10 mg/kg	0.9286 <3	9	6	7	4	1.1667	0.5292	2.5721	1.0000	1.5000	0.1950	11.5359	0.0952	-0.3836	0.5740
		>=3	25	17	25	14	1.2143	0.7825	1.8842	0.5607	1.6696	0.5270	5.2897	0.1200	-0.1470	0.3870
Prior AEDs	10 mg/kg	0.9909 <4	11	8	13	8	1.1818	0.6738	2.0728	0.6792	1.6667	0.2941	9.4453	0.1119	-0.2612	0.4850
		>=4	23	15	19	10	1.2391	0.7362	2.0855	0.5311	1.6875	0.4864	5.8541	0.1259	-0.1713	0.4230
Prior + Current AEDs	10 mg/kg	0.3433 <8	15	11	16	8	1.4667	0.8234	2.6123	0.2734	2.7500	0.6095	12.4067	0.2333	-0.0985	0.5652
		>=8	19	12	16	10	1.0105	0.6057	1.6859	1.0000	1.0286	0.2598	4.0720	0.0066	-0.3148	0.3280
Age Group	20 mg/kg	0.1773 2-5 years	8	6	11	8	1.0313	0.6013	1.7687	1.0000	1.1250	0.1407	8.9947	0.0227	-0.3764	0.4219
		6-12 years	16	12	14	6	1.7500	0.8975	3.4122	0.1349	4.0000	0.8494	18.8362	0.3214	-0.0136	0.6564
		13-18 years	4	1	7	4	0.4375	0.0713	2.6856	0.5455	0.2500	0.0166	3.7703	-0.3214	-0.8822	0.2393
Sex	20 mg/kg	0.4382 F	14	9	16	10	1.0286	0.5967	1.7730	1.0000	1.0800	0.2435	4.7911	0.0179	-0.3275	0.3632
		M	14	10	16	8	1.4286	0.7907	2.5809	0.2839	2.5000	0.5478	11.4098	0.2143	-0.1263	0.5549
Region	20 mg/kg	0.2296 REST OF THE WORLD	12	9	15	7	1.6071	0.8543	3.0235	0.2388	3.4286	0.6557	17.9271	0.2833	-0.0685	0.6351
		USA	16	10	17	11	0.9659	0.5760	1.6199	1.0000	0.9091	0.2199	3.7576	-0.0221	-0.3505	0.3064
Valproate Use	20 mg/kg	0.0585 N	8	3	6	4	0.5625	0.1952	1.6212	0.5921	0.3000	0.0326	2.7631	-0.2917	-0.7965	0.2131
		Y	20	16	26	14	1.4857	0.9782	2.2565	0.1173	3.4286	0.8980	13.0908	0.2615	0.0018	0.5213
Stiripentol Use	20 mg/kg	0.2684 N	20	12	18	10	1.0800	0.6252	1.8656	1.0000	1.2000	0.3303	4.3602	0.0444	-0.2699	0.3588

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		Y	8	7	14	8	1.5313	0.9069	2.5855	0.1932	5.2500	0.5020	54.9107	0.3036	-0.0424	0.6496
Levetiracetam Use	20 mg/kg	0.1556 N	20	15	28	15	1.4000	0.9128	2.1472	0.2261	2.6000	0.7409	9.1239	0.2143	-0.0505	0.4791
		Y	8	4	4	3	0.6667	0.2725	1.6309	0.5758	0.3333	0.0235	4.7360	-0.2500	-0.7978	0.2978
Topiramate Use	20 mg/kg	0.9174 N	19	13	25	14	1.2218	0.7693	1.9406	0.5351	1.7024	0.4884	5.9344	0.1242	-0.1614	0.4098
		Y	9	6	7	4	1.1667	0.5292	2.5721	1.0000	1.5000	0.1950	11.5359	0.0952	-0.3836	0.5740
Baseline Convulsive Seizure Frequency	20 mg/kg	0.8585 <=7	7	5	11	6	1.3095	0.6409	2.6756	0.6371	2.0833	0.2752	15.7716	0.1688	-0.2768	0.6145
		>7 to <=21	13	9	12	8	1.0385	0.6053	1.7817	1.0000	1.1250	0.2093	6.0458	0.0256	-0.3405	0.3918
		>21	8	5	9	4	1.4063	0.5681	3.4812	0.6372	2.0833	0.2983	14.5491	0.1806	-0.2863	0.6474
Current AEDs	20 mg/kg	0.3491 <3	8	4	7	4	0.8750	0.3403	2.2497	1.0000	0.7500	0.0975	5.7679	-0.0714	-0.5758	0.4330
		>=3	20	15	25	14	1.3393	0.8714	2.0585	0.2236	2.3571	0.6529	8.5096	0.1900	-0.0818	0.4618
Prior AEDs	20 mg/kg	0.1686 <4	11	10	13	8	1.4773	0.9246	2.3604	0.1660	6.2500	0.6022	64.8616	0.2937	-0.0206	0.6080
		>=4	17	9	19	10	1.0059	0.5418	1.8675	1.0000	1.0125	0.2730	3.7552	0.0031	-0.3236	0.3297
Prior + Current AEDs	20 mg/kg	0.5768 <8	16	11	16	8	1.3750	0.7615	2.4828	0.4725	2.2000	0.5205	9.2993	0.1875	-0.1466	0.5216
		>=8	12	8	16	10	1.0667	0.6145	1.8515	1.0000	1.2000	0.2497	5.7680	0.0417	-0.3153	0.3986
Non-Convulsive Seizures <=-75pct Age Group	10 mg/kg	0.3577 2-5 years	11	6	11	4	1.5000	0.5802	3.8779	0.6699	2.1000	0.3805	11.5890	0.1818	-0.2273	0.5910
		6-12 years	17	9	14	3	2.4706	0.8235	7.4118	0.1378	4.1250	0.8389	20.2828	0.3151	-0.0050	0.6353
		13-18 years	6	3	7	0	-	-	-	0.0699	-	-	-	0.5000	0.0999	0.9001
Sex	10 mg/kg	0.2159 F	19	8	16	4	1.6842	0.6201	4.5742	0.4759	2.1818	0.5105	9.3251	0.1711	-0.1360	0.4781
		M	15	10	16	3	3.5556	1.2063	10.4799	0.0113	8.6667	1.6615	45.2082	0.4792	0.1734	0.7849
Region	10 mg/kg	0.9447 REST OF THE WORLD	19	11	15	4	2.1711	0.8629	5.4623	0.0915	3.7813	0.8759	16.3232	0.3123	-0.0029	0.6275
		USA	15	7	17	3	2.6444	0.8284	8.4414	0.1283	4.0833	0.8183	20.3758	0.2902	-0.0206	0.6010
Valproate Use	10 mg/kg	0.2654 N	11	5	6	0	-	-	-	0.1023	-	-	-	0.4545	0.1603	0.7488
		Y	23	13	26	7	2.0994	1.0141	4.3463	0.0456	3.5286	1.0670	11.6694	0.2960	0.0312	0.5608
Stiripentol Use	10 mg/kg	0.1499 N	22	12	18	2	4.9091	1.2585	19.1494	0.0070	9.6000	1.7667	52.1654	0.4343	0.1806	0.6881
		Y	12	6	14	5	1.4000	0.5679	3.4511	0.6922	1.8000	0.3732	8.6815	0.1429	-0.2353	0.5210
Levetiracetam Use	10 mg/kg	0.9687 N	25	13	28	6	2.4267	1.0871	5.4171	0.0254	3.9722	1.2012	13.1359	0.3057	0.0578	0.5536
		Y	9	5	4	1	2.2222	0.3691	13.3786	0.5594	3.7500	0.2737	51.3734	0.3056	-0.2287	0.8398
Topiramate Use	10 mg/kg	0.9865 N	29	16	25	6	2.2989	1.0635	4.9692	0.0275	3.8974	1.2049	12.6064	0.3117	0.0652	0.5583
		Y	5	2	7	1	2.8000	0.3400	23.0569	0.5227	4.0000	0.2502	63.9500	0.2571	-0.2444	0.7587
Baseline Convulsive Seizure Frequency	10 mg/kg	0.8237 <=7	12	8	11	4	1.8333	0.7618	4.4120	0.2203	3.5000	0.6283	19.4964	0.3030	-0.0868	0.6928
		>7 to <=21	10	4	12	2	2.4000	0.5488	10.4948	0.3476	3.3333	0.4620	24.0516	0.2333	-0.1363	0.6030
		>21	12	6	9	1	4.5000	0.6515	31.0820	0.1588	8.0000	0.7502	85.3127	0.3889	0.0393	0.7384
Current AEDs	10 mg/kg	0.1319 <3	9	5	7	0	-	-	-	0.0337	-	-	-	0.5556	0.2309	0.8802
		>=3	25	13	25	7	1.8571	0.8925	3.8644	0.1482	2.7857	0.8613	9.0097	0.2400	-0.0233	0.5033
Prior AEDs	10 mg/kg	0.9842 <4	11	6	13	3	2.3636	0.7638	7.3141	0.2060	4.0000	0.6930	23.0886	0.3147	-0.0582	0.6876
		>=4	23	12	19	4	2.4783	0.9540	6.4377	0.0573	4.0909	1.0362	16.1515	0.3112	0.0368	0.5856
Prior + Current AEDs	10 mg/kg	0.7201 <8	15	8	16	3	2.8444	0.9239	8.7570	0.0659	4.9524	0.9860	24.8747	0.3458	0.0291	0.6626
		>=8	19	10	16	4	2.1053	0.8143	5.4428	0.1662	3.3333	0.7849	14.1563	0.2763	-0.0326	0.5852
Age Group	20 mg/kg	0.5759 2-5 years	8	4	11	4	1.3750	0.4837	3.9084	0.6577	1.7500	0.2746	11.1519	0.1364	-0.3118	0.5845
		6-12 years	16	5	14	3	1.4583	0.4226	5.0327	0.6887	1.6667	0.3177	8.7434	0.0982	-0.2145	0.4109
		13-18 years	4	1	7	0	-	-	-	0.3636	-	-	-	0.2500	-0.1743	0.6743
Sex	20 mg/kg	0.8245 F	14	6	16	4	1.7143	0.6046	4.8606	0.4421	2.2500	0.4778	10.5954	0.1786	-0.1564	0.5136
		M	14	4	16	3	1.5238	0.4095	5.6697	0.6746	1.7333	0.3138	9.5734	0.0982	-0.2060	0.4025

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Region	20 mg/kg	0.2482 REST OF THE WORLD	12	3	15	4	0.9375	0.2580	3.4064	1.0000	0.9167	0.1614	5.2065	-0.0167	-0.3485	0.3152
		USA	16	7	17	3	2.4792	0.7713	7.9684	0.1411	3.6296	0.7396	17.8121	0.2610	-0.0422	0.5642
Valproate Use	20 mg/kg	0.1742 N	8	3	6	0	-	-	-	0.2088	-	-	-	0.3750	0.0395	0.7105
		Y	20	7	26	7	1.3000	0.5444	3.1045	0.7476	1.4615	0.4133	5.1682	0.0808	-0.1890	0.3505
Stiripentol Use	20 mg/kg	0.0908 N	20	8	18	2	3.6000	0.8766	14.7838	0.0673	5.3333	0.9543	29.8077	0.2889	0.0297	0.5481
		Y	8	2	14	5	0.7000	0.1742	2.8128	1.0000	0.6000	0.0864	4.1672	-0.1071	-0.4983	0.2841
Levetiracetam Use	20 mg/kg	0.9514 N	20	7	28	6	1.6333	0.6462	4.1282	0.3389	1.9744	0.5445	7.1586	0.1357	-0.1227	0.3942
		Y	8	3	4	1	1.5000	0.2202	10.2181	1.0000	1.8000	0.1237	26.1960	0.1250	-0.4159	0.6659
Topiramate Use	20 mg/kg	0.4029 N	19	6	25	6	1.3158	0.5030	3.4419	0.7350	1.4615	0.3852	5.5454	0.0758	-0.1920	0.3436
		Y	9	4	7	1	3.1111	0.4400	22.0002	0.3077	4.8000	0.3971	58.0135	0.3016	-0.1138	0.7170
Baseline Convulsive Seizure Frequency	20 mg/kg	0.0157 <=7	7	0	11	4	-	-	-	0.1193	-	-	-	-0.3636	-0.6479	-0.0794
		>7 to <=21	13	5	12	2	2.3077	0.5468	9.7394	0.3783	3.1250	0.4745	20.5830	0.2179	-0.1203	0.5562
		>21	8	5	9	1	5.6250	0.8212	38.5313	0.0498	13.3333	1.0685	166.3736	0.5139	0.1206	0.9072
Current AEDs	20 mg/kg	0.2838 <3	8	2	7	0	-	-	-	0.4667	-	-	-	0.2500	-0.0501	0.5501
		>=3	20	8	25	7	1.4286	0.6251	3.2650	0.5273	1.7143	0.4912	5.9834	0.1200	-0.1576	0.3976
Prior AEDs	20 mg/kg	0.6263 <4	11	5	13	3	1.9697	0.6023	6.4418	0.3905	2.7778	0.4812	16.0338	0.2238	-0.1491	0.5967
		>=4	17	5	19	4	1.3971	0.4466	4.3700	0.7060	1.5625	0.3424	7.1311	0.0836	-0.2002	0.3673
Prior + Current AEDs	20 mg/kg	0.9428 <8	16	5	16	3	1.6667	0.4763	5.8314	0.6851	1.9697	0.3816	10.1662	0.1250	-0.1719	0.4219
		>=8	12	5	16	4	1.6667	0.5655	4.9124	0.4319	2.1429	0.4276	10.7385	0.1667	-0.1838	0.5171

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
All Data	10 mg/kg			45 / 41	1.275 [-27.5%] / 0.863 [13.7%]	1.478 [-47.8%]	(0.995, 2.195)	0.0529
	20 mg/kg			40 / 41	1.423 [-42.3%] / 0.863 [13.7%]	1.650 [-65.0%]	(1.089, 2.500)	0.0185
Age Group	10 mg/kg	0.0522	2-5 years	13 / 13	1.246 [-24.6%] / 1.735 [-73.5%]	0.718 [28.2%]	(0.358, 1.439)	0.3476
			6-12 years	23 / 16	1.303 [-30.3%] / 0.628 [37.2%]	2.075 [-107.5%]	(1.136, 3.788)	0.0179
			13-18 years	9 / 12	1.263 [-26.3%] / 0.635 [36.5%]	1.989 [-98.9%]	(0.923, 4.286)	0.0786
	20 mg/kg	0.3857	2-5 years	10 / 13	1.891 [-89.1%] / 1.735 [-73.5%]	1.090 [-9.0%]	(0.485, 2.451)	0.8334
			6-12 years	22 / 16	1.315 [-31.5%] / 0.628 [37.2%]	2.095 [-109.5%]	(1.139, 3.852)	0.0178
			13-18 years	8 / 12	1.352 [-35.2%] / 0.635 [36.5%]	2.130 [-113.0%]	(0.970, 4.679)	0.0595
Sex	10 mg/kg	0.5811	Female	22 / 22	1.219 [-21.9%] / 0.915 [8.5%]	1.333 [-33.3%]	(0.772, 2.302)	0.3002
			Male	23 / 19	1.330 [-33.0%] / 0.797 [20.3%]	1.668 [-66.8%]	(0.926, 3.004)	0.0877
	20 mg/kg	0.9375	Female	17 / 22	1.511 [-51.1%] / 0.915 [8.5%]	1.651 [-65.1%]	(0.916, 2.977)	0.0945
			Male	23 / 19	1.361 [-36.1%] / 0.797 [20.3%]	1.708 [-70.8%]	(0.933, 3.126)	0.0822
Region	10 mg/kg	0.6460	USA	22 / 23	1.507 [-50.7%] / 0.950 [5.0%]	1.585 [-58.5%]	(0.908, 2.767)	0.1039
			Rest of the World	23 / 18	1.061 [-6.1%] / 0.803 [19.7%]	1.321 [-32.1%]	(0.761, 2.293)	0.3192
	20 mg/kg	0.4987	USA	21 / 23	1.793 [-79.3%] / 0.950 [5.0%]	1.886 [-88.6%]	(1.040, 3.422)	0.0370
			Rest of the World	19 / 18	1.142 [-14.2%] / 0.803 [19.7%]	1.422 [-42.2%]	(0.805, 2.514)	0.2234

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
Valproic Acid Use	10 mg/kg	0.2690	Not Currently Taking	15 / 12	1.070 [-7.0%] / 1.049 [-4.9%]	1.020 [-2.0%]	(0.467, 2.225)	0.9602
			Currently Taking	30 / 29	1.396 [-39.6%] / 0.821 [17.9%]	1.700 [-70.0%]	(1.063, 2.717)	0.0271
	20 mg/kg	0.8667	Not Currently Taking	10 / 12	1.608 [-60.8%] / 1.049 [-4.9%]	1.533 [-53.3%]	(0.639, 3.673)	0.3354
			Currently Taking	30 / 29	1.370 [-37.0%] / 0.821 [17.9%]	1.668 [-66.8%]	(1.036, 2.685)	0.0355
Stiripentol Use	10 mg/kg	0.2093	Not Currently Taking	28 / 24	1.547 [-54.7%] / 0.897 [10.3%]	1.725 [-72.5%]	(1.019, 2.920)	0.0425
			Currently Taking	17 / 17	0.890 [11.0%] / 0.853 [14.7%]	1.042 [-4.2%]	(0.579, 1.879)	0.8890
	20 mg/kg	0.2465	Not Currently Taking	22 / 24	1.846 [-84.6%] / 0.897 [10.3%]	2.059 [-105.9%]	(1.150, 3.686)	0.0155
			Currently Taking	18 / 17	1.088 [-8.8%] / 0.853 [14.7%]	1.275 [-27.5%]	(0.721, 2.254)	0.3998
Levetiracetam Use	10 mg/kg	0.9334	Not Currently Taking	34 / 33	1.377 [-37.7%] / 0.914 [8.6%]	1.508 [-50.8%]	(0.961, 2.364)	0.0734
			Currently Taking	11 / 8	1.038 [-3.8%] / 0.660 [34.0%]	1.572 [-57.2%]	(0.649, 3.808)	0.3133
	20 mg/kg	0.5177	Not Currently Taking	31 / 33	1.415 [-41.5%] / 0.914 [8.6%]	1.548 [-54.8%]	(0.976, 2.457)	0.0631
			Currently Taking	9 / 8	1.460 [-46.0%] / 0.660 [34.0%]	2.212 [-121.2%]	(0.826, 5.922)	0.1132
Topiramate Use	10 mg/kg	0.8431	Not Currently Taking	37 / 30	1.348 [-34.8%] / 0.978 [2.2%]	1.379 [-37.9%]	(0.876, 2.172)	0.1638
			Currently Taking	8 / 11	0.964 [3.6%] / 0.635 [36.5%]	1.519 [-51.9%]	(0.651, 3.543)	0.3310
	20 mg/kg	0.3959	Not Currently Taking	30 / 30	1.432 [-43.2%] / 0.978 [2.2%]	1.465 [-46.5%]	(0.903, 2.375)	0.1207
			Currently Taking	10 / 11	1.402 [-40.2%] / 0.635 [36.5%]	2.209 [-120.9%]	(0.970, 5.032)	0.0591

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking Clobazam)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
Baseline Convulsive Seizure Frequency	10 mg/kg	0.0881	<=7	16 / 13	1.114 [-11.4%] / 1.024 [-2.4%]	1.089 [-8.9%]	(0.581, 2.039)	0.7893
			>7 to <=21	16 / 13	1.139 [-13.9%] / 0.911 [8.9%]	1.250 [-25.0%]	(0.660, 2.367)	0.4898
			>21	13 / 15	2.100 [-110.0%] / 0.626 [37.4%]	3.355 [-235.5%]	(1.452, 7.749)	0.0050
	20 mg/kg	0.1984	<=7	12 / 13	1.879 [-87.9%] / 1.024 [-2.4%]	1.836 [-83.6%]	(0.937, 3.598)	0.0764
			>7 to <=21	18 / 13	1.047 [-4.7%] / 0.911 [8.9%]	1.149 [-14.9%]	(0.608, 2.172)	0.6656
			>21	10 / 15	2.046 [-104.6%] / 0.626 [37.4%]	3.268 [-226.8%]	(1.230, 8.687)	0.0180
Number of concurrent AEDs	10 mg/kg	0.7144	<3	12 / 10	1.329 [-32.9%] / 1.065 [-6.5%]	1.247 [-24.7%]	(0.506, 3.072)	0.6281
			>=3	33 / 31	1.255 [-25.5%] / 0.835 [16.5%]	1.503 [-50.3%]	(0.959, 2.356)	0.0749
	20 mg/kg	0.8085	<3	8 / 10	1.963 [-96.3%] / 1.065 [-6.5%]	1.843 [-84.3%]	(0.652, 5.211)	0.2462
			>=3	32 / 31	1.339 [-33.9%] / 0.835 [16.5%]	1.604 [-60.4%]	(1.015, 2.535)	0.0433
Number of prior AEDs	10 mg/kg	0.4457	<4	17 / 17	1.404 [-40.4%] / 1.133 [-13.3%]	1.240 [-24.0%]	(0.679, 2.265)	0.4817
			>=4	28 / 24	1.191 [-19.1%] / 0.706 [29.4%]	1.687 [-68.7%]	(1.000, 2.846)	0.0499
	20 mg/kg	0.5405	<4	14 / 17	1.638 [-63.8%] / 1.133 [-13.3%]	1.446 [-44.6%]	(0.731, 2.863)	0.2869
			>=4	26 / 24	1.333 [-33.3%] / 0.706 [29.4%]	1.889 [-88.9%]	(1.117, 3.193)	0.0180
Number of prior and concurrent AEDs	10 mg/kg	0.3477	<8	23 / 22	1.327 [-32.7%] / 1.084 [-8.4%]	1.224 [-22.4%]	(0.710, 2.111)	0.4630
			>=8	22 / 19	1.220 [-22.0%] / 0.683 [31.7%]	1.788 [-78.8%]	(1.002, 3.188)	0.0491
	20 mg/kg	0.5406	<8	20 / 22	1.591 [-59.1%] / 1.084 [-8.4%]	1.468 [-46.8%]	(0.808, 2.667)	0.2057
			>=8	20 / 19	1.296 [-29.6%] / 0.683 [31.7%]	1.899 [-89.9%]	(1.065, 3.389)	0.0301

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 CGIC Responder [VMI, MI, SI] (subgroups) (ITT Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction p-Value	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference				
				N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI	
Last Visit (LOCF)	Age Group	10 mg/kg	0.8661	2-5 years	13	11	13	8	1.3750	0.8438	2.2406	0.3783	0.2909	0.0446	1.8984	0.2308	-0.0985	0.56
				6-12 years	23	15	16	5	2.0870	0.9513	4.5785	0.0536	0.2424	0.0621	0.946	0.3397	0.0406	0.6388
				13-18 years	9	7	12	4	2.3333	0.9746	5.5864	0.0805	0.1429	0.0198	1.032	0.4444	0.0638	0.8251
Last Visit (LOCF)	Sex	10 mg/kg	0.6317	F	22	17	22	9	1.8889	1.0887	3.2771	0.0305	0.2036	0.0549	0.7548	0.3636	0.0937	0.6336
				M	23	16	19	8	1.6522	0.9135	2.9880	0.1177	0.3182	0.0892	1.1354	0.2746	-0.0163	0.5655
Last Visit (LOCF)	Region	10 mg/kg	0.0192	REST OF THE WORLD	23	12	18	7	1.3416	0.6670	2.6987	0.5308	0.5833	0.1668	2.04	0.1329	-0.1711	0.4368
				USA	22	21	23	10	2.1955	1.3656	3.5296	0.0002	0.0366	0.0042	0.3205	0.5198	0.2993	0.7403
Last Visit (LOCF)	Valproate Use	10 mg/kg	0.3241	N	15	12	12	4	2.4000	1.0369	5.5549	0.0220	0.125	0.0219	0.7149	0.4667	0.1318	0.8015
				Y	30	21	29	13	1.5615	0.9791	2.4905	0.0673	0.3482	0.1194	1.0154	0.2517	0.0075	0.496
Last Visit (LOCF)	Stiripentol Use	10 mg/kg	0.4182	N	28	24	24	12	1.7143	1.1177	2.6292	0.0074	0.1667	0.0442	0.6282	0.3571	0.1188	0.5955
				Y	17	9	17	5	1.8000	0.7601	4.2626	0.2960	0.3704	0.0902	1.521	0.2353	-0.086	0.5566
Last Visit (LOCF)	Levetiracetam Use	10 mg/kg	0.0340	N	34	25	33	17	1.4273	0.9687	2.1031	0.0798	0.3825	0.1375	1.0639	0.2201	-0.0058	0.4461
				Y	11	8	8	0	-	-	-	0.0034	-	-	-	0.7273	0.4641	0.9905
Last Visit (LOCF)	Topiramate Use	10 mg/kg	0.2939	N	37	26	30	13	1.6216	1.0240	2.5681	0.0454	0.3235	0.1179	0.8876	0.2694	0.0389	0.4999
				Y	8	7	11	4	2.4063	1.0551	5.4878	0.0587	0.0816	0.0072	0.9262	0.5114	0.1462	0.8765
Last Visit (LOCF)	Baseline Convulsive Seizure Frequency	10 mg/kg	0.7040	<=7	16	11	13	6	1.4896	0.7594	2.9218	0.2742	0.3896	0.0853	1.7791	0.226	-0.1276	0.5795
				>7 to <=21	16	12	13	6	1.6250	0.8468	3.1182	0.1426	0.2857	0.0594	1.3753	0.2885	-0.0557	0.6326
				>21	13	10	15	5	2.3077	1.0630	5.0098	0.0296	0.15	0.028	0.8036	0.4359	0.1052	0.7666
Last Visit (LOCF)	Current AEDs	10 mg/kg	0.3857	<3	12	7	10	4	1.4583	0.5946	3.5767	0.6699	0.4762	0.0863	2.6279	0.1833	-0.229	0.5956
				>=3	33	26	31	13	1.8788	1.1974	2.9479	0.0044	0.1944	0.0649	0.5829	0.3685	0.1457	0.5913
Last Visit (LOCF)	Prior AEDs	10 mg/kg	0.7678	<4	17	13	17	7	1.8571	0.9927	3.4744	0.0799	0.2154	0.0491	0.9457	0.3529	0.0441	0.6618
				>=4	28	20	24	10	1.7143	1.0109	2.9071	0.0485	0.2857	0.0901	0.9056	0.2976	0.039	0.5563
Last Visit (LOCF)	Prior + Current AEDs	10 mg/kg	0.9056	<8	23	17	22	9	1.8068	1.0343	3.1562	0.0361	0.2443	0.0693	0.8617	0.33	0.0573	0.6028
				>=8	22	16	19	8	1.7273	0.9612	3.1038	0.0624	0.2727	0.0738	1.0083	0.3062	0.0165	0.5959
Last Visit (LOCF)	Age Group	20 mg/kg	0.8246	2-5 years	10	9	13	8	1.4625	0.9078	2.3560	0.1790	0.1778	0.017	1.8618	0.2846	-0.0387	0.6079
				6-12 years	21	16	16	5	2.4381	1.1344	5.2399	0.0090	0.142	0.0331	0.6104	0.4494	0.1583	0.7406
				13-18 years	8	5	12	4	1.8750	0.7154	4.9142	0.3618	0.3	0.0463	1.9425	0.2917	-0.1369	0.7202
Last Visit (LOCF)																		

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Sex	20 mg/kg	0.8938 F	16	12	22	9	1.8333	1.0302	3.2627	0.0516	0.2308	0.056	0.9502	0.3409	0.0456	0.6363
		M	23	18	19	8	1.8587	1.0516	3.2852	0.0258	0.202	0.0526	0.776	0.3616	0.0828	0.6403
Last Visit (LOCF)																
Region	20 mg/kg	0.0336 REST OF THE WORLD	18	10	18	7	1.4286	0.7014	2.9098	0.5051	0.5091	0.135	1.9201	0.1667	-0.1549	0.4882
		USA	21	20	23	10	2.1905	1.3613	3.5247	0.0003	0.0385	0.0044	0.3372	0.5176	0.2955	0.7397
Last Visit (LOCF)																
Valproate Use	20 mg/kg	0.6353 N	9	7	12	4	2.3333	0.9746	5.5864	0.0805	0.1429	0.0198	1.032	0.4444	0.0638	0.8251
		Y	30	23	29	13	1.7103	1.0911	2.6807	0.0169	0.2473	0.0808	0.7569	0.3184	0.0824	0.5543
Last Visit (LOCF)																
Stiripentol Use	20 mg/kg	0.8305 N	21	18	24	12	1.7143	1.1079	2.6525	0.0140	0.1667	0.0387	0.7183	0.3571	0.1073	0.607
		Y	18	12	17	5	2.2667	1.0128	5.0730	0.0437	0.2083	0.0498	0.8717	0.3725	0.0654	0.6797
Last Visit (LOCF)																
Levetiracetam Use	20 mg/kg	0.0141 N	31	23	33	17	1.4402	0.9744	2.1287	0.0749	0.3696	0.1287	1.0615	0.2268	-0.003	0.4566
		Y	8	7	8	0	-	-	-	0.0014	-	-	-	0.875	0.6458	1
Last Visit (LOCF)																
Topiramate Use	20 mg/kg	0.2458 N	29	21	30	13	1.6711	1.0478	2.6652	0.0352	0.2913	0.0981	0.8651	0.2908	0.0502	0.5314
		Y	10	9	11	4	2.4750	1.1026	5.5558	0.0237	0.0635	0.0057	0.7024	0.5364	0.1967	0.876
Last Visit (LOCF)																
Baseline Convulsive Seizure Frequency	20 mg/kg	0.3367 <=7	12	11	13	6	1.9861	1.0776	3.6605	0.0302	0.0779	0.0077	0.7924	0.4551	0.1423	0.768
		>7 to <=21	17	11	13	6	1.4020	0.7073	2.7787	0.4601	0.4675	0.1069	2.0456	0.1855	-0.1681	0.5391
		>21	10	8	15	5	2.4000	1.1003	5.2350	0.0414	0.125	0.019	0.8233	0.4667	0.1226	0.8107
Last Visit (LOCF)																
Current AEDs	20 mg/kg	0.5701 <3	7	6	10	4	2.1429	0.9465	4.8514	0.1340	0.1111	0.0094	1.3087	0.4571	0.0579	0.8564
		>=3	32	24	31	13	1.7885	1.1290	2.8330	0.0107	0.2407	0.0824	0.7032	0.3306	0.1011	0.5602
Last Visit (LOCF)																
Prior AEDs	20 mg/kg	0.4251 <4	14	12	17	7	2.0816	1.1344	3.8199	0.0245	0.1167	0.0196	0.6929	0.4454	0.1482	0.7426
		>=4	25	18	24	10	1.7280	1.0143	2.9439	0.0450	0.2778	0.0843	0.9149	0.3033	0.039	0.5677
Last Visit (LOCF)																
Prior + Current AEDs	20 mg/kg	0.8611 <8	20	15	22	9	1.8333	1.0448	3.2171	0.0334	0.2308	0.0615	0.8653	0.3409	0.0612	0.6206
		>=8	19	15	19	8	1.8750	1.0539	3.3359	0.0448	0.1939	0.0464	0.8107	0.3684	0.0805	0.6563

LOCF = last observation carried forward; MI = much improved; VMI = very much improved; SI = slightly improved.

Last visit = Last visit is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 CGIC Responder [VMI, MI] (subgroups) (ITT Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio	Odds Ratio		Risk Difference		
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI			95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Last Visit (LOCF)	Age Group	10 mg/kg	0.8554	2-5 years	13	8	13	3	2.6667	0.9042	7.8644	0.1107	0.1875	0.0340	1.0334	0.3846	0.0348	0.7345
				6-12 years	23	8	16	2	2.7826	0.6780	11.4205	0.1523	0.2679	0.0483	1.4841	0.2228	-0.0304	0.4761
				13-18 years	9	3	12	2	2.0000	0.4175	9.5808	0.6108	0.4000	0.0512	3.1247	0.1667	-0.2066	0.5399
Last Visit (LOCF)	Sex	10 mg/kg	0.7897	F	22	9	22	4	2.2500	0.8123	6.2323	0.1854	0.3210	0.0810	1.2721	0.2273	-0.0339	0.4884
				M	23	10	19	3	2.7536	0.8823	8.5942	0.0928	0.2438	0.0553	1.0743	0.2769	0.0163	0.5375
Last Visit (LOCF)	Region	10 mg/kg	0.1940	REST OF THE WORLD	23	6	18	3	1.5652	0.4525	5.4147	0.7061	0.5667	0.1203	2.6701	0.0942	-0.1545	0.3429
				USA	22	13	23	4	3.3977	1.3060	8.8398	0.0058	0.1457	0.0369	0.5752	0.4170	0.1597	0.6743
Last Visit (LOCF)	Valproate Use	10 mg/kg	0.2625	N	15	7	12	4	1.4000	0.5329	3.6779	0.6960	0.5714	0.1187	2.7507	0.1333	-0.2339	0.5006
				Y	30	12	29	3	3.8667	1.2150	12.3051	0.0153	0.1731	0.0427	0.7023	0.2966	0.0891	0.5040
Last Visit (LOCF)	Stiripentol Use	10 mg/kg	0.0255	N	28	17	24	4	3.6429	1.4189	9.3528	0.0018	0.1294	0.0348	0.4817	0.4405	0.2061	0.6749
				Y	17	2	17	3	0.6667	0.1270	3.4995	1.0000	1.6071	0.2329	11.0919	-0.0588	-0.2961	0.1784
Last Visit (LOCF)	Levetiracetam Use	10 mg/kg	0.0867	N	34	13	33	7	1.8025	0.8229	3.9485	0.1826	0.4349	0.1471	1.2857	0.1702	-0.0446	0.3850
				Y	11	6	8	0	-	-	-	0.0181	-	-	-	0.5455	0.2512	0.8397
Last Visit (LOCF)	Topiramate Use	10 mg/kg	0.3393	N	37	15	30	6	2.0270	0.8971	4.5801	0.1115	0.3667	0.1209	1.1121	0.2054	-0.0079	0.4187
				Y	8	4	11	1	5.5000	0.7495	40.3601	0.1108	0.1000	0.0084	1.1931	0.4091	0.0232	0.7950
Last Visit (LOCF)	Baseline Convulsive Seizure Frequency	10 mg/kg	0.6404	<=7	16	7	13	2	2.8438	0.7078	11.4247	0.1296	0.2338	0.0386	1.4164	0.2837	-0.0287	0.5960
				>7 to <=21	16	8	13	2	3.2500	0.8293	12.7359	0.1142	0.1818	0.0301	1.0970	0.3462	0.0323	0.6600
				>21	13	4	15	3	1.5385	0.4194	5.6435	0.6703	0.5625	0.0999	3.1682	0.1077	-0.2147	0.4301
Last Visit (LOCF)	Current AEDs	10 mg/kg	0.5769	<3	12	5	10	1	4.1667	0.5775	30.0645	0.1619	0.1556	0.0146	1.6530	0.3167	-0.0186	0.6519
				>=3	33	14	31	6	2.1919	0.9643	4.9825	0.0612	0.3257	0.1055	1.0054	0.2307	0.0121	0.4493
Last Visit (LOCF)	Prior AEDs	10 mg/kg	0.2024	<4	17	9	17	2	4.5000	1.1357	17.8302	0.0255	0.1185	0.0205	0.6862	0.4118	0.1294	0.6942
				>=4	28	10	24	5	1.7143	0.6799	4.3222	0.3582	0.4737	0.1354	1.6570	0.1488	-0.0918	0.3894
Last Visit (LOCF)	Prior + Current AEDs	10 mg/kg	0.1995	<8	23	10	22	2	4.7826	1.1780	19.4169	0.0165	0.1300	0.0244	0.6913	0.3439	0.1083	0.5794
				>=8	22	9	19	5	1.5545	0.6291	3.8412	0.5100	0.5159	0.1366	1.9477	0.1459	-0.1394	0.4313
End of Treatment	Age Group	20 mg/kg	0.9788	2-5 years	10	6	13	3	2.6000	0.8534	7.9213	0.1023	0.2000	0.0328	1.2184	0.3692	-0.0111	0.7496
				6-12 years	20	8	16	2	3.2000	0.7867	13.0172	0.1326	0.2143	0.0380	1.2096	0.2750	0.0060	0.5440
				13-18 years	7	3	12	2	2.5714	0.5584	11.8420	0.3047	0.2667	0.0316	2.2486	0.2619	-0.1610	0.6848
Last Visit (LOCF)	Age Group	20 mg/kg	0.9343	2-5 years	10	6	13	3	2.6000	0.8534	7.9213	0.1023	0.2000	0.0328	1.2184	0.3692	-0.0111	0.7496
				6-12 years	21	8	16	2	3.0476	0.7468	12.4378	0.1368	0.2321	0.0414	1.3011	0.2560	-0.0075	0.5194
				13-18 years	8	3	12	2	2.2500	0.4778	10.5954	0.3473	0.3333	0.0414	2.6857	0.2083	-0.1879	0.6046

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Last Visit (LOCF)																	
Sex	20 mg/kg	0.7982	F	16	8	22	4	2.7500	0.9988	7.5719	0.0751	0.2222	0.0516	0.9577	0.3182	0.0249	0.6114
			M	23	9	19	3	2.4783	0.7794	7.8800	0.1693	0.2917	0.0657	1.2949	0.2334	-0.0248	0.4916
Last Visit (LOCF)																	
Region	20 mg/kg	0.1213	REST OF THE WORLD	18	4	18	3	1.3333	0.3467	5.1271	1.0000	0.7000	0.1325	3.6990	0.0556	-0.2024	0.3135
			USA	21	13	23	4	3.5595	1.3741	9.2204	0.0047	0.1296	0.0322	0.5213	0.4451	0.1860	0.7042
Last Visit (LOCF)																	
Valproate Use	20 mg/kg	0.4666	N	9	5	12	4	1.6667	0.6188	4.4890	0.3964	0.4000	0.0674	2.3725	0.2222	-0.1979	0.6424
			Y	30	12	29	3	3.8667	1.2150	12.3051	0.0153	0.1731	0.0427	0.7023	0.2966	0.0891	0.5040
Last Visit (LOCF)																	
Stiripentol Use	20 mg/kg	0.2219	N	21	12	24	4	3.4286	1.3020	9.0285	0.0062	0.1500	0.0378	0.5952	0.4048	0.1459	0.6637
			Y	18	5	17	3	1.5741	0.4427	5.5973	0.6906	0.5571	0.1105	2.8103	0.1013	-0.1737	0.3764
Last Visit (LOCF)																	
Levetiracetam Use	20 mg/kg	0.2491	N	31	14	33	7	2.1290	0.9923	4.5682	0.0621	0.3269	0.1095	0.9763	0.2395	0.0156	0.4634
			Y	8	3	8	0	-	-	-	0.2000	-	-	-	0.3750	0.0395	0.7105
Last Visit (LOCF)																	
Topiramate Use	20 mg/kg	0.5961	N	29	13	30	6	2.2414	0.9855	5.0978	0.0539	0.3077	0.0969	0.9774	0.2483	0.0175	0.4790
			Y	10	4	11	1	4.4000	0.5854	33.0706	0.1486	0.1500	0.0134	1.6764	0.3091	-0.0388	0.6570
Last Visit (LOCF)																	
Baseline Convulsive Seizure Frequency	20 mg/kg	0.5315	<=7	12	7	13	2	3.7917	0.9716	14.7964	0.0414	0.1299	0.0195	0.8631	0.4295	0.0885	0.7705
			>7 to <=21	17	7	13	2	2.6765	0.6628	10.8073	0.2293	0.2597	0.0434	1.5552	0.2579	-0.0474	0.5632
			>21	10	3	15	3	1.5000	0.3751	5.9977	0.6532	0.5833	0.0915	3.7173	0.1000	-0.2488	0.4488
Last Visit (LOCF)																	
Current AEDs	20 mg/kg	0.0343	<3	7	6	10	1	8.5714	1.3029	56.3879	0.0037	0.0185	0.0010	0.3567	0.7571	0.4381	1.0000
			>=3	32	11	31	6	1.7760	0.7490	4.2115	0.2574	0.4582	0.1449	1.4493	0.1502	-0.0653	0.3657
Last Visit (LOCF)																	
Prior AEDs	20 mg/kg	0.3322	<4	14	7	17	2	4.2500	1.0446	17.2910	0.0439	0.1333	0.0218	0.8143	0.3824	0.0789	0.6858
			>=4	25	10	24	5	1.9200	0.7684	4.7977	0.2165	0.3947	0.1109	1.4044	0.1917	-0.0599	0.4432
Last Visit (LOCF)																	
Prior + Current AEDs	20 mg/kg	0.2059	<8	20	9	22	2	4.9500	1.2116	20.2230	0.0132	0.1222	0.0223	0.6688	0.3591	0.1102	0.6080
			>=8	19	8	19	5	1.6000	0.6384	4.0099	0.4951	0.4911	0.1250	1.9291	0.1579	-0.1396	0.4554

LOCF = last observation carried forward; MI = much improved; VMI = very much improved; SI = slightly improved.

Last visit = Last visit is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc Table: GWEP1424 Any AE (subgroups)(Safety Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]		
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI
Age Group	10 mg/kg	0.6909	2-5 years	13	11	13	13	0.8519	0.6541	1.1095	0.4800
			6-12 years	23	21	16	15	0.9825	0.8035	1.2015	1.0000
			13-18 years	8	8	12	12	0.9822	0.8105	1.1903	-
Sex	10 mg/kg	0.0881	F	22	22	22	21	1.0465	0.9245	1.1846	1.0000
			M	22	18	19	19	0.8250	0.6664	1.0212	0.1105
Region	10 mg/kg	0.4570	REST OF THE WORLD	23	23	18	18	1.0056	0.9152	1.1049	-
			USA	21	17	23	22	0.8485	0.6703	1.0740	0.1765
Valproate Use	10 mg/kg	0.5777	N	14	10	12	11	0.7913	0.5384	1.1630	0.3304
			Y	30	30	29	29	1.0005	0.9377	1.0676	-
Stiripentol Use	10 mg/kg	0.6510	N	28	24	24	23	0.8988	0.7471	1.0811	0.3577
			Y	16	16	17	17	0.9983	0.8910	1.1186	-
Levetiracetam Use	10 mg/kg	0.4599	N	33	31	33	33	0.9403	0.8481	1.0425	0.4923
			Y	11	9	8	7	0.9500	0.6293	1.4341	1.0000
Topiramate Use	10 mg/kg	0.6168	N	37	34	30	29	0.9541	0.8389	1.0851	0.6220
			Y	7	6	11	11	0.8478	0.5956	1.2069	0.3889
Baseline Convulsive Seizure Frequency	10 mg/kg	0.7498	<=7	16	15	13	13	0.9455	0.7906	1.1308	1.0000
			>7 to <=21	15	13	13	13	0.8750	0.6926	1.1054	0.4841
			>21	13	12	15	14	0.9852	0.7747	1.2529	1.0000
Current AEDs	10 mg/kg	0.5145	<3	12	10	10	9	0.9352	0.6562	1.3328	1.0000
			>=3	32	30	31	31	0.9389	0.8436	1.0449	0.4921
Prior AEDs	10 mg/kg	0.4862	<4	17	15	17	17	0.8857	0.7242	1.0832	0.4848
			>=4	27	25	24	23	0.9688	0.8318	1.1285	1.0000
Prior + Current AEDs	10 mg/kg	0.5582	<8	23	21	22	21	0.9583	0.8053	1.1404	1.0000
			>=8	21	19	19	19	0.9091	0.7706	1.0725	0.4885
Age Group	20 mg/kg	0.5521	2-5 years	10	9	13	13	0.8956	0.6937	1.1564	0.4348
			6-12 years	22	21	16	15	1.0252	0.8537	1.2312	1.0000

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

			13-18 years	9	8	12	12	0.8840	0.6667	1.1722	0.4286
Sex	20 mg/kg	0.9702	F	17	15	22	21	0.9212	0.7432	1.1417	0.5703
			M	24	23	19	19	0.9641	0.8539	1.0885	1.0000
Region	20 mg/kg	0.8022	REST OF THE WORLD	19	18	18	18	0.9500	0.8217	1.0983	1.0000
			USA	22	20	23	22	0.9507	0.7972	1.1339	0.6078
Valproate Use	20 mg/kg	0.5949	N	11	8	12	11	0.8007	0.5299	1.2099	0.3168
			Y	30	30	29	29	1.0005	0.9377	1.0676	-
Stiripentol Use	20 mg/kg	0.6054	N	22	19	24	23	0.9019	0.7388	1.1010	0.3364
			Y	19	19	17	17	1.0029	0.9029	1.1139	-
Levetiracetam Use	20 mg/kg	0.7457	N	32	31	33	33	0.9688	0.8898	1.0548	0.4923
			Y	9	7	8	7	0.9000	0.5670	1.4285	1.0000
Topiramate Use	20 mg/kg	0.7454	N	30	28	30	29	0.9661	0.8474	1.1014	1.0000
			Y	11	10	11	11	0.9130	0.7152	1.1656	1.0000
Baseline Convulsive Seizure Frequency	20 mg/kg	0.8523	<=7	12	12	13	13	0.9972	0.8597	1.1565	-
			>7 to <=21	19	17	13	13	0.9074	0.7475	1.1016	0.5020
			>21	10	9	15	14	0.9530	0.7182	1.2645	1.0000
Current AEDs	20 mg/kg	0.4832	<3	8	7	10	9	0.9649	0.6633	1.4037	1.0000
			>=3	33	31	31	31	0.9412	0.8480	1.0446	0.4926
Prior AEDs	20 mg/kg	0.7840	<4	14	14	17	17	0.9943	0.8799	1.1235	-
			>=4	27	24	24	23	0.9309	0.7842	1.1050	0.6123
Prior + Current AEDs	20 mg/kg	0.4321	<8	20	19	22	21	0.9934	0.8462	1.1662	1.0000
			>=8	21	19	19	19	0.9091	0.7706	1.0725	0.4885

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc Table: GWEP1424 Maximal AE Mild (subgroups) (Safety Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]			
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	p-value (vs. Placebo)
	Age Group	10 mg/kg	0.2801	2-5 years	13	5	13	5	1.0000	0.3782	2.6443	1.0000
				6-12 years	23	10	16	13	0.5351	0.3175	0.9019	0.0242
				13-18 years	8	6	12	11	0.8182	0.5296	1.2640	0.5368
	Sex	10 mg/kg	0.6246	F	22	11	22	15	0.7333	0.4421	1.2164	0.3580
				M	22	10	19	14	0.6169	0.3628	1.0489	0.1120
	Region	10 mg/kg	0.8958	REST OF THE WORLD	23	13	18	14	0.7267	0.4702	1.1230	0.1963
				USA	21	8	23	15	0.5841	0.3137	1.0875	0.1301
	Valproate Use	10 mg/kg	0.6799	N	14	7	12	8	0.7500	0.3880	1.4498	0.4527
				Y	30	14	29	21	0.6444	0.4135	1.0043	0.0641
	Stiripentol Use	10 mg/kg	0.3112	N	28	11	24	17	0.5546	0.3274	0.9396	0.0288
				Y	16	10	17	12	0.8854	0.5435	1.4425	0.7207
	Levetiracetam Use	10 mg/kg	0.3408	N	33	16	33	25	0.6400	0.4285	0.9559	0.0414
				Y	11	5	8	4	0.9091	0.3522	2.3466	1.0000
	Topiramate Use	10 mg/kg	0.3372	N	37	17	30	19	0.7255	0.4658	1.1299	0.2186
				Y	7	4	11	10	0.6286	0.3222	1.2262	0.2451
	Baseline Convulsive Seizure Frequency	10 mg/kg	0.9505	<=7	16	8	13	9	0.7222	0.3926	1.3285	0.4515
				>7 to <=21	15	7	13	9	0.6741	0.3515	1.2927	0.2761
				>21	13	6	15	11	0.6294	0.3247	1.2198	0.2458
	Current AEDs	10 mg/kg	0.4672	<3	12	4	10	7	0.4762	0.1942	1.1679	0.1984
				>=3	32	17	31	22	0.7486	0.5039	1.1120	0.1963
	Prior AEDs	10 mg/kg	0.0536	<4	17	9	17	9	1.0000	0.5306	1.8848	1.0000
				>=4	27	12	24	20	0.5333	0.3373	0.8432	0.0082
	Prior + Current AEDs	10 mg/kg	0.3286	<8	23	10	22	13	0.7358	0.4114	1.3160	0.3762
				>=8	21	11	19	16	0.6220	0.3959	0.9774	0.0455
	Age Group	20 mg/kg	0.3013	2-5 years	10	3	13	5	0.7800	0.2421	2.5134	1.0000
				6-12 years	22	8	16	13	0.4476	0.2454	0.8162	0.0088

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		13-18 years	9	5	12	11	0.6061	0.3297	1.1140	0.1194
Sex	20 mg/kg	0.9982 F	17	6	22	15	0.5176	0.2560	1.0467	0.0566
		M	24	10	19	14	0.5655	0.3281	0.9746	0.0628
Region	20 mg/kg	0.2080 REST OF THE WORLD	19	6	18	14	0.4060	0.2003	0.8229	0.0081
		USA	22	10	23	15	0.6970	0.4035	1.2037	0.2362
Valproate Use	20 mg/kg	0.5356 N	11	5	12	8	0.6818	0.3185	1.4594	0.4136
		Y	30	11	29	21	0.5063	0.3007	0.8527	0.0089
Stiripentol Use	20 mg/kg	0.0386 N	22	4	24	17	0.2567	0.1020	0.6459	0.0004
		Y	19	12	17	12	0.8947	0.5645	1.4181	0.7317
Levetiracetam Use	20 mg/kg	0.1972 N	32	12	33	25	0.4950	0.3041	0.8057	0.0026
		Y	9	4	8	4	0.8889	0.3248	2.4328	1.0000
Topiramate Use	20 mg/kg	0.1362 N	30	12	30	19	0.6316	0.3770	1.0580	0.1205
		Y	11	4	11	10	0.4000	0.1791	0.8936	0.0237
Baseline Convulsive Seizure Frequency	20 mg/kg	0.7311 <=7	12	3	13	9	0.3611	0.1270	1.0266	0.0472
		>7 to <=21	19	8	13	9	0.6082	0.3208	1.1532	0.1657
		>21	10	5	15	11	0.6818	0.3417	1.3605	0.3973
Current AEDs	20 mg/kg	0.1997 <3	8	1	10	7	0.1786	0.0273	1.1676	0.0248
		>=3	33	15	31	22	0.6405	0.4140	0.9909	0.0467
Prior AEDs	20 mg/kg	0.4315 <4	14	4	17	9	0.5397	0.2105	1.3840	0.2749
		>=4	27	12	24	20	0.5333	0.3373	0.8432	0.0082
Prior + Current AEDs	20 mg/kg	0.5812 <8	20	6	22	13	0.5077	0.2388	1.0795	0.0718
		>=8	21	10	19	16	0.5655	0.3468	0.9221	0.0219

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc Table: GWEP1424 Maximal AE Moderate (subgroups) (Safety Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]		
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI
Age Group	10 mg/kg	0.0571	2-5 years	13	4	13	7	0.5714	0.2192	1.4897	0.4283
			6-12 years	23	10	16	2	3.4783	0.8772	13.7925	0.0758
			13-18 years	8	2	12	1	3.0000	0.3234	27.8307	0.5368
Sex	10 mg/kg	0.9561	F	22	9	22	6	1.5000	0.6429	3.4999	0.5256
			M	22	7	19	4	1.5114	0.5215	4.3804	0.4993
Region	10 mg/kg	0.6336	REST OF THE WORLD	23	9	18	4	1.7609	0.6456	4.8027	0.3210
			USA	21	7	23	6	1.2778	0.5113	3.1936	0.7438
Valproate Use	10 mg/kg	0.3999	N	14	2	12	2	0.8571	0.1414	5.1954	1.0000
			Y	30	14	29	8	1.6917	0.8376	3.4165	0.1799
Stiripentol Use	10 mg/kg	0.4095	N	28	11	24	5	1.8857	0.7623	4.6645	0.2289
			Y	16	5	17	5	1.0625	0.3776	2.9900	1.0000
Levetiracetam Use	10 mg/kg	0.3132	N	33	14	33	8	1.7500	0.8498	3.6036	0.1912
			Y	11	2	8	2	0.7273	0.1282	4.1250	1.0000
Topiramate Use	10 mg/kg	0.1664	N	37	14	30	10	1.1266	0.5958	2.1301	0.8000
			Y	7	2	11	0	7.5000	0.4120	136.5223	0.1373
Baseline Convulsive Seizure Frequency	10 mg/kg	0.4396	<=7	16	7	13	4	1.4219	0.5301	3.8140	0.7021
			>7 to <=21	15	4	13	4	0.8667	0.2690	2.7927	1.0000
			>21	13	5	15	2	2.8846	0.6686	12.4458	0.1977
Current AEDs	10 mg/kg	0.3171	<3	12	6	10	2	2.5000	0.6400	9.7659	0.2043
			>=3	32	10	31	8	1.2109	0.5509	2.6619	0.7816
Prior AEDs	10 mg/kg	0.0033	<4	17	3	17	7	0.4286	0.1325	1.3858	0.2587
			>=4	27	13	24	3	3.8519	1.2461	11.9068	0.0076
Prior + Current AEDs	10 mg/kg	0.2884	<8	23	8	22	7	1.0932	0.4771	2.5046	1.0000
			>=8	21	8	19	3	2.4127	0.7467	7.7958	0.1628
Age Group	20 mg/kg	0.1742	2-5 years	10	5	13	7	0.9286	0.4179	2.0633	1.0000
			6-12 years	22	11	16	2	4.0000	1.0245	15.6172	0.0356

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		13-18 years	9	3	12	1	4.0000	0.4939	32.3930	0.2722
Sex	20 mg/kg	0.7646 F	17	8	22	6	1.7255	0.7387	4.0307	0.3137
		M	24	11	19	4	2.1771	0.8226	5.7621	0.1161
Region	20 mg/kg	0.4809 REST OF THE WORLD	19	10	18	4	2.3684	0.9034	6.2092	0.0911
		USA	22	9	23	6	1.5682	0.6691	3.6753	0.3534
Valproate Use	20 mg/kg	0.6868 N	11	3	12	2	1.6364	0.3333	8.0338	0.6404
		Y	30	16	29	8	1.9333	0.9814	3.8088	0.0641
Stiripentol Use	20 mg/kg	0.0376 N	22	14	24	5	3.0545	1.3168	7.0856	0.0063
		Y	19	5	17	5	0.8947	0.3122	2.5641	1.0000
Levetiracetam Use	20 mg/kg	0.2514 N	32	17	33	8	2.1914	1.1043	4.3487	0.0225
		Y	9	2	8	2	0.8889	0.1603	4.9295	1.0000
Topiramate Use	20 mg/kg	0.0437 N	30	13	30	10	1.2857	0.6817	2.4249	0.5959
		Y	11	6	11	0	13.0000	0.8204	205.9964	0.0124
Baseline Convulsive Seizure Frequency	20 mg/kg	0.6737 <=7	12	8	13	4	2.1667	0.8737	5.3733	0.1152
		>7 to <=21	19	8	13	4	1.3684	0.5182	3.6135	0.7128
		>21	10	3	15	2	2.2500	0.4541	11.1477	0.3577
Current AEDs	20 mg/kg	0.3374 <3	8	5	10	2	3.1250	0.8095	12.0642	0.1448
		>=3	33	14	31	8	1.6439	0.8025	3.3676	0.1948
Prior AEDs	20 mg/kg	0.3678 <4	14	8	17	7	1.3878	0.6707	2.8712	0.4795
		>=4	27	11	24	3	3.2593	1.0298	10.3152	0.0309
Prior + Current AEDs	20 mg/kg	0.8222 <8	20	11	22	7	1.7286	0.8339	3.5830	0.2118
		>=8	21	8	19	3	2.4127	0.7467	7.7958	0.1628

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count
(ITT Analysis Set, Patients Taking Clobazam)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data			40 / 38	0.460 [54.0%] / 0.727 [27.3%]	0.633 [36.7%]	(0.417, 0.961)	0.0321
Age Group	0.8498	2-5 years	14 / 10	0.295 [70.5%] / 0.547 [45.3%]	0.539 [46.1%]	(0.247, 1.178)	0.1195
		6-12 years	15 / 15	0.687 [31.3%] / 0.963 [3.7%]	0.714 [28.6%]	(0.362, 1.409)	0.3261
		13-18 years	11 / 13	0.388 [61.2%] / 0.669 [33.1%]	0.580 [42.0%]	(0.274, 1.231)	0.1534
Sex	0.5541	Female	18 / 22	0.485 [51.5%] / 0.840 [16.0%]	0.577 [42.3%]	(0.319, 1.044)	0.0687
		Male	22 / 16	0.437 [56.3%] / 0.587 [41.3%]	0.745 [25.5%]	(0.401, 1.383)	0.3459
Region	0.0662	USA	23 / 29	0.302 [69.8%] / 0.718 [28.2%]	0.420 [58.0%]	(0.251, 0.704)	0.0013
		Rest of the World	17 / 9	0.750 [25.0%] / 0.756 [24.4%]	0.993 [0.7%]	(0.464, 2.124)	0.9848
Valproic Acid Use	0.2498	Not Currently Taking	15 / 18	0.374 [62.6%] / 0.792 [20.8%]	0.473 [52.7%]	(0.247, 0.905)	0.0242
		Currently Taking	25 / 20	0.518 [48.2%] / 0.665 [33.5%]	0.778 [22.2%]	(0.445, 1.361)	0.3744
Stiripentol Use	0.0137	Not Currently Taking	17 / 24	0.190 [81.0%] / 0.634 [36.6%]	0.300 [70.0%]	(0.169, 0.534)	<.0001
		Currently Taking	23 / 14	0.765 [23.5%] / 0.888 [11.2%]	0.862 [13.8%]	(0.473, 1.574)	0.6255
Baseline Convulsive Seizure Frequency	0.8008	<=7	14 / 12	0.360 [64.0%] / 0.457 [54.3%]	0.789 [21.1%]	(0.364, 1.712)	0.5442
		>7 to <=21	16 / 11	0.494 [50.6%] / 0.875 [12.5%]	0.565 [43.5%]	(0.278, 1.149)	0.1133
		>21	10 / 15	0.594 [40.6%] / 0.821 [17.9%]	0.723 [27.7%]	(0.350, 1.495)	0.3767
Number of concurrent AEDs	<.0001	<3	12 / 9	0.107 [89.3%] / 0.820 [18.0%]	0.130 [87.0%]	(0.058, 0.289)	<.0001
		>=3	28 / 29	0.665 [33.5%] / 0.699 [30.1%]	0.951 [4.9%]	(0.602, 1.503)	0.8283
Number of prior AEDs	0.4657	<4	21 / 16	0.520 [48.0%] / 0.703 [29.7%]	0.739 [26.1%]	(0.399, 1.371)	0.3330
		>=4	19 / 22	0.404 [59.6%] / 0.747 [25.3%]	0.541 [45.9%]	(0.302, 0.969)	0.0393
SCN1A Mutation	0.0419	Truncation Variants	25 / 21	0.543 [45.7%] / 0.870 [13.0%]	0.624 [37.6%]	(0.361, 1.080)	0.0912
		No Known Mutation	3 / 2	0.143 [85.7%] / 1.690 [-69.0%]	0.085 [91.5%]	(0.015, 0.463)	0.0050
		Missense Variants	12 / 15	0.419 [58.1%] / 0.454 [54.6%]	0.922 [7.8%]	(0.445, 1.909)	0.8250

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.

Log transformed number of days seizures were reported by period is included as an offset.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B Total Seizure Responder (subgroups) (ITT Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Total Seizures <=25pct	Age Group	20 mg/kg	0.9609	2-5 years	14	8	10	4	1.4286	0.5900	3.4590	0.6802	2	0.3843	10.4093	0.1714	-0.2278	0.5707
				6-12 years	15	7	15	4	1.7500	0.6448	4.7497	0.4497	2.4063	0.5214	11.104	0.2	-0.1374	0.5374
				13-18 years	11	7	13	5	1.6545	0.7287	3.7565	0.4136	2.8	0.5321	14.735	0.2517	-0.1365	0.64
	Sex	20 mg/kg	0.4558	F	18	11	22	7	1.9206	0.9404	3.9227	0.1098	3.3673	0.9132	12.417	0.2929	-0.0047	0.5906
				M	22	11	16	6	1.3333	0.6247	2.8457	0.5205	1.6667	0.4485	6.1928	0.125	-0.1911	0.4411
	Region	20 mg/kg	0.3678	REST OF THE WORLD	17	7	9	3	1.2353	0.4176	3.6545	1.0000	1.4	0.2585	7.5818	0.0784	-0.3083	0.4652
				USA	23	15	29	10	1.8913	1.0550	3.3906	0.0495	3.5625	1.128	11.2516	0.3073	0.0469	0.5678
	Valproate Use	20 mg/kg	0.9416	N	15	9	18	7	1.5429	0.7575	3.1426	0.3028	2.3571	0.5802	9.576	0.2111	-0.1238	0.546
				Y	25	13	20	6	1.7333	0.8041	3.7366	0.2244	2.5278	0.7337	8.7091	0.22	-0.0605	0.5005
	Stiripentol Use	20 mg/kg	0.3189	N	17	15	24	11	1.9251	1.2053	3.0749	0.0082	8.8636	1.6524	47.5463	0.424	0.1726	0.6754
				Y	23	7	14	2	2.1304	0.5128	8.8502	0.4339	2.625	0.4605	14.9646	0.1615	-0.1011	0.4241
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.2195	<=8.0	14	9	12	6	1.2857	0.6465	2.5568	0.6922	1.8	0.3732	8.6815	0.1429	-0.2353	0.521
>8.0 to <=25.0				16	10	11	2	3.4375	0.9277	12.7373	0.0473	7.5	1.1956	47.049	0.4432	0.1142	0.7722	
>25.0				10	3	15	5	0.9000	0.2747	2.9490	1.0000	0.8571	0.1525	4.8192	-0.0333	-0.4043	0.3376	
Current AEDs	20 mg/kg	0.5430	<3	12	10	9	5	1.5000	0.7935	2.8356	0.3310	4	0.5368	29.8045	0.2778	-0.1093	0.6649	
			>=3	28	12	29	8	1.5536	0.7498	3.2188	0.2744	1.9688	0.6514	5.9503	0.1527	-0.0924	0.3978	
Prior AEDs	20 mg/kg	0.5978	<4	21	11	16	4	2.0952	0.8172	5.3722	0.1757	3.3	0.7984	13.6403	0.2738	-0.0273	0.5749	
			>=4	19	11	22	9	1.4152	0.7523	2.6622	0.3543	1.9861	0.5715	6.9024	0.1699	-0.1326	0.4723	
SCN1A Mutation-Positive	20 mg/kg	0.1770	Truncation Variants	25	12	21	6	1.6800	0.7626	3.7010	0.2318	2.3077	0.6748	7.8921	0.1943	-0.0808	0.4694	
			Missense Variants	12	7	15	7	1.2500	0.6072	2.5733	0.7036	1.6	0.3459	7.4015	0.1167	-0.2596	0.4929	
			No Known Mutation	3	3	2	0	-	-	-	0.1000	-	-	-	1	1	1	
Total Seizures <=50pct	Age Group	20 mg/kg	0.7678	2-5 years	14	8	10	4	1.4286	0.5900	3.4590	0.6802	2	0.3843	10.4093	0.1714	-0.2278	0.5707
				6-12 years	15	5	15	3	1.6667	0.4825	5.7570	0.6817	2	0.3806	10.5105	0.1333	-0.1795	0.4462
				13-18 years	11	5	13	2	2.9545	0.7072	12.3436	0.1819	4.5833	0.6733	31.1983	0.3007	-0.0529	0.6543
	Sex	20 mg/kg	0.1342	F	18	10	22	4	3.0556	1.1491	8.1251	0.0208	5.625	1.3493	23.4494	0.3737	0.0933	0.6542
				M	22	8	16	5	1.1636	0.4669	2.8999	1.0000	1.2571	0.32	4.9386	0.0511	-0.2522	0.3544
	Region	20 mg/kg	0.6012	REST OF THE WORLD	17	6	9	2	1.5882	0.3990	6.3217	0.6673	1.9091	0.2972	12.2614	0.1307	-0.2234	0.4848
				USA	23	12	29	7	2.1615	1.0163	4.5970	0.0469	3.4286	1.0534	11.1594	0.2804	0.0236	0.5371
	Valproate Use	20 mg/kg	0.2057	N	15	8	18	3	3.2000	1.0272	9.9686	0.0613	5.7143	1.1517	28.3521	0.3667	0.0611	0.6722
				Y	25	10	20	6	1.3333	0.5850	3.0389	0.5444	1.5556	0.447	5.4129	0.1	-0.1779	0.3779
	Stiripentol Use	20 mg/kg	0.9728	N	17	12	24	8	2.1176	1.1126	4.0307	0.0278	4.8	1.2507	18.421	0.3725	0.0854	0.6597
				Y	23	6	14	1	3.6522	0.4893	27.2586	0.2173	4.5882	0.49	42.9601	0.1894	-0.0351	0.4139
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.3216	<=8.0	14	7	12	5	1.2000	0.5129	2.8077	0.7127	1.4	0.296	6.6219	0.0833	-0.2993	0.466
>8.0 to <=25.0				16	8	11	1	5.5000	0.7968	37.9652	0.0417	10	1.0256	97.5005	0.4091	0.111	0.7072	
>25.0				10	3	15	3	1.5000	0.3751	5.9977	0.6532	1.7143	0.269	10.9243	0.1	-0.2488	0.4488	
Current AEDs	20 mg/kg	0.2949	<3	12	9	9	3	2.2500	0.8445	5.9949	0.0872	6	0.8932	40.3061	0.4167	0.0231	0.8102	
			>=3	28	9	29	6	1.5536	0.6361	3.7944	0.3786	1.8158	0.5478	6.0193	0.1145	-0.1128	0.3418	
Prior AEDs	20 mg/kg	0.7581	<4	21	9	16	4	1.7143	0.6422	4.5764	0.3149	2.25	0.5418	9.3447	0.1786	-0.1211	0.4783	
			>=4	19	9	22	5	2.0842	0.8435	5.1500	0.1147	3.06	0.7984	11.7283	0.2464	-0.0383	0.5311	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

SCN1A Mutation-Positive	20 mg/kg	0.2042 Truncation Variants	25	9	21	4	1.8900	0.6781	5.2676	0.3251	2.3906	0.6128	9.3268	0.1695	-0.0827	0.4217
		Missense Variants	12	6	15	5	1.5000	0.6024	3.7351	0.4517	2	0.4204	9.5156	0.1667	-0.2034	0.5367
		No Known Mutation	3	3	2	0	-	-	-	0.1000	-	-	-	1	1	1
Total Seizures <=75pct																
Age Group	20 mg/kg	0.3996 2-5 years	14	6	10	2	2.1429	0.5395	8.5116	0.3875	3	0.4594	19.5923	0.2286	-0.1301	0.5873
		6-12 years	15	2	15	3	0.6667	0.1293	3.4362	1.0000	0.6154	0.0872	4.3413	-0.0667	-0.3323	0.199
		13-18 years	11	4	13	2	2.3636	0.5298	10.5450	0.3572	3.1429	0.4498	21.9578	0.2098	-0.1356	0.5552
Sex	20 mg/kg	0.3418 F	18	6	22	3	2.4444	0.7088	8.4304	0.2534	3.1667	0.6634	15.1152	0.197	-0.0638	0.4577
		M	22	6	16	4	1.0909	0.3672	3.2414	1.0000	1.125	0.2587	4.8928	0.0227	-0.2595	0.305
Region	20 mg/kg	0.0891 REST OF THE WORLD	17	2	9	2	0.5294	0.0888	3.1572	0.5906	0.4667	0.0541	4.0285	-0.1046	-0.4164	0.2072
		USA	23	10	29	5	2.5217	1.0014	6.3503	0.0635	3.6923	1.0389	13.1224	0.2624	0.0175	0.5072
Valproate Use	20 mg/kg	0.0479 N	15	7	18	2	4.2000	1.0211	17.2756	0.0469	7	1.1734	41.7586	0.3556	0.0643	0.6468
		Y	25	5	20	5	0.8000	0.2686	2.3824	0.7310	0.75	0.1833	3.0683	-0.05	-0.2962	0.1962
Stiripentol Use	20 mg/kg	0.3784 N	17	10	24	6	2.3529	1.0583	5.2312	0.0505	4.2857	1.126	16.3123	0.3382	0.0471	0.6293
		Y	23	2	14	1	1.2174	0.1212	12.2239	1.0000	1.2381	0.1018	15.0548	0.0155	-0.1618	0.1929
Baseline Convulsive Seizure Frequency	20 mg/kg	0.3673 <=8.0	14	5	12	5	0.8571	0.3247	2.2625	1.0000	0.7778	0.1594	3.795	-0.0595	-0.4348	0.3157
		>8.0 to <=25.0	16	5	11	1	3.4375	0.4628	25.5298	0.3497	4.5455	0.4505	45.8625	0.2216	-0.062	0.5052
		>25.0	10	2	15	1	3.0000	0.3121	28.8406	0.5435	3.5	0.2725	44.9503	0.1333	-0.1449	0.4115
Current AEDs	20 mg/kg	0.0212 <3	12	9	9	2	3.3750	0.9524	11.9597	0.0300	10.5	1.3602	81.053	0.5278	0.162	0.8936
		>=3	28	3	29	5	0.6214	0.1637	2.3587	0.7057	0.576	0.1238	2.6789	-0.0653	-0.2442	0.1137
Prior AEDs	20 mg/kg	0.9320 <4	21	5	16	2	1.9048	0.4228	8.5821	0.6745	2.1875	0.3653	13.0997	0.1131	-0.1307	0.3569
		>=4	19	7	22	5	1.6211	0.6147	4.2749	0.4926	1.9833	0.5065	7.766	0.1411	-0.1376	0.4199
SCN1A Mutation-Positive	20 mg/kg	0.4576 Truncation Variants	25	5	21	2	2.1000	0.4530	9.7348	0.4285	2.375	0.4103	13.7484	0.1048	-0.0961	0.3056
		Missense Variants	12	5	15	5	1.2500	0.4691	3.3305	0.7063	1.4286	0.2968	6.8767	0.0833	-0.2837	0.4504
		No Known Mutation	3	2	2	0	0.3333	0.0673	1.6515	0.4000	-	-	-	0.6667	0.1332	1

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count (ITT Analysis Set, Patients Taking Clobazam)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data			40 / 38	0.462 [53.8%] / 0.811 [18.9%]	0.570 [43.0%]	(0.388, 0.839)	0.0049
Age Group	0.2551	2-5 years	14 / 10	0.253 [74.7%] / 0.657 [34.3%]	0.386 [61.4%]	(0.188, 0.790)	0.0100
		6-12 years	15 / 15	0.805 [19.5%] / 0.972 [2.8%]	0.828 [17.2%]	(0.452, 1.517)	0.5367
		13-18 years	11 / 13	0.393 [60.7%] / 0.766 [23.4%]	0.513 [48.7%]	(0.260, 1.013)	0.0545
Sex	0.8424	Female	18 / 22	0.475 [52.5%] / 0.856 [14.4%]	0.555 [44.5%]	(0.321, 0.960)	0.0356
		Male	22 / 16	0.451 [54.9%] / 0.751 [24.9%]	0.601 [39.9%]	(0.341, 1.057)	0.0766
Region	0.2564	USA	23 / 29	0.358 [64.2%] / 0.805 [19.5%]	0.445 [55.5%]	(0.275, 0.720)	0.0013
		Rest of the World	17 / 9	0.608 [39.2%] / 0.832 [16.8%]	0.730 [27.0%]	(0.357, 1.496)	0.3855
Valproic Acid Use	0.7080	Not Currently Taking	15 / 18	0.434 [56.6%] / 0.833 [16.7%]	0.522 [47.8%]	(0.284, 0.958)	0.0362
		Currently Taking	25 / 20	0.480 [52.0%] / 0.791 [20.9%]	0.607 [39.3%]	(0.360, 1.022)	0.0601
Stiripentol Use	0.0345	Not Currently Taking	17 / 24	0.226 [77.4%] / 0.731 [26.9%]	0.309 [69.1%]	(0.182, 0.524)	<.0001
		Currently Taking	23 / 14	0.682 [31.8%] / 0.963 [3.7%]	0.708 [29.2%]	(0.406, 1.234)	0.2198
Baseline Convulsive Seizure Frequency	0.8737	<=7	14 / 12	0.422 [57.8%] / 0.765 [23.5%]	0.551 [44.9%]	(0.267, 1.137)	0.1054
		>7 to <=21	16 / 11	0.460 [54.0%] / 0.850 [15.0%]	0.541 [45.9%]	(0.288, 1.019)	0.0568
		>21	10 / 15	0.608 [39.2%] / 0.910 [9.0%]	0.668 [33.2%]	(0.361, 1.237)	0.1957
Number of concurrent AEDs	<.0001	<3	12 / 9	0.117 [88.3%] / 0.902 [9.8%]	0.130 [87.0%]	(0.063, 0.266)	<.0001
		>=3	28 / 29	0.682 [31.8%] / 0.787 [21.3%]	0.866 [13.4%]	(0.570, 1.317)	0.4969
Number of prior AEDs	0.9103	<4	21 / 16	0.446 [55.4%] / 0.760 [24.0%]	0.587 [41.3%]	(0.331, 1.041)	0.0680
		>=4	19 / 22	0.479 [52.1%] / 0.853 [14.7%]	0.562 [43.8%]	(0.328, 0.961)	0.0355
SCN1A Mutation	0.0496	Truncation Variants	25 / 21	0.510 [49.0%] / 0.858 [14.2%]	0.595 [40.5%]	(0.361, 0.979)	0.0414
		No Known Mutation	3 / 2	0.159 [84.1%] / 1.617 [-61.7%]	0.098 [90.2%]	(0.022, 0.437)	0.0028
		Missense Variants	12 / 15	0.498 [50.2%] / 0.660 [34.0%]	0.754 [24.6%]	(0.391, 1.453)	0.3939

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.
 Log transformed number of days seizures were reported by period is included as an offset.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B Convulsive Seizure Responder (subgroups)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI	
Convulsive Seizures <=25pct	Age Group	20 mg/kg	0.9642	2-5 years	14	10	10	5	1.4286	0.7074	2.8848	0.4028	2.5	0.4579	13.649	0.2143	-0.1756	0.6042
				6-12 years	15	8	15	5	1.6000	0.6784	3.7738	0.4621	2.2857	0.5219	10.0105	0.2	-0.1473	0.5473
				13-18 years	11	8	13	6	1.5758	0.7906	3.1407	0.2397	3.1111	0.5585	17.3301	0.2657	-0.112	0.6435
	Sex	20 mg/kg	0.7863	F	18	13	22	10	1.5889	0.9259	2.7266	0.1159	3.12	0.8254	11.7931	0.2677	-0.0258	0.5611
				M	22	13	16	6	1.5758	0.7656	3.2432	0.3245	2.4074	0.6421	9.0267	0.2159	-0.0979	0.5297
	Region	20 mg/kg	0.3800	REST OF THE WORLD	17	12	9	3	2.1176	0.7999	5.6061	0.1034	4.8	0.847	27.2024	0.3725	-0.004	0.7491
				USA	23	14	29	13	1.3579	0.8073	2.2840	0.2781	1.9145	0.6296	5.8217	0.1604	-0.1089	0.4298
	Valproate Use	20 mg/kg	0.9460	N	15	10	18	8	1.5000	0.8002	2.8118	0.2964	2.5	0.6042	10.3441	0.2222	-0.1088	0.5533
				Y	25	16	20	8	1.6000	0.8676	2.9506	0.1397	2.6667	0.7942	8.9542	0.24	-0.0455	0.5255
	Stiripentol Use	20 mg/kg	0.6072	N	17	14	24	12	1.6471	1.0433	2.6002	0.0502	4.6667	1.0606	20.5331	0.3235	0.0536	0.5934
				Y	23	12	14	4	1.8261	0.7306	4.5639	0.1908	2.7273	0.6598	11.2729	0.236	-0.0765	0.5486
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.9690	<=8.0	14	10	12	6	1.4286	0.7416	2.7520	0.4216	2.5	0.4947	12.6351	0.2143	-0.1545	0.5831
				>8.0 to <=25.0	16	11	11	5	1.5125	0.7312	3.1285	0.2638	2.64	0.5387	12.9376	0.233	-0.1388	0.6047
				>25.0	10	5	15	5	1.5000	0.5820	3.8660	0.4422	2	0.388	10.3085	0.1667	-0.2244	0.5578
	Current AEDs	20 mg/kg	0.6207	<3	12	9	9	4	1.6875	0.7581	3.7562	0.2031	3.75	0.5875	23.9362	0.3056	-0.1012	0.7123
				>=3	28	17	29	12	1.4673	0.8673	2.4822	0.1885	2.1894	0.7594	6.3125	0.1933	-0.0613	0.448
	Prior AEDs	20 mg/kg	0.9680	<4	21	14	16	7	1.5238	0.8095	2.8685	0.1964	2.5714	0.6725	9.832	0.2292	-0.0866	0.545
				>=4	19	12	22	9	1.5439	0.8402	2.8368	0.2146	2.4762	0.7014	8.7422	0.2225	-0.0763	0.5212
	SCN1A Mutation-Positive	20 mg/kg	0.1903	Truncation Variants	25	15	21	8	1.5750	0.8370	2.9638	0.2362	2.4375	0.7416	8.0117	0.219	-0.0638	0.5019
				Missense Variants	12	8	15	8	1.2500	0.6726	2.3232	0.6960	1.75	0.3635	8.424	0.1333	-0.2339	0.5006
No Known Mutation				3	3	2	0	-	-	-	0.1000	-	-	-	1	1	1	
Convulsive Seizures <=50pct	Age Group	20 mg/kg	0.2332	2-5 years	14	9	10	5	1.2857	0.6180	2.6747	0.6785	1.8	0.3447	9.3987	0.1429	-0.2559	0.5416
				6-12 years	15	4	15	3	1.3333	0.3580	4.9653	1.0000	1.4545	0.2642	8.0095	0.0667	-0.2351	0.3684
				13-18 years	11	6	13	1	7.0909	1.0000	50.2814	0.0233	14.4	1.3595	152.5264	0.4685	0.1406	0.7965
	Sex	20 mg/kg	0.1907	F	18	10	22	4	3.0556	1.1491	8.1251	0.0208	5.625	1.3493	23.4494	0.3737	0.0933	0.6542
				M	22	9	16	5	1.3091	0.5411	3.1669	0.7352	1.5231	0.3923	5.9129	0.0966	-0.2097	0.4028
	Region	20 mg/kg	0.4965	REST OF THE WORLD	17	6	9	2	1.5882	0.3990	6.3217	0.6673	1.9091	0.2972	12.2614	0.1307	-0.2234	0.4848
				USA	23	13	29	7	2.3416	1.1193	4.8986	0.0233	4.0857	1.2498	13.3564	0.3238	0.0683	0.5794
	Valproate Use	20 mg/kg	0.1268	N	15	9	18	3	3.6000	1.1834	10.9518	0.0143	7.5	1.4938	37.6558	0.4333	0.1315	0.7352
				Y	25	10	20	6	1.3333	0.5850	3.0389	0.5444	1.5556	0.447	5.4129	0.1	-0.1779	0.3779
	Stiripentol Use	20 mg/kg	0.7947	N	17	13	24	8	2.2941	1.2289	4.2826	0.0109	6.5	1.5937	26.5108	0.4314	0.1553	0.7075
				Y	23	6	14	1	3.6522	0.4893	27.2586	0.2173	4.5882	0.49	42.9601	0.1894	-0.0351	0.4139
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.7639	<=8.0	14	8	12	4	1.7143	0.6833	4.3008	0.2671	2.6667	0.5382	13.2121	0.2381	-0.1338	0.61
				>8.0 to <=25.0	16	8	11	2	2.7500	0.7158	10.5651	0.1241	4.5	0.73	27.7392	0.3182	-0.0164	0.6528
				>25.0	10	3	15	3	1.5000	0.3751	5.9977	0.6532	1.7143	0.269	10.9243	0.1	-0.2488	0.4488
	Current AEDs	20 mg/kg	0.3632	<3	12	9	9	3	2.2500	0.8445	5.9949	0.0872	6	0.8932	40.3061	0.4167	0.0231	0.8102
				>=3	28	10	29	6	1.7262	0.7241	4.1151	0.2483	2.1296	0.651	6.9671	0.1502	-0.0805	0.381
	Prior AEDs	20 mg/kg	0.2659	<4	21	9	16	5	1.3714	0.5696	3.3021	0.5154	1.65	0.4212	6.4639	0.1161	-0.1944	0.4265
				>=4	19	10	22	4	2.8947	1.0824	7.7417	0.0262	5	1.2222	20.4555	0.3445	0.0681	0.6209

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

SCN1A Mutation-Positive	20 mg/kg	0.2106 Truncation Variants	25	10	21	4	2.1000	0.7695	5.7310	0.1988	2.8333	0.7334	10.9459	0.2095	-0.0456	0.4646
		Missense Variants	12	6	15	5	1.5000	0.6024	3.7351	0.4517	2	0.4204	9.5156	0.1667	-0.2034	0.5367
		No Known Mutation	3	3	2	0	-	-	-	0.1000	-	-	-	1	1	1
Convulsive Seizures <=75pct Age Group	20 mg/kg	0.0641 2-5 years	14	6	10	2	2.1429	0.5395	8.5116	0.3875	3	0.4594	19.5923	0.2286	-0.1301	0.5873
		6-12 years	15	1	15	3	0.3333	0.0389	2.8531	0.5977	0.2857	0.0262	3.121	-0.1333	-0.3719	0.1052
		13-18 years	11	3	13	0	0.7273	0.5064	1.0444	0.0815	-	-	-	0.2727	0.0095	0.5359
Sex	20 mg/kg	0.6454 F	18	4	22	2	2.4444	0.5040	11.8552	0.3810	2.8571	0.4585	17.8046	0.1313	-0.0952	0.3578
		M	22	6	16	3	1.4545	0.4263	4.9624	0.7060	1.625	0.339	7.7895	0.0852	-0.1816	0.3521
Region	20 mg/kg	0.1658 REST OF THE WORLD	17	1	9	1	0.5294	0.0373	7.5041	1.0000	0.5	0.0275	9.0764	-0.0523	-0.2861	0.1815
		USA	23	9	29	4	2.8370	0.9998	8.0499	0.0538	4.0179	1.0444	15.4569	0.2534	0.0177	0.489
Valproate Use	20 mg/kg	0.3942 N	15	5	18	2	3.0000	0.6763	13.3086	0.2028	4	0.648	24.6933	0.2222	-0.057	0.5015
		Y	25	5	20	3	1.3333	0.3616	4.9170	0.7157	1.4167	0.2946	6.8136	0.05	-0.1715	0.2715
Stiripentol Use	20 mg/kg	0.6969 N	17	9	24	5	2.5412	1.0337	6.2471	0.0476	4.275	1.0861	16.8272	0.3211	0.0335	0.6086
		Y	23	1	14	0	0.9565	0.8767	1.0436	1.0000	-	-	-	0.0435	-0.0399	0.1268
Baseline Convulsive Seizure Frequency	20 mg/kg	0.9014 <=8.0	14	4	12	2	1.7143	0.3779	7.7768	0.6522	2	0.2961	13.5107	0.119	-0.1979	0.436
		>8.0 to <=25.0	16	4	11	1	2.7500	0.3532	21.4139	0.6185	3.3333	0.319	34.83	0.1591	-0.1127	0.4309
		>25.0	10	2	15	2	1.5000	0.2506	8.9769	1.0000	1.625	0.1895	13.933	0.0667	-0.2351	0.3684
Current AEDs	20 mg/kg	0.0992 <3	12	9	9	3	2.2500	0.8445	5.9949	0.0872	6	0.8932	40.3061	0.4167	0.0231	0.8102
		>=3	28	1	29	2	0.5179	0.0497	5.3955	1.0000	0.5	0.0428	5.8466	-0.0333	-0.1483	0.0818
Prior AEDs	20 mg/kg	0.9781 <4	21	5	16	2	1.9048	0.4228	8.5821	0.6745	2.1875	0.3653	13.0997	0.1131	-0.1307	0.3569
		>=4	19	5	22	3	1.9298	0.5296	7.0321	0.4362	2.2619	0.4617	11.0822	0.1268	-0.1177	0.3713
SCN1A Mutation-Positive	20 mg/kg	0.5171 Truncation Variants	25	4	21	2	1.6800	0.3408	8.2808	0.6734	1.8095	0.2969	11.0268	0.0648	-0.1261	0.2556
		Missense Variants	12	4	15	3	1.6667	0.4587	6.0559	0.6618	2	0.3497	11.4391	0.1333	-0.2015	0.4682
		No Known Mutation	3	2	2	0	0.3333	0.0673	1.6515	0.4000	-	-	-	0.6667	0.1332	1

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count
(ITT Analysis Set, Patients Taking Clobazam)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data			40 / 38	0.591 [40.9%] / 0.439 [56.1%]	1.346 [-34.6%]	(0.684, 2.648)	0.3850
Age Group	0.4825	2-5 years	14 / 10	0.789 [21.1%] / 0.322 [67.8%]	2.452 [-145.2%]	(0.634, 9.479)	0.1904
		6-12 years	15 / 15	0.622 [37.8%] / 0.730 [27.0%]	0.852 [14.8%]	(0.285, 2.540)	0.7703
		13-18 years	11 / 13	0.433 [56.7%] / 0.349 [65.1%]	1.241 [-24.1%]	(0.339, 4.541)	0.7409
Sex	0.0656	Female	18 / 22	0.436 [56.4%] / 0.586 [41.4%]	0.743 [25.7%]	(0.288, 1.916)	0.5344
		Male	22 / 16	0.776 [22.4%] / 0.285 [71.5%]	2.726 [-172.6%]	(0.991, 7.496)	0.0519
Region	0.0705	USA	23 / 29	0.308 [69.2%] / 0.425 [57.5%]	0.724 [27.6%]	(0.306, 1.715)	0.4581
		Rest of the World	17 / 9	1.360 [-36.0%] / 0.482 [51.8%]	2.820 [-182.0%]	(0.851, 9.348)	0.0889
Valproic Acid Use	0.0359	Not Currently Taking	15 / 18	0.300 [70.0%] / 0.503 [49.7%]	0.596 [40.4%]	(0.218, 1.626)	0.3073
		Currently Taking	25 / 20	0.975 [2.5%] / 0.374 [62.6%]	2.607 [-160.7%]	(1.016, 6.684)	0.0463
Stiripentol Use	0.0262	Not Currently Taking	17 / 24	0.256 [74.4%] / 0.453 [54.7%]	0.566 [43.4%]	(0.220, 1.455)	0.2335
		Currently Taking	23 / 14	1.176 [-17.6%] / 0.417 [58.3%]	2.820 [-182.0%]	(0.989, 8.038)	0.0524
Baseline Convulsive Seizure Frequency	0.2419	<=7	14 / 12	0.273 [72.7%] / 0.062 [93.8%]	4.389 [-338.9%]	(1.012, 19.034)	0.0482
		>7 to <=21	16 / 11	0.712 [28.8%] / 0.709 [29.1%]	1.004 [-0.4%]	(0.343, 2.939)	0.9936
		>21	10 / 15	1.177 [-17.7%] / 0.470 [53.0%]	2.503 [-150.3%]	(0.737, 8.496)	0.1390
Number of concurrent AEDs	0.0423	<3	12 / 9	0.172 [82.8%] / 0.550 [45.0%]	0.312 [68.8%]	(0.068, 1.426)	0.1310
		>=3	28 / 29	0.747 [25.3%] / 0.409 [59.1%]	1.829 [-82.9%]	(0.844, 3.966)	0.1243
Number of prior AEDs	0.1210	<4	21 / 16	0.909 [9.1%] / 0.377 [62.3%]	2.415 [-141.5%]	(0.889, 6.560)	0.0830
		>=4	19 / 22	0.418 [58.2%] / 0.514 [48.6%]	0.814 [18.6%]	(0.313, 2.112)	0.6678
SCN1A Mutation	0.4708	Truncation Variants	25 / 21	0.741 [25.9%] / 0.620 [38.0%]	1.194 [-19.4%]	(0.416, 3.423)	0.7386
		No Known Mutation	3 / 2	0.000 [100.0%] / 1.679 [-67.9%]	0.000 [100.0%]	(0.000, .)	0.9827
		Missense Variants	12 / 15	0.478 [52.2%] / 0.121 [87.9%]	3.959 [-295.9%]	(0.779, 20.111)	0.0958

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.

Log transformed number of days seizures were reported by period is included as an offset.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B Non-Convulsive Seizure Responder (subgroups)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Non-Convulsive Seizures <=25pct	Age Group	20 mg/kg	0.6622	2-5 years	5	3	8	5	0.9600	0.3924	2.3485	1.0000	0.9	0.091	8.8989	-0.025	-0.5699	0.5199
				6-12 years	11	8	9	5	1.3091	0.6584	2.6030	0.6424	2.1333	0.3295	13.8137	0.1717	-0.2462	0.5896
				13-18 years	6	3	8	5	0.8000	0.3052	2.0967	1.0000	0.6	0.0701	5.1357	-0.125	-0.6471	0.3971
	Sex	20 mg/kg	0.3033	F	12	8	14	7	1.3333	0.6897	2.5775	0.4527	2	0.4066	9.8384	0.1667	-0.2071	0.5405
				M	10	6	11	8	0.8250	0.4429	1.5369	0.6594	0.5625	0.0899	3.5184	-0.1273	-0.5291	0.2746
	Region	20 mg/kg	0.0920	REST OF THE WORLD	9	3	5	3	0.5556	0.1727	1.7877	0.5804	0.3333	0.0347	3.2045	-0.2667	-0.7951	0.2618
				USA	13	11	20	12	1.4103	0.9207	2.1600	0.2455	3.6667	0.6358	21.147	0.2462	-0.0446	0.537
	Valproate Use	20 mg/kg	0.3226	N	10	8	13	8	1.3000	0.7653	2.2082	0.4050	2.5	0.3701	16.8884	0.1846	-0.1779	0.5471
				Y	12	6	12	7	0.8571	0.4086	1.7979	1.0000	0.7143	0.1425	3.5795	-0.0833	-0.4806	0.314
	Stiripentol Use	20 mg/kg	0.0352	N	11	10	17	10	1.5455	0.9959	2.3983	0.0987	7	0.7223	67.8399	0.3209	0.0317	0.61
				Y	11	4	8	5	0.5818	0.2254	1.5018	0.3698	0.3429	0.052	2.261	-0.2614	-0.7011	0.1784
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.2590	<=8.0	9	7	4	4	0.7778	0.5485	1.1029	1.0000	-	-	-	-0.2222	-0.4938	0.0494
				>8.0 to <=25.0	8	5	10	4	1.5625	0.6167	3.9590	0.6372	2.5	0.3701	16.8884	0.225	-0.2275	0.6775
				>25.0	5	2	11	7	0.6286	0.1965	2.0106	0.5962	0.381	0.0435	3.3376	-0.2364	-0.7513	0.2786
	Current AEDs	20 mg/kg	0.5233	<3	6	5	6	4	1.2500	0.6400	2.4415	1.0000	2.5	0.1619	38.5992	0.1667	-0.3142	0.6475
				>=3	16	9	19	11	0.9716	0.5452	1.7314	1.0000	0.9351	0.244	3.5836	-0.0164	-0.3456	0.3127
	Prior AEDs	20 mg/kg	0.5524	<4	9	5	13	8	0.9028	0.4371	1.8647	1.0000	0.7813	0.1391	4.3867	-0.0598	-0.4786	0.3589
				>=4	13	9	12	7	1.1868	0.6513	2.1625	0.6882	1.6071	0.3104	8.3222	0.109	-0.2662	0.4841
	SCN1A Mutation-Positive	20 mg/kg	0.6230	Truncation Variants	13	8	13	7	1.1429	0.5896	2.2152	1.0000	1.3714	0.2878	6.5345	0.0769	-0.3017	0.4556
				Missense Variants	8	5	10	7	0.8929	0.4556	1.7499	1.0000	0.7143	0.0997	5.1182	-0.075	-0.5146	0.3646
No Known Mutation				1	1	2	1	2.0000	0.5002	7.9969	1.0000	-	-	-	0.5	-0.193	1	
Non-Convulsive Seizures <=50pct	Age Group	20 mg/kg	0.7050	2-5 years	5	3	8	5	0.9600	0.3924	2.3485	1.0000	0.9	0.091	8.8989	-0.025	-0.5699	0.5199
				6-12 years	11	5	9	3	1.3636	0.4413	4.2136	0.6699	1.6667	0.2688	10.3341	0.1212	-0.3047	0.5472
				13-18 years	6	2	8	4	0.6667	0.1769	2.5129	0.6270	0.5	0.0559	4.4734	-0.1667	-0.6788	0.3455
	Sex	20 mg/kg	0.1702	F	12	7	14	6	1.3611	0.6296	2.9428	0.6951	1.8667	0.3918	8.8942	0.1548	-0.226	0.5356
				M	10	3	11	6	0.5500	0.1850	1.6353	0.3870	0.3571	0.0591	2.1593	-0.2455	-0.6544	0.1635
	Region	20 mg/kg	0.7445	REST OF THE WORLD	9	3	5	2	0.8333	0.2022	3.4351	1.0000	0.75	0.078	7.2101	-0.0667	-0.5951	0.4618
				USA	13	7	20	10	1.0769	0.5525	2.0990	1.0000	1.1667	0.288	4.7265	0.0385	-0.31	0.387
	Valproate Use	20 mg/kg	0.1113	N	10	6	13	5	1.5600	0.6643	3.6636	0.4136	2.4	0.4438	12.9798	0.2154	-0.1873	0.618
				Y	12	4	12	7	0.5714	0.2250	1.4514	0.4136	0.3571	0.0679	1.8795	-0.25	-0.6359	0.1359
	Stiripentol Use	20 mg/kg	0.1839	N	11	7	17	8	1.3523	0.6895	2.6523	0.4601	1.9688	0.416	9.3166	0.1658	-0.2045	0.5361
				Y	11	3	8	4	0.5455	0.1663	1.7894	0.3765	0.375	0.055	2.5545	-0.2273	-0.6624	0.2078
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.0219	<=8.0	9	6	4	4	0.6667	0.4200	1.0581	0.4965	-	-	-	-0.3333	-0.6413	-0.0254
				>8.0 to <=25.0	8	4	10	2	2.5000	0.6042	10.3441	0.3213	4	0.5003	31.9813	0.3	-0.126	0.726
				>25.0	5	0	11	6	2.2000	1.1515	4.2031	0.0934	-	-	-	-0.5455	-0.8397	-0.2512
	Current AEDs	20 mg/kg	0.1223	<3	6	5	6	3	1.6667	0.6937	4.0042	0.5455	5	0.3436	72.7667	0.3333	-0.1656	0.8323
				>=3	16	5	19	9	0.6597	0.2770	1.5710	0.4906	0.5051	0.126	2.0251	-0.1612	-0.4805	0.1582
	Prior AEDs	20 mg/kg	0.6374	<4	9	4	13	7	0.8254	0.3400	2.0040	1.0000	0.6857	0.1243	3.7842	-0.094	-0.5169	0.3289
				>=4	13	6	12	5	1.1077	0.4547	2.6986	1.0000	1.2	0.2464	5.8438	0.0449	-0.344	0.4338

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

SCN1A Mutation-Positive	20 mg/kg	0.1529 Truncation Variants	13	5	13	5	1.0000	0.3782	2.6443	1.0000	1	0.2059	4.8558	0	-0.374	0.374
		Missense Variants	8	4	10	7	0.7143	0.3200	1.5945	0.6305	0.4286	0.0618	2.9719	-0.2	-0.648	0.248
		No Known Mutation	1	1	2	0	-	-	-	0.3333	-	-	-	1	1	1
Non-Convulsive Seizures <=75pct																
Age Group	20 mg/kg	0.9571 2-5 years	5	2	8	3	1.0667	0.2637	4.3143	1.0000	1.1111	0.1124	10.9863	0.025	-0.5199	0.5699
		6-12 years	11	3	9	2	1.2273	0.2586	5.8246	1.0000	1.3125	0.1678	10.2643	0.0505	-0.3277	0.4287
		13-18 years	6	2	8	3	0.8889	0.2101	3.7611	1.0000	0.8333	0.0905	7.6753	-0.0417	-0.5465	0.4631
Sex	20 mg/kg	0.2780 F	12	5	14	4	1.4583	0.5027	4.2302	0.6828	1.7857	0.3494	9.1272	0.131	-0.2348	0.4967
		M	10	2	11	4	0.5500	0.1270	2.3814	0.6351	0.4375	0.0606	3.1604	-0.1636	-0.5408	0.2136
Region	20 mg/kg	0.3865 REST OF THE WORLD	9	2	5	2	0.5556	0.1092	2.8263	0.5804	0.4286	0.0396	4.6368	-0.1778	-0.6859	0.3303
		USA	13	5	20	6	1.2821	0.4911	3.3472	0.7136	1.4583	0.3351	6.3474	0.0846	-0.2475	0.4167
Valproate Use	20 mg/kg	0.0571 N	10	5	13	3	2.1667	0.6724	6.9817	0.2213	3.3333	0.557	19.9488	0.2692	-0.1161	0.6546
		Y	12	2	12	5	0.4000	0.0956	1.6737	0.3707	0.28	0.0417	1.8779	-0.25	-0.5997	0.0997
Stiripentol Use	20 mg/kg	0.2017 N	11	5	17	5	1.5455	0.5797	4.1199	0.4443	2	0.4119	9.7116	0.1604	-0.2049	0.5258
		Y	11	2	8	3	0.4848	0.1039	2.2618	0.6027	0.3704	0.0455	3.0147	-0.1932	-0.5988	0.2124
Baseline Convulsive Seizure Frequency	20 mg/kg	0.0961 <=8.0	9	5	4	4	0.5556	0.3097	0.9966	0.2280	-	-	-	-0.4444	-0.7691	-0.1198
		>8.0 to <=25.0	8	2	10	1	2.5000	0.2734	22.8603	0.5588	3	0.2199	40.9314	0.15	-0.203	0.503
		>25.0	5	0	11	3	1.3750	0.9575	1.9745	0.5089	-	-	-	-0.2727	-0.5359	-0.0095
Current AEDs	20 mg/kg	0.1494 <3	6	4	6	2	2.0000	0.5644	7.0873	0.5671	4	0.3627	44.1128	0.3333	-0.2001	0.8668
		>=3	16	3	19	6	0.5938	0.1760	2.0029	0.4605	0.5	0.1025	2.4393	-0.1283	-0.4116	0.155
Prior AEDs	20 mg/kg	0.6097 <4	9	2	13	4	0.7222	0.1662	3.1388	1.0000	0.6429	0.0902	4.5815	-0.0855	-0.4552	0.2843
		>=4	13	5	12	4	1.1538	0.4018	3.3138	1.0000	1.25	0.2425	6.4428	0.0513	-0.3243	0.4269
SCN1A Mutation-Positive	20 mg/kg	0.1277 Truncation Variants	13	3	13	2	1.5000	0.2982	7.5465	1.0000	1.65	0.227	11.9934	0.0769	-0.2246	0.3785
		Missense Variants	8	3	10	6	0.6250	0.2236	1.7468	0.6372	0.4	0.0592	2.7021	-0.225	-0.6775	0.2275
		No Known Mutation	1	1	2	0	-	-	-	0.3333	-	-	-	1	1	1

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc: GWEP 1332B - Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking Clobazam)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
All Data			40 / 38	1.177 [-17.7%] / 0.683 [31.7%]	1.724 [-72.4%]	(1.152, 2.579)	0.0087
Age Group	0.6903	2-5 years	14 / 10	1.280 [-28.0%] / 0.645 [35.5%]	1.985 [-98.5%]	(0.954, 4.131)	0.0662
		6-12 years	15 / 15	1.199 [-19.9%] / 0.639 [36.1%]	1.876 [-87.6%]	(0.972, 3.617)	0.0603
		13-18 years	11 / 13	1.027 [-2.7%] / 0.788 [21.2%]	1.304 [-30.4%]	(0.608, 2.797)	0.4909
Sex	0.6213	Female	18 / 22	1.095 [-9.5%] / 0.706 [29.4%]	1.552 [-55.2%]	(0.872, 2.763)	0.1332
		Male	22 / 16	1.249 [-24.9%] / 0.656 [34.4%]	1.903 [-90.3%]	(1.063, 3.407)	0.0307
Region	0.1958	USA	23 / 29	1.461 [-46.1%] / 0.683 [31.7%]	2.141 [-114.1%]	(1.325, 3.459)	0.0023
		Rest of the World	17 / 9	0.837 [16.3%] / 0.691 [30.9%]	1.212 [-21.2%]	(0.588, 2.499)	0.5978
Valproic Acid Use	0.7800	Not Currently Taking	15 / 18	1.043 [-4.3%] / 0.652 [34.8%]	1.601 [-60.1%]	(0.841, 3.051)	0.1497
		Currently Taking	25 / 20	1.275 [-27.5%] / 0.708 [29.2%]	1.801 [-80.1%]	(1.060, 3.060)	0.0301
Stiripentol Use	0.2076	Not Currently Taking	17 / 24	2.019 [-101.9%] / 0.845 [15.5%]	2.390 [-139.0%]	(1.487, 3.841)	0.0005
		Currently Taking	23 / 14	0.730 [27.0%] / 0.483 [51.7%]	1.512 [-51.2%]	(0.883, 2.590)	0.1302
Baseline Convulsive Seizure Frequency	0.3041	<=7	14 / 12	1.238 [-23.8%] / 0.741 [25.9%]	1.671 [-67.1%]	(0.881, 3.168)	0.1141
		>7 to <=21	16 / 11	0.976 [2.4%] / 0.760 [24.0%]	1.285 [-28.5%]	(0.624, 2.645)	0.4917
		>21	10 / 15	1.749 [-74.9%] / 0.570 [43.0%]	3.071 [-207.1%]	(1.291, 7.306)	0.0119
Number of concurrent AEDs	0.6648	<3	12 / 9	1.514 [-51.4%] / 0.796 [20.4%]	1.901 [-90.1%]	(0.896, 4.036)	0.0931
		>=3	28 / 29	1.024 [-2.4%] / 0.653 [34.7%]	1.567 [-56.7%]	(0.983, 2.498)	0.0588
Number of prior AEDs	0.9646	<4	21 / 16	1.208 [-20.8%] / 0.698 [30.2%]	1.732 [-73.2%]	(0.945, 3.174)	0.0751
		>=4	19 / 22	1.142 [-14.2%] / 0.672 [32.8%]	1.700 [-70.0%]	(0.973, 2.971)	0.0621
SCN1A Mutation	0.2742	Truncation Variants	25 / 21	0.922 [7.8%] / 0.642 [35.8%]	1.436 [-43.6%]	(0.855, 2.413)	0.1686
		No Known Mutation	3 / 2	1.254 [-25.4%] / 0.402 [59.8%]	3.117 [-211.7%]	(0.497, 19.565)	0.2213
		Missense Variants	12 / 15	2.071 [-107.1%] / 0.759 [24.1%]	2.728 [-172.8%]	(1.410, 5.277)	0.0034

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B CGIC Responder [VMI, MI, SI] (subgroups) (ITT Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Last Visit (LOCF)	Age Group	20 mg/kg	0.9100	2-5 years	13	10	9	5	1.3846	0.7186	2.6678	0.3762	0.3750	0.0594	2.3661	0.2137	-0.1836	0.6110
				6-12 years	15	9	15	4	2.2500	0.8830	5.7336	0.1394	0.2424	0.0519	1.1327	0.3333	-0.0006	0.6673
				13-18 years	11	5	13	2	2.9545	0.7072	12.3436	0.1819	0.2182	0.0321	1.4851	0.3007	-0.0529	0.6543
Last Visit (LOCF)	Sex	20 mg/kg	0.7816	F	17	12	21	8	1.8529	0.9912	3.4639	0.0585	0.2564	0.0655	1.0044	0.3249	0.0248	0.6250
				M	22	12	16	3	2.9091	0.9791	8.6437	0.0435	0.1923	0.0425	0.8706	0.3580	0.0753	0.6406
Last Visit (LOCF)	Region	20 mg/kg	0.7600	REST OF THE WORLD	17	9	8	2	2.1176	0.5881	7.6254	0.2337	0.2963	0.0460	1.9076	0.2794	-0.1031	0.6619
				USA	22	15	29	9	2.1970	1.1901	4.0558	0.0117	0.2100	0.0637	0.6925	0.3715	0.1141	0.6288
Last Visit (LOCF)	Valproate Use	20 mg/kg	0.7024	N	15	8	18	5	1.9200	0.7943	4.6409	0.1686	0.3365	0.0792	1.4299	0.2556	-0.0709	0.5820
				Y	24	16	19	6	2.1111	1.0278	4.3362	0.0329	0.2308	0.0637	0.8357	0.3509	0.0694	0.6324
Last Visit (LOCF)	Stiripentol Use	20 mg/kg	0.3398	N	16	13	24	8	2.4375	1.3207	4.4986	0.0041	0.1154	0.0254	0.5251	0.4792	0.2106	0.7478
				Y	23	11	13	3	2.0725	0.7035	6.1050	0.1750	0.3273	0.0710	1.5080	0.2475	-0.0593	0.5543
Last Visit (LOCF)	Baseline Convulsive Seizure Frequency	20 mg/kg	0.4901	<=8.0	14	10	12	4	2.1429	0.9013	5.0945	0.1131	0.2000	0.0377	1.0612	0.3810	0.0244	0.7375
				>8.0 to <=25.0	16	11	10	3	2.2917	0.8408	6.2464	0.1054	0.1948	0.0350	1.0842	0.3875	0.0238	0.7512
				>25.0	9	3	15	4	1.2500	0.3588	4.3549	1.0000	0.7273	0.1205	4.3879	0.0667	-0.3140	0.4474
Last Visit (LOCF)	Current AEDs	20 mg/kg	0.5618	<3	12	9	9	3	2.2500	0.8445	5.9949	0.0872	0.1667	0.0248	1.1196	0.4167	0.0231	0.8102
				>=3	27	15	28	8	1.9444	0.9892	3.8223	0.0577	0.3200	0.1047	0.9782	0.2698	0.0186	0.5211
Last Visit (LOCF)	Prior AEDs	20 mg/kg	0.9895	<4	20	13	15	5	1.9500	0.8898	4.2735	0.0922	0.2692	0.0655	1.1061	0.3167	-0.0005	0.6339
				>=4	19	11	22	6	2.1228	0.9705	4.6435	0.0624	0.2727	0.0738	1.0083	0.3062	0.0165	0.5959
Last Visit (LOCF)	SCN1A Mutation-Positive	20 mg/kg	0.6513	Truncation Variants	25	15	20	6	2.0000	0.9523	4.2004	0.0715	0.2857	0.0821	0.9942	0.3000	0.0221	0.5779
				Missense Variants	11	7	15	5	1.9091	0.8212	4.4383	0.2329	0.2857	0.0559	1.4603	0.3030	-0.0681	0.6741
				No Known Mutation	3	2	2	0	-	-	-	0.4000	-	-	-	0.6667	0.1332	1.0000

LOCF = last observation carried forward; MI = much improved; VMI = very much improved; SI = slightly improved.

Last visit = Last visit is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B CGIC Responder [VMI, MI] (subgroups) (ITT Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Last Visit (LOCF)	Age Group	20 mg/kg	0.8134	2-5 years	13	6	9	2	2.0769	0.5352	8.0595	0.3802	0.3333	0.0492	2.2572	0.2393	-0.1444	0.6230
				6-12 years	15	5	15	1	5.0000	0.6605	37.8519	0.1686	0.1429	0.0144	1.4182	0.2667	-0.0032	0.5366
				13-18 years	11	2	13	1	2.3636	0.2461	22.7004	0.5761	0.3750	0.0292	4.8089	0.1049	-0.1652	0.3750
Last Visit (LOCF)	Sex	20 mg/kg	0.3647	F	17	5	21	3	2.0588	0.5721	7.4091	0.4258	0.4000	0.0802	1.9950	0.1513	-0.1120	0.4145
				M	22	8	16	1	5.8182	0.8060	41.9965	0.0525	0.1167	0.0129	1.0558	0.3011	0.0677	0.5345
Last Visit (LOCF)	Region	20 mg/kg	0.5589	REST OF THE WORLD	17	3	8	0	-	-	-	0.5270	-	-	-	0.1765	-0.0047	0.3577
				USA	22	10	29	4	3.2955	1.1901	9.1257	0.0246	0.1920	0.0499	0.7395	0.3166	0.0736	0.5596
Last Visit (LOCF)	Valproate Use	20 mg/kg	0.3461	N	15	5	18	3	2.0000	0.5692	7.0275	0.4184	0.4000	0.0776	2.0617	0.1667	-0.1275	0.4609
				Y	24	8	19	1	6.3333	0.8659	46.3235	0.0551	0.1111	0.0125	0.9881	0.2807	0.0670	0.4944
Last Visit (LOCF)	Stiripentol Use	20 mg/kg	0.4969	N	16	9	24	4	3.3750	1.2497	9.1148	0.0154	0.1556	0.0362	0.6690	0.3958	0.1107	0.6810
				Y	23	4	13	0	-	-	-	0.2741	-	-	-	0.1739	0.0190	0.3288
Last Visit (LOCF)	Baseline Convulsive Seizure Frequency	20 mg/kg	0.6027	<=8.0	14	5	12	1	4.2857	0.5778	31.7881	0.1696	0.1636	0.0161	1.6663	0.2738	-0.0219	0.5695
				>8.0 to <=25.0	16	5	10	2	1.5625	0.3713	6.5747	0.6680	0.5500	0.0843	3.5891	0.1125	-0.2237	0.4487
				>25.0	9	3	15	1	5.0000	0.6081	41.1135	0.1304	0.1429	0.0122	1.6670	0.2667	-0.0662	0.5995
Last Visit (LOCF)	Current AEDs	20 mg/kg	0.1298	<3	12	8	9	1	6.0000	0.9058	39.7434	0.0244	0.0625	0.0057	0.6893	0.5556	0.2190	0.8921
				>=3	27	5	28	3	1.7284	0.4571	6.5361	0.4688	0.5280	0.1130	2.4673	0.0780	-0.1079	0.2640
Last Visit (LOCF)	Prior AEDs	20 mg/kg	0.1414	<4	20	6	15	3	1.5000	0.4457	5.0478	0.7003	0.5833	0.1194	2.8490	0.1000	-0.1852	0.3852
				>=4	19	7	22	1	8.1053	1.0933	60.0917	0.0157	0.0816	0.0089	0.7457	0.3230	0.0893	0.5567
Last Visit (LOCF)	SCN1A Mutation-Positive	20 mg/kg	0.6621	Truncation Variants	25	7	20	2	2.8000	0.6520	12.0244	0.2604	0.2857	0.0521	1.5669	0.1800	-0.0397	0.3997
				Missense Variants	11	4	15	2	2.7273	0.6033	12.3279	0.3478	0.2692	0.0391	1.8551	0.2303	-0.1020	0.5626
				No Known Mutation	3	2	2	0	-	-	-	0.4000	-	-	-	0.6667	0.1332	1.0000

LOCF = last observation carried forward; MI = much improved; VMI = very much improved; SI = slightly improved.

Last visit = Last visit is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc Table: GWEP1332B Any AE (subgroups) (Safety Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]		
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI
Age Group	20 mg/kg	0.7727	2-5 years	14	14	10	9	1.1193	0.8692	1.4414	0.4167
				15	15	15	11	1.3478	0.9798	1.8541	0.0996
				11	10	13	9	1.2895	0.8479	1.9609	0.3271
Sex	20 mg/kg	0.2397	F	18	17	22	18	1.1451	0.9001	1.4568	0.3555
				22	22	16	11	1.4461	1.0352	2.0203	0.0087
Region	20 mg/kg	0.3983	REST OF THE WORLD	17	17	9	6	1.4957	0.9429	2.3728	0.0323
				23	22	29	23	1.1968	0.9656	1.4834	0.1170
Valproate Use	20 mg/kg	0.4762	N	15	14	18	13	1.2755	0.9193	1.7696	0.1861
				25	25	20	16	1.2483	0.9920	1.5707	0.0325
Stiripentol Use	20 mg/kg	0.8093	N	17	17	24	19	1.2464	0.9979	1.5568	0.0650
				23	22	14	10	1.3393	0.9466	1.8949	0.0574
Baseline Convulsive Seizure	20 mg/kg	0.6985	<=8.0	14	13	12	10	1.1143	0.8323	1.4918	0.5800
				16	16	11	10	1.1000	0.9125	1.3260	0.4074
				10	10	15	9	1.6667	1.1026	2.5194	0.0508
Current AEDs	20 mg/kg	0.8680	<3	12	12	9	7	1.2821	0.8820	1.8635	0.1714
				28	27	29	22	1.2644	1.0112	1.5809	0.0517
Prior AEDs	20 mg/kg	0.7722	<4	21	21	16	15	1.0718	0.9124	1.2591	0.4324
				19	18	22	14	1.4672	1.0476	2.0550	0.0238
SCN1A Mutation-Positive	20 mg/kg	0.7099	Truncation Variants	25	24	21	18	1.1206	0.9128	1.3757	0.3180
				12	12	15	10	1.4652	1.0111	2.1232	0.0470
				3	3	2	1	1.7500	0.5320	5.7562	0.4000

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc Table: GWEP1332B Maximal AE Mild (subgroups) (Safety Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	
Age Group	20 mg/kg	0.8354	2-5 years	14	7	10	8	0.6250	0.3401	1.1487	0.2099	
			6-12 years	15	5	15	8	0.6250	0.2650	1.4741	0.4621	
			13-18 years	11	5	13	8	0.7386	0.3396	1.6065	0.6824	
Sex	20 mg/kg	0.9185	F	18	8	22	14	0.6984	0.3812	1.2795	0.3391	
			M	22	9	16	10	0.6545	0.3488	1.2284	0.3245	
Region	20 mg/kg	0.6223	REST OF THE WORLD	17	6	9	4	0.7941	0.3000	2.1023	0.6924	
			USA	23	11	29	20	0.6935	0.4241	1.1340	0.1595	
Valproate Use	20 mg/kg	0.1649	N	15	10	18	12	1.0000	0.6160	1.6234	1.0000	
			Y	25	7	20	12	0.4667	0.2264	0.9619	0.0389	
Stiripentol Use	20 mg/kg	0.9315	N	17	8	24	16	0.7059	0.3960	1.2584	0.3349	
			Y	23	9	14	8	0.6848	0.3461	1.3549	0.3277	
Baseline Convulsive Seizure	20 mg/kg	0.8183	<=8.0	14	6	12	8	0.6429	0.3113	1.3276	0.2671	
			>8.0 to <=25.0	16	9	11	8	0.7734	0.4402	1.3590	0.4475	
			>25.0	10	2	15	8	0.3750	0.0995	1.4135	0.2107	
Current AEDs	20 mg/kg	0.4975	<3	12	7	9	6	0.8750	0.4500	1.7012	1.0000	
			>=3	28	10	29	18	0.5754	0.3245	1.0201	0.0650	
Prior AEDs	20 mg/kg	0.3063	<4	21	10	16	13	0.5861	0.3531	0.9727	0.0475	
			>=4	19	7	22	11	0.7368	0.3580	1.5167	0.5308	
SCN1A Mutation-Positive	20 mg/kg	0.6899	Truncation Variants	25	13	21	14	0.7800	0.4812	1.2643	0.3769	
			Missense Variants	12	3	15	9	0.4167	0.1438	1.2069	0.1207	
			No Known Mutation	3	1	2	1	0.6667	0.0803	5.5375	1.0000	

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc Table: GWEP1332B Maximal AE Moderate (subgroups) (Safety Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]		
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI
Age Group	20 mg/kg	0.8117	2-5 years	14	4	10	0	6.6000	0.3949	110.3126	0.1140
			6-12 years	15	7	15	3	2.1429	0.7403	6.2025	0.2451
			13-18 years	11	4	13	1	3.5000	0.6528	18.7667	0.1421
Sex	20 mg/kg	0.3768	F	18	6	22	3	2.4444	0.7088	8.4304	0.2534
			M	22	9	16	1	6.5455	0.9192	46.6105	0.0250
Region	20 mg/kg	0.8898	REST OF THE WORLD	17	7	9	1	3.7059	0.5362	25.6147	0.1902
			USA	23	8	29	3	3.3623	1.0038	11.2619	0.0439
Valproate Use	20 mg/kg	0.5597	N	15	2	18	1	2.4000	0.2405	23.9520	0.5794
			Y	25	13	20	3	3.4667	1.1434	10.5104	0.0133
Stiripentol Use	20 mg/kg	0.7986	N	17	7	24	3	3.2941	0.9908	10.9516	0.0632
			Y	23	8	14	1	4.8696	0.6792	34.9122	0.1120
Baseline Convulsive Seizure	20 mg/kg	0.7139	<=8.0	14	5	12	2	2.1429	0.5040	9.1101	0.3913
			>8.0 to <=25.0	16	6	11	1	4.1250	0.5736	29.6653	0.1832
			>25.0	10	4	15	1	6.0000	0.7802	46.1434	0.1206
Current AEDs	20 mg/kg	0.9034	<3	12	5	9	1	3.7500	0.5254	26.7666	0.1778
			>=3	28	10	29	3	3.4524	1.0597	11.2476	0.0295
Prior AEDs	20 mg/kg	0.9701	<4	21	6	16	1	4.5714	0.6097	34.2759	0.1131
			>=4	19	9	22	3	3.4737	1.0961	11.0088	0.0367
SCN1A Mutation-Positive	20 mg/kg	0.6513	Truncation Variants	25	8	21	3	2.0549	0.6787	6.2215	0.1878
			Missense Variants	12	5	15	1	4.5128	0.8663	23.5076	0.0602
			No Known Mutation	3	2	2	0	3.7500	0.2671	52.6396	0.4000

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count during Baseline and Treatment Periods
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data	10 mg/kg			45 / 65	0.341 [65.9%] / 0.704 [29.6%]	0.484 [51.6%]	(0.368, 0.636)	<.0001
	20 mg/kg			40 / 65	0.424 [57.6%] / 0.704 [29.6%]	0.602 [39.8%]	(0.452, 0.800)	0.0006
Age Group	10 mg/kg	0.8426	2-5 years	13 / 18	0.280 [72.0%] / 0.520 [48.0%]	0.539 [46.1%]	(0.319, 0.911)	0.0214
			6-12 years	23 / 28	0.342 [65.8%] / 0.758 [24.2%]	0.451 [54.9%]	(0.302, 0.672)	0.0001
			13-18 years	9 / 19	0.437 [56.3%] / 0.839 [16.1%]	0.521 [47.9%]	(0.292, 0.930)	0.0277
	20 mg/kg	0.7350	2-5 years	10 / 18	0.377 [62.3%] / 0.520 [48.0%]	0.725 [27.5%]	(0.415, 1.267)	0.2563
			6-12 years	22 / 28	0.439 [56.1%] / 0.758 [24.2%]	0.578 [42.2%]	(0.385, 0.870)	0.0089
			13-18 years	8 / 19	0.448 [55.2%] / 0.839 [16.1%]	0.534 [46.6%]	(0.289, 0.987)	0.0453
Sex	10 mg/kg	0.5164	Female	22 / 34	0.372 [62.8%] / 0.704 [29.6%]	0.529 [47.1%]	(0.358, 0.781)	0.0015
			Male	23 / 31	0.310 [69.0%] / 0.704 [29.6%]	0.441 [55.9%]	(0.297, 0.654)	<.0001
	20 mg/kg	0.7992	Female	17 / 34	0.444 [55.6%] / 0.704 [29.6%]	0.630 [37.0%]	(0.408, 0.972)	0.0371
			Male	23 / 31	0.411 [58.9%] / 0.704 [29.6%]	0.584 [41.6%]	(0.395, 0.863)	0.0074
Region	10 mg/kg	0.2463	USA	22 / 32	0.259 [74.1%] / 0.645 [35.5%]	0.401 [59.9%]	(0.270, 0.596)	<.0001
			Rest of the World	23 / 33	0.430 [57.0%] / 0.774 [22.6%]	0.555 [44.5%]	(0.378, 0.815)	0.0029
	20 mg/kg	0.9381	USA	21 / 32	0.387 [61.3%] / 0.645 [35.5%]	0.600 [40.0%]	(0.405, 0.889)	0.0112
			Rest of the World	19 / 33	0.475 [52.5%] / 0.774 [22.6%]	0.614 [38.6%]	(0.404, 0.933)	0.0225

Total seizures include all seizure types combined.
Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 1 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count during Baseline and Treatment Periods
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Valproic Acid Use	10 mg/kg	0.0606	Not Currently Taking Currently Taking	15 / 17 30 / 48	0.486 [51.4%] / 0.685 [31.5%] 0.286 [71.4%] / 0.712 [28.8%]	0.709 [29.1%] 0.402 [59.8%]	(0.433, 1.162) (0.290, 0.559)	0.1716 <.0001
	20 mg/kg	0.5337	Not Currently Taking Currently Taking	10 / 17 30 / 48	0.480 [52.0%] / 0.685 [31.5%] 0.408 [59.2%] / 0.712 [28.8%]	0.701 [29.9%] 0.573 [42.7%]	(0.406, 1.210) (0.411, 0.798)	0.2006 0.0011
Stiripentol Use	10 mg/kg	0.0008	Not Currently Taking Currently Taking	28 / 41 17 / 24	0.242 [75.8%] / 0.718 [28.2%] 0.601 [39.9%] / 0.680 [32.0%]	0.337 [66.3%] 0.884 [11.6%]	(0.241, 0.472) (0.569, 1.373)	<.0001 0.5812
	20 mg/kg	0.9652	Not Currently Taking Currently Taking	22 / 41 18 / 24	0.432 [56.8%] / 0.718 [28.2%] 0.415 [58.5%] / 0.680 [32.0%]	0.602 [39.8%] 0.610 [39.0%]	(0.420, 0.863) (0.393, 0.947)	0.0060 0.0278
Levetiracetam Use	10 mg/kg	0.5272	Not Currently Taking Currently Taking	34 / 51 11 / 14	0.341 [65.9%] / 0.673 [32.7%] 0.336 [66.4%] / 0.819 [18.1%]	0.507 [49.3%] 0.411 [58.9%]	(0.370, 0.696) (0.230, 0.734)	<.0001 0.0029
	20 mg/kg	0.9440	Not Currently Taking Currently Taking	31 / 51 9 / 14	0.408 [59.2%] / 0.673 [32.7%] 0.484 [51.6%] / 0.819 [18.1%]	0.606 [39.4%] 0.591 [40.9%]	(0.436, 0.840) (0.322, 1.084)	0.0029 0.0887
Topiramate Use	10 mg/kg	0.2016	Not Currently Taking Currently Taking	37 / 48 8 / 17	0.304 [69.6%] / 0.680 [32.0%] 0.543 [45.7%] / 0.782 [21.8%]	0.447 [55.3%] 0.694 [30.6%]	(0.327, 0.610) (0.380, 1.267)	<.0001 0.2324
	20 mg/kg	0.3787	Not Currently Taking Currently Taking	30 / 48 10 / 17	0.441 [55.9%] / 0.680 [32.0%] 0.378 [62.2%] / 0.782 [21.8%]	0.648 [35.2%] 0.483 [51.7%]	(0.465, 0.903) (0.273, 0.853)	0.0106 0.0125

Total seizures include all seizure types combined.
Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 2 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count during Baseline and Treatment Periods
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Baseline Convulsive Seizure Frequency	10 mg/kg	0.9743	<=7	16 / 17	0.338 [66.2%] / 0.658 [34.2%]	0.515 [48.5%]	(0.302, 0.876)	0.0148
			>7 to <=21	16 / 24	0.315 [68.5%] / 0.649 [35.1%]	0.484 [51.6%]	(0.304, 0.773)	0.0026
			>21	13 / 24	0.376 [62.4%] / 0.791 [20.9%]	0.475 [52.5%]	(0.297, 0.759)	0.0021
	20 mg/kg	0.3174	<=7	12 / 17	0.362 [63.8%] / 0.658 [34.2%]	0.551 [44.9%]	(0.306, 0.992)	0.0471
			>7 to <=21	18 / 24	0.507 [49.3%] / 0.649 [35.1%]	0.780 [22.0%]	(0.498, 1.221)	0.2749
			>21	10 / 24	0.371 [62.9%] / 0.791 [20.9%]	0.469 [53.1%]	(0.281, 0.783)	0.0041
Number of concurrent AEDs	10 mg/kg	0.5343	<3	12 / 19	0.293 [70.7%] / 0.698 [30.2%]	0.419 [58.1%]	(0.249, 0.705)	0.0012
			>=3	33 / 46	0.360 [64.0%] / 0.708 [29.2%]	0.509 [49.1%]	(0.368, 0.703)	<.0001
	20 mg/kg	0.1409	<3	8 / 19	0.620 [38.0%] / 0.698 [30.2%]	0.888 [11.2%]	(0.504, 1.566)	0.6802
			>=3	32 / 46	0.385 [61.5%] / 0.708 [29.2%]	0.543 [45.7%]	(0.390, 0.757)	0.0004
Number of prior AEDs	10 mg/kg	0.3839	<4	17 / 26	0.275 [72.5%] / 0.676 [32.4%]	0.407 [59.3%]	(0.257, 0.643)	0.0002
			>=4	28 / 39	0.379 [62.1%] / 0.724 [27.6%]	0.524 [47.6%]	(0.372, 0.737)	0.0003
	20 mg/kg	0.2375	<4	14 / 26	0.323 [67.7%] / 0.676 [32.4%]	0.478 [52.2%]	(0.296, 0.769)	0.0026
			>=4	26 / 39	0.494 [50.6%] / 0.724 [27.6%]	0.682 [31.8%]	(0.478, 0.974)	0.0355

Total seizures include all seizure types combined.
Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 3 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count during Baseline and Treatment Periods
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Number of prior and concurrent AEDs	10 mg/kg	0.4140	<8	23 / 32	0.291 [70.9%] / 0.680 [32.0%]	0.428 [57.2%]	(0.287, 0.637)	<.0001
			>=8	22 / 33	0.393 [60.7%] / 0.730 [27.0%]	0.538 [46.2%]	(0.367, 0.789)	0.0017
	20 mg/kg	0.6548	<8	20 / 32	0.436 [56.4%] / 0.680 [32.0%]	0.642 [35.8%]	(0.426, 0.967)	0.0343
			>=8	20 / 33	0.412 [58.8%] / 0.730 [27.0%]	0.564 [43.6%]	(0.377, 0.842)	0.0055

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 4 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Total Seizure Responder (ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			Odds Ratio			Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	p-value (vs. Placebo)	Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Total Seizures <=25pct	Age Group	10 mg/kg	0.5303	2-5 years	13	11	18	12	1.2692	0.8503	1.8945	0.4120	2.7500	0.4558	16.5918	0.1795	-0.1136	0.4726
				6-12 years	23	19	28	13	1.7793	1.1461	2.7622	0.0100	5.4808	1.4799	20.2975	0.3618	0.1207	0.6029
				13-18 years	9	5	19	8	1.3194	0.6006	2.8987	0.6891	1.7188	0.3472	8.5079	0.1345	-0.2588	0.5278
	Sex	10 mg/kg	0.3787	F	22	18	34	16	1.7386	1.1569	2.6128	0.0122	5.0625	1.4137	18.1290	0.3476	0.1149	0.5802
				M	23	17	31	17	1.3478	0.9023	2.0132	0.1694	2.3333	0.7249	7.5105	0.1907	-0.0600	0.4415
	Region	10 mg/kg	0.3600	REST OF THE WORLD	23	16	33	16	1.4348	0.9208	2.2358	0.1708	2.4286	0.7922	7.4450	0.2108	-0.0430	0.4646
				USA	22	19	32	17	1.6257	1.1281	2.3427	0.0178	5.5882	1.3757	22.6997	0.3324	0.1078	0.5570
	Valproate Use	10 mg/kg	0.0884	N	15	9	17	9	1.1333	0.6161	2.0850	0.7345	1.3333	0.3271	5.4341	0.0706	-0.2726	0.4137
				Y	30	26	48	24	1.7333	1.2640	2.3770	0.0014	6.5000	1.9674	21.4750	0.3667	0.1801	0.5532
	Stiripentol Use	10 mg/kg	0.0024	N	28	26	41	19	2.0038	1.4191	2.8294	<.0001	15.0526	3.1513	71.9009	0.4652	0.2852	0.6452
				Y	17	9	24	14	0.9076	0.5177	1.5911	0.7598	0.8036	0.2299	2.8082	-0.0539	-0.3625	0.2546
	Levetiracetam Use	10 mg/kg	0.3339	N	34	28	51	26	1.6154	1.1838	2.2044	0.0053	4.4872	1.5881	12.6784	0.3137	0.1260	0.5015
				Y	11	7	14	7	1.2727	0.6394	2.5335	0.6887	1.7500	0.3482	8.7947	0.1364	-0.2502	0.5229
	Topiramate Use	10 mg/kg	0.0752	N	37	31	48	24	1.6757	1.2211	2.2994	0.0014	5.1667	1.8238	14.6365	0.3378	0.1531	0.5225
				Y	8	4	17	9	0.9444	0.4138	2.1557	1.0000	0.8889	0.1654	4.7770	-0.0294	-0.4493	0.3905
	Baseline Convulsive Seizure Frequency	10 mg/kg	0.6579	<=7	16	12	17	9	1.4167	0.8339	2.4068	0.2818	2.6667	0.6076	11.7030	0.2206	-0.0977	0.5389
				>7 to <=21	16	12	24	13	1.3846	0.8704	2.2025	0.3176	2.5385	0.6338	10.1663	0.2083	-0.0828	0.4995
				>21	13	11	24	11	1.8462	1.1278	3.0221	0.0353	6.5000	1.1789	35.8392	0.3878	0.1082	0.6675
	Current AEDs	10 mg/kg	0.2759	<3	12	11	19	10	1.7417	1.1001	2.7573	0.0464	9.9000	1.0577	92.6634	0.3904	0.1167	0.6640
				>=3	33	24	46	23	1.4545	1.0183	2.0778	0.0627	2.6667	1.0214	6.9621	0.2273	0.0176	0.4370
Prior AEDs	10 mg/kg	0.5123	<4	17	13	26	15	1.3255	0.8694	2.0209	0.3274	2.3833	0.6091	9.3255	0.1878	-0.0892	0.4648	
			>=4	28	22	39	18	1.7024	1.1523	2.5151	0.0113	4.2778	1.4232	12.8581	0.3242	0.1061	0.5423	
Prior + Current AEDs	10 mg/kg	0.8708	<8	23	19	32	18	1.4686	1.0261	2.1019	0.0474	3.6944	1.0224	13.3496	0.2636	0.0322	0.4950	
			>=8	22	16	33	15	1.6000	1.0172	2.5167	0.0567	3.2000	1.0013	10.2265	0.2727	0.0207	0.5247	
Age Group	20 mg/kg	0.5403	2-5 years	10	8	18	12	1.2000	0.7649	1.8825	0.6692	2.0000	0.3197	12.5100	0.1333	-0.1966	0.4633	
			6-12 years	22	19	28	13	1.8601	1.2087	2.8627	0.0067	7.3077	1.7553	30.4231	0.3994	0.1655	0.6332	
			13-18 years	8	6	19	8	1.7813	0.9189	3.4528	0.2087	4.1250	0.6543	26.0070	0.3289	-0.0443	0.7022	
Sex	20 mg/kg	0.6775	F	17	13	34	16	1.6250	1.0430	2.5318	0.0718	3.6563	0.9891	13.5159	0.2941	0.0318	0.5564	
			M	23	20	31	17	1.5857	1.1102	2.2649	0.0174	5.4902	1.3476	22.3666	0.3212	0.0984	0.5440	
Region	20 mg/kg	0.6717	REST OF THE WORLD	19	16	33	16	1.7368	1.1619	2.5962	0.0171	5.6667	1.3842	23.1984	0.3573	0.1207	0.5938	
			USA	21	17	32	17	1.5238	1.0359	2.2416	0.0463	3.7500	1.0305	13.6456	0.2783	0.0372	0.5193	
Valproate Use	20 mg/kg	0.0631	N	10	6	17	9	1.1333	0.5765	2.2281	1.0000	1.3333	0.2737	6.4963	0.0706	-0.3148	0.4559	
			Y	30	27	48	24	1.8000	1.3242	2.4468	0.0003	9.0000	2.4038	33.6970	0.4000	0.2224	0.5776	
Stiripentol Use	20 mg/kg	0.2563	N	22	16	41	19	1.5694	1.0342	2.3816	0.0633	3.0877	1.0062	9.4749	0.2639	0.0232	0.5045	
			Y	18	17	24	14	1.6190	1.1339	2.3118	0.0122	12.1429	1.3810	106.7692	0.3611	0.1373	0.5849	
Levetiracetam Use	20 mg/kg	0.7489	N	31	26	51	26	1.6452	1.2063	2.2436	0.0041	5.0000	1.6587	15.0717	0.3289	0.1403	0.5175	
			Y	9	7	14	7	1.5556	0.8288	2.9194	0.2283	3.5000	0.5295	23.1370	0.2778	-0.0995	0.6551	
Topiramate Use	20 mg/kg	0.7538	N	30	25	48	24	1.6667	1.2042	2.3068	0.0038	5.0000	1.6404	15.2400	0.3333	0.1389	0.5277	
			Y	10	8	17	9	1.5111	0.8763	2.6058	0.2305	3.5556	0.5768	21.9174	0.2706	-0.0726	0.6137	
Baseline Convulsive Seizure Frequency	20 mg/kg	0.6166	<=7	12	10	17	9	1.5741	0.9408	2.6336	0.1261	4.4444	0.7404	26.6777	0.3039	-0.0135	0.6213	
			>7 to <=21	18	14	24	13	1.4359	0.9218	2.2366	0.1930	2.9615	0.7518	11.6656	0.2361	-0.0407	0.5129	
			>21	10	9	24	11	1.9636	1.2132	3.1782	0.0240	10.6364	1.1592	97.5933	0.4417	0.1691	0.7143	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Current AEDs	20 mg/kg	0.0226 <3 >=3	8	4	19	10	0.9500	0.4210	2.1435	1.0000	0.9000	0.1724	4.6994	-0.0263	-0.4392	0.3865
			32	29	46	23	1.8125	1.3297	2.4705	0.0002	9.6667	2.5778	36.2493	0.4063	0.2300	0.5825
Prior AEDs	20 mg/kg	0.0992 <4 >=4	14	14	26	15	1.7333	1.2472	2.4090	0.0036	-	-	-	0.4231	0.2332	0.6130
			26	19	39	18	1.5833	1.0492	2.3894	0.0421	3.1667	1.0850	9.2424	0.2692	0.0378	0.5006
Prior + Current AEDs	20 mg/kg	0.4215 <8 >=8	20	16	32	18	1.4222	0.9765	2.0714	0.1335	3.1111	0.8484	11.4080	0.2375	-0.0080	0.4830
			20	17	33	15	1.8700	1.2328	2.8365	0.0082	6.8000	1.6673	27.7327	0.3955	0.1645	0.6264
Total Seizures <=50pct																
Age Group	10 mg/kg	0.7186 2-5 years 6-12 years 13-18 years	13	10	18	9	1.5385	0.8880	2.6655	0.1581	3.3333	0.6819	16.2954	0.2692	-0.0561	0.5945
			23	15	28	6	3.0435	1.4099	6.5699	0.0021	6.8750	1.9787	23.8871	0.4379	0.1909	0.6848
			9	5	19	5	2.1111	0.8143	5.4733	0.2096	3.5000	0.6623	18.4949	0.2924	-0.0879	0.6727
Sex	10 mg/kg	0.8724 F M	22	14	34	10	2.1636	1.1767	3.9782	0.0147	4.2000	1.3437	13.1277	0.3422	0.0895	0.5950
			23	16	31	10	2.1565	1.2107	3.8413	0.0125	4.8000	1.4981	15.3800	0.3731	0.1232	0.6230
Region	10 mg/kg	0.6975 REST OF THE WORLD USA	23	13	33	8	2.3315	1.1559	4.7027	0.0240	4.0625	1.2914	12.7799	0.3228	0.0729	0.5726
			22	17	32	12	2.0606	1.2480	3.4022	0.0056	5.6667	1.6607	19.3362	0.3977	0.1552	0.6402
Valproate Use	10 mg/kg	0.1919 N Y	15	8	17	6	1.5111	0.6797	3.3596	0.4765	2.0952	0.5061	8.6744	0.1804	-0.1592	0.5200
			30	22	48	14	2.5143	1.5390	4.1076	0.0002	6.6786	2.4062	18.5370	0.4417	0.2378	0.6456
Stiripentol Use	10 mg/kg	0.0181 N Y	28	23	41	12	2.8065	1.6917	4.6561	<.0001	11.1167	3.4224	36.1088	0.5287	0.3299	0.7275
			17	7	24	8	1.2353	0.5540	2.7542	0.7449	1.4000	0.3870	5.0644	0.0784	-0.2221	0.3789
Levetiracetam Use	10 mg/kg	0.2834 N Y	34	24	51	19	1.8947	1.2486	2.8752	0.0038	4.0421	1.5935	10.2532	0.3333	0.1307	0.5360
			11	6	14	1	7.6364	1.0711	54.4413	0.0213	15.6000	1.4805	164.3762	0.4740	0.1503	0.7977
Topiramate Use	10 mg/kg	0.7143 N Y	37	26	48	16	2.1081	1.3420	3.3116	0.0010	4.7273	1.8730	11.9311	0.3694	0.1707	0.5681
			8	4	17	4	2.1250	0.7059	6.3971	0.3592	3.2500	0.5468	19.3164	0.2647	-0.1362	0.6656
Baseline Convulsive Seizure Frequency	10 mg/kg	0.4249 <=7 >7 to <=21 >21	16	11	17	5	2.3375	1.0428	5.2394	0.0381	5.2800	1.1956	23.3165	0.3934	0.0795	0.7072
			16	10	24	10	1.5000	0.8177	2.7517	0.3332	2.3333	0.6376	8.5384	0.2083	-0.1002	0.5168
			13	9	24	5	3.3231	1.4062	7.8528	0.0058	8.5500	1.8413	39.7020	0.4840	0.1851	0.7829
Current AEDs	10 mg/kg	0.3844 <3 >=3	12	9	19	5	2.8500	1.2549	6.4726	0.0119	8.4000	1.5999	44.1037	0.4868	0.1718	0.8018
			33	21	46	15	1.9515	1.1968	3.1823	0.0112	3.6167	1.4132	9.2560	0.3103	0.0975	0.5231
Prior AEDs	10 mg/kg	0.9901 <4 >=4	17	12	26	9	2.0392	1.1070	3.7565	0.0305	4.5333	1.2116	16.9625	0.3597	0.0763	0.6432
			28	18	39	11	2.2792	1.2867	4.0375	0.0056	4.5818	1.6176	12.9778	0.3608	0.1340	0.5876
Prior + Current AEDs	10 mg/kg	0.7888 <8 >=8	23	16	32	10	2.2261	1.2456	3.9785	0.0067	5.0286	1.5750	16.0548	0.3832	0.1359	0.6304
			22	14	33	10	2.1000	1.1453	3.8504	0.0256	4.0250	1.2838	12.6191	0.3333	0.0784	0.5883
Age Group	20 mg/kg	0.1878 2-5 years 6-12 years 13-18 years	10	6	18	9	1.2000	0.6048	2.3810	0.7055	1.5000	0.3131	7.1856	0.1000	-0.2815	0.4815
			22	16	28	6	3.3939	1.5968	7.2138	0.0005	9.7778	2.6594	35.9492	0.5130	0.2727	0.7533
			8	5	19	5	2.3750	0.9425	5.9849	0.1019	4.6667	0.8043	27.0774	0.3618	-0.0277	0.7514
Sex	20 mg/kg	0.5261 F M	17	10	34	10	2.0000	1.0386	3.8512	0.0676	3.4286	1.0169	11.5596	0.2941	0.0145	0.5737
			23	17	31	10	2.2913	1.3023	4.0313	0.0054	5.9500	1.7971	19.6994	0.4165	0.1731	0.6600
Region	20 mg/kg	0.7727 REST OF THE WORLD USA	19	12	33	8	2.6053	1.3014	5.2153	0.0081	5.3571	1.5723	18.2524	0.3892	0.1276	0.6507
			21	15	32	12	1.9048	1.1293	3.2126	0.0244	4.1667	1.2716	13.6526	0.3393	0.0834	0.5952
Valproate Use	20 mg/kg	0.1766 N Y	10	5	17	6	1.4167	0.5797	3.4620	0.6868	1.8333	0.3741	8.9844	0.1471	-0.2372	0.5313
			30	22	48	14	2.5143	1.5390	4.1076	0.0002	6.6786	2.4062	18.5370	0.4417	0.2378	0.6456
Stiripentol Use	20 mg/kg	0.7677 N Y	22	15	41	12	2.3295	1.3375	4.0575	0.0038	5.1786	1.6874	15.8933	0.3891	0.1498	0.6285
			18	12	24	8	2.0000	1.0406	3.8438	0.0600	4.0000	1.0941	14.6244	0.3333	0.0452	0.6214
Levetiracetam Use	20 mg/kg	0.2902 N Y	31	22	51	19	1.9049	1.2499	2.9032	0.0058	4.1170	1.5747	10.7638	0.3371	0.1294	0.5448
			9	5	14	1	7.7778	1.0771	56.1637	0.0183	16.2500	1.4422	183.0932	0.4841	0.1326	0.8357
Topiramate Use	20 mg/kg	0.5309 N	30	20	48	16	2.0000	1.2458	3.2108	0.0053	4.0000	1.5199	10.5271	0.3333	0.1183	0.5484

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		Y	10	7	17	4	2.9750	1.1527	7.6784	0.0402	7.5833	1.3093	43.9216	0.4647	0.1164	0.8130
Baseline Convulsive Seizure Frequency	20 mg/kg	0.6304 <=7	12	9	17	5	2.5500	1.1394	5.7071	0.0253	7.2000	1.3526	38.3258	0.4559	0.1289	0.7829
		>7 to <=21	18	12	24	10	1.6000	0.9002	2.8438	0.1309	2.8000	0.7845	9.9939	0.2500	-0.0438	0.5438
		>21	10	6	24	5	2.8800	1.1367	7.2971	0.0447	5.7000	1.1468	28.3301	0.3917	0.0473	0.7360
Current AEDs	20 mg/kg	0.5297 <3	8	4	19	5	1.9000	0.6832	5.2843	0.3748	2.8000	0.5007	15.6595	0.2368	-0.1622	0.6359
		>=3	32	23	46	15	2.2042	1.3796	3.5216	0.0011	5.2815	1.9687	14.1689	0.3927	0.1862	0.5991
Prior AEDs	20 mg/kg	0.2392 <4	14	12	26	9	2.4762	1.4005	4.3782	0.0028	11.3333	2.0682	62.1046	0.5110	0.2521	0.7699
		>=4	26	15	39	11	2.0455	1.1234	3.7242	0.0220	3.4711	1.2209	9.8683	0.2949	0.0582	0.5315
Prior + Current AEDs	20 mg/kg	0.7523 <8	20	13	32	10	2.0800	1.1344	3.8137	0.0233	4.0857	1.2498	13.3564	0.3375	0.0739	0.6011
		>=8	20	14	33	10	2.3100	1.2784	4.1741	0.0096	5.3667	1.5992	18.0097	0.3970	0.1422	0.6518
Total Seizures <=75pct																
Age Group	10 mg/kg	0.2331 2-5 years	13	5	18	2	3.4615	0.7907	15.1535	0.0994	5.0000	0.7890	31.6857	0.2735	-0.0282	0.5752
		6-12 years	23	8	28	0	-	-	-	0.0008	-	-	-	0.3478	0.1532	0.5425
		13-18 years	9	2	19	0	-	-	-	0.0952	-	-	-	0.2222	-0.0494	0.4938
Sex	10 mg/kg	0.1156 F	22	6	34	2	4.6364	1.0265	20.9409	0.0466	6.0000	1.0861	33.1448	0.2139	0.0117	0.4161
		M	23	9	31	0	-	-	-	0.0002	-	-	-	0.3913	0.1919	0.5908
Region	10 mg/kg	0.0537 REST OF THE WORLD	23	5	33	2	3.5870	0.7606	16.9167	0.1104	4.3056	0.7560	24.5214	0.1568	-0.0304	0.3440
		USA	22	10	32	0	-	-	-	<.0001	-	-	-	0.4545	0.2465	0.6626
Valproate Use	10 mg/kg	0.4932 N	15	4	17	0	-	-	-	0.0380	-	-	-	0.2667	0.0429	0.4905
		Y	30	11	48	2	8.8000	2.0935	36.9910	0.0003	13.3158	2.6921	65.8638	0.3250	0.1435	0.5065
Stiripentol Use	10 mg/kg	0.0043 N	28	13	41	0	-	-	-	<.0001	-	-	-	0.4643	0.2796	0.6490
		Y	17	2	24	2	1.4118	0.2200	9.0586	1.0000	1.4667	0.1856	11.5874	0.0343	-0.1546	0.2232
Levetiracetam Use	10 mg/kg	0.4242 N	34	11	51	2	8.2500	1.9492	34.9181	0.0005	11.7174	2.3991	57.2293	0.2843	0.1183	0.4503
		Y	11	4	14	0	-	-	-	0.0261	-	-	-	0.3636	0.0794	0.6479
Topiramate Use	10 mg/kg	0.6800 N	37	14	48	2	9.0811	2.1990	37.5016	0.0001	14.0000	2.9306	66.8810	0.3367	0.1705	0.5029
		Y	8	1	17	0	-	-	-	0.3200	-	-	-	0.1250	-0.1042	0.3542
Baseline Convulsive Seizure Frequency	10 mg/kg	0.0635 <=7	16	4	17	2	2.1250	0.4492	10.0524	0.3983	2.5000	0.3894	16.0495	0.1324	-0.1293	0.3940
		>7 to <=21	16	7	24	0	-	-	-	0.0006	-	-	-	0.4375	0.1944	0.6806
		>21	13	4	24	0	-	-	-	0.0108	-	-	-	0.3077	0.0568	0.5586
Current AEDs	10 mg/kg	0.2767 <3	12	5	19	0	-	-	-	0.0047	-	-	-	0.4167	0.1377	0.6956
		>=3	33	10	46	2	6.9697	1.6335	29.7378	0.0028	9.5652	1.9317	47.3650	0.2596	0.0920	0.4271
Prior AEDs	10 mg/kg	0.9286 <4	17	7	26	1	10.7059	1.4429	79.4335	0.0037	17.5000	1.9008	161.1153	0.3733	0.1280	0.6187
		>=4	28	8	39	1	11.1429	1.4761	84.1139	0.0030	15.2000	1.7737	130.2564	0.2601	0.0855	0.4346
Prior + Current AEDs	10 mg/kg	0.7463 <8	23	9	32	1	12.5217	1.7026	92.0900	0.0009	19.9286	2.2977	172.8432	0.3601	0.1517	0.5684
		>=8	22	6	33	1	9.0000	1.1620	69.7098	0.0130	12.0000	1.3291	108.3454	0.2424	0.0473	0.4375
Age Group	20 mg/kg	0.1493 2-5 years	10	2	18	2	1.8000	0.2972	10.9012	0.6015	2.0000	0.2363	16.9280	0.0889	-0.1984	0.3762
		6-12 years	22	5	28	0	-	-	-	0.0124	-	-	-	0.2273	0.0522	0.4024
		13-18 years	8	2	19	0	-	-	-	0.0798	-	-	-	0.2500	-0.0501	0.5501
Sex	20 mg/kg	0.2191 F	17	4	34	2	4.0000	0.8121	19.7017	0.0865	4.9231	0.8011	30.2531	0.1765	-0.0401	0.3931
		M	23	5	31	0	-	-	-	0.0106	-	-	-	0.2174	0.0488	0.3860
Region	20 mg/kg	0.0912 REST OF THE WORLD	19	3	33	2	2.6053	0.4770	14.2302	0.3419	2.9063	0.4399	19.2026	0.0973	-0.0858	0.2803
		USA	21	6	32	0	-	-	-	0.0024	-	-	-	0.2857	0.0925	0.4789
Valproate Use	20 mg/kg	0.1832 N	10	4	17	0	-	-	-	0.0120	-	-	-	0.4000	0.0964	0.7036
		Y	30	5	48	2	4.0000	0.8279	19.3249	0.1003	4.6000	0.8315	25.4488	0.1250	-0.0198	0.2698
Stiripentol Use	20 mg/kg	0.0187 N	22	7	41	0	-	-	-	0.0003	-	-	-	0.3182	0.1236	0.5128
		Y	18	2	24	2	1.3333	0.2071	8.5843	1.0000	1.3750	0.1747	10.8211	0.0278	-0.1547	0.2103

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Levetiracetam Use	20 mg/kg	0.3174 N	31	6	51	2	4.9355	1.0615	22.9483	0.0482	5.8800	1.1055	31.2742	0.1543	0.0054	0.3033
		Y	9	3	14	0	-	-	-	0.0474	-	-	-	0.3333	0.0254	0.6413
Topiramate Use	20 mg/kg	0.1832 N	30	5	48	2	4.0000	0.8279	19.3249	0.1003	4.6000	0.8315	25.4488	0.1250	-0.0198	0.2698
		Y	10	4	17	0	-	-	-	0.0120	-	-	-	0.4000	0.0964	0.7036
Baseline Convulsive Seizure Frequency	20 mg/kg	0.1876 <=7	12	3	17	2	2.1250	0.4166	10.8398	0.6221	2.5000	0.3484	17.9414	0.1324	-0.1566	0.4213
		>7 to <=21	18	3	24	0	-	-	-	0.0711	-	-	-	0.1667	-0.0055	0.3388
		>21	10	3	24	0	-	-	-	0.0201	-	-	-	0.3000	0.0160	0.5840
Current AEDs	20 mg/kg	0.5558 <3	8	1	19	0	-	-	-	0.2963	-	-	-	0.1250	-0.1042	0.3542
		>=3	32	8	46	2	5.7500	1.3058	25.3188	0.0130	7.3333	1.4406	37.3295	0.2065	0.0453	0.3677
Prior AEDs	20 mg/kg	0.9510 <4	14	4	26	1	7.4286	0.9163	60.2259	0.0426	10.0000	0.9919	100.8212	0.2473	-0.0007	0.4952
		>=4	26	5	39	1	7.5000	0.9287	60.5702	0.0338	9.0476	0.9904	82.6560	0.1667	0.0073	0.3261
Prior + Current AEDs	20 mg/kg	0.8748 <8	20	5	32	1	8.0000	1.0064	63.5937	0.0263	10.3333	1.1069	96.4624	0.2188	0.0196	0.4179
		>=8	20	4	33	1	6.6000	0.7924	54.9718	0.0611	8.0000	0.8249	77.5898	0.1697	-0.0151	0.3545
Total Seizures <=100pct																
Age Group	10 mg/kg	0.1086 2-5 years	13	0	18	1	-	-	-	1.0000	-	-	-	-0.0556	-0.1614	0.0503
		6-12 years	23	0	28	0	-	-	-	-	-	-	-	-	-	-
		13-18 years	9	1	19	0	-	-	-	0.3214	-	-	-	0.1111	-0.0942	0.3164
Sex	10 mg/kg	. F	22	1	34	1	1.5455	0.1019	23.4472	1.0000	1.5714	0.0932	26.5034	0.0160	-0.0879	0.1200
		M	23	0	31	0	-	-	-	-	-	-	-	-	-	-
Region	10 mg/kg	0.1519 REST OF THE WORLD	23	0	33	1	-	-	-	1.0000	-	-	-	-0.0303	-0.0888	0.0282
		USA	22	1	32	0	-	-	-	0.4074	-	-	-	0.0455	-0.0416	0.1325
Valproate Use	10 mg/kg	. N	15	0	17	0	-	-	-	-	-	-	-	-	-	-
		Y	30	1	48	1	1.6000	0.1039	24.6313	1.0000	1.6207	0.0976	26.9244	0.0125	-0.0634	0.0884
Stiripentol Use	10 mg/kg	0.1497 N	28	1	41	0	-	-	-	0.4058	-	-	-	0.0357	-0.0330	0.1045
		Y	17	0	24	1	-	-	-	1.0000	-	-	-	-0.0417	-0.1216	0.0383
Levetiracetam Use	10 mg/kg	. N	34	1	51	1	1.5000	0.0971	23.1755	1.0000	1.5152	0.0915	25.0773	0.0098	-0.0586	0.0782
		Y	11	0	14	0	-	-	-	-	-	-	-	-	-	-
Topiramate Use	10 mg/kg	. N	37	1	48	1	1.2973	0.0839	20.0599	1.0000	1.3056	0.0789	21.5898	0.0062	-0.0599	0.0722
		Y	8	0	17	0	-	-	-	-	-	-	-	-	-	-
Baseline Convulsive Seizure Frequency	10 mg/kg	0.1180 <=7	16	0	17	1	-	-	-	1.0000	-	-	-	-0.0588	-0.1707	0.0530
		>7 to <=21	16	1	24	0	-	-	-	0.4000	-	-	-	0.0625	-0.0561	0.1811
		>21	13	0	24	0	-	-	-	-	-	-	-	-	-	-
Current AEDs	10 mg/kg	. <3	12	0	19	0	-	-	-	-	-	-	-	-	-	-
		>=3	33	1	46	1	1.3939	0.0904	21.4911	1.0000	1.4063	0.0848	23.3254	0.0086	-0.0635	0.0807
Prior AEDs	10 mg/kg	0.1433 <4	17	1	26	0	-	-	-	0.3953	-	-	-	0.0588	-0.0530	0.1707
		>=4	28	0	39	1	-	-	-	1.0000	-	-	-	-0.0256	-0.0752	0.0240
Prior + Current AEDs	10 mg/kg	0.1612 <8	23	1	32	0	-	-	-	0.4182	-	-	-	0.0435	-0.0399	0.1268
		>=8	22	0	33	1	-	-	-	1.0000	-	-	-	-0.0303	-0.0888	0.0282
Age Group	20 mg/kg	0.1061 2-5 years	10	0	18	1	-	-	-	1.0000	-	-	-	-0.0556	-0.1614	0.0503
		6-12 years	22	2	28	0	-	-	-	0.1886	-	-	-	0.0909	-0.0292	0.2110
		13-18 years	8	0	19	0	-	-	-	-	-	-	-	-	-	-
Sex	20 mg/kg	0.4549 F	17	1	34	1	2.0000	0.1331	30.0578	1.0000	2.0625	0.1211	35.1388	0.0294	-0.0960	0.1549
		M	23	1	31	0	-	-	-	0.4259	-	-	-	0.0435	-0.0399	0.1268
Region	20 mg/kg	0.0889 REST OF THE WORLD	19	0	33	1	-	-	-	1.0000	-	-	-	-0.0303	-0.0888	0.0282
		USA	21	2	32	0	-	-	-	0.1524	-	-	-	0.0952	-0.0303	0.2208

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Valproate Use	20 mg/kg	. N Y	10 30	0 2	17 48	0 1	3.2000	0.3031	33.7799	0.5552	3.3571	0.2910	38.7342	0.0458	-0.0521	0.1438
Stiripentol Use	20 mg/kg	0.0583 N Y	22 18	2 0	41 24	0 1	- -	- -	- -	0.1183 1.0000	- -	- -	- -	0.0909 -0.0417	-0.0292 -0.1216	0.2110 0.0383
Levetiracetam Use	20 mg/kg	. N Y	31 9	2 0	51 14	1 0	3.2903	0.3111	34.7986	0.5537	3.4483	0.2995	39.7073	0.0449	-0.0496	0.1394
Topiramate Use	20 mg/kg	0.0705 N Y	30 10	0 2	48 17	1 0	- -	- -	- -	1.0000 0.1282	- -	- -	- -	-0.0208 0.2000	-0.0612 -0.0479	0.0196 0.4479
Baseline Convulsive Seizure Frequency	20 mg/kg	0.3979 <=7 >7 to <=21 >21	12 18 10	1 1 0	17 24 24	1 0 0	1.4167 - -	0.0980 - -	20.4870 - -	1.0000 0.4286	1.4545 - -	0.0820 - -	25.8121 - -	0.0245 0.0556	-0.1678 -0.0503	0.2168 0.1614
Current AEDs	20 mg/kg	. <3 >=3	8 32	0 2	19 46	0 1	2.8750	0.2721	30.3783	0.5646	3.0000	0.2603	34.5745	0.0408	-0.0531	0.1346
Prior AEDs	20 mg/kg	0.3441 <4 >=4	14 26	1 1	26 39	0 1	- 1.5000	- 0.0981	- 22.9310	0.3500 1.0000	- 1.5200	- 0.0908	- 25.4343	0.0714 0.0128	-0.0635 -0.0762	0.2063 0.1018
Prior + Current AEDs	20 mg/kg	0.3908 <8 >=8	20 20	1 1	32 33	0 1	- 1.6500	- 0.1092	- 24.9374	0.3846 1.0000	- 1.6842	- 0.0995	- 28.5208	0.0500 0.0197	-0.0455 -0.0923	0.1455 0.1317
Total seizures >0pct																
Age Group	10 mg/kg	0.2048 2-5 years 6-12 years 13-18 years	13 23 9	1 0 2	18 28 19	3 9 8	0.4615 1.4737 0.5278	0.0539 1.1421 0.1394	3.9535 1.9016 1.9978	0.6207 0.0025 0.4170	2.4000 - 2.5455	0.2206 - 0.4140	26.1161 - 15.6520	-0.0897 -0.3214 -0.1988	-0.3147 -0.4944 -0.5496	0.1353 -0.1484 0.1520
Sex	10 mg/kg	0.3673 F M	22 23	2 1	34 31	9 11	0.3434 0.1225	0.0818 0.0170	1.4427 0.8828	0.1707 0.0078	3.6000 12.1000	0.6975 1.4310	18.5795 102.3097	-0.1738 -0.3114	-0.3646 -0.4993	0.0170 -0.1234
Region	10 mg/kg	0.7428 REST OF THE WORLD USA	23 22	2 1	33 32	11 9	0.2609 0.1616	0.0637 0.0220	1.0679 1.1863	0.0519 0.0358	5.2500 8.2174	1.0380 0.9581	26.5540 70.4752	-0.2464 -0.2358	-0.4442 -0.4142	-0.0486 -0.0573
Valproate Use	10 mg/kg	0.3692 N Y	15 30	2 1	17 48	6 14	0.3778 0.1143	0.0893 0.0158	1.5974 0.8251	0.2293 0.0064	3.5455 11.9412	0.5917 1.4794	21.2448 96.3863	-0.2196 -0.2583	-0.5046 -0.4021	0.0653 -0.1146
Stiripentol Use	10 mg/kg	0.0188 N Y	28 17	0 3	41 24	14 6	1.5185 0.7059	1.2181 0.2045	1.8930 2.4364	0.0004 0.7113	- 1.5556	- 0.3295	- 7.3432	-0.3415 -0.0735	-0.4866 -0.3242	-0.1963 0.1772
Levetiracetam Use	10 mg/kg	0.2669 N Y	34 11	3 0	51 14	15 5	0.3000 1.5556	0.0939 1.0527	0.9581 2.2985	0.0299 0.0464	4.3056 -	1.1394 -	16.2691 -	-0.2059 -0.3571	-0.3631 -0.6081	-0.0486 -0.1061
Topiramate Use	10 mg/kg	0.0514 N Y	37 8	1 2	48 17	15 5	0.0865 0.8500	0.0120 0.2079	0.6253 3.4751	0.0006 1.0000	16.3636 1.2500	2.0471 0.1850	130.8019 8.4442	-0.2855 -0.0441	-0.4266 -0.4142	-0.1443 0.3259
Baseline Convulsive Seizure Frequency	10 mg/kg	0.3335 <=7 >7 to <=21 >21	16 16 13	0 1 2	17 24 24	6 6 8	1.5455 0.2500 0.4615	1.0879 0.0332 0.1144	2.1955 1.8851 1.8618	0.0184 0.2097 0.4395	- 5.0000 2.7500	- 0.5403 0.4879	- 46.2735 15.4998	-0.3529 -0.1875 -0.1795	-0.5801 -0.3975 -0.4516	-0.1258 0.0225 0.0926
Current AEDs	10 mg/kg	0.2839 <3 >=3	12 33	0 3	19 46	6 14	1.4615 0.2987	1.0768 0.0933	1.9837 0.9567	0.0585 0.0276	- 4.3750	- 1.1424	- 16.7543	-0.3158 -0.2134	-0.5248 -0.3787	-0.1068 -0.0482
Prior AEDs	10 mg/kg	0.1841 <4 >=4	17 28	0 3	26 39	8 12	1.4444 0.3482	1.1179 0.1083	1.8663 1.1200	0.0144 0.0751	- 3.7037	- 0.9344	- 14.6800	-0.3077 -0.2005	-0.4851 -0.3852	-0.1303 -0.0159
Prior + Current AEDs	10 mg/kg	0.1262 <8 >=8	23 22	0 3	32 33	9 11	1.3913 0.4091	1.1202 0.1286	1.7280 1.3011	0.0070 0.1245	- 3.1667	- 0.7681	- 13.0553	-0.2813 -0.1970	-0.4370 -0.4125	-0.1255 0.0185
Age Group	20 mg/kg	0.3359 2-5 years 6-12 years 13-18 years	10 22 8	0 3 0	18 28 19	3 9 8	1.2000 0.4242 1.7273	0.9760 0.1302 1.1771	1.4754 1.3825 2.5345	0.5330 0.1863 0.0607	- 3.0000 -	- 0.7015 -	- 12.8298 -	-0.1667 -0.1851 -0.4211	-0.3388 -0.4098 -0.6431	0.0055 0.0396 -0.1990
Sex	20 mg/kg	0.2628 F	17	2	34	9	0.4444	0.1077	1.8337	0.2972	2.7000	0.5131	14.2075	-0.1471	-0.3602	0.0661

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		M	23	1	31	11	0.1225	0.0170	0.8828	0.0078	12.1000	1.4310	102.3097	-0.3114	-0.4993	-0.1234
Region	20 mg/kg	0.6553 REST OF THE WORLD USA	19	2	33	11	0.3158	0.0781	1.2766	0.0987	4.2500	0.8292	21.7823	-0.2281	-0.4400	-0.0161
			21	1	32	9	0.1693	0.0231	1.2402	0.0688	7.8261	0.9106	67.2621	-0.2336	-0.4141	-0.0532
Valproate Use	20 mg/kg	0.2087 N Y	10	2	17	6	0.5667	0.1402	2.2904	0.6655	2.1818	0.3461	13.7557	-0.1529	-0.4892	0.1833
			30	1	48	14	0.1143	0.0158	0.8251	0.0064	11.9412	1.4794	96.3863	-0.2583	-0.4021	-0.1146
Stiripentol Use	20 mg/kg	0.2088 N Y	22	3	41	14	0.3994	0.1285	1.2415	0.1354	3.2840	0.8277	13.0294	-0.2051	-0.4091	-0.0011
			18	0	24	6	1.3333	1.0583	1.6798	0.0292	-	-	-	-0.2500	-0.4232	-0.0768
Levetiracetam Use	20 mg/kg	0.8303 N Y	31	2	51	15	0.2194	0.0538	0.8951	0.0130	6.0417	1.2768	28.5892	-0.2296	-0.3816	-0.0776
			9	1	14	5	0.3111	0.0431	2.2465	0.3401	4.4444	0.4244	46.5457	-0.2460	-0.5703	0.0782
Topiramate Use	20 mg/kg	0.7089 N Y	30	2	48	15	0.2133	0.0524	0.8678	0.0115	6.3636	1.3386	30.2526	-0.2458	-0.4045	-0.0872
			10	1	17	5	0.3400	0.0460	2.5121	0.3625	3.7500	0.3706	37.9478	-0.1941	-0.4796	0.0913
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4475 <=7 >7 to <=21 >21	12	1	17	6	0.2361	0.0325	1.7167	0.1872	6.0000	0.6162	58.4256	-0.2696	-0.5454	0.0062
			18	2	24	6	0.4444	0.1013	1.9505	0.4307	2.6667	0.4698	15.1357	-0.1389	-0.3649	0.0871
			10	0	24	8	1.5000	1.1304	1.9905	0.0720	-	-	-	-0.3333	-0.5219	-0.1447
Current AEDs	20 mg/kg	0.0051 <3 >=3	8	3	19	6	1.1875	0.3902	3.6135	1.0000	0.7692	0.1367	4.3285	0.0592	-0.3360	0.4545
			32	0	46	14	1.4375	1.1874	1.7403	0.0005	-	-	-	-0.3043	-0.4373	-0.1714
Prior AEDs	20 mg/kg	0.2049 <4 >=4	14	0	26	8	1.4444	1.1179	1.8663	0.0342	-	-	-	-0.3077	-0.4851	-0.1303
			26	3	39	12	0.3750	0.1171	1.2007	0.0821	3.4074	0.8555	13.5711	-0.1923	-0.3822	-0.0024
Prior + Current AEDs	20 mg/kg	0.4639 <8 >=8	20	2	32	9	0.3556	0.0854	1.4808	0.1697	3.5217	0.6752	18.3682	-0.1813	-0.3851	0.0226
			20	1	33	11	0.1500	0.0209	1.0760	0.0197	9.5000	1.1209	80.5161	-0.2833	-0.4704	-0.0963

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data	10 mg/kg			45 / 65	0.390 [61.0%] / 0.731 [26.9%]	0.533 [46.7%]	(0.398, 0.715)	<.0001
	20 mg/kg			40 / 65	0.431 [56.9%] / 0.731 [26.9%]	0.589 [41.1%]	(0.433, 0.801)	0.0009
Age Group	10 mg/kg	0.1346	2-5 years	13 / 18	0.349 [65.1%] / 0.494 [50.6%]	0.706 [29.4%]	(0.405, 1.230)	0.2176
			6-12 years	23 / 28	0.451 [54.9%] / 0.767 [23.3%]	0.588 [41.2%]	(0.385, 0.897)	0.0141
			13-18 years	9 / 19	0.319 [68.1%] / 1.001 [-0.1%]	0.319 [68.1%]	(0.175, 0.582)	0.0002
	20 mg/kg	0.6118	2-5 years	10 / 18	0.373 [62.7%] / 0.494 [50.6%]	0.755 [24.5%]	(0.416, 1.372)	0.3543
			6-12 years	22 / 28	0.434 [56.6%] / 0.767 [23.3%]	0.566 [43.4%]	(0.365, 0.876)	0.0110
			13-18 years	8 / 19	0.498 [50.2%] / 1.001 [-0.1%]	0.498 [50.2%]	(0.263, 0.940)	0.0318
Sex	10 mg/kg	0.1126	Female	22 / 34	0.479 [52.1%] / 0.713 [28.7%]	0.671 [32.9%]	(0.445, 1.012)	0.0571
			Male	23 / 31	0.314 [68.6%] / 0.753 [24.7%]	0.417 [58.3%]	(0.273, 0.637)	<.0001
	20 mg/kg	0.6882	Female	17 / 34	0.450 [55.0%] / 0.713 [28.7%]	0.632 [36.8%]	(0.396, 1.006)	0.0530
			Male	23 / 31	0.418 [58.2%] / 0.753 [24.7%]	0.556 [44.4%]	(0.366, 0.845)	0.0064
Region	10 mg/kg	0.0050	USA	22 / 32	0.230 [77.0%] / 0.695 [30.5%]	0.331 [66.9%]	(0.218, 0.501)	<.0001
			Rest of the World	23 / 33	0.589 [41.1%] / 0.774 [22.6%]	0.761 [23.9%]	(0.509, 1.137)	0.1814
	20 mg/kg	0.5298	USA	21 / 32	0.377 [62.3%] / 0.695 [30.5%]	0.543 [45.7%]	(0.358, 0.823)	0.0043
			Rest of the World	19 / 33	0.510 [49.0%] / 0.774 [22.6%]	0.658 [34.2%]	(0.423, 1.024)	0.0633

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 1 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Valproic Acid Use	10 mg/kg	0.4760	Not Currently Taking	15 / 17	0.423 [57.7%]	0.627 [37.3%]	(0.368, 1.066)	0.0841
			Currently Taking	30 / 48	0.376 [62.4%]	0.497 [50.3%]	(0.348, 0.710)	0.0002
	20 mg/kg	0.6890	Not Currently Taking	10 / 17	0.439 [56.1%]	0.651 [34.9%]	(0.361, 1.175)	0.1532
			Currently Taking	30 / 48	0.428 [57.2%]	0.565 [43.5%]	(0.393, 0.814)	0.0024
Stiripentol Use	10 mg/kg	0.0002	Not Currently Taking	28 / 41	0.251 [74.9%]	0.340 [66.0%]	(0.238, 0.485)	<.0001
			Currently Taking	17 / 24	0.763 [23.7%]	1.055 [-5.5%]	(0.660, 1.685)	0.8228
	20 mg/kg	0.9862	Not Currently Taking	22 / 41	0.438 [56.2%]	0.593 [40.7%]	(0.402, 0.875)	0.0088
			Currently Taking	18 / 24	0.426 [57.4%]	0.590 [41.0%]	(0.371, 0.937)	0.0256
Levetiracetam Use	10 mg/kg	0.8911	Not Currently Taking	34 / 51	0.378 [62.2%]	0.529 [47.1%]	(0.377, 0.742)	0.0003
			Currently Taking	11 / 14	0.436 [56.4%]	0.556 [44.4%]	(0.298, 1.039)	0.0653
	20 mg/kg	0.5757	Not Currently Taking	31 / 51	0.401 [59.9%]	0.561 [43.9%]	(0.392, 0.801)	0.0017
			Currently Taking	9 / 14	0.542 [45.8%]	0.690 [31.0%]	(0.364, 1.310)	0.2550
Topiramate Use	10 mg/kg	0.2780	Not Currently Taking	37 / 48	0.359 [64.1%]	0.491 [50.9%]	(0.351, 0.687)	<.0001
			Currently Taking	8 / 17	0.537 [46.3%]	0.733 [26.7%]	(0.385, 1.394)	0.3405
	20 mg/kg	0.6963	Not Currently Taking	30 / 48	0.445 [55.5%]	0.609 [39.1%]	(0.425, 0.872)	0.0071
			Currently Taking	10 / 17	0.387 [61.3%]	0.528 [47.2%]	(0.282, 0.988)	0.0456

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 2 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Baseline Convulsive Seizure Frequency	10 mg/kg	0.5653	<=7	16 / 17	0.521 [47.9%] / 0.748 [25.2%]	0.696 [30.4%]	(0.382, 1.268)	0.2346
			>7 to <=21	16 / 24	0.417 [58.3%] / 0.775 [22.5%]	0.538 [46.2%]	(0.329, 0.879)	0.0138
			>21	13 / 24	0.348 [65.2%] / 0.757 [24.3%]	0.459 [54.1%]	(0.284, 0.742)	0.0017
	20 mg/kg	0.1197	<=7	12 / 17	0.263 [73.7%] / 0.748 [25.2%]	0.351 [64.9%]	(0.176, 0.700)	0.0032
			>7 to <=21	18 / 24	0.639 [36.1%] / 0.775 [22.5%]	0.825 [17.5%]	(0.511, 1.331)	0.4282
			>21	10 / 24	0.400 [60.0%] / 0.757 [24.3%]	0.529 [47.1%]	(0.314, 0.890)	0.0169
Number of concurrent AEDs	10 mg/kg	0.0158	<3	12 / 19	0.236 [76.4%] / 0.792 [20.8%]	0.298 [70.2%]	(0.173, 0.514)	<.0001
			>=3	33 / 46	0.466 [53.4%] / 0.705 [29.5%]	0.661 [33.9%]	(0.468, 0.933)	0.0188
	20 mg/kg	0.6788	<3	8 / 19	0.536 [46.4%] / 0.792 [20.8%]	0.676 [32.4%]	(0.361, 1.268)	0.2208
			>=3	32 / 46	0.410 [59.0%] / 0.705 [29.5%]	0.582 [41.8%]	(0.409, 0.827)	0.0028
Number of prior AEDs	10 mg/kg	0.9044	<4	17 / 26	0.342 [65.8%] / 0.633 [36.7%]	0.540 [46.0%]	(0.332, 0.877)	0.0131
			>=4	28 / 39	0.418 [58.2%] / 0.805 [19.5%]	0.520 [48.0%]	(0.360, 0.752)	0.0006
	20 mg/kg	0.9527	<4	14 / 26	0.373 [62.7%] / 0.633 [36.7%]	0.589 [41.1%]	(0.350, 0.990)	0.0457
			>=4	26 / 39	0.465 [53.5%] / 0.805 [19.5%]	0.577 [42.3%]	(0.393, 0.848)	0.0054

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 3 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Number of prior and concurrent AEDs	10 mg/kg	0.3423	<8	23 / 32	0.405 [59.5%] / 0.659 [34.1%]	0.615 [38.5%]	(0.403, 0.938)	0.0244
			>=8	22 / 33	0.377 [62.3%] / 0.815 [18.5%]	0.463 [53.7%]	(0.306, 0.699)	0.0003
	20 mg/kg	0.4771	<8	20 / 32	0.433 [56.7%] / 0.659 [34.1%]	0.657 [34.3%]	(0.420, 1.027)	0.0651
			>=8	20 / 33	0.428 [57.2%] / 0.815 [18.5%]	0.525 [47.5%]	(0.342, 0.808)	0.0036

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 4 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Convulsive Seizure Responder (ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference	Risk Difference		
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		95% Lower CI	95% Upper CI		95% Lower CI	95% Upper CI	
Convulsive Seizures <=25pct	Age Group	10 mg/kg	0.1942	2-5 years	13	9	18	14	0.8901	0.5741	1.3800	0.6894	0.6429	0.1273	3.2460	-0.0855	-0.4014	0.2305
				6-12 years	23	16	28	12	1.6232	0.9787	2.6922	0.0896	3.0476	0.9540	9.7363	0.2671	0.0045	0.5297
				13-18 years	9	6	19	6	2.1111	0.9418	4.7320	0.1139	4.3333	0.7995	23.4870	0.3509	-0.0213	0.7231
	Sex	10 mg/kg	0.5036	F	22	14	34	17	1.2727	0.8024	2.0186	0.4119	1.7500	0.5835	5.2489	0.1364	-0.1257	0.3984
				M	23	17	31	15	1.5275	0.9866	2.3651	0.0927	3.0222	0.9406	9.7105	0.2553	0.0040	0.5066
	Region	10 mg/kg	0.1016	REST OF THE WORLD	23	12	33	15	1.1478	0.6682	1.9718	0.7864	1.3091	0.4503	3.8057	0.0672	-0.1984	0.3328
				USA	22	19	32	17	1.6257	1.1281	2.3427	0.0178	5.5882	1.3757	22.6997	0.3324	0.1078	0.5570
	Valproate Use	10 mg/kg	0.3556	N	15	9	17	9	1.1333	0.6161	2.0850	0.7345	1.3333	0.3271	5.4341	0.0706	-0.2726	0.4137
				Y	30	22	48	23	1.5304	1.0619	2.2056	0.0349	2.9891	1.1133	8.0256	0.2542	0.0420	0.4663
	Stiripentol Use	10 mg/kg	0.0024	N	28	25	41	20	1.8304	1.3042	2.5687	0.0007	8.7500	2.2796	33.5856	0.4051	0.2139	0.5962
				Y	17	6	24	12	0.7059	0.3308	1.5061	0.5239	0.5455	0.1522	1.9551	-0.1471	-0.4497	0.1556
	Levetiracetam Use	10 mg/kg	0.8348	N	34	23	51	25	1.3800	0.9591	1.9856	0.1190	2.1745	0.8804	5.3712	0.1863	-0.0224	0.3950
				Y	11	8	14	7	1.4545	0.7695	2.7493	0.4139	2.6667	0.4917	14.4610	0.2273	-0.1440	0.5986
	Topiramate Use	10 mg/kg	0.1162	N	37	27	48	22	1.5921	1.1055	2.2929	0.0153	3.1909	1.2700	8.0173	0.2714	0.0705	0.4723
				Y	8	4	17	10	0.8500	0.3823	1.8898	1.0000	0.7000	0.1293	3.7909	-0.0882	-0.5063	0.3298
	Baseline Convulsive Seizure Frequency	10 mg/kg	0.4842	<=7	16	10	17	10	1.0625	0.6132	1.8411	1.0000	1.1667	0.2880	4.7265	0.0368	-0.2964	0.3699
				>7 to <=21	16	11	24	9	1.8333	0.9931	3.3846	0.1053	3.6667	0.9584	14.0285	0.3125	0.0140	0.6110
				>21	13	10	24	13	1.4201	0.8846	2.2799	0.2882	2.8205	0.6171	12.8916	0.2276	-0.0761	0.5312
	Current AEDs	10 mg/kg	0.2486	<3	12	10	19	9	1.7593	1.0280	3.0107	0.0652	5.5556	0.9509	32.4589	0.3596	0.0516	0.6677
				>=3	33	21	46	23	1.2727	0.8640	1.8748	0.2582	1.7500	0.7010	4.3690	0.1364	-0.0823	0.3550
Prior AEDs	10 mg/kg	0.2487	<4	17	12	26	17	1.0796	0.7128	1.6352	1.0000	1.2706	0.3396	4.7542	0.0520	-0.2314	0.3355	
			>=4	28	19	39	15	1.7643	1.1007	2.8279	0.0258	3.3778	1.2152	9.3891	0.2940	0.0632	0.5247	
Prior + Current AEDs	10 mg/kg	0.2206	<8	23	16	32	20	1.1130	0.7605	1.6291	0.7745	1.3714	0.4383	4.2909	0.0707	-0.1813	0.3226	
			>=8	22	15	33	12	1.8750	1.0992	3.1984	0.0288	3.7500	1.1950	11.7682	0.3182	0.0636	0.5728	
Age Group	20 mg/kg	0.1227	2-5 years	10	8	18	14	1.0286	0.6921	1.5287	1.0000	1.1429	0.1698	7.6927	0.0222	-0.2914	0.3358	
			6-12 years	22	20	28	12	2.1212	1.3557	3.3189	0.0008	13.3333	2.5995	68.3884	0.4805	0.2614	0.6997	
			13-18 years	8	6	19	6	2.3750	1.0959	5.1468	0.0870	6.5000	1.0019	42.1718	0.4342	0.0685	0.7999	
Sex	20 mg/kg	0.6785	F	17	14	34	17	1.6471	1.1021	2.4614	0.0348	4.6667	1.1318	19.2414	0.3235	0.0764	0.5707	
			M	23	20	31	15	1.7971	1.2088	2.6717	0.0041	7.1111	1.7481	28.9271	0.3857	0.1623	0.6091	
Region	20 mg/kg	0.8519	REST OF THE WORLD	19	16	33	15	1.8526	1.2155	2.8237	0.0083	6.4000	1.5614	26.2326	0.3876	0.1515	0.6237	
			USA	21	18	32	17	1.6134	1.1152	2.3343	0.0186	5.2941	1.2981	21.5912	0.3259	0.0972	0.5546	
Valproate Use	20 mg/kg	0.1430	N	10	7	17	9	1.3222	0.7223	2.4203	0.4475	2.0741	0.3967	10.8448	0.1706	-0.1995	0.5407	
			Y	30	27	48	23	1.8783	1.3664	2.5818	0.0002	9.7826	2.6123	36.6349	0.4208	0.2434	0.5983	
Stiripentol Use	20 mg/kg	0.1974	N	22	17	41	20	1.5841	1.0758	2.3326	0.0347	3.5700	1.1078	11.5043	0.2849	0.0524	0.5175	
			Y	18	17	24	12	1.8889	1.2467	2.8618	0.0024	17.0000	1.9416	148.8486	0.4444	0.2181	0.6707	
Levetiracetam Use	20 mg/kg	0.5385	N	31	27	51	25	1.7768	1.3019	2.4248	0.0008	7.0200	2.1465	22.9585	0.3808	0.1998	0.5617	
			Y	9	7	14	7	1.5556	0.8288	2.9194	0.2283	3.5000	0.5295	23.1370	0.2778	-0.0995	0.6551	
Topiramate Use	20 mg/kg	0.9605	N	30	25	48	22	1.8182	1.2855	2.5716	0.0017	5.9091	1.9367	18.0289	0.3750	0.1810	0.5690	
			Y	10	9	17	10	1.5300	0.9774	2.3951	0.1895	6.3000	0.6440	61.6311	0.3118	0.0129	0.6106	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Baseline Convulsive Seizure Frequency	20 mg/kg	0.4263 <=7	12	12	17	10	1.7000	1.1422	2.5303	0.0230	-	-	-	0.4118	0.1778	0.6457
		>7 to <=21	18	13	24	9	1.9259	1.0669	3.4766	0.0334	4.3333	1.1557	16.2480	0.3472	0.0638	0.6306
		>21	10	9	24	13	1.6615	1.0895	2.5340	0.0607	7.6154	0.8300	69.8745	0.3583	0.0857	0.6309
Current AEDs	20 mg/kg	0.1228 <3	8	5	19	9	1.3194	0.6448	2.7001	0.6776	1.8519	0.3413	10.0469	0.1513	-0.2524	0.5550
		>=3	32	29	46	23	1.8125	1.3297	2.4705	0.0002	9.6667	2.5778	36.2493	0.4063	0.2300	0.5825
Prior AEDs	20 mg/kg	0.9848 <4	14	13	26	17	1.4202	1.0363	1.9463	0.0696	6.8824	0.7714	61.4062	0.2747	0.0475	0.5020
		>=4	26	21	39	15	2.1000	1.3537	3.2576	0.0009	6.7200	2.0870	21.6377	0.4231	0.2080	0.6382
Prior + Current AEDs	20 mg/kg	0.2924 <8	20	17	32	20	1.3600	0.9822	1.8831	0.1182	3.4000	0.8212	14.0773	0.2250	-0.0044	0.4544
		>=8	20	17	33	12	2.3375	1.4357	3.8058	0.0007	9.9167	2.4028	40.9268	0.4864	0.2596	0.7131
Convulsive Seizures <=50pct																
Age Group	10 mg/kg	0.6629 2-5 years	13	9	18	9	1.3846	0.7697	2.4907	0.4622	2.2500	0.5036	10.0531	0.1923	-0.1487	0.5333
		6-12 years	23	11	28	4	3.3478	1.2283	9.1248	0.0135	5.5000	1.4433	20.9591	0.3354	0.0936	0.5772
		13-18 years	9	5	19	4	2.6389	0.9247	7.5308	0.0968	4.6875	0.8426	26.0765	0.3450	-0.0278	0.7178
Sex	10 mg/kg	0.3094 F	22	10	34	9	1.7172	0.8330	3.5400	0.1614	2.3148	0.7452	7.1908	0.1898	-0.0657	0.4453
		M	23	15	31	8	2.5272	1.2966	4.9256	0.0055	5.3906	1.6627	17.4768	0.3941	0.1459	0.6423
Region	10 mg/kg	0.1071 REST OF THE WORLD	23	7	33	6	1.6739	0.6463	4.3353	0.3439	1.9688	0.5621	6.8961	0.1225	-0.1070	0.3520
		USA	22	18	32	11	2.3802	1.4184	3.9942	0.0008	8.5909	2.3270	31.7159	0.4744	0.2441	0.7048
Valproate Use	10 mg/kg	0.3933 N	15	7	17	5	1.5867	0.6363	3.9567	0.4670	2.1000	0.4901	8.9985	0.1725	-0.1601	0.5052
		Y	30	18	48	12	2.4000	1.3566	4.2459	0.0037	4.5000	1.6889	11.9898	0.3500	0.1361	0.5639
Stiripentol Use	10 mg/kg	0.0126 N	28	22	41	12	2.6845	1.6062	4.4869	<.0001	8.8611	2.8745	27.3162	0.4930	0.2869	0.6992
		Y	17	3	24	5	0.8471	0.2333	3.0756	1.0000	0.8143	0.1662	3.9896	-0.0319	-0.2753	0.2115
Levetiracetam Use	10 mg/kg	0.1617 N	34	19	51	16	1.7813	1.0761	2.9484	0.0421	2.7708	1.1277	6.8081	0.2451	0.0352	0.4550
		Y	11	6	14	1	7.6364	1.0711	54.4413	0.0213	15.6000	1.4805	164.3762	0.4740	0.1503	0.7977
Topiramate Use	10 mg/kg	0.6208 N	37	21	48	12	2.2703	1.2904	3.9943	0.0037	3.9375	1.5662	9.8988	0.3176	0.1164	0.5188
		Y	8	4	17	5	1.7000	0.6184	4.6731	0.3942	2.4000	0.4235	13.6012	0.2059	-0.2027	0.6145
Baseline Convulsive Seizure Frequency	10 mg/kg	0.5531 <=7	16	7	17	5	1.4875	0.5913	3.7419	0.4813	1.8667	0.4437	7.8524	0.1434	-0.1822	0.4690
		>7 to <=21	16	10	24	6	2.5000	1.1345	5.5090	0.0245	5.0000	1.2700	19.6850	0.3750	0.0813	0.6687
		>21	13	8	24	6	2.4615	1.0891	5.5632	0.0395	4.8000	1.1261	20.4604	0.3654	0.0492	0.6815
Current AEDs	10 mg/kg	0.2839 <3	12	8	19	4	3.1667	1.2146	8.2559	0.0220	7.5000	1.4694	38.2803	0.4561	0.1325	0.7798
		>=3	33	17	46	13	1.8228	1.0339	3.2138	0.0592	2.6971	1.0567	6.8839	0.2325	0.0181	0.4470
Prior AEDs	10 mg/kg	0.8024 <4	17	11	26	8	2.1029	1.0707	4.1304	0.0580	4.1250	1.1272	15.0955	0.3394	0.0511	0.6276
		>=4	28	14	39	9	2.1667	1.0952	4.2866	0.0361	3.3333	1.1658	9.5308	0.2692	0.0417	0.4968
Prior + Current AEDs	10 mg/kg	0.8832 <8	23	13	32	9	2.0097	1.0390	3.8873	0.0511	3.3222	1.0748	10.2689	0.2840	0.0284	0.5395
		>=8	22	12	33	8	2.2500	1.1022	4.5932	0.0437	3.7500	1.1794	11.9236	0.3030	0.0487	0.5573
Age Group	20 mg/kg	0.4657 2-5 years	10	7	18	9	1.4000	0.7570	2.5891	0.4343	2.3333	0.4535	12.0043	0.2000	-0.1661	0.5661
		6-12 years	22	13	28	4	4.1364	1.5655	10.9292	0.0021	8.6667	2.2300	33.6820	0.4481	0.2051	0.6910
		13-18 years	8	5	19	4	2.9688	1.0674	8.2567	0.0721	6.2500	1.0259	38.0758	0.4145	0.0322	0.7968
Sex	20 mg/kg	0.7242 F	17	10	34	9	2.2222	1.1179	4.4174	0.0338	3.9683	1.1596	13.5791	0.3235	0.0465	0.6005
		M	23	15	31	8	2.5272	1.2966	4.9256	0.0055	5.3906	1.6627	17.4768	0.3941	0.1459	0.6423
Region	20 mg/kg	0.9582 REST OF THE WORLD	19	10	33	6	2.8947	1.2495	6.7061	0.0138	5.0000	1.4150	17.6683	0.3445	0.0843	0.6047
		USA	21	15	32	11	2.0779	1.1990	3.6011	0.0119	4.7727	1.4444	15.7701	0.3705	0.1167	0.6243
Valproate Use	20 mg/kg	0.7091 N	10	6	17	5	2.0400	0.8348	4.9853	0.2238	3.6000	0.6985	18.5553	0.3059	-0.0671	0.6789
		Y	30	19	48	12	2.5333	1.4463	4.4375	0.0010	5.1818	1.9273	13.9323	0.3833	0.1718	0.5949
Stiripentol Use	20 mg/kg	0.6997 N	22	14	41	12	2.1742	1.2282	3.8490	0.0148	4.2292	1.4096	12.6887	0.3437	0.0991	0.5882

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		Y	18	11	24	5	2.9333	1.2381	6.9498	0.0114	5.9714	1.5221	23.4275	0.4028	0.1251	0.6805
Levetiracetam Use	20 mg/kg	0.2764 N	31	20	51	16	2.0565	1.2692	3.3321	0.0055	3.9773	1.5474	10.2226	0.3314	0.1203	0.5426
		Y	9	5	14	1	7.7778	1.0771	56.1637	0.0183	16.2500	1.4422	183.0932	0.4841	0.1326	0.8357
Topiramate Use	20 mg/kg	0.7091 N	30	19	48	12	2.5333	1.4463	4.4375	0.0010	5.1818	1.9273	13.9323	0.3833	0.1718	0.5949
		Y	10	6	17	5	2.0400	0.8348	4.9853	0.2238	3.6000	0.6985	18.5553	0.3059	-0.0671	0.6789
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4770 <=7	12	10	17	5	2.8333	1.3005	6.1727	0.0078	12.0000	1.9018	75.7164	0.5392	0.2369	0.8415
		>7 to <=21	18	9	24	6	2.0000	0.8696	4.5996	0.1156	3.0000	0.8122	11.0813	0.2500	-0.0387	0.5387
		>21	10	6	24	6	2.4000	1.0176	5.6606	0.1122	4.5000	0.9394	21.5567	0.3500	0.0004	0.6996
Current AEDs	20 mg/kg	0.7084 <3	8	5	19	4	2.9688	1.0674	8.2567	0.0721	6.2500	1.0259	38.0758	0.4145	0.0322	0.7968
		>=3	32	20	46	13	2.2115	1.2979	3.7683	0.0048	4.2308	1.6178	11.0639	0.3424	0.1301	0.5547
Prior AEDs	20 mg/kg	0.8153 <4	14	10	26	8	2.3214	1.1939	4.5139	0.0208	5.6250	1.3493	23.4494	0.4066	0.1108	0.7023
		>=4	26	15	39	9	2.5000	1.2911	4.8409	0.0081	4.5455	1.5481	13.3465	0.3462	0.1147	0.5776
Prior + Current AEDs	20 mg/kg	0.9885 <8	20	13	32	9	2.3111	1.2181	4.3851	0.0114	4.7460	1.4306	15.7451	0.3688	0.1081	0.6294
		>=8	20	12	33	8	2.4750	1.2275	4.9905	0.0181	4.6875	1.4153	15.5251	0.3576	0.0978	0.6173
Convulsive Seizures <=75pct Age Group	10 mg/kg	0.7413 2-5 years	13	5	18	2	3.4615	0.7907	15.1535	0.0994	5.0000	0.7890	31.6857	0.2735	-0.0282	0.5752
		6-12 years	23	7	28	1	8.5217	1.1289	64.3291	0.0164	11.8125	1.3291	104.9819	0.2686	0.0684	0.4688
		13-18 years	9	4	19	1	8.4444	1.0950	65.1215	0.0256	14.4000	1.3000	159.5130	0.3918	0.0520	0.7316
Sex	10 mg/kg	0.1665 F	22	6	34	3	3.0909	0.8612	11.0940	0.1327	3.8750	0.8547	17.5680	0.1845	-0.0246	0.3936
		M	23	10	31	1	13.4783	1.8542	97.9716	0.0004	23.0769	2.6715	199.3420	0.4025	0.1906	0.6145
Region	10 mg/kg	0.0076 REST OF THE WORLD	23	3	33	3	1.4348	0.3172	6.4894	0.6811	1.5000	0.2747	8.1894	0.0395	-0.1295	0.2085
		USA	22	13	32	1	18.9091	2.6630	134.2657	<.0001	44.7778	5.1377	390.2635	0.5597	0.3455	0.7738
Valproate Use	10 mg/kg	0.2992 N	15	5	17	2	2.8333	0.6414	12.5164	0.2095	3.7500	0.6048	23.2518	0.2157	-0.0678	0.4992
		Y	30	11	48	2	8.8000	2.0935	36.9910	0.0003	13.3158	2.6921	65.8638	0.3250	0.1435	0.5065
Stiripentol Use	10 mg/kg	0.0003 N	28	14	41	0	-	-	-	<.0001	-	-	-	0.5000	0.3148	0.6852
		Y	17	2	24	4	0.7059	0.1455	3.4256	1.0000	0.6667	0.1075	4.1337	-0.0490	-0.2628	0.1647
Levetiracetam Use	10 mg/kg	0.9082 N	34	12	51	3	6.0000	1.8282	19.6910	0.0009	8.7273	2.2353	34.0738	0.2941	0.1210	0.4672
		Y	11	4	14	1	5.0909	0.6593	39.3118	0.1333	7.4286	0.6902	79.9568	0.2922	-0.0225	0.6069
Topiramate Use	10 mg/kg	0.3370 N	37	15	48	3	6.4865	2.0272	20.7551	0.0003	10.2273	2.6770	39.0724	0.3429	0.1705	0.5153
		Y	8	1	17	1	2.1250	0.1514	29.8185	1.0000	2.2857	0.1244	41.9850	0.0662	-0.1888	0.3212
Baseline Convulsive Seizure Frequency	10 mg/kg	0.1024 <=7	16	5	17	3	1.7708	0.5033	6.2308	0.4384	2.1212	0.4136	10.8779	0.1360	-0.1545	0.4266
		>7 to <=21	16	6	24	1	9.0000	1.1936	67.8642	0.0109	13.8000	1.4641	130.0702	0.3333	0.0830	0.5837
		>21	13	5	24	0	-	-	-	0.0030	-	-	-	0.3846	0.1202	0.6491
Current AEDs	10 mg/kg	0.0887 <3	12	6	19	0	-	-	-	0.0013	-	-	-	0.5000	0.2171	0.7829
		>=3	33	10	46	4	3.4848	1.1955	10.1582	0.0177	4.5652	1.2871	16.1927	0.2161	0.0394	0.3928
Prior AEDs	10 mg/kg	0.9722 <4	17	7	26	2	5.3529	1.2586	22.7674	0.0179	8.4000	1.4803	47.6669	0.3348	0.0795	0.5902
		>=4	28	9	39	2	6.2679	1.4655	26.8069	0.0057	8.7632	1.7187	44.6803	0.2701	0.0838	0.4565
Prior + Current AEDs	10 mg/kg	0.9327 <8	23	8	32	2	5.5652	1.3003	23.8180	0.0115	8.0000	1.5077	42.4485	0.2853	0.0734	0.4973
		>=8	22	8	33	2	6.0000	1.4038	25.6439	0.0095	8.8571	1.6622	47.1961	0.3030	0.0862	0.5199
Age Group	20 mg/kg	0.8275 2-5 years	10	4	18	2	3.6000	0.7944	16.3148	0.1472	5.3333	0.7669	37.0926	0.2889	-0.0477	0.6254
		6-12 years	22	5	28	1	6.3636	0.8005	50.5897	0.0748	7.9412	0.8529	73.9363	0.1916	0.0034	0.3797
		13-18 years	8	1	19	1	2.3750	0.1685	33.4768	0.5128	2.5714	0.1406	47.0170	0.0724	-0.1778	0.3226
Sex	20 mg/kg	0.6310 F	17	5	34	3	3.3333	0.9016	12.3243	0.0986	4.3056	0.8878	20.8796	0.2059	-0.0308	0.4425
		M	23	5	31	1	6.7391	0.8435	53.8448	0.0728	8.3333	0.9004	77.1226	0.1851	0.0055	0.3648

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Region	20 mg/kg	0.2572 REST OF THE WORLD USA	19	4	33	3	2.3158	0.5789	9.2647	0.4003	2.6667	0.5276	13.4774	0.1196	-0.0883	0.3275
			21	6	32	1	9.1429	1.1839	70.6097	0.0120	12.4000	1.3672	112.4633	0.2545	0.0521	0.4569
Valproate Use	20 mg/kg	0.5539 N Y	10	3	17	2	2.5500	0.5099	12.7532	0.3261	3.2143	0.4343	23.7867	0.1824	-0.1403	0.5050
			30	7	48	2	5.6000	1.2448	25.1931	0.0234	7.0000	1.3454	36.4217	0.1917	0.0301	0.3532
Stiripentol Use	20 mg/kg	0.0015 N Y	22	8	41	0	-	-	-	<.0001	-	-	-	0.3636	0.1626	0.5646
			18	2	24	4	0.6667	0.1368	3.2481	0.6852	0.6250	0.1012	3.8583	-0.0556	-0.2637	0.1526
Levetiracetam Use	20 mg/kg	0.3812 N Y	31	9	51	3	4.9355	1.4454	16.8523	0.0077	6.5455	1.6130	26.5617	0.2315	0.0592	0.4038
			9	1	14	1	1.5556	0.1108	21.8483	1.0000	1.6250	0.0887	29.7811	0.0397	-0.2060	0.2854
Topiramate Use	20 mg/kg	0.4595 N Y	30	6	48	3	3.2000	0.8646	11.8441	0.0797	3.7500	0.8607	16.3388	0.1375	-0.0212	0.2962
			10	4	17	1	6.8000	0.8777	52.6828	0.0473	10.6667	0.9835	115.6827	0.3412	0.0176	0.6648
Baseline Convulsive Seizure Frequency	20 mg/kg	0.5090 <=7 >7 to <=21 >21	12	6	17	3	2.8333	0.8772	9.1514	0.1059	4.6667	0.8664	25.1359	0.3235	-0.0124	0.6595
			18	2	24	1	2.6667	0.2617	27.1721	0.5672	2.8750	0.2398	34.4621	0.0694	-0.0963	0.2352
			10	2	24	0	-	-	-	0.0802	-	-	-	0.2000	-0.0479	0.4479
Current AEDs	20 mg/kg	0.1051 <3 >=3	8	3	19	0	-	-	-	0.0191	-	-	-	0.3750	0.0395	0.7105
			32	7	46	4	2.5156	0.8024	7.8864	0.1840	2.9400	0.7819	11.0552	0.1318	-0.0330	0.2966
Prior AEDs	20 mg/kg	0.9095 <4 >=4	14	4	26	2	3.7143	0.7742	17.8195	0.1591	4.8000	0.7542	30.5502	0.2088	-0.0491	0.4666
			26	6	39	2	4.5000	0.9828	20.6043	0.0514	5.5500	1.0239	30.0850	0.1795	0.0034	0.3556
Prior + Current AEDs	20 mg/kg	0.3983 <8 >=8	20	7	32	2	5.6000	1.2891	24.3267	0.0192	8.0769	1.4742	44.2524	0.2875	0.0623	0.5127
			20	3	33	2	2.4750	0.4518	13.5589	0.3536	2.7353	0.4155	18.0055	0.0894	-0.0870	0.2658
Convulsive Seizures >0pct Age Group	10 mg/kg	0.0938 2-5 years 6-12 years 13-18 years	13	3	18	2	2.0769	0.4025	10.7157	0.6254	0.4167	0.0589	2.9459	0.1197	-0.1515	0.3908
			23	4	28	9	0.5411	0.1911	1.5318	0.3355	2.2500	0.5900	8.5799	-0.1475	-0.3797	0.0847
			9	0	19	6	1.4615	1.0768	1.9837	0.1358	-	-	-	-0.3158	-0.5248	-0.1068
Sex	10 mg/kg	0.1461 F M	22	6	34	10	0.9273	0.3930	2.1877	1.0000	1.1111	0.3368	3.6653	-0.0214	-0.2624	0.2196
			23	1	31	7	0.1925	0.0254	1.4583	0.1186	6.4167	0.7299	56.4065	-0.1823	-0.3515	-0.0132
Region	10 mg/kg	0.1380 REST OF THE WORLD USA	23	5	33	7	1.0248	0.3708	2.8327	1.0000	0.9692	0.2653	3.5403	0.0053	-0.2135	0.2241
			22	2	32	10	0.2909	0.0705	1.2009	0.0941	4.5455	0.8866	23.3038	-0.2216	-0.4221	-0.0210
Valproate Use	10 mg/kg	0.9070 N Y	15	3	17	6	0.5667	0.1708	1.8804	0.4440	2.1818	0.4364	10.9084	-0.1529	-0.4572	0.1513
			30	4	48	11	0.5818	0.2037	1.6618	0.3827	1.9324	0.5539	6.7412	-0.0958	-0.2659	0.0743
Stiripentol Use	10 mg/kg	0.0420 N Y	28	2	41	12	0.2440	0.0591	1.0074	0.0330	5.3793	1.0994	26.3204	-0.2213	-0.3901	-0.0524
			17	5	24	5	1.4118	0.4830	4.1267	0.7143	0.6316	0.1504	2.6521	0.0858	-0.1850	0.3565
Levetiracetam Use	10 mg/kg	0.7642 N Y	34	5	51	12	0.6250	0.2420	1.6140	0.4112	1.7846	0.5658	5.6285	-0.0882	-0.2547	0.0783
			11	2	14	5	0.5091	0.1210	2.1426	0.4065	2.5000	0.3806	16.4199	-0.1753	-0.5144	0.1637
Topiramate Use	10 mg/kg	0.9309 N Y	37	6	48	13	0.5988	0.2516	1.4251	0.2978	1.9190	0.6508	5.6589	-0.1087	-0.2816	0.0643
			8	1	17	4	0.5312	0.0702	4.0199	1.0000	2.1538	0.2001	23.1827	-0.1103	-0.4155	0.1950
Baseline Convulsive Seizure Frequency	10 mg/kg	0.6476 <=7 >7 to <=21 >21	16	3	17	3	1.0625	0.2499	4.5177	1.0000	0.9286	0.1583	5.4484	0.0110	-0.2524	0.2745
			16	2	24	6	0.5000	0.1150	2.1746	0.4390	2.3333	0.4071	13.3748	-0.1250	-0.3622	0.1122
			13	2	24	8	0.4615	0.1144	1.8618	0.4395	2.7500	0.4879	15.4998	-0.1795	-0.4516	0.0926
Current AEDs	10 mg/kg	0.3082 <3 >=3	12	1	19	6	0.2639	0.0361	1.9301	0.2015	5.0769	0.5276	48.8554	-0.2325	-0.4935	0.0286
			33	6	46	11	0.7603	0.3127	1.8488	0.5907	1.4143	0.4641	4.3096	-0.0573	-0.2376	0.1230
Prior AEDs	10 mg/kg	0.6086 <4 >=4	17	3	26	6	0.7647	0.2205	2.6526	1.0000	1.4000	0.2986	6.5635	-0.0543	-0.2973	0.1887
			28	4	39	11	0.5065	0.1797	1.4277	0.2395	2.3571	0.6635	8.3734	-0.1392	-0.3309	0.0525
Prior + Current AEDs	10 mg/kg	0.4682 <8	23	4	32	7	0.7950	0.2632	2.4015	0.7452	1.3300	0.3394	5.2113	-0.0448	-0.2558	0.1661

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		>=8	22	3	33	10	0.4500	0.1394	1.4528	0.2038	2.7536	0.6615	11.4621	-0.1667	-0.3792	0.0458
Age Group	20 mg/kg	0.0898 2-5 years	10	2	18	2	1.8000	0.2972	10.9012	0.6015	0.5000	0.0591	4.2320	0.0889	-0.1984	0.3762
		6-12 years	22	2	28	9	0.2828	0.0679	1.1781	0.0846	4.7368	0.9044	24.8092	-0.2305	-0.4411	-0.0199
		13-18 years	8	0	19	6	1.4615	1.0768	1.9837	0.1358	-	-	-	-0.3158	-0.5248	-0.1068
Sex	20 mg/kg	0.3598 F	17	3	34	10	0.6000	0.1897	1.8975	0.5020	1.9444	0.4566	8.2796	-0.1176	-0.3549	0.1196
		M	23	1	31	7	0.1925	0.0254	1.4583	0.1186	6.4167	0.7299	56.4065	-0.1823	-0.3515	-0.0132
Region	20 mg/kg	0.5951 REST OF THE WORLD	19	2	33	7	0.4962	0.1145	2.1509	0.4582	2.2885	0.4239	12.3551	-0.1069	-0.3031	0.0893
		USA	21	2	32	10	0.3048	0.0740	1.2544	0.0954	4.3182	0.8397	22.2072	-0.2173	-0.4211	-0.0134
Valproate Use	20 mg/kg	0.5999 N	10	2	17	6	0.5667	0.1402	2.2904	0.6655	2.1818	0.3461	13.7557	-0.1529	-0.4892	0.1833
		Y	30	2	48	11	0.2909	0.0692	1.2228	0.0702	4.1622	0.8534	20.3004	-0.1625	-0.3112	-0.0138
Stiripentol Use	20 mg/kg	0.1488 N	22	4	41	12	0.6212	0.2271	1.6989	0.3815	1.8621	0.5202	6.6657	-0.1109	-0.3239	0.1021
		Y	18	0	24	5	1.2632	1.0288	1.5509	0.0600	-	-	-	-0.2083	-0.3708	-0.0459
Levetiracetam Use	20 mg/kg	0.5067 N	31	2	51	12	0.2742	0.0657	1.1445	0.0683	4.4615	0.9262	21.4923	-0.1708	-0.3158	-0.0258
		Y	9	2	14	5	0.6222	0.1519	2.5483	0.6570	1.9444	0.2867	13.1879	-0.1349	-0.5047	0.2349
Topiramate Use	20 mg/kg	0.8917 N	30	3	48	13	0.3692	0.1146	1.1892	0.0878	3.3429	0.8648	12.9212	-0.1708	-0.3361	-0.0055
		Y	10	1	17	4	0.4250	0.0549	3.2927	0.6210	2.7692	0.2640	29.0472	-0.1353	-0.4096	0.1390
Baseline Convulsive Seizure Frequency	20 mg/kg	0.1166 <=7	12	0	17	3	1.2143	0.9744	1.5132	0.2463	-	-	-	-0.1765	-0.3577	0.0047
		>7 to <=21	18	4	24	6	0.8889	0.2936	2.6912	1.0000	1.1667	0.2750	4.9495	-0.0278	-0.2864	0.2309
		>21	10	0	24	8	1.5000	1.1304	1.9905	0.0720	-	-	-	-0.3333	-0.5219	-0.1447
Current AEDs	20 mg/kg	0.0495 <3	8	3	19	6	1.1875	0.3902	3.6135	1.0000	0.7692	0.1367	4.3285	0.0592	-0.3360	0.4545
		>=3	32	1	46	11	0.1307	0.0177	0.9625	0.0222	9.7429	1.1890	79.8340	-0.2079	-0.3451	-0.0707
Prior AEDs	20 mg/kg	0.8468 <4	14	1	26	6	0.3095	0.0413	2.3213	0.3870	3.9000	0.4197	36.2400	-0.1593	-0.3701	0.0514
		>=4	26	3	39	11	0.4091	0.1262	1.3263	0.1339	3.0119	0.7497	12.1003	-0.1667	-0.3538	0.0205
Prior + Current AEDs	20 mg/kg	0.1970 <8	20	3	32	7	0.6857	0.2001	2.3500	0.7225	1.5867	0.3589	7.0137	-0.0688	-0.2809	0.1434
		>=8	20	1	33	10	0.1650	0.0228	1.1941	0.0371	8.2609	0.9685	70.4624	-0.2530	-0.4366	-0.0694

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data	10 mg/kg			45 / 65	0.256 [74.4%] / 0.581 [41.9%]	0.440 [56.0%]	(0.283, 0.685)	0.0003
	20 mg/kg			40 / 65	0.394 [60.6%] / 0.581 [41.9%]	0.678 [32.2%]	(0.425, 1.082)	0.1024
Age Group	10 mg/kg	0.3396	2-5 years	13 / 18	0.205 [79.5%] / 0.548 [45.2%]	0.373 [62.7%]	(0.165, 0.844)	0.0183
			6-12 years	23 / 28	0.235 [76.5%] / 0.603 [39.7%]	0.391 [60.9%]	(0.207, 0.736)	0.0040
			13-18 years	9 / 19	0.528 [47.2%] / 0.578 [42.2%]	0.913 [8.7%]	(0.320, 2.609)	0.8645
	20 mg/kg	0.9141	2-5 years	10 / 18	0.320 [68.0%] / 0.548 [45.2%]	0.584 [41.6%]	(0.238, 1.431)	0.2371
			6-12 years	22 / 28	0.414 [58.6%] / 0.603 [39.7%]	0.687 [31.3%]	(0.359, 1.318)	0.2568
			13-18 years	8 / 19	0.458 [54.2%] / 0.578 [42.2%]	0.792 [20.8%]	(0.249, 2.515)	0.6900
Sex	10 mg/kg	0.1827	Female	22 / 34	0.314 [68.6%] / 0.552 [44.8%]	0.568 [43.2%]	(0.310, 1.041)	0.0670
			Male	23 / 31	0.190 [81.0%] / 0.615 [38.5%]	0.309 [69.1%]	(0.159, 0.601)	0.0006
	20 mg/kg	0.6285	Female	17 / 34	0.425 [57.5%] / 0.552 [44.8%]	0.770 [23.0%]	(0.385, 1.541)	0.4578
			Male	23 / 31	0.375 [62.5%] / 0.615 [38.5%]	0.610 [39.0%]	(0.319, 1.167)	0.1341
Region	10 mg/kg	0.4327	USA	22 / 32	0.281 [71.9%] / 0.531 [46.9%]	0.529 [47.1%]	(0.277, 1.012)	0.0541
			Rest of the World	23 / 33	0.236 [76.4%] / 0.637 [36.3%]	0.371 [62.9%]	(0.201, 0.686)	0.0018
	20 mg/kg	0.8956	USA	21 / 32	0.374 [62.6%] / 0.531 [46.9%]	0.705 [29.5%]	(0.371, 1.338)	0.2822
			Rest of the World	19 / 33	0.421 [57.9%] / 0.637 [36.3%]	0.662 [33.8%]	(0.330, 1.328)	0.2434

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 1 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Valproic Acid Use	10 mg/kg	0.2127	Not Currently Taking	15 / 17	0.439 [56.1%]	0.660 [34.0%]	(0.291, 1.499)	0.3187
			Currently Taking	30 / 48	0.198 [80.2%]	0.356 [64.4%]	(0.210, 0.605)	0.0002
	20 mg/kg	0.6117	Not Currently Taking	10 / 17	0.541 [45.9%]	0.814 [18.6%]	(0.342, 1.936)	0.6389
			Currently Taking	30 / 48	0.347 [65.3%]	0.624 [37.6%]	(0.357, 1.092)	0.0977
Stiripentol Use	10 mg/kg	0.2242	Not Currently Taking	28 / 41	0.227 [77.3%]	0.359 [64.1%]	(0.204, 0.632)	0.0005
			Currently Taking	17 / 24	0.319 [68.1%]	0.635 [36.5%]	(0.306, 1.318)	0.2211
	20 mg/kg	0.8395	Not Currently Taking	22 / 41	0.435 [56.5%]	0.690 [31.0%]	(0.388, 1.226)	0.2040
			Currently Taking	18 / 24	0.312 [68.8%]	0.621 [37.9%]	(0.268, 1.441)	0.2653
Levetiracetam Use	10 mg/kg	0.6853	Not Currently Taking	34 / 51	0.253 [74.7%]	0.455 [54.5%]	(0.274, 0.754)	0.0025
			Currently Taking	11 / 14	0.263 [73.7%]	0.362 [63.8%]	(0.135, 0.972)	0.0438
	20 mg/kg	0.9655	Not Currently Taking	31 / 51	0.368 [63.2%]	0.663 [33.7%]	(0.384, 1.144)	0.1390
			Currently Taking	9 / 14	0.470 [53.0%]	0.647 [35.3%]	(0.240, 1.747)	0.3877
Topiramate Use	10 mg/kg	0.7874	Not Currently Taking	37 / 48	0.236 [76.4%]	0.440 [56.0%]	(0.268, 0.723)	0.0014
			Currently Taking	8 / 17	0.385 [61.5%]	0.514 [48.6%]	(0.185, 1.428)	0.1999
	20 mg/kg	0.2927	Not Currently Taking	30 / 48	0.426 [57.4%]	0.794 [20.6%]	(0.450, 1.400)	0.4227
			Currently Taking	10 / 17	0.341 [65.9%]	0.456 [54.4%]	(0.191, 1.087)	0.0762

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 2 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Baseline Convulsive Seizure Frequency	10 mg/kg	0.4288	<=7	16 / 17	0.153 [84.7%] / 0.520 [48.0%]	0.294 [70.6%]	(0.124, 0.698)	0.0059
			>7 to <=21	16 / 24	0.315 [68.5%] / 0.499 [50.1%]	0.630 [37.0%]	(0.293, 1.354)	0.2347
			>21	13 / 24	0.324 [67.6%] / 0.726 [27.4%]	0.447 [55.3%]	(0.211, 0.946)	0.0356
	20 mg/kg	0.2387	<=7	12 / 17	0.525 [47.5%] / 0.520 [48.0%]	1.009 [-0.9%]	(0.403, 2.527)	0.9838
			>7 to <=21	18 / 24	0.409 [59.1%] / 0.499 [50.1%]	0.820 [18.0%]	(0.393, 1.708)	0.5933
			>21	10 / 24	0.265 [73.5%] / 0.726 [27.4%]	0.366 [63.4%]	(0.151, 0.887)	0.0263
Number of concurrent AEDs	10 mg/kg	0.8612	<3	12 / 19	0.253 [74.7%] / 0.610 [39.0%]	0.414 [58.6%]	(0.174, 0.989)	0.0472
			>=3	33 / 46	0.257 [74.3%] / 0.567 [43.3%]	0.453 [54.7%]	(0.270, 0.760)	0.0029
	20 mg/kg	0.1897	<3	8 / 19	0.689 [31.1%] / 0.610 [39.0%]	1.129 [-12.9%]	(0.486, 2.622)	0.7760
			>=3	32 / 46	0.326 [67.4%] / 0.567 [43.3%]	0.574 [42.6%]	(0.326, 1.010)	0.0542
Number of prior AEDs	10 mg/kg	0.0771	<4	17 / 26	0.184 [81.6%] / 0.735 [26.5%]	0.250 [75.0%]	(0.115, 0.545)	0.0006
			>=4	28 / 39	0.295 [70.5%] / 0.501 [49.9%]	0.588 [41.2%]	(0.342, 1.012)	0.0551
	20 mg/kg	0.0367	<4	14 / 26	0.271 [72.9%] / 0.735 [26.5%]	0.369 [63.1%]	(0.173, 0.785)	0.0100
			>=4	26 / 39	0.516 [48.4%] / 0.501 [49.9%]	1.031 [-3.1%]	(0.567, 1.877)	0.9190

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 3 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Adhoc: GWEP1424 - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Number of prior and concurrent AEDs	10 mg/kg	0.1403	<8	23 / 32	0.210 [79.0%] / 0.684 [31.6%]	0.307 [69.3%]	(0.158, 0.596)	0.0006
			>=8	22 / 33	0.300 [70.0%] / 0.499 [50.1%]	0.601 [39.9%]	(0.330, 1.096)	0.0963
	20 mg/kg	0.8147	<8	20 / 32	0.429 [57.1%] / 0.684 [31.6%]	0.628 [37.2%]	(0.330, 1.193)	0.1539
			>=8	20 / 33	0.351 [64.9%] / 0.499 [50.1%]	0.703 [29.7%]	(0.349, 1.413)	0.3196

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

Source: Listings 8.1.1 and 8.2.1

01-NOV-2023 12:24

Page 4 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 NBR (subgroups).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Non-Convulsive Seizure Responder (ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference	Risk Difference		
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		95% Lower CI	95% Upper CI		95% Lower CI	95% Upper CI	
Non-Convulsive Seizures <=25pct	Age Group	10 mg/kg	0.4748	2-5 years	11	9	16	10	1.3091	0.8175	2.0962	0.4048	2.7000	0.4304	16.9376	0.1932	-0.1358	0.5222
				6-12 years	17	15	22	12	1.6176	1.0638	2.4598	0.0365	6.2500	1.1448	34.1226	0.3369	0.0785	0.5953
				13-18 years	6	4	13	8	1.0833	0.5323	2.2046	1.0000	1.2500	0.1638	9.5379	0.0513	-0.4094	0.5120
	Sex	10 mg/kg	0.4780	F	19	15	26	16	1.2829	0.8752	1.8805	0.3296	2.3438	0.6035	9.1018	0.1741	-0.0878	0.4360
				M	15	13	25	14	1.5476	1.0372	2.3092	0.0801	5.1071	0.9469	27.5450	0.3067	0.0469	0.5664
	Region	10 mg/kg	0.2971	REST OF THE WORLD	19	16	28	14	1.6842	1.1083	2.5593	0.0291	5.3333	1.2655	22.4772	0.3421	0.0948	0.5895
				USA	15	12	23	16	1.1500	0.7941	1.6653	0.7085	1.7500	0.3730	8.2105	0.1043	-0.1719	0.3806
	Valproate Use	10 mg/kg	0.0441	N	11	7	10	7	0.9091	0.4972	1.6622	1.0000	0.7500	0.1207	4.6620	-0.0636	-0.4655	0.3382
				Y	23	21	41	23	1.6276	1.2073	2.1942	0.0044	8.2174	1.6992	39.7398	0.3521	0.1614	0.5427
	Stiripentol Use	10 mg/kg	0.2234	N	22	19	30	16	1.6193	1.1144	2.3529	0.0169	5.5417	1.3486	22.7713	0.3303	0.1013	0.5593
				Y	12	9	21	14	1.1250	0.7208	1.7558	0.7098	1.5000	0.3057	7.3611	0.0833	-0.2340	0.4006
	Levetiracetam Use	10 mg/kg	0.6377	N	25	21	43	25	1.4448	1.0640	1.9619	0.0338	3.7800	1.1060	12.9189	0.2586	0.0527	0.4645
				Y	9	7	8	5	1.2444	0.6560	2.3609	0.6199	2.1000	0.2507	17.5941	0.1528	-0.2789	0.5844
	Topiramate Use	10 mg/kg	0.4405	N	29	25	39	24	1.4009	1.0507	1.8678	0.0307	3.9063	1.1338	13.4581	0.2467	0.0490	0.4443
				Y	5	3	12	6	1.2000	0.4819	2.9881	1.0000	1.5000	0.1806	12.4593	0.1000	-0.4142	0.6142
	Baseline Convulsive Seizure Frequency	10 mg/kg	0.6533	<=7	12	11	14	10	1.2833	0.8841	1.8628	0.3304	4.4000	0.4185	46.2612	0.2024	-0.0813	0.4860
				>7 to <=21	10	7	21	12	1.2250	0.7072	2.1219	0.6972	1.7500	0.3515	8.7118	0.1286	-0.2256	0.4828
				>21	12	10	16	8	1.6667	0.9602	2.8930	0.1144	5.0000	0.8207	30.4606	0.3333	0.0101	0.6566
	Current AEDs	10 mg/kg	0.7777	<3	9	8	14	9	1.3827	0.8785	2.1764	0.3401	4.4444	0.4244	46.5457	0.2460	-0.0782	0.5703
				>=3	25	20	37	21	1.4095	1.0004	1.9859	0.0996	3.0476	0.9401	9.8802	0.2324	0.0087	0.4562
Prior AEDs	10 mg/kg	0.3132	<4	11	10	20	11	1.6529	1.0664	2.5620	0.0550	8.1818	0.8741	76.5813	0.3591	0.0827	0.6355	
			>=4	23	18	31	19	1.2769	0.8970	1.8176	0.2418	2.2737	0.6670	7.7507	0.1697	-0.0707	0.4102	
Prior + Current AEDs	10 mg/kg	0.4050	<8	15	13	24	13	1.6000	1.0532	2.4306	0.0449	5.5000	1.0134	29.8499	0.3250	0.0617	0.5883	
			>=8	19	15	27	17	1.2539	0.8653	1.8170	0.3352	2.2059	0.5710	8.5219	0.1598	-0.0986	0.4183	
Age Group	20 mg/kg	0.8217	2-5 years	8	6	16	10	1.2000	0.6913	2.0830	0.6674	1.8000	0.2710	11.9567	0.1250	-0.2575	0.5075	
			6-12 years	16	13	22	12	1.4896	0.9515	2.3320	0.1650	3.6111	0.7977	16.3473	0.2670	-0.0156	0.5497	
			13-18 years	4	3	13	8	1.2188	0.5989	2.4802	1.0000	1.8750	0.1503	23.3963	0.1346	-0.3654	0.6346	
Sex	20 mg/kg	0.3203	F	14	10	26	16	1.1607	0.7404	1.8196	0.7305	1.5625	0.3841	6.3561	0.0989	-0.2027	0.4005	
			M	14	12	25	14	1.5306	1.0178	2.3017	0.0826	4.7143	0.8677	25.6122	0.2971	0.0298	0.5645	
Region	20 mg/kg	0.2314	REST OF THE WORLD	12	10	28	14	1.6667	1.0642	2.6101	0.0788	5.0000	0.9233	27.0778	0.3333	0.0527	0.6140	
			USA	16	12	23	16	1.0781	0.7290	1.5944	1.0000	1.3125	0.3114	5.5315	0.0543	-0.2292	0.3379	
Valproate Use	20 mg/kg	0.0224	N	8	4	10	7	0.7143	0.3200	1.5945	0.6305	0.4286	0.0618	2.9719	-0.2000	-0.6480	0.2480	
			Y	20	18	41	23	1.6043	1.1794	2.1823	0.0092	7.0435	1.4425	34.3927	0.3390	0.1381	0.5399	
Stiripentol Use	20 mg/kg	0.1919	N	20	14	30	16	1.3125	0.8446	2.0397	0.3771	2.0417	0.6177	6.7478	0.1667	-0.1020	0.4354	
			Y	8	8	21	14	1.5000	1.1085	2.0297	0.1421	-	-	-	0.3333	0.1317	0.5350	
Levetiracetam Use	20 mg/kg	0.7103	N	20	16	43	25	1.3760	0.9841	1.9239	0.1547	2.8800	0.8235	10.0724	0.2186	-0.0105	0.4477	
			Y	8	6	8	5	1.2000	0.6144	2.3438	1.0000	1.8000	0.2103	15.4070	0.1250	-0.3251	0.5751	
Topiramate Use	20 mg/kg	0.7345	N	19	15	39	24	1.2829	0.9133	1.8021	0.2405	2.3438	0.6531	8.4106	0.1741	-0.0645	0.4127	
			Y	9	7	12	6	1.5556	0.8001	3.0244	0.3666	3.5000	0.5047	24.2703	0.2778	-0.1144	0.6700	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Baseline Convulsive Seizure Frequency	20 mg/kg	0.4411 <=7	7	5	14	10	1.0000	0.5634	1.7750	1.0000	1.0000	0.1342	7.4511	0.0000	-0.4099	0.4099
		>7 to <=21	13	10	21	12	1.3462	0.8370	2.1651	0.2919	2.5000	0.5291	11.8132	0.1978	-0.1141	0.5097
		>21	8	7	16	8	1.7500	1.0040	3.0502	0.1782	7.0000	0.6927	70.7426	0.3750	0.0395	0.7105
Current AEDs	20 mg/kg	0.0320 <3	8	4	14	9	0.7778	0.3511	1.7230	0.6619	0.5556	0.0951	3.2459	-0.1429	-0.5707	0.2850
		>=3	20	18	37	21	1.5857	1.1550	2.1770	0.0156	6.8571	1.3857	33.9335	0.3324	0.1256	0.5392
Prior AEDs	20 mg/kg	0.0289 <4	11	11	20	11	1.8182	1.2231	2.7027	0.0116	-	-	-	0.4500	0.2320	0.6680
		>=4	17	11	31	19	1.0557	0.6739	1.6539	1.0000	1.1579	0.3386	3.9596	0.0342	-0.2505	0.3188
Prior + Current AEDs	20 mg/kg	0.8955 <8	16	12	24	13	1.3846	0.8704	2.2025	0.3176	2.5385	0.6338	10.1663	0.2083	-0.0828	0.4995
		>=8	12	10	27	17	1.3235	0.9012	1.9438	0.2755	2.9412	0.5334	16.2184	0.2037	-0.0749	0.4823
Non-Convulsive Seizures <=50pct																
Age Group	10 mg/kg	0.2990 2-5 years	11	7	16	9	1.1313	0.6077	2.1062	1.0000	1.3611	0.2814	6.5838	0.0739	-0.3002	0.4479
		6-12 years	17	13	22	9	1.8693	1.0601	3.2962	0.0496	4.6944	1.1502	19.1607	0.3556	0.0677	0.6435
		13-18 years	6	3	13	7	0.9286	0.3608	2.3897	1.0000	0.8571	0.1236	5.9437	-0.0385	-0.5217	0.4448
Sex	10 mg/kg	0.3546 F	19	12	26	14	1.1729	0.7153	1.9233	0.5593	1.4694	0.4383	4.9262	0.0931	-0.1963	0.3825
		M	15	11	25	11	1.6667	0.9739	2.8523	0.1040	3.5000	0.8714	14.0575	0.2933	-0.0032	0.5899
Region	10 mg/kg	0.4978 REST OF THE WORLD	19	13	28	12	1.5965	0.9439	2.7004	0.1364	2.8889	0.8503	9.8155	0.2556	-0.0224	0.5336
		USA	15	10	23	13	1.1795	0.7108	1.9573	0.7356	1.5385	0.3974	5.9556	0.1014	-0.2115	0.4144
Valproate Use	10 mg/kg	0.0547 N	11	5	10	6	0.7576	0.3331	1.7230	0.6699	0.5556	0.0980	3.1484	-0.1455	-0.5683	0.2774
		Y	23	18	41	19	1.6888	1.1394	2.5032	0.0178	4.1684	1.2995	13.3709	0.3192	0.0918	0.5466
Stiripentol Use	10 mg/kg	0.2037 N	22	16	30	13	1.6783	1.0358	2.7194	0.0493	3.4872	1.0673	11.3938	0.2939	0.0369	0.5510
		Y	12	7	21	12	1.0208	0.5575	1.8691	1.0000	1.0500	0.2496	4.4170	0.0119	-0.3382	0.3621
Levetiracetam Use	10 mg/kg	0.2197 N	25	18	43	20	1.5480	1.0344	2.3165	0.0475	2.9571	1.0256	8.5261	0.2549	0.0242	0.4855
		Y	9	5	8	5	0.8889	0.4020	1.9654	1.0000	0.7500	0.1074	5.2377	-0.0694	-0.5363	0.3974
Topiramate Use	10 mg/kg	0.9965 N	29	20	39	20	1.3448	0.9093	1.9890	0.2129	2.1111	0.7716	5.7763	0.1768	-0.0533	0.4070
		Y	5	3	12	5	1.4400	0.5405	3.8367	0.6199	2.1000	0.2507	17.5941	0.1833	-0.3287	0.6954
Baseline Convulsive Seizure Frequency	10 mg/kg	0.3419 <=7	12	10	14	7	1.6667	0.9315	2.9819	0.1100	5.0000	0.7905	31.6269	0.3333	-0.0029	0.6696
		>7 to <=21	10	5	21	11	0.9545	0.4546	2.0045	1.0000	0.9091	0.2015	4.1014	-0.0238	-0.4002	0.3526
		>21	12	8	16	7	1.5238	0.7684	3.0218	0.2761	2.5714	0.5434	12.1686	0.2292	-0.1317	0.5900
Current AEDs	10 mg/kg	0.9120 <3	9	6	14	7	1.3333	0.6632	2.6808	0.6693	2.0000	0.3520	11.3642	0.1667	-0.2376	0.5710
		>=3	25	17	37	18	1.3978	0.9125	2.1412	0.1922	2.2431	0.7778	6.4686	0.1935	-0.0502	0.4372
Prior AEDs	10 mg/kg	0.7711 <4	11	8	20	10	1.4545	0.8239	2.5678	0.2755	2.6667	0.5437	13.0802	0.2273	-0.1152	0.5697
		>=4	23	15	31	15	1.3478	0.8421	2.1573	0.2738	2.0000	0.6590	6.0697	0.1683	-0.0941	0.4307
Prior AEDs	10 mg/kg	0.4466 <8	15	11	24	11	1.6000	0.9405	2.7219	0.1116	3.2500	0.8031	13.1526	0.2750	-0.0247	0.5747
		>=8	19	12	27	14	1.2180	0.7387	2.0083	0.5510	1.5918	0.4797	5.2824	0.1131	-0.1743	0.4004
Age Group	20 mg/kg	0.1440 2-5 years	8	6	16	9	1.3333	0.7399	2.4027	0.6570	2.3333	0.3558	15.3004	0.1875	-0.1987	0.5737
		6-12 years	16	12	22	9	1.8333	1.0302	3.2627	0.0516	4.3333	1.0525	17.8418	0.3409	0.0456	0.6363
		13-18 years	4	1	13	7	0.4643	0.0791	2.7269	0.5765	0.2857	0.0232	3.5233	-0.2885	-0.7920	0.2150
Sex	20 mg/kg	0.4633 F	14	9	26	14	1.1939	0.7039	2.0248	0.7385	1.5429	0.4049	5.8791	0.1044	-0.2114	0.4202
		M	14	10	25	11	1.6234	0.9342	2.8209	0.1799	3.1818	0.7824	12.9404	0.2743	-0.0321	0.5807
Region	20 mg/kg	0.2602 REST OF THE WORLD	12	9	28	12	1.7500	1.0217	2.9975	0.0888	4.0000	0.8873	18.0316	0.3214	0.0155	0.6274
		USA	16	10	23	13	1.1058	0.6561	1.8637	0.7521	1.2821	0.3475	4.7296	0.0598	-0.2522	0.3717
Valproate Use	20 mg/kg	0.0313 N	8	3	10	6	0.6250	0.2236	1.7468	0.6372	0.4000	0.0592	2.7021	-0.2250	-0.6775	0.2275
		Y	20	16	41	19	1.7263	1.1623	2.5641	0.0148	4.6316	1.3192	16.2612	0.3366	0.1041	0.5690
Stiripentol Use	20 mg/kg	0.4396 N	20	12	30	13	1.3846	0.8040	2.3846	0.3868	1.9615	0.6213	6.1929	0.1667	-0.1118	0.4451

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		Y	8	7	21	12	1.5313	0.9728	2.4102	0.2008	5.2500	0.5443	50.6412	0.3036	-0.0084	0.6155
Levetiracetam Use	20 mg/kg	0.1327 N	20	15	43	20	1.6125	1.0719	2.4258	0.0556	3.4500	1.0641	11.1852	0.2849	0.0436	0.5262
		Y	8	4	8	5	0.8000	0.3330	1.9220	1.0000	0.6000	0.0818	4.3997	-0.1250	-0.6073	0.3573
Topiramate Use	20 mg/kg	0.7777 N	19	13	39	20	1.3342	0.8659	2.0558	0.2663	2.0583	0.6496	6.5218	0.1714	-0.0899	0.4327
		Y	9	6	12	5	1.6000	0.7094	3.6088	0.3870	2.8000	0.4631	16.9287	0.2500	-0.1655	0.6655
Baseline Convulsive Seizure Frequency	20 mg/kg	0.9867 <=7	7	5	14	7	1.4286	0.7074	2.8848	0.6424	2.5000	0.3571	17.5001	0.2143	-0.2107	0.6392
		>7 to <=21	13	9	21	11	1.3217	0.7659	2.2806	0.4774	2.0455	0.4768	8.7744	0.1685	-0.1610	0.4980
		>21	8	5	16	7	1.4286	0.6598	3.0932	0.6668	2.1429	0.3765	12.1973	0.1875	-0.2268	0.6018
Current AEDs	20 mg/kg	0.2815 <3	8	4	14	7	1.0000	0.4195	2.3837	1.0000	1.0000	0.1760	5.6821	0.0000	-0.4343	0.4343
		>=3	20	15	37	18	1.5417	1.0163	2.3386	0.0908	3.1667	0.9538	10.5136	0.2635	0.0146	0.5124
Prior AEDs	20 mg/kg	0.0830 <4	11	10	20	10	1.8182	1.1291	2.9279	0.0472	10.0000	1.0702	93.4370	0.4091	0.1318	0.6864
		>=4	17	9	31	15	1.0941	0.6144	1.9485	1.0000	1.2000	0.3671	3.9231	0.0455	-0.2498	0.3409
Prior + Current AEDs	20 mg/kg	0.7341 <8	16	11	24	11	1.5000	0.8688	2.5899	0.2026	2.6000	0.6894	9.8061	0.2292	-0.0730	0.5314
		>=8	12	8	27	14	1.2857	0.7488	2.2075	0.4940	1.8571	0.4498	7.6671	0.1481	-0.1784	0.4747
Non-Convulsive Seizures <=-75pct																
Age Group	10 mg/kg	0.9939 2-5 years	11	6	16	4	2.1818	0.7981	5.9643	0.2238	3.6000	0.6985	18.5553	0.2955	-0.0673	0.6582
		6-12 years	17	9	22	5	2.3294	0.9553	5.6802	0.0914	3.8250	0.9634	15.1868	0.3021	0.0072	0.5970
		13-18 years	6	3	13	3	2.1667	0.6055	7.7527	0.3201	3.3333	0.4267	26.0391	0.2692	-0.1918	0.7302
Sex	10 mg/kg	0.3236 F	19	8	26	6	1.8246	0.7585	4.3891	0.2063	2.4242	0.6679	8.7986	0.1903	-0.0845	0.4651
		M	15	10	25	6	2.7778	1.2683	6.0838	0.0180	6.3333	1.5425	26.0033	0.4267	0.1352	0.7181
Region	10 mg/kg	0.8464 REST OF THE WORLD	19	11	28	8	2.0263	1.0062	4.0806	0.0695	3.4375	1.0094	11.7068	0.2932	0.0152	0.5712
		USA	15	7	23	4	2.6833	0.9464	7.6079	0.0733	4.1563	0.9458	18.2650	0.2928	-0.0034	0.5890
Valproate Use	10 mg/kg	0.5706 N	11	5	10	1	4.5455	0.6346	32.5566	0.1486	7.5000	0.6923	81.2484	0.3545	0.0065	0.7026
		Y	23	13	41	11	2.1067	1.1337	3.9150	0.0305	3.5455	1.2093	10.3944	0.2969	0.0531	0.5407
Stiripentol Use	10 mg/kg	0.1149 N	22	12	30	4	4.0909	1.5218	10.9970	0.0023	7.8000	2.0297	29.9752	0.4121	0.1711	0.6531
		Y	12	6	21	8	1.3125	0.5982	2.8796	0.7157	1.6250	0.3874	6.8171	0.1190	-0.2319	0.4700
Levetiracetam Use	10 mg/kg	0.5503 N	25	13	43	9	2.4844	1.2432	4.9649	0.0146	4.0926	1.3969	11.9902	0.3107	0.0802	0.5412
		Y	9	5	8	3	1.4815	0.5089	4.3128	0.6372	2.0833	0.2983	14.5491	0.1806	-0.2863	0.6474
Topiramate Use	10 mg/kg	0.9582 N	29	16	39	10	2.1517	1.1493	4.0285	0.0224	3.5692	1.2796	9.9554	0.2953	0.0683	0.5223
		Y	5	2	12	2	2.4000	0.4567	12.6126	0.5378	3.3333	0.3190	34.8300	0.2333	-0.2451	0.7117
Baseline Convulsive Seizure Frequency	10 mg/kg	0.6367 <=7	12	8	14	5	1.8667	0.8315	4.1906	0.2377	3.6000	0.7100	18.2544	0.3095	-0.0567	0.6758
		>7 to <=21	10	4	21	5	1.6800	0.5718	4.9360	0.4174	2.1333	0.4242	10.7287	0.1619	-0.1922	0.5160
		>21	12	6	16	2	4.0000	0.9722	16.4574	0.0441	7.0000	1.0850	45.1598	0.3750	0.0490	0.7010
Current AEDs	10 mg/kg	0.1548 <3	9	5	14	1	7.7778	1.0771	56.1637	0.0183	16.2500	1.4422	183.0932	0.4841	0.1326	0.8357
		>=3	25	13	37	11	1.7491	0.9388	3.2589	0.1114	2.5606	0.8918	7.3525	0.2227	-0.0223	0.4677
Prior AEDs	10 mg/kg	0.3677 <4	11	6	20	3	3.6364	1.1235	11.7691	0.0377	6.8000	1.2332	37.4968	0.3955	0.0622	0.7287
		>=4	23	12	31	9	1.7971	0.9147	3.5306	0.0994	2.6667	0.8638	8.2328	0.2314	-0.0278	0.4907
Prior + Current AEDs	10 mg/kg	0.4286 <8	15	8	24	4	3.2000	1.1630	8.8046	0.0306	5.7143	1.3048	25.0263	0.3667	0.0735	0.6599
		>=8	19	10	27	8	1.7763	0.8637	3.6530	0.1371	2.6389	0.7775	8.9565	0.2300	-0.0529	0.5130
Age Group	20 mg/kg	0.7828 2-5 years	8	4	16	4	2.0000	0.6686	5.9823	0.3625	3.0000	0.5013	17.9539	0.2500	-0.1563	0.6563
		6-12 years	16	5	22	5	1.3750	0.4768	3.9655	0.7127	1.5455	0.3614	6.6095	0.0852	-0.2016	0.3720
		13-18 years	4	1	13	3	1.0833	0.1516	7.7390	1.0000	1.1111	0.0821	15.0363	0.0192	-0.4630	0.5014
Sex	20 mg/kg	0.5117 F	14	6	26	6	1.8571	0.7353	4.6904	0.2808	2.5000	0.6181	10.1117	0.1978	-0.1079	0.5035
		M	14	4	25	6	1.1905	0.4031	3.5156	1.0000	1.2667	0.2887	5.5579	0.0457	-0.2442	0.3356

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Region	20 mg/kg	0.1655 REST OF THE WORLD USA	12	3	28	8	0.8750	0.2794	2.7404	1.0000	0.8333	0.1782	3.8972	-0.0357	-0.3324	0.2610
			16	7	23	4	2.5156	0.8805	7.1872	0.1461	3.6944	0.8561	15.9439	0.2636	-0.0246	0.5518
Valproate Use	20 mg/kg	0.3459 N Y	8	3	10	1	3.7500	0.4763	29.5226	0.2745	5.4000	0.4374	66.6714	0.2750	-0.1086	0.6586
			20	7	41	11	1.3045	0.5965	2.8528	0.5585	1.4685	0.4652	4.6360	0.0817	-0.1675	0.3309
Stiripentol Use	20 mg/kg	0.0682 N Y	20	8	30	4	3.0000	1.0409	8.6461	0.0445	4.3333	1.0886	17.2496	0.2667	0.0199	0.5134
			8	2	21	8	0.6563	0.1756	2.4523	0.6749	0.5417	0.0872	3.3654	-0.1310	-0.4959	0.2340
Levetiracetam Use	20 mg/kg	0.5510 N Y	20	7	43	9	1.6722	0.7269	3.8472	0.3509	2.0342	0.6273	6.5967	0.1407	-0.1011	0.3825
			8	3	8	3	1.0000	0.2822	3.5436	1.0000	1.0000	0.1321	7.5704	0.0000	-0.4744	0.4744
Topiramate Use	20 mg/kg	0.3558 N Y	19	6	39	10	1.2316	0.5260	2.8835	0.7563	1.3385	0.4011	4.4667	0.0594	-0.1906	0.3093
			9	4	12	2	2.6667	0.6188	11.4926	0.3310	4.0000	0.5368	29.8045	0.2778	-0.1093	0.6649
Baseline Convulsive Seizure Frequency	20 mg/kg	0.0122 <=7 >7 to <=21 >21	7	0	14	5	-	-	-	0.1235	-	-	-	-0.3571	-0.6081	-0.1061
			13	5	21	5	1.6154	0.5775	4.5188	0.4505	2.0000	0.4452	8.9839	0.1465	-0.1746	0.4676
			8	5	16	2	5.0000	1.2291	20.3394	0.0207	11.6667	1.4869	91.5429	0.5000	0.1274	0.8726
Current AEDs	20 mg/kg	0.4764 <3 >=3	8	2	14	1	3.5000	0.3734	32.8034	0.5273	4.3333	0.3257	57.6490	0.1786	-0.1504	0.5076
			20	8	37	11	1.3455	0.6481	2.7931	0.5578	1.5758	0.5045	4.9220	0.1027	-0.1577	0.3631
Prior AEDs	20 mg/kg	0.1564 <4 >=4	11	5	20	3	3.0303	0.8877	10.3445	0.0947	4.7222	0.8564	26.0395	0.3045	-0.0287	0.6378
			17	5	31	9	1.0131	0.4040	2.5405	1.0000	1.0185	0.2776	3.7370	0.0038	-0.2654	0.2730
Prior + Current AEDs	20 mg/kg	0.7814 <8 >=8	16	5	24	4	1.8750	0.5921	5.9371	0.4414	2.2727	0.5038	10.2535	0.1458	-0.1259	0.4175
			12	5	27	8	1.4063	0.5794	3.4128	0.4859	1.6964	0.4125	6.9764	0.1204	-0.2075	0.4482
Non-Convulsive Seizures >0pct Age Group	10 mg/kg	0.0582 2-5 years 6-12 years 13-18 years	11	2	16	5	0.5818	0.1366	2.4780	0.6618	2.0455	0.3180	13.1588	-0.1307	-0.4524	0.1911
			17	0	22	8	1.5714	1.1458	2.1552	0.0056	-	-	-	-0.3636	-0.5646	-0.1626
			6	2	13	3	1.4444	0.3206	6.5070	1.0000	0.6000	0.0712	5.0594	0.1026	-0.3387	0.5438
Sex	10 mg/kg	0.4421 F M	19	3	26	8	0.5132	0.1565	1.6830	0.3093	2.3704	0.5353	10.4967	-0.1498	-0.3914	0.0918
			15	1	25	8	0.2083	0.0288	1.5057	0.1166	6.5882	0.7330	59.2159	-0.2533	-0.4755	-0.0311
Region	10 mg/kg	0.5558 REST OF THE WORLD USA	19	2	28	10	0.2947	0.0725	1.1976	0.0875	4.7222	0.9010	24.7508	-0.2519	-0.4767	-0.0271
			15	2	23	6	0.5111	0.1184	2.2055	0.4398	2.2941	0.3964	13.2770	-0.1275	-0.3761	0.1211
Valproate Use	10 mg/kg	0.1101 N Y	11	3	10	3	0.9091	0.2352	3.5134	1.0000	1.1429	0.1718	7.6007	-0.0273	-0.4145	0.3599
			23	1	41	13	0.1371	0.0191	0.9821	0.0120	10.2143	1.2393	84.1833	-0.2736	-0.4386	-0.1086
Stiripentol Use	10 mg/kg	0.0193 N Y	22	1	30	12	0.1136	0.0159	0.8103	0.0037	14.0000	1.6555	118.3902	-0.3545	-0.5503	-0.1588
			12	3	21	4	1.3125	0.3512	4.9047	0.6856	0.7059	0.1288	3.8681	0.0595	-0.2375	0.3566
Levetiracetam Use	10 mg/kg	0.7778 N Y	25	3	43	13	0.3969	0.1251	1.2593	0.1378	3.1778	0.8070	12.5136	-0.1823	-0.3696	0.0049
			9	1	8	3	0.2963	0.0380	2.3086	0.2941	4.8000	0.3847	59.8945	-0.2639	-0.6572	0.1294
Topiramate Use	10 mg/kg	0.1134 N Y	29	2	39	12	0.2241	0.0543	0.9252	0.0178	6.0000	1.2246	29.3975	-0.2387	-0.4104	-0.0670
			5	2	12	4	1.2000	0.3146	4.5779	1.0000	0.7500	0.0870	6.4675	0.0667	-0.4388	0.5722
Baseline Convulsive Seizure Frequency	10 mg/kg	0.4418 <=7 >7 to <=21 >21	12	0	14	3	1.2727	0.9681	1.6732	0.2246	-	-	-	-0.2143	-0.4292	0.0007
			10	2	21	6	0.7000	0.1705	2.8731	1.0000	1.6000	0.2603	9.8339	-0.0857	-0.4000	0.2286
			12	2	16	7	0.3810	0.0957	1.5169	0.2232	3.8889	0.6357	23.7916	-0.2708	-0.5926	0.0510
Current AEDs	10 mg/kg	0.1773 <3 >=3	9	0	14	5	1.5556	1.0527	2.2985	0.1157	-	-	-	-0.3571	-0.6081	-0.1061
			25	4	37	11	0.5382	0.1930	1.5010	0.2452	2.2212	0.6171	7.9945	-0.1373	-0.3431	0.0685
Prior AEDs	10 mg/kg	0.6151 <4 >=4	11	1	20	7	0.2597	0.0365	1.8474	0.2028	5.3846	0.5666	51.1716	-0.2591	-0.5285	0.0103
			23	3	31	9	0.4493	0.1367	1.4770	0.2003	2.7273	0.6461	11.5126	-0.1599	-0.3708	0.0510
Prior + Current AEDs	10 mg/kg	0.3917 <8 >=8	15	1	24	8	0.2000	0.0277	1.4431	0.1152	7.0000	0.7763	63.1194	-0.2667	-0.4936	-0.0397
			19	3	27	8	0.5329	0.1621	1.7517	0.3198	2.2456	0.5090	9.9067	-0.1384	-0.3762	0.0994

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Age Group	20 mg/kg	0.7907 2-5 years	8	1	16	5	0.4000	0.0557	2.8745	0.6214	3.1818	0.3044	33.2586	-0.1875	-0.5101	0.1351
		6-12 years	16	3	22	8	0.5156	0.1616	1.6451	0.2960	2.4762	0.5380	11.3968	-0.1761	-0.4536	0.1013
		13-18 years	4	0	13	3	1.3000	0.9652	1.7509	0.5412	-	-	-	-0.2308	-0.4598	-0.0017
Sex	20 mg/kg	0.3212 F	14	3	26	8	0.6964	0.2190	2.2148	0.7152	1.6296	0.3549	7.4827	-0.0934	-0.3721	0.1853
		M	14	1	25	8	0.2232	0.0310	1.6058	0.1189	6.1176	0.6774	55.2508	-0.2486	-0.4758	-0.0213
Region	20 mg/kg	0.9250 REST OF THE WORLD	12	2	28	10	0.4667	0.1199	1.8169	0.2848	2.7778	0.5056	15.2611	-0.1905	-0.4661	0.0851
		USA	16	2	23	6	0.4792	0.1104	2.0790	0.4318	2.4706	0.4295	14.2125	-0.1359	-0.3777	0.1059
Valproate Use	20 mg/kg	0.3742 N	8	2	10	3	0.8333	0.1807	3.8434	1.0000	1.2857	0.1582	10.4500	-0.0500	-0.4632	0.3632
		Y	20	2	41	13	0.3154	0.0786	1.2655	0.1114	4.1786	0.8418	20.7408	-0.2171	-0.4109	-0.0232
Stiripentol Use	20 mg/kg	0.4082 N	20	4	30	12	0.5000	0.1877	1.3322	0.2165	2.6667	0.7146	9.9507	-0.2000	-0.4479	0.0479
		Y	8	0	21	4	1.2353	1.0039	1.5201	0.5520	-	-	-	-0.1905	-0.3584	-0.0225
Levetiracetam Use	20 mg/kg	0.7152 N	20	3	43	13	0.4962	0.1590	1.5479	0.2316	2.4556	0.6121	9.8512	-0.1523	-0.3605	0.0558
		Y	8	1	8	3	0.3333	0.0433	2.5635	0.5692	4.2000	0.3321	53.1228	-0.2500	-0.6563	0.1563
Topiramate Use	20 mg/kg	0.7116 N	19	3	39	12	0.5132	0.1641	1.6048	0.3399	2.3704	0.5798	9.6913	-0.1498	-0.3686	0.0690
		Y	9	1	12	4	0.3333	0.0445	2.4969	0.3383	4.0000	0.3627	44.1128	-0.2222	-0.5588	0.1144
Baseline Convulsive Seizure Frequency	20 mg/kg	0.1388 <=7	7	2	14	3	1.3333	0.2852	6.2325	1.0000	0.6818	0.0853	5.4475	0.0714	-0.3263	0.4692
		>7 to <=21	13	2	21	6	0.5385	0.1272	2.2797	0.4438	2.2000	0.3712	13.0380	-0.1319	-0.4072	0.1434
		>21	8	0	16	7	1.7778	1.1540	2.7387	0.0538	-	-	-	-0.4375	-0.6806	-0.1944
Current AEDs	20 mg/kg	0.0110 <3	8	4	14	5	1.4000	0.5218	3.7563	0.6619	0.5556	0.0951	3.2459	0.1429	-0.2850	0.5707
		>=3	20	0	37	11	1.4231	1.1540	1.7549	0.0053	-	-	-	-0.2973	-0.4446	-0.1500
Prior AEDs	20 mg/kg	0.0772 <4	11	0	20	7	1.5385	1.1154	2.1220	0.0331	-	-	-	-0.3500	-0.5590	-0.1410
		>=4	17	4	31	9	0.8105	0.2927	2.2441	0.7470	1.3295	0.3403	5.1948	-0.0550	-0.3123	0.2022
Prior + Current AEDs	20 mg/kg	0.5737 <8	16	3	24	8	0.5625	0.1752	1.8059	0.4732	2.1667	0.4761	9.8604	-0.1458	-0.4144	0.1228
		>=8	12	1	27	8	0.2813	0.0394	2.0057	0.2276	4.6316	0.5094	42.1147	-0.2130	-0.4456	0.0197

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc: Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
All Data	10 mg/kg			45 / 65	1.274 [-27.4%] / 0.692 [30.8%]	1.841 [-84.1%]	(1.300, 2.606)	0.0007
	20 mg/kg			40 / 65	1.424 [-42.4%] / 0.692 [30.8%]	2.057 [-105.7%]	(1.422, 2.977)	0.0002
Age Group	10 mg/kg	0.0167	2-5 years	13 / 18	1.242 [-24.2%] / 1.504 [-50.4%]	0.826 [17.4%]	(0.438, 1.558)	0.5528
			6-12 years	23 / 28	1.304 [-30.4%] / 0.495 [50.5%]	2.633 [-163.3%]	(1.610, 4.306)	0.0002
			13-18 years	9 / 19	1.273 [-27.3%] / 0.605 [39.5%]	2.105 [-110.5%]	(1.060, 4.180)	0.0337
	20 mg/kg	0.2568	2-5 years	10 / 18	1.881 [-88.1%] / 1.504 [-50.4%]	1.251 [-25.1%]	(0.590, 2.654)	0.5570
			6-12 years	22 / 28	1.318 [-31.8%] / 0.495 [50.5%]	2.660 [-166.0%]	(1.612, 4.389)	0.0002
			13-18 years	8 / 19	1.355 [-35.5%] / 0.605 [39.5%]	2.240 [-124.0%]	(1.109, 4.528)	0.0249
Sex	10 mg/kg	0.5678	Female	22 / 34	1.218 [-21.8%] / 0.729 [27.1%]	1.670 [-67.0%]	(1.025, 2.720)	0.0395
			Male	23 / 31	1.330 [-33.0%] / 0.650 [35.0%]	2.047 [-104.7%]	(1.235, 3.393)	0.0058
	20 mg/kg	0.9815	Female	17 / 34	1.514 [-51.4%] / 0.729 [27.1%]	2.076 [-107.6%]	(1.218, 3.539)	0.0076
			Male	23 / 31	1.361 [-36.1%] / 0.650 [35.0%]	2.094 [-109.4%]	(1.240, 3.536)	0.0060
Region	10 mg/kg	0.4306	USA	22 / 32	1.506 [-50.6%] / 0.724 [27.6%]	2.080 [-108.0%]	(1.266, 3.416)	0.0041
			Rest of the World	23 / 33	1.061 [-6.1%] / 0.673 [32.7%]	1.577 [-57.7%]	(0.975, 2.553)	0.0634
	20 mg/kg	0.3104	USA	21 / 32	1.796 [-79.6%] / 0.724 [27.6%]	2.481 [-148.1%]	(1.448, 4.251)	0.0011
			Rest of the World	19 / 33	1.142 [-14.2%] / 0.673 [32.7%]	1.699 [-69.9%]	(1.029, 2.804)	0.0385

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

31-OCT-2023 11:32

Page 1 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 LSFI NBR (subgroups).sas

Adhoc: Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
Valproic Acid Use	10 mg/kg	0.2097	Not Currently Taking	15 / 17	1.070 [-7.0%] / 0.837 [16.3%]	1.279 [-27.9%]	(0.651, 2.511)	0.4729
			Currently Taking	30 / 48	1.397 [-39.7%] / 0.659 [34.1%]	2.119 [-111.9%]	(1.400, 3.206)	0.0005
	20 mg/kg	0.8715	Not Currently Taking	10 / 17	1.615 [-61.5%] / 0.837 [16.3%]	1.931 [-93.1%]	(0.887, 4.204)	0.0968
			Currently Taking	30 / 48	1.369 [-36.9%] / 0.659 [34.1%]	2.076 [-107.6%]	(1.361, 3.166)	0.0008
Stiripentol Use	10 mg/kg	0.0418	Not Currently Taking	28 / 41	1.545 [-54.5%] / 0.644 [35.6%]	2.398 [-139.8%]	(1.546, 3.720)	0.0001
			Currently Taking	17 / 24	0.890 [11.0%] / 0.766 [23.4%]	1.161 [-16.1%]	(0.675, 1.998)	0.5865
	20 mg/kg	0.0570	Not Currently Taking	22 / 41	1.850 [-85.0%] / 0.644 [35.6%]	2.871 [-187.1%]	(1.736, 4.748)	<.0001
			Currently Taking	18 / 24	1.088 [-8.8%] / 0.766 [23.4%]	1.420 [-42.0%]	(0.843, 2.394)	0.1864
Levetiracetam Use	10 mg/kg	0.9342	Not Currently Taking	34 / 51	1.378 [-37.8%] / 0.736 [26.4%]	1.872 [-87.2%]	(1.255, 2.792)	0.0023
			Currently Taking	11 / 14	1.038 [-3.8%] / 0.535 [46.5%]	1.939 [-93.9%]	(0.929, 4.045)	0.0773
	20 mg/kg	0.4582	Not Currently Taking	31 / 51	1.414 [-41.4%] / 0.736 [26.4%]	1.920 [-92.0%]	(1.272, 2.900)	0.0021
			Currently Taking	9 / 14	1.467 [-46.7%] / 0.535 [46.5%]	2.740 [-174.0%]	(1.171, 6.413)	0.0205
Topiramate Use	10 mg/kg	0.7922	Not Currently Taking	37 / 48	1.347 [-34.7%] / 0.736 [26.4%]	1.831 [-83.1%]	(1.233, 2.719)	0.0029
			Currently Taking	8 / 17	0.965 [3.5%] / 0.592 [40.8%]	1.630 [-63.0%]	(0.751, 3.539)	0.2145
	20 mg/kg	0.6538	Not Currently Taking	30 / 48	1.432 [-43.2%] / 0.736 [26.4%]	1.947 [-94.7%]	(1.270, 2.987)	0.0025
			Currently Taking	10 / 17	1.402 [-40.2%] / 0.592 [40.8%]	2.370 [-137.0%]	(1.120, 5.016)	0.0244

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

31-OCT-2023 11:32

Page 2 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 LSFI NBR (subgroups).sas

Adhoc: Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Periods (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
Baseline Convulsive Seizure Frequency	10 mg/kg	0.0401	<=7	16 / 17	1.114 [-11.4%] / 0.866 [13.4%]	1.287 [-28.7%]	(0.729, 2.272)	0.3824
			>7 to <=21	16 / 24	1.142 [-14.2%] / 0.706 [29.4%]	1.618 [-61.8%]	(0.938, 2.791)	0.0834
			>21	13 / 24	2.099 [-109.9%] / 0.503 [49.7%]	4.172 [-317.2%]	(1.996, 8.723)	0.0002
	20 mg/kg	0.1591	<=7	12 / 17	1.876 [-87.6%] / 0.866 [13.4%]	2.167 [-116.7%]	(1.170, 4.012)	0.0143
			>7 to <=21	18 / 24	1.048 [-4.8%] / 0.706 [29.4%]	1.485 [-48.5%]	(0.862, 2.557)	0.1525
			>21	10 / 24	2.048 [-104.8%] / 0.503 [49.7%]	4.070 [-307.0%]	(1.671, 9.911)	0.0022
Number of concurrent AEDs	10 mg/kg	0.9393	<3	12 / 19	1.327 [-32.7%] / 0.746 [25.4%]	1.778 [-77.8%]	(0.865, 3.655)	0.1163
			>=3	33 / 46	1.255 [-25.5%] / 0.684 [31.6%]	1.836 [-83.6%]	(1.228, 2.745)	0.0033
	20 mg/kg	0.5441	<3	8 / 19	1.971 [-97.1%] / 0.746 [25.4%]	2.641 [-164.1%]	(1.092, 6.387)	0.0313
			>=3	32 / 46	1.338 [-33.8%] / 0.684 [31.6%]	1.957 [-95.7%]	(1.297, 2.954)	0.0016
Number of prior AEDs	10 mg/kg	0.5785	<4	17 / 26	1.403 [-40.3%] / 0.860 [14.0%]	1.632 [-63.2%]	(0.957, 2.785)	0.0719
			>=4	28 / 39	1.191 [-19.1%] / 0.598 [40.2%]	1.990 [-99.0%]	(1.258, 3.149)	0.0035
	20 mg/kg	0.6784	<4	14 / 26	1.632 [-63.2%] / 0.860 [14.0%]	1.899 [-89.9%]	(1.020, 3.533)	0.0431
			>=4	26 / 39	1.336 [-33.6%] / 0.598 [40.2%]	2.234 [-123.4%]	(1.409, 3.543)	0.0007

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

31-OCT-2023 11:32

Page 3 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 LSFI NBR (subgroups).sas

Adhoc: Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Periods
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Treatment	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
Number of prior and concurrent AEDs	10 mg/kg	0.3359	<8	23 / 32	1.326 [-32.6%] / 0.866 [13.4%]	1.532 [-53.2%]	(0.946, 2.482)	0.0825
			>=8	22 / 33	1.221 [-22.1%] / 0.566 [43.4%]	2.155 [-115.5%]	(1.300, 3.572)	0.0031
	20 mg/kg	0.5548	<8	20 / 32	1.591 [-59.1%] / 0.866 [13.4%]	1.838 [-83.8%]	(1.071, 3.152)	0.0273
			>=8	20 / 33	1.298 [-29.8%] / 0.566 [43.4%]	2.293 [-129.3%]	(1.383, 3.800)	0.0015

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

31-OCT-2023 11:32

Page 4 of 4

C:\SASData\elypdc\CBD\PhaseIII\GWEP1424 Dravet\Reporting\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1424 LSFI NBR (subgroups).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 CGIC Responder [VMI, MI, SI](ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference	Risk Difference		
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI		95% Upper CI	95% Lower CI	95% Upper CI
End of Treatment	Age Group	10 mg/kg	0.9406	2-5 years	12	10	18	11	1.3636	0.8721	2.1323	0.2487	0.3143	0.0525	1.8818	0.2222	-0.0863	0.5307
				6-12 years	22	15	28	9	2.1212	1.1535	3.9008	0.0216	0.2211	0.0667	0.7321	0.3604	0.1000	0.6208
				13-18 years	8	6	18	7	1.9286	0.9540	3.8987	0.2016	0.2121	0.0330	1.3624	0.3611	-0.0141	0.7363
Last Visit (LOCF)	Age Group	10 mg/kg	0.9061	2-5 years	13	11	18	11	1.3846	0.8959	2.1399	0.2374	0.2857	0.0482	1.6940	0.2350	-0.0636	0.5337
				6-12 years	23	15	28	9	2.0290	1.0965	3.7544	0.0256	0.2526	0.0785	0.8127	0.3307	0.0703	0.5912
				13-18 years	9	7	19	7	2.1111	1.0647	4.1859	0.1032	0.1667	0.0268	1.0360	0.4094	0.0618	0.7569
End of Treatment	Sex	10 mg/kg	0.6942	F	20	16	33	15	1.7600	1.1412	2.7144	0.0209	0.2083	0.0572	0.7586	0.3455	0.1013	0.5896
				M	22	15	31	12	1.7614	1.0399	2.9834	0.0514	0.2947	0.0931	0.9327	0.2947	0.0353	0.5541
Last Visit (LOCF)	Sex	10 mg/kg	0.8375	F	22	17	34	15	1.7515	1.1269	2.7223	0.0259	0.2322	0.0696	0.7750	0.3316	0.0896	0.5735
				M	23	16	31	12	1.7971	1.0696	3.0195	0.0309	0.2763	0.0879	0.8684	0.3086	0.0541	0.5630
End of Treatment	Region	10 mg/kg	0.0084	REST OF THE WORLD	20	10	32	13	1.2308	0.6713	2.2566	0.5736	0.6842	0.2221	2.1078	0.0938	-0.1837	0.3712
				USA	22	21	32	14	2.1818	1.4577	3.2657	<.0001	0.0370	0.0044	0.3099	0.5170	0.3244	0.7097
Last Visit (LOCF)	Region	10 mg/kg	0.0114	REST OF THE WORLD	23	12	33	13	1.3244	0.7442	2.3569	0.4175	0.5958	0.2032	1.7468	0.1278	-0.1358	0.3914
				USA	22	21	32	14	2.1818	1.4577	3.2657	<.0001	0.0370	0.0044	0.3099	0.5170	0.3244	0.7097
End of Treatment	Valproate Use	10 mg/kg	0.3064	N	14	11	16	5	2.5143	1.1565	5.4660	0.0136	0.1240	0.0236	0.6503	0.4732	0.1605	0.7859
				Y	28	20	48	22	1.5584	1.0587	2.2940	0.0348	0.3385	0.1248	0.9176	0.2560	0.0372	0.4747
Last Visit (LOCF)	Valproate Use	10 mg/kg	0.1953	N	15	12	17	5	2.7200	1.2485	5.9258	0.0060	0.1042	0.0202	0.5369	0.5059	0.2094	0.8023
				Y	30	21	48	22	1.5273	1.0376	2.2481	0.0604	0.3626	0.1381	0.9523	0.2417	0.0254	0.4579
End of Treatment	Stiripentol Use	10 mg/kg	0.1866	N	26	23	41	20	1.8135	1.2869	2.5555	0.0014	0.1242	0.0322	0.4792	0.3968	0.2006	0.5930
				Y	16	8	23	7	1.6429	0.7467	3.6147	0.3178	0.4375	0.1166	1.6420	0.1957	-0.1132	0.5045
Last Visit (LOCF)	Stiripentol Use	10 mg/kg	0.3559	N	28	24	41	20	1.7571	1.2405	2.4890	0.0021	0.1587	0.0467	0.5392	0.3693	0.1688	0.5699
				Y	17	9	24	7	1.8151	0.8422	3.9118	0.1945	0.3660	0.1001	1.3388	0.2377	-0.0612	0.5367
End of Treatment	Levetiracetam Use	10 mg/kg	0.6257	N	32	24	50	23	1.6304	1.1366	2.3389	0.0122	0.2840	0.1072	0.7524	0.2900	0.0861	0.4939
				Y	10	7	14	4	2.4500	0.9741	6.1618	0.0953	0.1714	0.0289	1.0181	0.4143	0.0446	0.7840

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Last Visit (LOCF)	Levetiracetam Use	10 mg/kg	0.5043 N	34	25	51	23	1.6304	1.1332	2.3459	0.0138	0.2957	0.1154	0.7575	0.2843	0.0827	0.4859
			Y	11	8	14	4	2.5455	1.0309	6.2849	0.0472	0.1500	0.0258	0.8737	0.4416	0.0876	0.7955
End of Treatment	Topiramate Use	10 mg/kg	0.2855 N	34	24	48	21	1.6134	1.0954	2.3765	0.0240	0.3241	0.1276	0.8234	0.2684	0.0607	0.4761
			Y	8	7	16	6	2.3333	1.1766	4.6272	0.0335	0.0857	0.0084	0.8783	0.5000	0.1702	0.8298
Last Visit (LOCF)	Topiramate Use	10 mg/kg	0.2421 N	37	26	48	21	1.6062	1.0949	2.3562	0.0170	0.3291	0.1329	0.8148	0.2652	0.0618	0.4686
			Y	8	7	17	6	2.4792	1.2374	4.9670	0.0302	0.0779	0.0077	0.7924	0.5221	0.1994	0.8447
End of Treatment	Baseline Convulsive Seizure Frequency	10 mg/kg	0.7606 <=7	15	10	16	7	1.5238	0.7869	2.9508	0.2852	0.3889	0.0904	1.6725	0.2292	-0.1114	0.5697
			>7 to <=21	15	12	24	10	1.9200	1.1225	3.2841	0.0244	0.1786	0.0397	0.8027	0.3833	0.1007	0.6660
			>21	12	9	24	10	1.8000	1.0127	3.1993	0.0830	0.2381	0.0511	1.1085	0.3333	0.0188	0.6479
Last Visit (LOCF)	Baseline Convulsive Seizure Frequency	10 mg/kg	0.9271 <=7	16	11	17	7	1.6696	0.8654	3.2215	0.1663	0.3182	0.0760	1.3322	0.2757	-0.0503	0.6018
			>7 to <=21	16	12	24	10	1.8000	1.0370	3.1244	0.0545	0.2381	0.0592	0.9583	0.3333	0.0436	0.6230
			>21	13	10	24	10	1.8462	1.0554	3.2295	0.0823	0.2143	0.0467	0.9839	0.3526	0.0503	0.6548
End of Treatment	Current AEDs	10 mg/kg	0.2157 <3	10	6	19	9	1.2667	0.6332	2.5339	0.6999	0.6000	0.1270	2.8352	0.1263	-0.2513	0.5039
			>=3	32	25	45	18	1.9531	1.3065	2.9198	0.0011	0.1867	0.0667	0.5222	0.3813	0.1788	0.5837
Last Visit (LOCF)	Current AEDs	10 mg/kg	0.1457 <3	12	7	19	9	1.2315	0.6281	2.4145	0.7160	0.6429	0.1495	2.7647	0.1096	-0.2484	0.4677
			>=3	33	26	46	18	2.0135	1.3476	3.0084	0.0006	0.1731	0.0622	0.4816	0.3966	0.1982	0.5949
End of Treatment	Prior AEDs	10 mg/kg	0.8458 <4	16	12	26	12	1.6250	0.9833	2.6856	0.1087	0.2857	0.0727	1.1236	0.2885	0.0026	0.5744
			>=4	26	19	38	15	1.8513	1.1714	2.9257	0.0111	0.2403	0.0813	0.7100	0.3360	0.1053	0.5667
Last Visit (LOCF)	Prior AEDs	10 mg/kg	0.9512 <4	17	13	26	12	1.6569	1.0132	2.7095	0.0637	0.2637	0.0677	1.0279	0.3032	0.0250	0.5813
			>=4	28	20	39	15	1.8571	1.1713	2.9447	0.0127	0.2500	0.0881	0.7096	0.3297	0.1031	0.5562
End of Treatment	Prior + Current AEDs	10 mg/kg	0.7767 <8	22	16	32	14	1.6623	1.0402	2.6567	0.0517	0.2917	0.0906	0.9394	0.2898	0.0364	0.5431
			>=8	20	15	32	13	1.8462	1.1317	3.0116	0.0226	0.2281	0.0664	0.7832	0.3438	0.0889	0.5986
Last Visit (LOCF)	Prior + Current AEDs	10 mg/kg	0.8877 <8	23	17	32	14	1.6894	1.0646	2.6811	0.0314	0.2745	0.0857	0.8788	0.3016	0.0531	0.5501
			>=8	22	16	33	13	1.8462	1.1259	3.0272	0.0266	0.2438	0.0757	0.7850	0.3333	0.0835	0.5832
End of Treatment	Age Group	20 mg/kg	0.5927 2-5 years	10	9	18	11	1.4727	0.9653	2.2470	0.1937	0.1746	0.0180	1.6950	0.2889	-0.0032	0.5809
			6-12 years	20	15	28	9	2.3333	1.2874	4.2291	0.0077	0.1579	0.0436	0.5712	0.4286	0.1718	0.6854
			13-18 years	7	4	18	7	1.4694	0.6191	3.4872	0.6564	0.4773	0.0812	2.8067	0.1825	-0.2477	0.6128

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Last Visit (LOCF)																		
Age Group	20 mg/kg	0.7251 2-5 years	10	9	18	11	1.4727	0.9653	2.2470	0.1937	0.1746	0.0180	1.6950	0.2889	-0.0032	0.5809		
		6-12 years	21	16	28	9	2.3704	1.3154	4.2714	0.0037	0.1480	0.0412	0.5322	0.4405	0.1893	0.6917		
		13-18 years	8	5	19	7	1.6964	0.7648	3.7630	0.3981	0.3500	0.0634	1.9315	0.2566	-0.1429	0.6561		
End of Treatment																		
Sex	20 mg/kg	0.5968 F	15	11	33	15	1.6133	0.9958	2.6138	0.1179	0.3030	0.0798	1.1502	0.2788	-0.0022	0.5598		
		M	22	17	31	12	1.9962	1.2137	3.2832	0.0109	0.1858	0.0542	0.6365	0.3856	0.1405	0.6307		
Last Visit (LOCF)																		
Sex	20 mg/kg	0.6587 F	16	12	34	15	1.7000	1.0600	2.7265	0.0673	0.2632	0.0704	0.9838	0.3088	0.0389	0.5788		
		M	23	18	31	12	2.0217	1.2354	3.3085	0.0056	0.1754	0.0515	0.5980	0.3955	0.1551	0.6360		
End of Treatment																		
Region	20 mg/kg	0.0115 REST OF THE WORLD	16	8	32	13	1.2308	0.6460	2.3450	0.5553	0.6842	0.2045	2.2887	0.0938	-0.2045	0.3920		
		USA	21	20	32	14	2.1769	1.4529	3.2616	0.0001	0.0389	0.0046	0.3261	0.5149	0.3204	0.7094		
Last Visit (LOCF)																		
Region	20 mg/kg	0.0223 REST OF THE WORLD	18	10	33	13	1.4103	0.7806	2.5478	0.3784	0.5200	0.1626	1.6633	0.1616	-0.1221	0.4453		
		USA	21	20	32	14	2.1769	1.4529	3.2616	0.0001	0.0389	0.0046	0.3261	0.5149	0.3204	0.7094		
End of Treatment																		
Valproate Use	20 mg/kg	0.4785 N	9	7	16	5	2.4889	1.1113	5.5742	0.0414	0.1299	0.0195	0.8631	0.4653	0.1112	0.8193		
		Y	28	21	48	22	1.6364	1.1251	2.3799	0.0170	0.2821	0.1010	0.7874	0.2917	0.0781	0.5052		
Last Visit (LOCF)																		
Valproate Use	20 mg/kg	0.4786 N	9	7	17	5	2.6444	1.1705	5.9744	0.0375	0.1190	0.0181	0.7851	0.4837	0.1363	0.8311		
		Y	30	23	48	22	1.6727	1.1607	2.4107	0.0096	0.2575	0.0930	0.7134	0.3083	0.1015	0.5152		
End of Treatment																		
Stiripentol Use	20 mg/kg	0.7184 N	20	17	41	20	1.7425	1.2112	2.5068	0.0110	0.1681	0.0426	0.6625	0.3622	0.1433	0.5811		
		Y	17	11	23	7	2.1261	1.0446	4.3272	0.0534	0.2386	0.0629	0.9055	0.3427	0.0478	0.6376		
Last Visit (LOCF)																		
Stiripentol Use	20 mg/kg	0.7875 N	21	18	41	20	1.7571	1.2272	2.5160	0.0058	0.1587	0.0405	0.6228	0.3693	0.1553	0.5834		
		Y	18	12	24	7	2.2857	1.1307	4.6207	0.0277	0.2059	0.0552	0.7686	0.3750	0.0913	0.6587		
End of Treatment																		
Levetiracetam Use	20 mg/kg	0.2348 N	30	22	50	23	1.5942	1.1014	2.3075	0.0209	0.3098	0.1160	0.8269	0.2733	0.0633	0.4834		
		Y	7	6	14	4	3.0000	1.2422	7.2452	0.0237	0.0667	0.0060	0.7451	0.5714	0.2204	0.9224		
Last Visit (LOCF)																		
Levetiracetam Use	20 mg/kg	0.2086 N	31	23	51	23	1.6452	1.1396	2.3750	0.0122	0.2857	0.1077	0.7578	0.2910	0.0851	0.4968		
		Y	8	7	14	4	3.0625	1.2848	7.3001	0.0237	0.0571	0.0052	0.6266	0.5893	0.2599	0.9187		
End of Treatment																		
Topiramate Use	20 mg/kg	0.2547 N	28	20	48	21	1.6327	1.0975	2.4288	0.0311	0.3111	0.1146	0.8446	0.2768	0.0584	0.4952		
		Y	9	8	16	6	2.3704	1.2088	4.6482	0.0330	0.0750	0.0074	0.7572	0.5139	0.2002	0.8276		
Last Visit (LOCF)																		
Topiramate Use	20 mg/kg	0.1976 N	29	21	48	21	1.6552	1.1188	2.4486	0.0187	0.2963	0.1096	0.8007	0.2866	0.0718	0.5015		

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		Y		10	9	17	6	2.5500	1.2971	5.0132	0.0140	0.0606	0.0061	0.6003	0.5471	0.2535	0.8406
End of Treatment	Baseline Convulsive Seizure Frequency	20 mg/kg	0.4519 <=7	11	10	16	7	2.0779	1.1563	3.7343	0.0183	0.0778	0.0080	0.7609	0.4716	0.1750	0.7681
			>7 to <=21	17	11	24	10	1.5529	0.8614	2.7997	0.2082	0.3896	0.1079	1.4065	0.2304	-0.0705	0.5312
			>21	9	7	24	10	1.8667	1.0366	3.3616	0.1175	0.2041	0.0348	1.1965	0.3611	0.0254	0.6968
Last Visit (LOCF)	Baseline Convulsive Seizure Frequency	20 mg/kg	0.3539 <=7	12	11	17	7	2.2262	1.2301	4.0290	0.0080	0.0636	0.0066	0.6120	0.5049	0.2235	0.7863
			>7 to <=21	17	11	24	10	1.5529	0.8614	2.7997	0.2082	0.3896	0.1079	1.4065	0.2304	-0.0705	0.5312
			>21	10	8	24	10	1.9200	1.0904	3.3808	0.0630	0.1786	0.0311	1.0267	0.3833	0.0665	0.7001
End of Treatment	Current AEDs	20 mg/kg	0.7061 <3	7	6	19	9	1.8095	1.0313	3.1750	0.1783	0.1500	0.0150	1.4970	0.3835	0.0405	0.7264
			>=3	30	22	45	18	1.8333	1.2072	2.7843	0.0053	0.2424	0.0887	0.6624	0.3333	0.1200	0.5467
Last Visit (LOCF)	Current AEDs	20 mg/kg	0.7794 <3	7	6	19	9	1.8095	1.0313	3.1750	0.1783	0.1500	0.0150	1.4970	0.3835	0.0405	0.7264
			>=3	32	24	46	18	1.9167	1.2692	2.8945	0.0026	0.2143	0.0792	0.5798	0.3587	0.1528	0.5646
End of Treatment	Prior AEDs	20 mg/kg	0.5951 <4	13	11	26	12	1.8333	1.1396	2.9495	0.0371	0.1558	0.0287	0.8467	0.3846	0.1104	0.6588
			>=4	24	17	38	15	1.7944	1.1215	2.8711	0.0204	0.2685	0.0899	0.8023	0.3136	0.0744	0.5528
Last Visit (LOCF)	Prior AEDs	20 mg/kg	0.6015 <4	14	12	26	12	1.8571	1.1642	2.9626	0.0199	0.1429	0.0265	0.7695	0.3956	0.1304	0.6608
			>=4	25	18	39	15	1.8720	1.1744	2.9839	0.0112	0.2431	0.0821	0.7197	0.3354	0.1024	0.5684
End of Treatment	Prior + Current AEDs	20 mg/kg	0.7029 <8	19	14	32	14	1.6842	1.0464	2.7109	0.0467	0.2778	0.0806	0.9571	0.2993	0.0371	0.5615
			>=8	18	14	32	13	1.9145	1.1773	3.1134	0.0177	0.1955	0.0524	0.7290	0.3715	0.1149	0.6281
Last Visit (LOCF)	Prior + Current AEDs	20 mg/kg	0.6597 <8	20	15	32	14	1.7143	1.0743	2.7354	0.0441	0.2593	0.0758	0.8867	0.3125	0.0565	0.5685
			>=8	19	15	33	13	2.0040	1.2367	3.2475	0.0090	0.1733	0.0470	0.6394	0.3955	0.1478	0.6433

LOCF = last observation carried forward; MI = much improved; VMI = very much improved; SI = slightly improved.

End of treatment = The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF page (Visit 8: Day 99).

Last visit = Last visit is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table:		GWEP1424 CGIC Responder [VMI, MI] (ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)																
Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Last Visit (LOCF)	Age Group	10 mg/kg	0.6834	2-5 years	13	8	18	3	3.6923	1.2061	11.3030	0.0209	0.1250	0.0236	0.6633	0.4487	0.1332	0.7643
				6-12 years	23	8	28	3	3.2464	0.9711	10.8523	0.0477	0.2250	0.0516	0.9817	0.2407	0.0148	0.4665
				13-18 years	9	3	19	3	2.1111	0.5259	8.4754	0.3518	0.3750	0.0587	2.3971	0.1754	-0.1735	0.5243
End of Treatment	Sex	10 mg/kg	0.8148	F	20	8	33	5	2.6400	1.0012	6.9609	0.0541	0.2679	0.0726	0.9888	0.2485	0.0014	0.4956
				M	22	9	31	4	3.1705	1.1168	9.0004	0.0264	0.2140	0.0554	0.8262	0.2801	0.0431	0.5170
Last Visit (LOCF)	Sex	10 mg/kg	0.7847	F	22	9	34	5	2.7818	1.0730	7.2120	0.0554	0.2490	0.0697	0.8904	0.2620	0.0246	0.4995
				M	23	10	31	4	3.3696	1.2073	9.4048	0.0257	0.1926	0.0507	0.7319	0.3058	0.0713	0.5402
End of Treatment	Region	10 mg/kg	0.0422	REST OF THE WORLD	20	4	32	5	1.2800	0.3893	4.2082	0.7192	0.7407	0.1732	3.1671	0.0438	-0.1720	0.2595
				USA	22	13	32	4	4.7273	1.7735	12.6008	0.0007	0.0989	0.0257	0.3811	0.4659	0.2307	0.7012
Last Visit (LOCF)	Region	10 mg/kg	0.0874	REST OF THE WORLD	23	6	33	5	1.7217	0.5961	4.9731	0.3305	0.5060	0.1337	1.9150	0.1094	-0.1078	0.3265
				USA	22	13	32	4	4.7273	1.7735	12.6008	0.0007	0.0989	0.0257	0.3811	0.4659	0.2307	0.7012
End of Treatment	Valproate Use	10 mg/kg	0.3629	N	14	6	16	4	1.7143	0.6046	4.8606	0.4421	0.4444	0.0944	2.0929	0.1786	-0.1564	0.5136
				Y	28	11	48	5	3.7714	1.4603	9.7405	0.0070	0.1797	0.0543	0.5949	0.2887	0.0882	0.4892
Last Visit (LOCF)	Valproate Use	10 mg/kg	0.4725	N	15	7	17	4	1.9833	0.7199	5.4643	0.2662	0.3516	0.0776	1.5943	0.2314	-0.0917	0.5545
				Y	30	12	48	5	3.8400	1.5026	9.8133	0.0039	0.1744	0.0536	0.5673	0.2958	0.1004	0.4913
End of Treatment	Stiripentol Use	10 mg/kg	0.0019	N	26	16	41	5	5.0462	2.1020	12.1142	<.0001	0.0868	0.0255	0.2953	0.4934	0.2813	0.7056
				Y	16	1	23	4	0.3594	0.0442	2.9240	0.6309	3.1579	0.3187	31.2931	-0.1114	-0.3065	0.0837
Last Visit (LOCF)	Stiripentol Use	10 mg/kg	0.0070	N	28	17	41	5	4.9786	2.0781	11.9276	<.0001	0.0899	0.0270	0.2996	0.4852	0.2784	0.6920
				Y	17	2	24	4	0.7059	0.1455	3.4256	1.0000	1.5000	0.2419	9.3007	-0.0490	-0.2628	0.1647
End of Treatment	Levetiracetam Use	10 mg/kg	0.0617	N	32	12	50	9	2.0833	0.9923	4.3738	0.0693	0.3659	0.1324	1.0108	0.1950	-0.0037	0.3937
				Y	10	5	14	0	-	-	-	0.0059	-	-	-	0.5000	0.1901	0.8099
Last Visit (LOCF)	Levetiracetam Use	10 mg/kg	0.0493	N	34	13	51	9	2.1667	1.0433	4.4995	0.0443	0.3462	0.1276	0.9394	0.2059	0.0119	0.3999

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

		Y	11	6	14	0	-	-	-	0.0026	-	-	-	0.5455	0.2512	0.8397
End of Treatment																
Topiramate Use	10 mg/kg	0.2306 N	34	13	48	8	2.2941	1.0693	4.9218	0.0397	0.3231	0.1157	0.9022	0.2157	0.0213	0.4101
		Y	8	4	16	1	8.0000	1.0609	60.3238	0.0277	0.0667	0.0057	0.7750	0.4375	0.0713	0.8037
Last Visit (LOCF)																
Topiramate Use	10 mg/kg	0.2382 N	37	15	48	8	2.4324	1.1568	5.1148	0.0254	0.2933	0.1075	0.8001	0.2387	0.0486	0.4288
		Y	8	4	17	1	8.5000	1.1233	64.3182	0.0235	0.0625	0.0054	0.7242	0.4412	0.0771	0.8053
End of Treatment																
Baseline Convulsive Seizure Frequency	10 mg/kg	0.3981 <=7	15	6	16	2	3.2000	0.7605	13.4649	0.1134	0.2143	0.0352	1.3044	0.2750	-0.0212	0.5712
		>7 to <=21	15	8	24	3	4.2667	1.3382	13.6040	0.0101	0.1250	0.0258	0.6061	0.4083	0.1233	0.6934
		>21	12	3	24	4	1.5000	0.3979	5.6540	0.6639	0.6000	0.1106	3.2552	0.0833	-0.2035	0.3701
Last Visit (LOCF)																
Baseline Convulsive Seizure Frequency	10 mg/kg	0.5596 <=7	16	7	17	2	3.7187	0.9030	15.3148	0.0570	0.1714	0.0290	1.0120	0.3199	0.0326	0.6072
		>7 to <=21	16	8	24	3	4.0000	1.2459	12.8418	0.0138	0.1429	0.0301	0.6777	0.3750	0.0966	0.6534
		>21	13	4	24	4	1.8462	0.5503	6.1938	0.4132	0.4500	0.0914	2.2147	0.1410	-0.1508	0.4329
End of Treatment																
Current AEDs	10 mg/kg	0.8335 <3	10	4	19	3	2.5333	0.6999	9.1689	0.1929	0.2813	0.0481	1.6457	0.2421	-0.1030	0.5872
		>=3	32	13	45	6	3.0469	1.2963	7.1614	0.0081	0.2249	0.0740	0.6836	0.2729	0.0759	0.4699
Last Visit (LOCF)																
Current AEDs	10 mg/kg	0.8044 <3	12	5	19	3	2.6389	0.7671	9.0781	0.2055	0.2625	0.0487	1.4149	0.2588	-0.0648	0.5823
		>=3	33	14	46	6	3.2525	1.3966	7.5749	0.0041	0.2036	0.0677	0.6124	0.2938	0.0991	0.4885
End of Treatment																
Prior AEDs	10 mg/kg	0.3140 <4	16	8	26	3	4.3333	1.3427	13.9854	0.0105	0.1304	0.0276	0.6156	0.3846	0.1106	0.6587
		>=4	26	9	38	6	2.1923	0.8873	5.4169	0.1318	0.3542	0.1079	1.1627	0.1883	-0.0283	0.4048
Last Visit (LOCF)																
Prior AEDs	10 mg/kg	0.2882 <4	17	9	26	3	4.5882	1.4458	14.5605	0.0052	0.1159	0.0250	0.5378	0.4140	0.1469	0.6812
		>=4	28	10	39	6	2.3214	0.9551	5.6422	0.0811	0.3273	0.1022	1.0479	0.2033	-0.0072	0.4138
End of Treatment																
Prior AEDs	10 mg/kg	0.3915 <8	22	9	32	3	4.3636	1.3294	14.3229	0.0089	0.1494	0.0347	0.6442	0.3153	0.0864	0.5443
		>=8	20	8	32	6	2.1333	0.8682	5.2422	0.1164	0.3462	0.0982	1.2207	0.2125	-0.0412	0.4662
Last Visit (LOCF)																
Prior + Current AEDs	10 mg/kg	0.3664 <8	23	10	32	3	4.6377	1.4341	14.9979	0.0082	0.1345	0.0317	0.5714	0.3410	0.1147	0.5674
		>=8	22	9	33	6	2.2500	0.9324	5.4296	0.1206	0.3210	0.0941	1.0946	0.2273	-0.0167	0.4713
End of Treatment																
Age Group	20 mg/kg	0.8745 2-5 years	10	6	18	3	3.6000	1.1396	11.3728	0.0346	0.1333	0.0227	0.7837	0.4333	0.0843	0.7824
		6-12 years	20	8	28	3	3.7333	1.1285	12.3507	0.0339	0.1800	0.0404	0.8025	0.2929	0.0495	0.5362

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

			13-18 years	7	3	18	3	2.5714	0.6725	9.8320	0.2985	0.2667	0.0382	1.8623	0.2619	-0.1431	0.6669
Last Visit (LOCF)																	
	Age Group	20 mg/kg	0.8113 2-5 years	10	6	18	3	3.6000	1.1396	11.3728	0.0346	0.1333	0.0227	0.7837	0.4333	0.0843	0.7824
			6-12 years	21	8	28	3	3.5556	1.0707	11.8076	0.0372	0.1950	0.0441	0.8623	0.2738	0.0366	0.5110
			13-18 years	8	3	19	3	2.3750	0.6031	9.3523	0.3191	0.3125	0.0472	2.0671	0.2171	-0.1563	0.5905
End of Treatment																	
	Sex	20 mg/kg	0.7503 F	15	8	33	5	3.5200	1.3806	8.9746	0.0120	0.1563	0.0389	0.6279	0.3818	0.1013	0.6624
			M	22	9	31	4	3.1705	1.1168	9.0004	0.0264	0.2140	0.0554	0.8262	0.2801	0.0431	0.5170
Last Visit (LOCF)																	
	Sex	20 mg/kg	0.7662 F	16	8	34	5	3.4000	1.3199	8.7586	0.0143	0.1724	0.0441	0.6746	0.3529	0.0806	0.6253
			M	23	9	31	4	3.0326	1.0644	8.6404	0.0509	0.2305	0.0602	0.8828	0.2623	0.0305	0.4940
End of Treatment																	
	Region	20 mg/kg	0.0686 REST OF THE WORLD	16	4	32	5	1.6000	0.4967	5.1544	0.4566	0.5556	0.1264	2.4411	0.0938	-0.1529	0.3404
			USA	21	13	32	4	4.9524	1.8658	13.1448	0.0003	0.0879	0.0224	0.3455	0.4940	0.2568	0.7313
Last Visit (LOCF)																	
	Region	20 mg/kg	0.0506 REST OF THE WORLD	18	4	33	5	1.4667	0.4494	4.7861	0.7029	0.6250	0.1447	2.6992	0.0707	-0.1570	0.2984
			USA	21	13	32	4	4.9524	1.8658	13.1448	0.0003	0.0879	0.0224	0.3455	0.4940	0.2568	0.7313
End of Treatment																	
	Valproate Use	20 mg/kg	0.6130 N	9	5	16	4	2.2222	0.7930	6.2271	0.1998	0.2667	0.0471	1.5112	0.3056	-0.0823	0.6934
			Y	28	12	48	5	4.1143	1.6178	10.4629	0.0017	0.1550	0.0471	0.5100	0.3244	0.1218	0.5271
Last Visit (LOCF)																	
	Valproate Use	20 mg/kg	0.7467 N	9	5	17	4	2.3611	0.8369	6.6617	0.1937	0.2462	0.0437	1.3851	0.3203	-0.0619	0.7024
			Y	30	12	48	5	3.8400	1.5026	9.8133	0.0039	0.1744	0.0536	0.5673	0.2958	0.1004	0.4913
End of Treatment																	
	Stiripentol Use	20 mg/kg	0.0888 N	20	12	41	5	4.9200	2.0085	12.0518	0.0002	0.0926	0.0254	0.3378	0.4780	0.2411	0.7150
			Y	17	5	23	4	1.6912	0.5324	5.3717	0.4561	0.5053	0.1127	2.2652	0.1202	-0.1461	0.3865
Last Visit (LOCF)																	
	Stiripentol Use	20 mg/kg	0.1031 N	21	12	41	5	4.6857	1.9032	11.5365	0.0005	0.1042	0.0291	0.3722	0.4495	0.2153	0.6836
			Y	18	5	24	4	1.6667	0.5203	5.3385	0.4620	0.5200	0.1173	2.3043	0.1111	-0.1439	0.3662
End of Treatment																	
	Levetiracetam Use	20 mg/kg	0.1539 N	30	14	50	9	2.5926	1.2816	5.2445	0.0101	0.2509	0.0907	0.6939	0.2867	0.0788	0.4945
			Y	7	3	14	0	-	-	-	0.0263	-	-	-	0.4286	0.0620	0.7952
Last Visit (LOCF)																	
	Levetiracetam Use	20 mg/kg	0.1819 N	31	14	51	9	2.5591	1.2601	5.1975	0.0109	0.2602	0.0948	0.7139	0.2751	0.0711	0.4792
			Y	8	3	14	0	-	-	-	0.0364	-	-	-	0.3750	0.0395	0.7105

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

End of Treatment																
Topiramate Use	20 mg/kg	0.4425 N	28	13	48	8	2.7857	1.3194	5.8814	0.0077	0.2308	0.0798	0.6674	0.2976	0.0849	0.5103
		Y	9	4	16	1	7.1111	0.9307	54.3315	0.0403	0.0833	0.0075	0.9313	0.3819	0.0363	0.7276
Last Visit (LOCF)																
Topiramate Use	20 mg/kg	0.4617 N	29	13	48	8	2.6897	1.2699	5.6966	0.0094	0.2462	0.0858	0.7065	0.2816	0.0721	0.4911
		Y	10	4	17	1	6.8000	0.8777	52.6828	0.0473	0.0938	0.0086	1.0167	0.3412	0.0176	0.6648
End of Treatment																
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4811 <=7	11	7	16	2	5.0909	1.2921	20.0586	0.0115	0.0816	0.0119	0.5594	0.5114	0.1841	0.8386
		>7 to <=21	17	7	24	3	3.2941	0.9908	10.9516	0.0632	0.2041	0.0434	0.9596	0.2868	0.0180	0.5555
		>21	9	3	24	4	2.0000	0.5527	7.2370	0.3583	0.4000	0.0693	2.3089	0.1667	-0.1755	0.5088
Last Visit (LOCF)																
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4628 <=7	12	7	17	2	4.9583	1.2389	19.8448	0.0140	0.0952	0.0147	0.6174	0.4657	0.1475	0.7839
		>7 to <=21	17	7	24	3	3.2941	0.9908	10.9516	0.0632	0.2041	0.0434	0.9596	0.2868	0.0180	0.5555
		>21	10	3	24	4	1.8000	0.4893	6.6216	0.3943	0.4667	0.0830	2.6238	0.1333	-0.1874	0.4541
End of Treatment																
Current AEDs	20 mg/kg	0.1057 <3	7	6	19	3	5.4286	1.8406	16.0103	0.0022	0.0313	0.0027	0.3621	0.6992	0.3925	1.0000
		>=3	30	11	45	6	2.7500	1.1396	6.6362	0.0250	0.2657	0.0853	0.8274	0.2333	0.0343	0.4323
Last Visit (LOCF)																
Current AEDs	20 mg/kg	0.0926 <3	7	6	19	3	5.4286	1.8406	16.0103	0.0022	0.0313	0.0027	0.3621	0.6992	0.3925	1.0000
		>=3	32	11	46	6	2.6354	1.0860	6.3953	0.0488	0.2864	0.0929	0.8832	0.2133	0.0221	0.4045
End of Treatment																
Prior AEDs	20 mg/kg	0.4044 <4	13	7	26	3	4.6667	1.4379	15.1460	0.0077	0.1118	0.0220	0.5671	0.4231	0.1256	0.7206
		>=4	24	10	38	6	2.6389	1.1016	6.3217	0.0364	0.2625	0.0798	0.8638	0.2588	0.0300	0.4876
Last Visit (LOCF)																
Prior AEDs	20 mg/kg	0.4653 <4	14	7	26	3	4.3333	1.3233	14.1903	0.0180	0.1304	0.0265	0.6430	0.3846	0.0953	0.6739
		>=4	25	10	39	6	2.6000	1.0798	6.2606	0.0387	0.2727	0.0836	0.8892	0.2462	0.0232	0.4691
End of Treatment																
Prior AEDs	20 mg/kg	0.3576 <8	19	9	32	3	5.0526	1.5574	16.3922	0.0046	0.1149	0.0259	0.5107	0.3799	0.1338	0.6261
		>=8	18	8	32	6	2.3704	0.9762	5.7555	0.0986	0.2885	0.0798	1.0431	0.2569	-0.0095	0.5234
Last Visit (LOCF)																
Prior + Current AEDs	20 mg/kg	0.3730 <8	20	9	32	3	4.8000	1.4732	15.6395	0.0056	0.1264	0.0288	0.5552	0.3563	0.1160	0.5965
		>=8	19	8	33	6	2.3158	0.9458	5.6701	0.1030	0.3056	0.0858	1.0876	0.2392	-0.0188	0.4973

LOCF = last observation carried forward; MI = much improved; VMI = very much improved; SI = slightly improved.

End of treatment = The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF page (Visit 8: Day 99).

Last visit = Last visit is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Any AE (subgroups) (Safety Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	
Age Group	10 mg/kg	0.4730	2-5 years	13	11	18	17	0.8918	0.6758	1.1770	0.5575	
				23	21	28	23	1.1055	0.8848	1.3813	0.4362	
				8	8	19	18	1.0210	0.8345	1.2492	1.0000	
Sex	10 mg/kg	0.0348	F	22	22	34	29	1.1606	0.9935	1.3559	0.1448	
			M	22	18	31	29	0.8725	0.6964	1.0931	0.2190	
Region	10 mg/kg	0.0704	REST OF THE WORLD	23	23	33	29	1.1285	0.9775	1.3029	0.1355	
			USA	21	17	32	29	0.8898	0.6984	1.1338	0.4154	
Valproate Use	10 mg/kg	0.0505	N	14	10	17	15	0.8129	0.5561	1.1883	0.3697	
			Y	30	30	48	43	1.1083	0.9935	1.2363	0.1502	
Stiripentol Use	10 mg/kg	0.3632	N	28	24	41	36	0.9721	0.7997	1.1817	1.0000	
			Y	16	16	24	22	1.0784	0.9239	1.2588	0.5077	
Levetiracetam Use	10 mg/kg	0.9575	N	33	31	51	47	1.0193	0.9059	1.1470	1.0000	
			Y	11	9	14	11	1.0413	0.7047	1.5387	1.0000	
Topiramate Use	10 mg/kg	0.3623	N	37	34	48	42	1.0502	0.9098	1.2123	0.7253	
			Y	7	6	17	16	0.9107	0.6581	1.2604	0.5072	
Baseline Convulsive Seizure Frequency	10 mg/kg	0.4379	<=7	16	15	17	17	0.9378	0.7934	1.1085	0.4848	
			>7 to <=21	15	13	24	22	0.9375	0.7315	1.2014	0.6309	
			>21	13	12	24	19	1.1447	0.8685	1.5088	0.3945	
Current AEDs	10 mg/kg	0.8569	<3	12	10	19	15	1.0556	0.7487	1.4881	1.0000	
			>=3	32	30	46	43	1.0029	0.8916	1.1281	1.0000	
Prior AEDs	10 mg/kg	0.4258	<4	17	15	26	24	0.9559	0.7779	1.1746	1.0000	
			>=4	27	25	39	34	1.0621	0.9043	1.2474	0.6911	
Prior + Current AEDs	10 mg/kg	0.8873	<8	23	21	32	29	1.0075	0.8514	1.1922	1.0000	
			>=8	21	19	33	29	1.0296	0.8532	1.2424	1.0000	
Age Group	20 mg/kg	0.3073	2-5 years	10	9	18	17	0.9529	0.7533	1.2054	1.0000	
			6-12 years	22	21	28	23	1.1621	0.9559	1.4127	0.2109	
			13-18 years	9	8	19	18	0.9383	0.7277	1.2098	1.0000	
Sex	20 mg/kg	0.8946	F	17	15	34	29	1.0345	0.8279	1.2926	1.0000	
			M	24	23	31	29	1.0244	0.9045	1.1603	1.0000	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Region	20 mg/kg	0.5562 REST OF THE WORLD	19	18	33	29	1.0780	0.9139	1.2717	0.6410	
			USA	22	20	32	29	1.0031	0.8439	1.1924	1.0000
Valproate Use	20 mg/kg	0.0583 N	11	8	17	15	0.8226	0.5472	1.2367	0.3531	
			Y	30	30	48	43	1.1083	0.9935	1.2363	0.1502
Stiripentol Use	20 mg/kg	0.3216 N	22	19	41	36	0.9756	0.7914	1.2026	1.0000	
			Y	19	19	24	22	1.0833	0.9340	1.2565	0.4950
Levetiracetam Use	20 mg/kg	0.5040 N	32	31	51	47	1.0512	0.9498	1.1634	0.6442	
			Y	9	7	14	11	0.9899	0.6352	1.5426	1.0000
Topiramate Use	20 mg/kg	0.4841 N	30	28	48	42	1.0667	0.9241	1.2312	0.7035	
			Y	11	10	17	16	0.9659	0.7740	1.2054	1.0000
Baseline Convulsive Seizure Frequency	20 mg/kg	0.8115 <=7	12	12	17	17	0.9890	0.8651	1.1307		
			>7 to <=21	19	17	24	22	0.9722	0.7873	1.2006	1.0000
			>21	10	9	24	19	1.1072	0.8090	1.5154	0.6445
Current AEDs	20 mg/kg	0.7207 <3	8	7	19	15	1.1083	0.7810	1.5728	1.0000	
			>=3	33	31	46	43	1.0049	0.8953	1.1280	1.0000
Prior AEDs	20 mg/kg	0.5681 <4	14	14	26	24	1.0653	0.9144	1.2412	0.5333	
			>=4	27	24	39	34	1.0145	0.8416	1.2229	1.0000
Prior + Current AEDs	20 mg/kg	0.7868 <8	20	19	32	29	1.0483	0.9022	1.2180	1.0000	
			>=8	21	19	33	29	1.0296	0.8532	1.2424	1.0000

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Maximal AE mild (subgroups) (Safety Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	
	Age Group	10 mg/kg	0.5154	2-5 years	13	5	18	6	1.1538	0.4469	2.9790	1.0000
				6-12 years	23	10	28	18	0.6763	0.3935	1.1625	0.1659
				13-18 years	8	6	19	15	0.9500	0.5982	1.5088	1.0000
	Sex	10 mg/kg	0.4913	F	22	11	34	19	0.8947	0.5353	1.4954	0.7856
				M	22	10	31	20	0.7045	0.4160	1.1933	0.2606
	Region	10 mg/kg	0.5815	REST OF THE WORLD	23	13	33	21	0.8882	0.5711	1.3813	0.7814
				USA	21	8	32	18	0.6772	0.3625	1.2653	0.2641
	Valproate Use	10 mg/kg	0.8175	N	14	7	17	10	0.8500	0.4403	1.6408	0.7247
				Y	30	14	48	29	0.7724	0.4946	1.2064	0.2525
	Stiripentol Use	10 mg/kg	0.3481	N	28	11	41	24	0.6711	0.3960	1.1375	0.1449
				Y	16	10	24	15	1.0000	0.6126	1.6323	1.0000
	Levetiracetam Use	10 mg/kg	0.6658	N	33	16	51	32	0.7727	0.5126	1.1648	0.2598
				Y	11	5	14	7	0.9091	0.3953	2.0906	1.0000
	Topiramate Use	10 mg/kg	0.5918	N	37	17	48	26	0.8482	0.5486	1.3114	0.5151
				Y	7	4	17	13	0.7473	0.3734	1.4952	0.3742
	Baseline Convulsive Seizure Frequency	10 mg/kg	0.9890	<=7	16	8	17	11	0.7727	0.4229	1.4119	0.4905
				>7 to <=21	15	7	24	14	0.8000	0.4227	1.5141	0.5254
				>21	13	6	24	14	0.7912	0.4018	1.5579	0.5119
	Current AEDs	10 mg/kg	0.9252	<3	12	4	19	9	0.7037	0.2777	1.7835	0.4840
				>=3	32	17	46	30	0.8146	0.5527	1.2006	0.3492
	Prior AEDs	10 mg/kg	0.1063	<4	17	9	26	12	1.1471	0.6227	2.1130	0.7597
				>=4	27	12	39	27	0.6420	0.4009	1.0279	0.0738
	Prior + Current AEDs	10 mg/kg	0.7910	<8	23	10	32	17	0.8184	0.4636	1.4448	0.5875
				>=8	21	11	33	22	0.7857	0.4892	1.2619	0.3924
	Age Group	20 mg/kg	0.6045	2-5 years	10	3	18	6	0.9000	0.2849	2.8432	1.0000
				6-12 years	22	8	28	18	0.5657	0.3049	1.0493	0.0863
				13-18 years	9	5	19	15	0.7037	0.3752	1.3197	0.3715
	Sex	20 mg/kg	0.9120	F	17	6	34	19	0.6316	0.3106	1.2841	0.2367
				M	24	10	31	20	0.6458	0.3761	1.1089	0.1090

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Region	20 mg/kg	0.2760	REST OF THE WORLD	19	6	33	21	0.4962	0.2439	1.0097	0.0430
			USA	22	10	32	18	0.8081	0.4661	1.4011	0.5804
Valproate Use	20 mg/kg	0.6384	N	11	5	17	10	0.7727	0.3615	1.6519	0.7000
			Y	30	11	48	29	0.6069	0.3597	1.0240	0.0621
Stiripentol Use	20 mg/kg	0.0343	N	22	4	41	24	0.3106	0.1234	0.7818	0.0031
			Y	19	12	24	15	1.0105	0.6363	1.6049	1.0000
Levetiracetam Use	20 mg/kg	0.4055	N	32	12	51	32	0.5977	0.3644	0.9802	0.0413
			Y	9	4	14	7	0.8889	0.3618	2.1838	1.0000
Topiramate Use	20 mg/kg	0.2266	N	30	12	48	26	0.7385	0.4436	1.2294	0.2518
			Y	11	4	17	13	0.4755	0.2084	1.0851	0.0527
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4448	<=7	12	3	17	11	0.3864	0.1364	1.0942	0.0604
			>7 to <=21	19	8	24	14	0.7218	0.3858	1.3503	0.3640
			>21	10	5	24	14	0.8571	0.4231	1.7365	0.7176
Current AEDs	20 mg/kg	0.4016	<3	8	1	19	9	0.2639	0.0397	1.7532	0.1895
			>=3	33	15	46	30	0.6970	0.4537	1.0706	0.1077
Prior AEDs	20 mg/kg	0.7573	<4	14	4	26	12	0.6190	0.2451	1.5635	0.3295
			>=4	27	12	39	27	0.6420	0.4009	1.0279	0.0738
Prior + Current AEDs	20 mg/kg	0.8248	<8	20	6	32	17	0.5647	0.2683	1.1888	0.1523
			>=8	21	10	33	22	0.7143	0.4292	1.1887	0.2558

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc Table: GWEP1424 Maximal AE Moderate (Safety Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	
	Age Group	10 mg/kg	0.0377	2-5 years	13	4	18	10	0.5538	0.2220	1.3816	0.2749
				6-12 years	23	10	28	4	3.0435	1.0975	8.4397	0.0286
				13-18 years	8	2	19	3	1.5833	0.3238	7.7417	0.6159
	Sex	10 mg/kg	0.6706	F	22	9	34	9	1.5455	0.7283	3.2795	0.3800
				M	22	7	31	8	1.2330	0.5245	2.8981	0.7593
	Region	10 mg/kg	0.5927	REST OF THE WORLD	23	9	33	8	1.6141	0.7328	3.5554	0.2543
				USA	21	7	32	9	1.1852	0.5219	2.6914	0.7642
	Valproate Use	10 mg/kg	0.1605	N	14	2	17	4	0.6071	0.1298	2.8405	0.6638
				Y	30	14	48	13	1.7231	0.9442	3.1444	0.0913
	Stiripentol Use	10 mg/kg	0.4967	N	28	11	41	10	1.6107	0.7928	3.2724	0.2865
				Y	16	5	24	7	1.0714	0.4112	2.7914	1.0000
	Levetiracetam Use	10 mg/kg	0.4331	N	33	14	51	14	1.5455	0.8503	2.8091	0.1654
				Y	11	2	14	3	0.8485	0.1704	4.2257	1.0000
	Topiramate Use	10 mg/kg	-	N	37	14	48	15	-	-	-	0.6453
				Y	7	2	17	2	-	-	-	0.5520
	Baseline Convulsive Seizure Frequency	10 mg/kg	0.3736	<=7	16	7	17	5	1.4875	0.5913	3.7419	0.4813
				>7 to <=21	15	4	24	8	0.8000	0.2908	2.2011	0.7342
				>21	13	5	24	4	2.3077	0.7467	7.1318	0.2293
	Current AEDs	10 mg/kg	0.6593	<3	12	6	19	6	1.5833	0.6629	3.7821	0.4521
				>=3	32	10	46	11	1.3068	0.6311	2.7060	0.6047
	Prior AEDs	10 mg/kg	0.0059	<4	17	3	26	10	0.4588	0.1473	1.4292	0.1874
				>=4	27	13	39	7	2.6825	1.2336	5.8335	0.0137
	Prior + Current AEDs	10 mg/kg	0.4313	<8	23	8	32	10	1.1130	0.5206	2.3795	1.0000
				>=8	21	8	33	7	1.7959	0.7644	4.2194	0.2201
	Age Group	20 mg/kg	0.1483	2-5 years	10	5	18	10	0.9000	0.4273	1.8956	1.0000
				6-12 years	22	11	28	4	3.5000	1.2890	9.5034	0.0117
				13-18 years	9	3	19	3	2.1111	0.5259	8.4754	0.3518
	Sex	20 mg/kg	0.9861	F	17	8	34	9	1.7778	0.8367	3.7775	0.2084
				M	24	11	31	8	1.7760	0.8486	3.7170	0.1574

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Region	20 mg/kg	0.4257 REST OF THE WORLD	19	10	33	8	2.1711	1.0371	4.5447	0.0679
		USA	22	9	32	9	1.4545	0.6887	3.0721	0.3863
Valproate Use	20 mg/kg	0.3570 N	11	3	17	4	1.1591	0.3189	4.2133	1.0000
		Y	30	16	48	13	1.9692	1.1111	3.4901	0.0298
Stiripentol Use	20 mg/kg	0.0379 N	22	14	41	10	2.6091	1.3970	4.8729	0.0031
		Y	19	5	24	7	0.9023	0.3396	2.3972	1.0000
Levetiracetam Use	20 mg/kg	0.3493 N	32	17	51	14	1.9353	1.1140	3.3619	0.0220
		Y	9	2	14	3	1.0370	0.2134	5.0405	1.0000
Topiramate Use	20 mg/kg	- N	30	13	48	15	-	-	-	0.3354
		Y	11	6	17	2	-	-	-	0.0299
Baseline Convulsive Seizure Frequency	20 mg/kg	0.5066 <=7	12	8	17	5	2.2667	0.9804	5.2404	0.0667
		>7 to <=21	19	8	24	8	1.2632	0.5829	2.7374	0.7516
		>21	10	3	24	4	1.8000	0.4893	6.6216	0.3943
Current AEDs	20 mg/kg	0.6686 <3	8	5	19	6	1.9792	0.8441	4.6405	0.2064
		>=3	33	14	46	11	1.7741	0.9253	3.4015	0.0923
Prior AEDs	20 mg/kg	0.6610 <4	14	8	26	10	1.4857	0.7641	2.8889	0.3267
		>=4	27	11	39	7	2.2698	1.0091	5.1059	0.0524
Prior + Current AEDs	20 mg/kg	0.8493 <8	20	11	32	10	1.7600	0.9197	3.3681	0.1458
		>=8	21	8	33	7	1.7959	0.7644	4.2194	0.2201

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1424 Any SAE (subgroups) (Safety Analysis Set, Patients Taking Clobazam)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	
	Age Group	10 mg/kg	0.8042	2-5 years	13	5	18	4	1.6587	0.5880	4.6792	0.4328
				6-12 years	23	5	28	5	1.2083	0.4225	3.4561	0.7389
				13-18 years	8	0	19	1	0.7407	0.0333	16.4827	1.0000
	Sex	10 mg/kg	0.4910	F	22	7	34	6	1.8030	0.6977	4.6595	0.3316
				M	22	3	31	4	1.0568	0.2623	4.2586	1.0000
	Region	10 mg/kg	0.1498	REST OF THE WORLD	23	7	33	4	2.5109	0.8299	7.5970	0.1696
				USA	21	3	32	6	0.7619	0.2136	2.7182	1.0000
	Valproate Use	10 mg/kg	0.1848	N	14	3	17	5	0.7286	0.2099	2.5287	0.6980
				Y	30	7	48	5	2.2400	0.7814	6.4209	0.1957
	Stiripentol Use	10 mg/kg	0.8802	N	28	4	41	4	1.4643	0.3991	5.3726	0.7064
				Y	16	6	24	6	1.5000	0.5870	3.8333	0.4898
	Levetiracetam Use	10 mg/kg	0.7057	N	33	7	51	8	1.3523	0.5416	3.3763	0.5677
				Y	11	3	14	2	1.9091	0.3833	9.5079	0.6232
	Topiramate Use	10 mg/kg	0.5148	N	37	9	48	7	1.6680	0.6851	4.0609	0.2770
				Y	7	1	17	3	0.8095	0.1006	6.5122	1.0000
	Baseline Convulsive Seizure Frequency	10 mg/kg	0.5519	<=7	16	3	17	4	0.7969	0.2103	3.0197	1.0000
				>7 to <=21	15	4	24	3	2.1333	0.5526	8.2359	0.3955
				>21	13	3	24	3	1.8462	0.4326	7.8783	0.6435
	Current AEDs	10 mg/kg	0.4440	<3	12	1	19	0	4.6154	0.2031	104.8894	0.3871
				>=3	32	9	46	10	1.2886	0.6048	2.7454	0.5959
	Prior AEDs	10 mg/kg	0.3959	<4	17	5	26	7	1.0924	0.4136	2.8854	1.0000
				>=4	27	5	39	3	2.4074	0.6275	9.2366	0.2561
	Prior + Current AEDs	10 mg/kg	0.9519	<8	23	7	32	7	1.3913	0.5655	3.4230	0.5393
				>=8	21	3	33	3	1.5714	0.3493	7.0700	0.6673
	Age Group	20 mg/kg		- 2-5 years	10	3	18	4	-	-	-	0.6744
				6-12 years	22	6	28	5	-	-	-	0.5025
				13-18 years	9	2	19	1	-	-	-	0.2344
	Sex	20 mg/kg	0.5117	F	17	4	34	6	1.3333	0.4336	4.0997	0.7137
				M	24	7	31	4	2.2604	0.7473	6.8375	0.1804

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Region	20 mg/kg	0.9644 REST OF THE WORLD	19	4	33	4	1.7368	0.4898	6.1584	0.4427
		USA	22	7	32	6	1.6970	0.6591	4.3691	0.3383
Valproate Use	20 mg/kg	0.2384 N	11	3	17	5	0.9273	0.2754	3.1218	1.0000
		Y	30	8	48	5	2.5600	0.9231	7.0994	0.1157
Stiripentol Use	20 mg/kg	0.0275 N	22	8	41	4	3.7273	1.2624	11.0053	0.0173
		Y	19	3	24	6	0.6316	0.1812	2.2009	0.7079
Levetiracetam Use	20 mg/kg	0.6621 N	32	8	51	8	1.5938	0.6646	3.8218	0.3925
		Y	9	3	14	2	2.3333	0.4801	11.3411	0.3428
Topiramate Use	20 mg/kg	0.8577 N	30	8	48	7	1.8286	0.7390	4.5247	0.2410
		Y	11	3	17	3	1.5455	0.3776	6.3249	0.6525
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4917 <=7	12	6	17	4	2.1250	0.7610	5.9338	0.2359
		>7 to <=21	19	2	24	3	0.8421	0.1562	4.5407	1.0000
		>21	10	3	24	3	2.4000	0.5800	9.9304	0.3284
Current AEDs	20 mg/kg	0.0076 <3	8	4	19	0	20.0000	1.1995	333.4751	0.0040
		>=3	33	7	46	10	0.9874	0.4320	2.2568	1.0000
Prior AEDs	20 mg/kg	0.7796 <4	14	6	26	7	1.5918	0.6631	3.8214	0.4802
		>=4	27	5	39	3	2.4074	0.6275	9.2366	0.2561
Prior + Current AEDs	20 mg/kg	0.7388 <8	20	8	32	7	1.8286	0.7842	4.2640	0.2128
		>=8	21	3	33	3	1.5714	0.3493	7.0700	0.6673

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data			40 / 59	0.462 [53.8%] / 0.730 [27.0%]	0.633 [36.7%]	(0.444, 0.903)	0.0123
Age Group	0.4948	2-5 years	14 / 17	0.299 [70.1%] / 0.654 [34.6%]	0.457 [54.3%]	(0.240, 0.869)	0.0174
		6-12 years	15 / 24	0.689 [31.1%] / 0.901 [9.9%]	0.765 [23.5%]	(0.432, 1.354)	0.3534
		13-18 years	11 / 18	0.387 [61.3%] / 0.627 [37.3%]	0.618 [38.2%]	(0.321, 1.190)	0.1477
Sex	0.9343	Female	18 / 32	0.486 [51.4%] / 0.774 [22.6%]	0.628 [37.2%]	(0.375, 1.051)	0.0763
		Male	22 / 27	0.439 [56.1%] / 0.679 [32.1%]	0.647 [35.3%]	(0.389, 1.078)	0.0937
Region	0.1014	USA	23 / 37	0.304 [69.6%] / 0.650 [35.0%]	0.468 [53.2%]	(0.295, 0.741)	0.0015
		Rest of the World	17 / 22	0.751 [24.9%] / 0.878 [12.2%]	0.855 [14.5%]	(0.489, 1.495)	0.5797
Valproic Acid Use	0.3206	Not Currently Taking	15 / 27	0.376 [62.4%] / 0.746 [25.4%]	0.503 [49.7%]	(0.287, 0.884)	0.0173
		Currently Taking	25 / 32	0.519 [48.1%] / 0.714 [28.6%]	0.727 [27.3%]	(0.456, 1.160)	0.1789
Stiripentol Use	0.0102	Not Currently Taking	17 / 38	0.194 [80.6%] / 0.619 [38.1%]	0.313 [68.7%]	(0.190, 0.517)	<.0001
		Currently Taking	23 / 21	0.765 [23.5%] / 0.956 [4.4%]	0.801 [19.9%]	(0.484, 1.325)	0.3832
Baseline Convulsive Seizure Frequency	0.7429	<=7	14 / 20	0.366 [63.4%] / 0.543 [45.7%]	0.674 [32.6%]	(0.354, 1.281)	0.2253
		>7 to <=21	16 / 16	0.497 [50.3%] / 0.900 [10.0%]	0.552 [44.8%]	(0.303, 1.004)	0.0514
		>21	10 / 23	0.595 [40.5%] / 0.773 [22.7%]	0.770 [23.0%]	(0.412, 1.439)	0.4091

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.

Log transformed number of days seizures were reported by period is included as an offset.

27-OCT-2023 13:43

Page 1 of 2

C:\SASData\elypdc\CBD\PhaseII\GWEP1332 Dravet\Reporting\Part B\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1332B NBR (subgroups).sas

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Total Seizure Count
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Number of concurrent AEDs	<.0001	<3	12 / 19	0.109 [89.1%] / 0.768 [23.2%]	0.142 [85.8%]	(0.074, 0.271)	<.0001
		>=3	28 / 40	0.665 [33.5%] / 0.711 [28.9%]	0.935 [6.5%]	(0.625, 1.401)	0.7435
Number of prior AEDs	0.4998	<4	21 / 27	0.523 [47.7%] / 0.733 [26.7%]	0.713 [28.7%]	(0.427, 1.191)	0.1935
		>=4	19 / 32	0.406 [59.4%] / 0.727 [27.3%]	0.558 [44.2%]	(0.338, 0.923)	0.0235
SCN1A Mutation	0.1285	Truncation Variants	25 / 27	0.542 [45.8%] / 0.829 [17.1%]	0.654 [34.6%]	(0.404, 1.059)	0.0836
		No Known Mutation	3 / 3	0.146 [85.4%] / 1.019 [-1.9%]	0.143 [85.7%]	(0.034, 0.609)	0.0090
		Missense Variants	12 / 29	0.423 [57.7%] / 0.614 [38.6%]	0.690 [31.0%]	(0.376, 1.266)	0.2277

Total seizures include all seizure types combined.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.
 Log transformed number of days seizures were reported by period is included as an offset.

27-OCT-2023 13:43

Page 2 of 2

C:\SASData\elypdc\CBD\PhaseII\GWEP1332 Dravet\Reporting\Part B\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1332B NBR (subgroups).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B Total Seizure Responder (ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Total Seizures <=25pct	Age Group	20 mg/kg	0.9897	2-5 years	14	8	17	6	1.6190	0.7367	3.5583	0.2895	2.4444	0.5719	10.4475	0.2185	-0.1262	0.5632
				6-12 years	15	7	24	7	1.6000	0.7008	3.6527	0.3182	2.1250	0.5547	8.1400	0.1750	-0.1361	0.4861
				13-18 years	11	7	18	8	1.4318	0.7233	2.8344	0.4497	2.1875	0.4687	10.2100	0.1919	-0.1735	0.5573
	Sex	20 mg/kg	0.7498	F	18	11	32	12	1.6296	0.9128	2.9093	0.1438	2.6190	0.7988	8.5877	0.2361	-0.0447	0.5169
				M	22	11	27	9	1.5000	0.7617	2.9538	0.2602	2.0000	0.6288	6.3609	0.1667	-0.1077	0.4410
	Region	20 mg/kg	0.4080	REST OF THE WORLD	17	7	22	7	1.2941	0.5616	2.9823	0.7376	1.5000	0.4014	5.6054	0.0936	-0.2107	0.3979
				USA	23	15	37	14	1.7236	1.0355	2.8690	0.0624	3.0804	1.0406	9.1181	0.2738	0.0242	0.5234
	Valproate Use	20 mg/kg	0.9180	N	15	9	27	11	1.4727	0.7966	2.7228	0.3357	2.1818	0.6024	7.9024	0.1926	-0.1169	0.5021
				Y	25	13	32	10	1.6640	0.8799	3.1467	0.1736	2.3833	0.8064	7.0441	0.2075	-0.0458	0.4608
	Stiripentol Use	20 mg/kg	0.1319	N	17	15	38	17	1.9723	1.3304	2.9239	0.0030	9.2647	1.8556	46.2578	0.4350	0.2149	0.6551
				Y	23	7	21	4	1.5978	0.5444	4.6894	0.4941	1.8594	0.4560	7.5811	0.1139	-0.1383	0.3660
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.1092	<=8.0	14	9	20	9	1.4286	0.7668	2.6616	0.3151	2.2000	0.5404	8.9571	0.1929	-0.1396	0.5253
				>8.0 to <=25.0	16	10	16	3	3.3333	1.1226	9.8976	0.0290	7.2222	1.4399	36.2243	0.4375	0.1328	0.7422
				>25.0	10	3	23	9	0.7667	0.2616	2.2469	0.7098	0.6667	0.1358	3.2716	-0.0913	-0.4384	0.2558
	Current AEDs	20 mg/kg	0.1450	<3	12	10	19	8	1.9792	1.1028	3.5520	0.0317	6.8750	1.1706	40.3779	0.4123	0.1061	0.7185
>=3				28	12	40	13	1.3187	0.7105	2.4474	0.4482	1.5577	0.5736	4.2300	0.1036	-0.1302	0.3374	
Prior AEDs	20 mg/kg	0.4993	<4	21	11	27	7	2.0204	0.9479	4.3065	0.0773	3.1429	0.9333	10.5836	0.2646	-0.0055	0.5346	
			>=4	19	11	32	14	1.3233	0.7643	2.2913	0.3929	1.7679	0.5611	5.5704	0.1414	-0.1393	0.4222	
SCN1A Mutation-Positive	20 mg/kg	0.4209	Truncation Variants	25	12	27	8	1.6200	0.7963	3.2957	0.2547	2.1923	0.7016	6.8500	0.1837	-0.0771	0.4445	
			Missense Variants	12	7	29	12	1.4097	0.7395	2.6875	0.4926	1.9833	0.5065	7.7660	0.1695	-0.1620	0.5011	
			No Known Mutation	3	3	3	1	3.0000	0.6055	14.8636	0.4000	-	-	-	0.6667	0.1332	1.0000	
Total Seizures <=50pct	Age Group	20 mg/kg	0.8789	2-5 years	14	8	17	5	1.9429	0.8181	4.6140	0.1570	3.2000	0.7239	14.1451	0.2773	-0.0605	0.6151
				6-12 years	15	5	24	5	1.6000	0.5552	4.6113	0.4633	1.9000	0.4426	8.1570	0.1250	-0.1636	0.4136
				13-18 years	11	5	18	5	1.6364	0.6099	4.3901	0.4320	2.1667	0.4497	10.4390	0.1768	-0.1830	0.5365
	Sex	20 mg/kg	0.3456	F	18	10	32	8	2.2222	1.0724	4.6049	0.0381	3.7500	1.0998	12.7862	0.3056	0.0313	0.5798
				M	22	8	27	7	1.4026	0.6032	3.2614	0.5377	1.6327	0.4806	5.5460	0.1044	-0.1559	0.3646
	Region	20 mg/kg	0.9578	REST OF THE WORLD	17	6	22	4	1.9412	0.6491	5.8052	0.2819	2.4545	0.5639	10.6839	0.1711	-0.1074	0.4497
				USA	23	12	37	11	1.7549	0.9335	3.2993	0.1052	2.5785	0.8757	7.5926	0.2244	-0.0273	0.4762
	Valproate Use	20 mg/kg	0.3397	N	15	8	27	6	2.4000	1.0261	5.6137	0.0854	4.0000	1.0257	15.5993	0.3111	0.0139	0.6083
				Y	25	10	32	9	1.4222	0.6833	2.9601	0.4036	1.7037	0.5610	5.1743	0.1188	-0.1285	0.3660
	Stiripentol Use	20 mg/kg	0.6733	N	17	12	38	14	1.9160	1.1423	3.2136	0.0392	4.1143	1.1977	14.1330	0.3375	0.0721	0.6029
				Y	23	6	21	1	5.4783	0.7176	41.8236	0.0973	7.0588	0.7716	64.5742	0.2133	0.0120	0.4145
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.3232	<=8.0	14	7	20	7	1.4286	0.6455	3.1616	0.4867	1.8571	0.4610	7.4823	0.1500	-0.1851	0.4851
				>8.0 to <=25.0	16	8	16	2	4.0000	1.0004	15.9938	0.0538	7.0000	1.1848	41.3585	0.3750	0.0813	0.6687
				>25.0	10	3	23	6	1.1500	0.3568	3.7063	1.0000	1.2143	0.2351	6.2711	0.0391	-0.2968	0.3751
	Current AEDs	20 mg/kg	0.1620	<3	12	9	19	6	2.3750	1.1353	4.9683	0.0290	6.5000	1.2790	33.0344	0.4342	0.1122	0.7562
>=3				28	9	40	9	1.4286	0.6499	3.1404	0.4130	1.6316	0.5507	4.8342	0.0964	-0.1196	0.3125	
Prior AEDs	20 mg/kg	0.8806	<4	21	9	27	6	1.9286	0.8150	4.5635	0.2089	2.6250	0.7498	9.1901	0.2063	-0.0571	0.4698	
			>=4	19	9	32	9	1.6842	0.8125	3.4914	0.2279	2.3000	0.7030	7.5245	0.1924	-0.0808	0.4657	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

SCN1A Mutation-Positive	20 mg/kg	0.4511 Truncation Variants	25	9	27	5	1.9440	0.7531	5.0179	0.2147	2.4750	0.6959	8.8024	0.1748	-0.0637	0.4133
		Missense Variants	12	6	29	9	1.6111	0.7357	3.5283	0.2999	2.2222	0.5601	8.8171	0.1897	-0.1396	0.5189
		No Known Mutation	3	3	3	1	3.0000	0.6055	14.8636	0.4000	-	-	-	0.6667	0.1332	1.0000
Total Seizures <=75pct																
Age Group	20 mg/kg	0.1398 2-5 years	14	6	17	2	3.6429	0.8670	15.3061	0.0971	5.6250	0.9152	34.5724	0.3109	0.0098	0.6120
		6-12 years	15	2	24	5	0.6400	0.1417	2.8902	0.6857	0.5846	0.0981	3.4845	-0.0750	-0.3116	0.1616
		13-18 years	11	4	18	2	3.2727	0.7139	15.0033	0.1638	4.5714	0.6731	31.0482	0.2525	-0.0667	0.5717
Sex	20 mg/kg	0.4530 F	18	6	32	4	2.6667	0.8652	8.2195	0.1381	3.5000	0.8338	14.6921	0.2083	-0.0377	0.4544
		M	22	6	27	5	1.4727	0.5180	4.1868	0.5095	1.6500	0.4276	6.3665	0.0875	-0.1493	0.3244
Region	20 mg/kg	0.1686 REST OF THE WORLD	17	2	22	3	0.8627	0.1618	4.5992	1.0000	0.8444	0.1247	5.7196	-0.0187	-0.2285	0.1911
		USA	23	10	37	6	2.6812	1.1254	6.3874	0.0342	3.9744	1.1952	13.2163	0.2726	0.0378	0.5075
Valproate Use	20 mg/kg	0.0195 N	15	7	27	2	6.3000	1.4939	26.5676	0.0055	10.9375	1.8787	63.6774	0.3926	0.1215	0.6637
		Y	25	5	32	7	0.9143	0.3292	2.5392	1.0000	0.8929	0.2459	3.2419	-0.0187	-0.2311	0.1936
Stiripentol Use	20 mg/kg	0.4557 N	17	10	38	8	2.7941	1.3425	5.8154	0.0114	5.3571	1.5481	18.5388	0.3777	0.1102	0.6452
		Y	23	2	21	1	1.8261	0.1783	18.7014	1.0000	1.9048	0.1599	22.6847	0.0393	-0.1075	0.1862
Baseline Convulsive Seizure Frequency	20 mg/kg	0.5488 <=8.0	14	5	20	6	1.1905	0.4510	3.1423	1.0000	1.2963	0.3033	5.5401	0.0571	-0.2643	0.3786
		>8.0 to <=25.0	16	5	16	2	2.5000	0.5656	11.0508	0.3944	3.1818	0.5155	19.6390	0.1875	-0.0915	0.4665
		>25.0	10	2	23	1	4.6000	0.4692	45.0973	0.2117	5.5000	0.4367	69.2639	0.1565	-0.1050	0.4181
Current AEDs	20 mg/kg	0.0056 <3	12	9	19	3	4.7500	1.5993	14.1078	0.0019	16.0000	2.6537	96.4691	0.5921	0.2973	0.8869
		>=3	28	3	40	6	0.7143	0.1949	2.6184	0.7266	0.6800	0.1550	2.9841	-0.0429	-0.2021	0.1164
Prior AEDs	20 mg/kg	0.9915 <4	21	5	27	3	2.1429	0.5765	7.9645	0.2724	2.5000	0.5228	11.9556	0.1270	-0.0904	0.3443
		>=4	19	7	32	6	1.9649	0.7745	4.9852	0.1919	2.5278	0.6978	9.1572	0.1809	-0.0747	0.4365
SCN1A Mutation-Positive	20 mg/kg	0.4403 Truncation Variants	25	5	27	3	1.8000	0.4789	6.7648	0.4583	2.0000	0.4247	9.4181	0.0889	-0.1077	0.2855
		Missense Variants	12	5	29	6	2.0139	0.7576	5.3537	0.2474	2.7381	0.6375	11.7608	0.2098	-0.1057	0.5253
		No Known Mutation	3	2	3	0	-	-	-	0.4000	-	-	-	0.6667	0.1332	1.0000
Total Seizures >0pct																
Age Group	20 mg/kg	0.7371 2-5 years	14	2	17	7	0.3469	0.0853	1.4115	0.1317	4.2000	0.7072	24.9430	-0.2689	-0.5661	0.0283
		6-12 years	15	5	24	14	0.5714	0.2589	1.2610	0.1908	2.8000	0.7290	10.7547	-0.2500	-0.5595	0.0595
		13-18 years	11	1	18	2	0.8182	0.0837	8.0011	1.0000	1.2500	0.0999	15.6470	-0.0202	-0.2437	0.2033
Sex	20 mg/kg	0.9166 F	18	4	32	13	0.5470	0.2094	1.4292	0.2272	2.3947	0.6421	8.9307	-0.1840	-0.4406	0.0726
		M	22	4	27	10	0.4909	0.1781	1.3529	0.2074	2.6471	0.6962	10.0651	-0.1886	-0.4318	0.0547
Region	20 mg/kg	0.5468 REST OF THE WORLD	17	5	22	10	0.6471	0.2719	1.5400	0.3429	2.0000	0.5243	7.6298	-0.1604	-0.4608	0.1399
		USA	23	3	37	13	0.3712	0.1184	1.1636	0.0764	3.6111	0.9007	14.4773	-0.2209	-0.4273	-0.0145
Valproate Use	20 mg/kg	0.7537 N	15	2	27	7	0.5143	0.1220	2.1688	0.4508	2.2750	0.4075	12.6999	-0.1259	-0.3645	0.1126
		Y	25	6	32	16	0.4800	0.2203	1.0459	0.0583	3.1667	1.0026	10.0014	-0.2600	-0.5009	-0.0191
Stiripentol Use	20 mg/kg	0.9201 N	17	2	38	12	0.3725	0.0934	1.4859	0.1829	3.4615	0.6808	17.6012	-0.1981	-0.4110	0.0147
		Y	23	6	21	11	0.4980	0.2238	1.1080	0.1210	3.1167	0.8799	11.0398	-0.2629	-0.5419	0.0160
Baseline Convulsive Seizure Frequency	20 mg/kg	0.3189 <=8.0	14	2	20	7	0.4082	0.0991	1.6807	0.2502	3.2308	0.5578	18.7122	-0.2071	-0.4852	0.0709
		>8.0 to <=25.0	16	3	16	9	0.3333	0.1101	1.0092	0.0659	5.5714	1.1278	27.5230	-0.3750	-0.6843	-0.0657
		>25.0	10	3	23	7	0.9857	0.3182	3.0531	1.0000	1.0208	0.2024	5.1484	-0.0043	-0.3450	0.3363
Current AEDs	20 mg/kg	0.5103 <3	12	1	19	6	0.2639	0.0361	1.9301	0.2015	5.0769	0.5276	48.8554	-0.2325	-0.4935	0.0286
		>=3	28	7	40	17	0.5882	0.2818	1.2278	0.1979	2.2174	0.7678	6.4035	-0.1750	-0.3968	0.0468
Prior AEDs	20 mg/kg	0.9284 <4	21	5	27	12	0.5357	0.2236	1.2833	0.2238	2.5600	0.7270	9.0143	-0.2063	-0.4677	0.0550
		>=4	19	3	32	11	0.4593	0.1464	1.4412	0.2023	2.7937	0.6667	11.7058	-0.1859	-0.4182	0.0464
SCN1A Mutation-Positive	20 mg/kg	0.5905 Truncation Variants	25	5	27	12	0.4500	0.1848	1.0960	0.0799	3.2000	0.9264	11.0534	-0.2444	-0.4888	-0.0001

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Missense Variants	12	3	29	10	0.7250	0.2411	2.1800	0.7186	1.5789	0.3472	7.1795	-0.0948	-0.3947	0.2051
No Known Mutation	3	0	3	1	1.5000	0.6739	3.3388	1.0000	-	-	-	-0.3333	-0.8668	0.2001

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data			40 / 59	0.463 [53.7%] / 0.765 [23.5%]	0.605 [39.5%]	(0.432, 0.847)	0.0038
Age Group	0.2006	2-5 years	14 / 17	0.256 [74.4%] / 0.609 [39.1%]	0.420 [58.0%]	(0.231, 0.765)	0.0050
		6-12 years	15 / 24	0.807 [19.3%] / 0.948 [5.2%]	0.852 [14.8%]	(0.508, 1.427)	0.5381
		13-18 years	11 / 18	0.393 [60.7%] / 0.706 [29.4%]	0.556 [44.4%]	(0.305, 1.014)	0.0553
Sex	0.9260	Female	18 / 32	0.477 [52.3%] / 0.795 [20.5%]	0.599 [40.1%]	(0.369, 0.975)	0.0393
		Male	22 / 27	0.452 [54.8%] / 0.731 [26.9%]	0.619 [38.1%]	(0.385, 0.994)	0.0473
Region	0.2723	USA	23 / 37	0.358 [64.2%] / 0.727 [27.3%]	0.493 [50.7%]	(0.318, 0.765)	0.0019
		Rest of the World	17 / 22	0.609 [39.1%] / 0.841 [15.9%]	0.724 [27.6%]	(0.425, 1.232)	0.2306
Valproic Acid Use	0.6510	Not Currently Taking	15 / 27	0.433 [56.7%] / 0.788 [21.2%]	0.549 [45.1%]	(0.319, 0.945)	0.0307
		Currently Taking	25 / 32	0.479 [52.1%] / 0.744 [25.6%]	0.644 [35.6%]	(0.414, 1.002)	0.0509
Stiripentol Use	0.0359	Not Currently Taking	17 / 38	0.228 [77.2%] / 0.668 [33.2%]	0.341 [65.9%]	(0.213, 0.545)	<.0001
		Currently Taking	23 / 21	0.683 [31.7%] / 0.980 [2.0%]	0.697 [30.3%]	(0.434, 1.118)	0.1327
Baseline Convulsive Seizure Frequency	0.5496	<=7	14 / 20	0.415 [58.5%] / 0.777 [22.3%]	0.534 [46.6%]	(0.284, 1.007)	0.0525
		>7 to <=21	16 / 16	0.459 [54.1%] / 0.872 [12.8%]	0.526 [47.4%]	(0.301, 0.920)	0.0247
		>21	10 / 23	0.601 [39.9%] / 0.772 [22.8%]	0.779 [22.1%]	(0.445, 1.361)	0.3764

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.
Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.
Log transformed number of days seizures were reported by period is included as an offset.

27-OCT-2023 13:43

Page 1 of 2

C:\SASData\elypdc\CBD\PhaseII\GWEP1332 Dravet\Reporting\Part B\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1332B NBR (subgroups).sas

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Convulsive Seizure Count
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Number of concurrent AEDs	<.0001	<3	12 / 19	0.117 [88.3%] / 0.782 [21.8%]	0.150 [85.0%]	(0.082, 0.275)	<.0001
		>=3	28 / 40	0.682 [31.8%] / 0.759 [24.1%]	0.899 [10.1%]	(0.615, 1.313)	0.5771
Number of prior AEDs	0.7430	<4	21 / 27	0.448 [55.2%] / 0.783 [21.7%]	0.572 [42.8%]	(0.352, 0.929)	0.0244
		>=4	19 / 32	0.480 [52.0%] / 0.751 [24.9%]	0.639 [36.1%]	(0.398, 1.026)	0.0636
SCN1A Mutation	0.0778	Truncation Variants	25 / 27	0.509 [49.1%] / 0.762 [23.8%]	0.668 [33.2%]	(0.424, 1.052)	0.0810
		No Known Mutation	3 / 3	0.159 [84.1%] / 1.131 [-13.1%]	0.141 [85.9%]	(0.038, 0.521)	0.0037
		Missense Variants	12 / 29	0.497 [50.3%] / 0.732 [26.8%]	0.678 [32.2%]	(0.387, 1.188)	0.1724

Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.
 Log transformed number of days seizures were reported by period is included as an offset.

27-OCT-2023 13:43

Page 2 of 2

C:\SASData\elypdc\CBD\PhaseII\GWEP1332 Dravet\Reporting\Part B\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1332B NBR (subgroups).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B Convulsive Seizure Responder (ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Convulsive Seizures <=25pct	Age Group	20 mg/kg	0.8917	2-5 years	14	10	17	10	1.2143	0.7236	2.0376	0.7074	1.7500	0.3869	7.9148	0.1261	-0.2067	0.4588
				6-12 years	15	8	24	7	1.8286	0.8359	4.0002	0.1817	2.7755	0.7246	10.6319	0.2417	-0.0695	0.5528
				13-18 years	11	8	18	9	1.4545	0.8089	2.6157	0.2732	2.6667	0.5294	13.4330	0.2273	-0.1229	0.5774
	Sex	20 mg/kg	0.6947	F	18	13	32	15	1.5407	0.9658	2.4579	0.1373	2.9467	0.8499	10.2164	0.2535	-0.0162	0.5231
				M	22	13	27	11	1.4504	0.8181	2.5713	0.2563	2.1010	0.6684	6.6041	0.1835	-0.0932	0.4602
	Region	20 mg/kg	0.2831	REST OF THE WORLD	17	12	22	8	1.9412	1.0315	3.6529	0.0536	4.2000	1.0806	16.3242	0.3422	0.0467	0.6377
				USA	23	14	37	18	1.2512	0.7853	1.9935	0.4299	1.6420	0.5707	4.7242	0.1222	-0.1341	0.3786
	Valproate Use	20 mg/kg	0.8286	N	15	10	27	13	1.3846	0.8147	2.3532	0.3371	2.1538	0.5798	8.0015	0.1852	-0.1188	0.4892
				Y	25	16	32	13	1.5754	0.9444	2.6281	0.1108	2.5983	0.8831	7.6448	0.2338	-0.0199	0.4874
	Stiripentol Use	20 mg/kg	0.6513	N	17	14	38	20	1.5647	1.0772	2.2729	0.0418	4.2000	1.0356	17.0341	0.2972	0.0563	0.5381
				Y	23	12	21	6	1.8261	0.8360	3.9887	0.1359	2.7273	0.7804	9.5312	0.2360	-0.0451	0.5171
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.6728	<=8.0	14	10	20	9	1.5873	0.8826	2.8548	0.1706	3.0556	0.7123	13.1074	0.2643	-0.0575	0.5861
				>8.0 to <=25.0	16	11	16	7	1.5714	0.8233	2.9993	0.2852	2.8286	0.6656	12.0196	0.2500	-0.0827	0.5827
				>25.0	10	5	23	10	1.1500	0.5296	2.4972	1.0000	1.3000	0.2934	5.7607	0.0652	-0.3050	0.4355
	Current AEDs	20 mg/kg	0.6239	<3	12	9	19	9	1.5833	0.8904	2.8156	0.1581	3.3333	0.6819	16.2954	0.2763	-0.0560	0.6086
				>=3	28	17	40	17	1.4286	0.8950	2.2804	0.2177	2.0909	0.7816	5.5932	0.1821	-0.0549	0.4192
	Prior AEDs	20 mg/kg	0.4203	<4	21	14	27	10	1.8000	1.0105	3.2064	0.0798	3.4000	1.0269	11.2568	0.2963	0.0246	0.5680
				>=4	19	12	32	16	1.2632	0.7755	2.0574	0.3984	1.7143	0.5366	5.4767	0.1316	-0.1460	0.4092
	SCN1A Mutation-Positive	20 mg/kg	0.4307	Truncation Variants	25	15	27	11	1.4727	0.8444	2.5685	0.2668	2.1818	0.7199	6.6128	0.1926	-0.0743	0.4595
Missense Variants				12	8	29	14	1.3810	0.7971	2.3924	0.3246	2.1429	0.5263	8.7240	0.1839	-0.1389	0.5067	
No Known Mutation				3	3	3	1	3.0000	0.6055	14.8636	0.4000	-	-	-	0.6667	0.1332	1.0000	
Convulsive Seizures <=50pct	Age Group	20 mg/kg	0.4291	2-5 years	14	9	17	8	1.3661	0.7220	2.5848	0.4730	2.0250	0.4751	8.6317	0.1723	-0.1731	0.5177
				6-12 years	15	4	24	5	1.2800	0.4071	4.0249	0.7110	1.3818	0.3053	6.2550	0.0583	-0.2182	0.3349
				13-18 years	11	6	18	3	3.2727	1.0205	10.4960	0.0478	6.0000	1.0786	33.3779	0.3788	0.0379	0.7197
	Sex	20 mg/kg	0.1781	F	18	10	32	7	2.5397	1.1709	5.5085	0.0282	4.4643	1.2769	15.6085	0.3368	0.0662	0.6074
				M	22	9	27	9	1.2273	0.5899	2.5534	0.7665	1.3846	0.4309	4.4492	0.0758	-0.1960	0.3475
	Region	20 mg/kg	0.3234	REST OF THE WORLD	17	6	22	6	1.2941	0.5065	3.3064	0.7302	1.4545	0.3706	5.7093	0.0802	-0.2135	0.3739
				USA	23	13	37	10	2.0913	1.1034	3.9636	0.0304	3.5100	1.1705	10.5258	0.2949	0.0469	0.5430
	Valproate Use	20 mg/kg	0.1527	N	15	9	27	6	2.7000	1.1919	6.1165	0.0210	5.2500	1.3276	20.7613	0.3778	0.0844	0.6711
				Y	25	10	32	10	1.2800	0.6336	2.5860	0.5804	1.4667	0.4907	4.3841	0.0875	-0.1628	0.3378
	Stiripentol Use	20 mg/kg	0.6447	N	17	13	38	14	2.0756	1.2681	3.3975	0.0090	5.5714	1.5182	20.4457	0.3963	0.1429	0.6496
				Y	23	6	21	2	2.7391	0.6192	12.1168	0.2451	3.3529	0.5951	18.8921	0.1656	-0.0534	0.3846
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.6434	<=8.0	14	8	20	6	1.9048	0.8485	4.2761	0.1627	3.1111	0.7471	12.9557	0.2714	-0.0565	0.5994
				>8.0 to <=25.0	16	8	16	4	2.0000	0.7506	5.3288	0.2734	3.0000	0.6714	13.4041	0.2500	-0.0741	0.5741
				>25.0	10	3	23	6	1.1500	0.3568	3.7063	1.0000	1.2143	0.2351	6.2711	0.0391	-0.2968	0.3751
	Current AEDs	20 mg/kg	0.1647	<3	12	9	19	6	2.3750	1.1353	4.9683	0.0290	6.5000	1.2790	33.0344	0.4342	0.1122	0.7562
				>=3	28	10	40	10	1.4286	0.6874	2.9688	0.4206	1.6667	0.5812	4.7792	0.1071	-0.1154	0.3296
	Prior AEDs	20 mg/kg	0.7456	<4	21	9	27	7	1.6531	0.7380	3.7029	0.2373	2.1429	0.6328	7.2565	0.1693	-0.0992	0.4379
				>=4	19	10	32	9	1.8713	0.9301	3.7651	0.1334	2.8395	0.8679	9.2895	0.2451	-0.0282	0.5183

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

SCN1A Mutation-Positive	20 mg/kg	0.1334 Truncation Variants	25	10	27	7	1.5429	0.6946	3.4272	0.3775	1.9048	0.5881	6.1691	0.1407	-0.1126	0.3941
		Missense Variants	12	6	29	9	1.6111	0.7357	3.5283	0.2999	2.2222	0.5601	8.8171	0.1897	-0.1396	0.5189
		No Known Mutation	3	3	3	0	-	-	-	0.1000	-	-	-	1.0000	1.0000	1.0000
Convulsive Seizures <=75pct Age Group	20 mg/kg	0.0182 2-5 years	14	6	17	2	3.6429	0.8670	15.3061	0.0971	5.6250	0.9152	34.5724	0.3109	0.0098	0.6120
		6-12 years	15	1	24	5	0.3200	0.0413	2.4803	0.3758	0.2714	0.0285	2.5889	-0.1417	-0.3474	0.0641
		13-18 years	11	3	18	0	-	-	-	0.0452	-	-	-	0.2727	0.0095	0.5359
Sex	20 mg/kg	0.8220 F	18	4	32	3	2.3704	0.5957	9.4322	0.2345	2.7619	0.5427	14.0567	0.1285	-0.0885	0.3455
		M	22	6	27	4	1.8409	0.5929	5.7160	0.3114	2.1563	0.5228	8.8934	0.1246	-0.1047	0.3539
Region	20 mg/kg	0.1620 REST OF THE WORLD	17	1	22	2	0.6471	0.0639	6.5548	1.0000	0.6250	0.0519	7.5296	-0.0321	-0.1962	0.1321
		USA	23	9	37	5	2.8957	1.1072	7.5731	0.0306	4.1143	1.1661	14.5159	0.2562	0.0283	0.4840
Valproate Use	20 mg/kg	0.1762 N	15	5	27	2	4.5000	0.9906	20.4415	0.0772	6.2500	1.0369	37.6720	0.2593	0.0011	0.5175
		Y	25	5	32	5	1.2800	0.4161	3.9379	0.7345	1.3500	0.3438	5.3012	0.0438	-0.1573	0.2448
Stiripentol Use	20 mg/kg	0.6593 N	17	9	38	7	2.8739	1.2845	6.4302	0.0219	4.9821	1.4176	17.5092	0.3452	0.0778	0.6126
		Y	23	1	21	0	-	-	-	1.0000	-	-	-	0.0435	-0.0399	0.1268
Baseline Convulsive Seizure Frequency	20 mg/kg	0.9941 <=8.0	14	4	20	3	1.9048	0.5027	7.2169	0.4099	2.2667	0.4189	12.2655	0.1357	-0.1480	0.4194
		>8.0 to <=25.0	16	4	16	2	2.0000	0.4247	9.4181	0.6539	2.3333	0.3617	15.0533	0.1250	-0.1420	0.3920
		>25.0	10	2	23	2	2.3000	0.3749	14.1092	0.5672	2.6250	0.3143	21.9217	0.1130	-0.1603	0.3864
Current AEDs	20 mg/kg	0.0176 <3	12	9	19	4	3.5625	1.4056	9.0291	0.0075	11.2500	2.0349	62.1949	0.5395	0.2335	0.8455
		>=3	28	1	40	3	0.4762	0.0522	4.3453	0.6380	0.4568	0.0450	4.6338	-0.0393	-0.1460	0.0674
Prior AEDs	20 mg/kg	1.0000 <4	21	5	27	3	2.1429	0.5765	7.9645	0.2724	2.5000	0.5228	11.9556	0.1270	-0.0904	0.3443
		>=4	19	5	32	4	2.1053	0.6431	6.8921	0.2656	2.5000	0.5789	10.7968	0.1382	-0.0906	0.3669
SCN1A Mutation-Positive	20 mg/kg	0.3639 Truncation Variants	25	4	27	3	1.4400	0.3570	5.8081	0.6983	1.5238	0.3054	7.6038	0.0489	-0.1374	0.2352
		Missense Variants	12	4	29	4	2.4167	0.7194	8.1178	0.2024	3.1250	0.6320	15.4520	0.1954	-0.0994	0.4902
		No Known Mutation	3	2	3	0	-	-	-	0.4000	-	-	-	0.6667	0.1332	1.0000
Convulsive Seizures >0pct Age Group	20 mg/kg	0.5522 2-5 years	14	1	17	5	0.2429	0.0320	1.8439	0.1848	5.4167	0.5508	53.2707	-0.2227	-0.4779	0.0325
		6-12 years	15	4	24	14	0.4571	0.1850	1.1298	0.0978	3.8500	0.9467	15.6578	-0.3167	-0.6150	-0.0184
		13-18 years	11	2	18	4	0.8182	0.1785	3.7508	1.0000	1.2857	0.1937	8.5336	-0.0404	-0.3385	0.2577
Sex	20 mg/kg	0.9753 F	18	3	32	12	0.4444	0.1442	1.3699	0.1990	3.0000	0.7170	12.5531	-0.2083	-0.4487	0.0320
		M	22	4	27	11	0.4463	0.1648	1.2087	0.1231	3.0938	0.8200	11.6721	-0.2256	-0.4712	0.0200
Region	20 mg/kg	0.9120 REST OF THE WORLD	17	3	22	9	0.4314	0.1375	1.3530	0.1685	3.2308	0.7144	14.6108	-0.2326	-0.5066	0.0413
		USA	23	4	37	14	0.4596	0.1722	1.2269	0.1471	2.8913	0.8148	10.2593	-0.2045	-0.4245	0.0156
Valproate Use	20 mg/kg	0.4756 N	15	3	27	9	0.6000	0.1911	1.8837	0.4848	2.0000	0.4476	8.9361	-0.1333	-0.4028	0.1361
		Y	25	4	32	14	0.3657	0.1372	0.9748	0.0432	4.0833	1.1386	14.6444	-0.2775	-0.5015	-0.0535
Stiripentol Use	20 mg/kg	0.8991 N	17	2	38	12	0.3725	0.0934	1.4859	0.1829	3.4615	0.6808	17.6012	-0.1981	-0.4110	0.0147
		Y	23	5	21	11	0.4150	0.1728	0.9967	0.0592	3.9600	1.0689	14.6707	-0.3064	-0.5785	-0.0343
Baseline Convulsive Seizure Frequency	20 mg/kg	0.2474 <=8.0	14	2	20	8	0.3571	0.0889	1.4351	0.1413	4.0000	0.6994	22.8782	-0.2571	-0.5394	0.0252
		>8.0 to <=25.0	16	2	16	8	0.2500	0.0625	0.9996	0.0538	7.0000	1.1848	41.3585	-0.3750	-0.6687	-0.0813
		>25.0	10	3	23	7	0.9857	0.3182	3.0531	1.0000	1.0208	0.2024	5.1484	-0.0043	-0.3450	0.3363
Current AEDs	20 mg/kg	0.4424 <3	12	1	19	7	0.2262	0.0316	1.6166	0.1082	6.4167	0.6768	60.8402	-0.2851	-0.5525	-0.0177
		>=3	28	6	40	16	0.5357	0.2396	1.1975	0.1231	2.4444	0.8118	7.3602	-0.1857	-0.4005	0.0291
Prior AEDs	20 mg/kg	0.1348 <4	21	3	27	14	0.2755	0.0909	0.8351	0.0137	6.4615	1.5361	27.1793	-0.3757	-0.6163	-0.1350
		>=4	19	4	32	9	0.7485	0.2667	2.1008	0.7432	1.4674	0.3821	5.6348	-0.0707	-0.3113	0.1698
SCN1A Mutation-Positive	20 mg/kg	0.7845 Truncation Variants	25	5	27	12	0.4500	0.1848	1.0960	0.0799	3.2000	0.9264	11.0534	-0.2444	-0.4888	-0.0001

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Missense Variants	12	2	29	10	0.4833	0.1239	1.8850	0.4521	2.6316	0.4806	14.4102	-0.1782	-0.4509	0.0946
No Known Mutation	3	0	3	1	1.5000	0.6739	3.3388	1.0000	-	-	-	-0.3333	-0.8668	0.2001

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
All Data			40 / 59	0.593 [40.7%] / 0.466 [53.4%]	1.272 [-27.2%]	(0.707, 2.289)	0.4181
Age Group	0.6829	2-5 years	14 / 17	0.790 [21.0%] / 0.467 [53.3%]	1.690 [-69.0%]	(0.531, 5.377)	0.3701
		6-12 years	15 / 24	0.625 [37.5%] / 0.664 [33.6%]	0.940 [6.0%]	(0.380, 2.326)	0.8927
		13-18 years	11 / 18	0.438 [56.2%] / 0.290 [71.0%]	1.513 [-51.3%]	(0.479, 4.781)	0.4766
Sex	0.1726	Female	18 / 32	0.442 [55.8%] / 0.526 [47.4%]	0.841 [15.9%]	(0.369, 1.916)	0.6776
		Male	22 / 27	0.773 [22.7%] / 0.403 [59.7%]	1.918 [-91.8%]	(0.811, 4.537)	0.1363
Region	0.1607	USA	23 / 37	0.313 [68.7%] / 0.370 [63.0%]	0.846 [15.4%]	(0.389, 1.841)	0.6708
		Rest of the World	17 / 22	1.346 [-34.6%] / 0.680 [32.0%]	1.980 [-98.0%]	(0.800, 4.897)	0.1377
Valproic Acid Use	0.0278	Not Currently Taking	15 / 27	0.303 [69.7%] / 0.504 [49.6%]	0.600 [40.0%]	(0.250, 1.440)	0.2497
		Currently Taking	25 / 32	0.978 [2.2%] / 0.425 [57.5%]	2.303 [-130.3%]	(1.021, 5.196)	0.0446
Stiripentol Use	0.0432	Not Currently Taking	17 / 38	0.262 [73.8%] / 0.431 [56.9%]	0.609 [39.1%]	(0.263, 1.410)	0.2439
		Currently Taking	23 / 21	1.165 [-16.5%] / 0.542 [45.8%]	2.151 [-115.1%]	(0.884, 5.229)	0.0903
Baseline Convulsive Seizure Frequency	0.5522	<=7	14 / 20	0.278 [72.2%] / 0.170 [83.0%]	1.634 [-63.4%]	(0.539, 4.950)	0.3814
		>7 to <=21	16 / 16	0.708 [29.2%] / 0.691 [30.9%]	1.025 [-2.5%]	(0.393, 2.678)	0.9588
		>21	10 / 23	1.170 [-17.0%] / 0.519 [48.1%]	2.254 [-125.4%]	(0.759, 6.691)	0.1413

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.
Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.
Log transformed number of days seizures were reported by period is included as an offset.

27-OCT-2023 13:43

Page 1 of 2

C:\SASData\elypcd\CBD\PhaseII\GWEP1332 Dravet\Reporting\Part B\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1332B NBR (subgroups).sas

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Non-Convulsive Seizure Count
(ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio (Percentage Reduction)	95% CI	P-value
Number of concurrent AEDs	0.0183	<3	12 / 19	0.182 [81.8%] / 0.573 [42.7%]	0.317 [68.3%]	(0.089, 1.126)	0.0751
		>=3	28 / 40	0.742 [25.8%] / 0.409 [59.1%]	1.816 [-81.6%]	(0.909, 3.629)	0.0902
Number of prior AEDs	0.0771	<4	21 / 27	0.908 [9.2%] / 0.396 [60.4%]	2.295 [-129.5%]	(0.959, 5.490)	0.0617
		>=4	19 / 32	0.422 [57.8%] / 0.538 [46.2%]	0.785 [21.5%]	(0.348, 1.769)	0.5552
SCN1A Mutation	0.8152	Truncation Variants	25 / 27	0.735 [26.5%] / 0.588 [41.2%]	1.250 [-25.0%]	(0.472, 3.314)	0.6503
		No Known Mutation	3 / 3	0.001 [99.9%] / 0.788 [21.2%]	0.001 [99.9%]	(0.000, 1226130)	0.5848
		Missense Variants	12 / 29	0.483 [51.7%] / 0.304 [69.6%]	1.587 [-58.7%]	(0.420, 5.990)	0.4918

Non-convulsive seizures include myoclonic, countable partial, other partial and absence seizures.
 Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.
 Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect.
 Log transformed number of days seizures were reported by period is included as an offset.

27-OCT-2023 13:43

Page 2 of 2

C:\SASData\elypdc\CBD\PhaseII\GWEP1332 Dravet\Reporting\Part B\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1332B NBR (subgroups).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B Non-Convulsive Seizure Responder (ITT Analysis Set, Patients Taking CBZ + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio		Risk Difference			
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
Non-Convulsive Seizures <=25pct	Age Group	20 mg/kg	0.4976	2-5 years	5	3	15	8	1.1250	0.4770	2.6534	1.0000	1.3125	0.1678	10.2643	0.0667	-0.4315	0.5648
				6-12 years	11	8	15	9	1.2121	0.6998	2.0994	0.6828	1.7778	0.3308	9.5539	0.1273	-0.2343	0.4888
				13-18 years	6	3	11	8	0.6875	0.2857	1.6545	0.6000	0.3750	0.0469	2.9982	-0.2273	-0.7062	0.2516
	Sex	20 mg/kg	0.3446	F	12	8	21	11	1.2727	0.7188	2.2534	0.4861	1.8182	0.4162	7.9427	0.1429	-0.1989	0.4846
				M	10	6	20	14	0.8571	0.4791	1.5335	0.6904	0.6429	0.1316	3.1397	-0.1000	-0.4640	0.2640
	Region	20 mg/kg	0.1090	REST OF THE WORLD	9	3	13	7	0.6190	0.2162	1.7728	0.4149	0.4286	0.0735	2.4997	-0.2051	-0.6154	0.2051
				USA	13	11	28	18	1.3162	0.9179	1.8875	0.2756	3.0556	0.5619	16.6155	0.2033	-0.0612	0.4678
	Valproate Use	20 mg/kg	0.2595	N	10	8	21	13	1.2923	0.8185	2.0404	0.4285	2.4615	0.4142	14.6302	0.1810	-0.1425	0.5044
				Y	12	6	20	12	0.8333	0.4267	1.6276	0.7178	0.6667	0.1576	2.8208	-0.1000	-0.4551	0.2551
	Stiripentol Use	20 mg/kg	0.0156	N	11	10	29	17	1.5508	1.0837	2.2192	0.0678	7.0588	0.7944	62.7212	0.3229	0.0759	0.5699
				Y	11	4	12	8	0.5455	0.2267	1.3126	0.2203	0.2857	0.0513	1.5915	-0.3030	-0.6928	0.0868
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.3057	<=8.0	9	7	10	9	0.8642	0.5760	1.2967	0.5820	0.3889	0.0290	5.2136	-0.1222	-0.4514	0.2069
				>8.0 to <=25.0	8	5	13	5	1.6250	0.6792	3.8877	0.3870	2.6667	0.4339	16.3899	0.2404	-0.1868	0.6676
				>25.0	5	2	18	11	0.6545	0.2104	2.0364	0.6175	0.4242	0.0560	3.2130	-0.2111	-0.6960	0.2738
	Current AEDs	20 mg/kg	0.2060	<3	6	5	16	9	1.4815	0.8453	2.5963	0.3512	3.8889	0.3660	41.3247	0.2708	-0.1139	0.6556
				>=3	16	9	25	16	0.8789	0.5211	1.4823	0.7461	0.7232	0.2008	2.6053	-0.0775	-0.3849	0.2299
	Prior AEDs	20 mg/kg	0.4047	<4	9	5	20	13	0.8547	0.4387	1.6653	0.6942	0.6731	0.1353	3.3473	-0.0944	-0.4806	0.2917
				>=4	13	9	21	12	1.2115	0.7216	2.0342	0.7178	1.6875	0.3916	7.2726	0.1209	-0.2074	0.4491
	SCN1A Mutation-Positive	20 mg/kg	0.8060	Truncation Variants	13	8	19	11	1.0629	0.5975	1.8908	1.0000	1.1636	0.2753	4.9187	0.0364	-0.3089	0.3817
				Missense Variants	8	5	19	12	0.9896	0.5233	1.8715	1.0000	0.9722	0.1762	5.3653	-0.0066	-0.4061	0.3929
No Known Mutation				1	1	3	2	1.5000	0.6739	3.3388	1.0000	-	-	-	0.3333	-0.2001	0.8668	
Non-Convulsive Seizures <=50pct	Age Group	20 mg/kg	0.5215	2-5 years	5	3	15	7	1.2857	0.5242	3.1533	1.0000	1.7143	0.2192	13.4065	0.1333	-0.3648	0.6315
				6-12 years	11	5	15	5	1.3636	0.5195	3.5793	0.6891	1.6667	0.3364	8.2576	0.1212	-0.2576	0.5000
				13-18 years	6	2	11	6	0.6111	0.1745	2.1407	0.6199	0.4167	0.0525	3.3058	-0.2121	-0.6905	0.2663
	Sex	20 mg/kg	0.2461	F	12	7	21	9	1.3611	0.6845	2.7067	0.4813	1.8667	0.4437	7.8524	0.1548	-0.1954	0.5049
				M	10	3	20	9	0.6667	0.2302	1.9311	0.6942	0.5238	0.1043	2.6313	-0.1500	-0.5081	0.2081
	Region	20 mg/kg	0.6708	REST OF THE WORLD	9	3	13	3	1.4444	0.3722	5.6052	0.6550	1.6667	0.2509	11.0710	0.1026	-0.2812	0.4864
				USA	13	7	28	15	1.0051	0.5461	1.8500	1.0000	1.0111	0.2703	3.7825	0.0027	-0.3252	0.3307
	Valproate Use	20 mg/kg	0.1435	N	10	6	21	8	1.5750	0.7485	3.3139	0.4414	2.4375	0.5218	11.3872	0.2190	-0.1488	0.5869
				Y	12	4	20	10	0.6667	0.2677	1.6601	0.4709	0.5000	0.1131	2.2102	-0.1667	-0.5119	0.1785
	Stiripentol Use	20 mg/kg	0.4310	N	11	7	29	14	1.3182	0.7348	2.3646	0.4882	1.8750	0.4495	7.8206	0.1536	-0.1839	0.4911
				Y	11	3	12	4	0.8182	0.2336	2.8660	1.0000	0.7500	0.1253	4.4885	-0.0606	-0.4353	0.3141
	Baseline Convulsive Seizure Frequency	20 mg/kg	0.0787	<=8.0	9	6	10	7	0.9524	0.5150	1.7613	1.0000	0.8571	0.1236	5.9437	-0.0333	-0.4523	0.3856
				>8.0 to <=25.0	8	4	13	3	2.1667	0.6458	7.2691	0.3458	3.3333	0.5018	22.1420	0.2692	-0.1461	0.6846
				>25.0	5	0	18	8	-	-	-	0.1221	-	-	-	-0.4444	-0.6740	-0.2149
	Current AEDs	20 mg/kg	0.0664	<3	6	5	16	7	1.9048	0.9836	3.6885	0.1619	6.4286	0.6050	68.3122	0.3958	0.0111	0.7806
				>=3	16	5	25	11	0.7102	0.3033	1.6629	0.5193	0.5785	0.1546	2.1646	-0.1275	-0.4266	0.1716
	Prior AEDs	20 mg/kg	0.6065	<4	9	4	20	10	0.8889	0.3792	2.0835	1.0000	0.8000	0.1648	3.8846	-0.0556	-0.4472	0.3361
				>=4	13	6	21	8	1.2115	0.5437	2.6997	0.7282	1.3929	0.3429	5.6578	0.0806	-0.2608	0.4220

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

SCN1A Mutation-Positive	20 mg/kg	0.5237 Truncation Variants	13	5	19	7	1.0440	0.4222	2.5811	1.0000	1.0714	0.2500	4.5911	0.0162	-0.3258	0.3582
		Missense Variants	8	4	19	10	0.9500	0.4210	2.1435	1.0000	0.9000	0.1724	4.6994	-0.0263	-0.4392	0.3865
		No Known Mutation	1	1	3	1	3.0000	0.6055	14.8636	1.0000	-	-	-	0.6667	0.1332	1.0000
Non-Convulsive Seizures <=75pct																
Age Group	20 mg/kg	0.8605 2-5 years	5	2	15	5	1.2000	0.3303	4.3602	1.0000	1.3333	0.1655	10.7427	0.0667	-0.4246	0.5579
		6-12 years	11	3	15	4	1.0227	0.2847	3.6743	1.0000	1.0313	0.1788	5.9476	0.0061	-0.3394	0.3515
		13-18 years	6	2	11	5	0.7333	0.1991	2.7007	1.0000	0.6000	0.0756	4.7603	-0.1212	-0.5996	0.3572
Sex	20 mg/kg	0.3389 F	12	5	21	7	1.2500	0.5071	3.0814	0.7161	1.4286	0.3308	6.1696	0.0833	-0.2608	0.4275
		M	10	2	20	7	0.5714	0.1443	2.2622	0.6749	0.4643	0.0766	2.8128	-0.1500	-0.4743	0.1743
Region	20 mg/kg	0.9910 REST OF THE WORLD	9	2	13	3	0.9630	0.1995	4.6493	1.0000	0.9524	0.1247	7.2752	-0.0085	-0.3638	0.3467
		USA	13	5	28	11	0.9790	0.4280	2.2397	1.0000	0.9659	0.2503	3.7275	-0.0082	-0.3287	0.3122
Valproate Use	20 mg/kg	0.0709 N	10	5	21	6	1.7500	0.6993	4.3795	0.4232	2.5000	0.5255	11.8945	0.2143	-0.1509	0.5795
		Y	12	2	20	8	0.4167	0.1054	1.6468	0.2479	0.3000	0.0515	1.7475	-0.2333	-0.5343	0.0676
Stiripentol Use	20 mg/kg	0.5664 N	11	5	29	11	1.1983	0.5399	2.6600	0.7275	1.3636	0.3349	5.5519	0.0752	-0.2679	0.4184
		Y	11	2	12	3	0.7273	0.1481	3.5706	1.0000	0.6667	0.0890	4.9938	-0.0682	-0.4028	0.2664
Baseline Convulsive Seizure Frequency	20 mg/kg	0.3347 <=8.0	9	5	10	7	0.7937	0.3896	1.6165	0.6499	0.5357	0.0812	3.5328	-0.1444	-0.5758	0.2869
		>8.0 to <=25.0	8	2	13	2	1.6250	0.2821	9.3600	0.6177	1.8333	0.2036	16.5118	0.0962	-0.2623	0.4546
		>25.0	5	0	18	5	-	-	-	0.5453	-	-	-	-0.2778	-0.4847	-0.0709
Current AEDs	20 mg/kg	0.1236 <3	6	4	16	6	1.7778	0.7608	4.1539	0.3476	3.3333	0.4620	24.0516	0.2917	-0.1539	0.7373
		>=3	16	3	25	8	0.5859	0.1820	1.8863	0.4783	0.4904	0.1083	2.2213	-0.1325	-0.3971	0.1321
Prior AEDs	20 mg/kg	0.4672 <4	9	2	20	7	0.6349	0.1629	2.4747	0.6749	0.5306	0.0859	3.2761	-0.1278	-0.4705	0.2150
		>=4	13	5	21	7	1.1538	0.4618	2.8831	1.0000	1.2500	0.2964	5.2723	0.0513	-0.2813	0.3838
SCN1A Mutation-Positive	20 mg/kg	0.4561 Truncation Variants	13	3	19	4	1.0962	0.2927	4.1046	1.0000	1.1250	0.2061	6.1421	0.0202	-0.2731	0.3136
		Missense Variants	8	3	19	9	0.7917	0.2876	2.1788	0.6957	0.6667	0.1229	3.6169	-0.0987	-0.5024	0.3050
		No Known Mutation	1	1	3	1	3.0000	0.6055	14.8636	1.0000	-	-	-	0.6667	0.1332	1.0000
Non-Convulsive Seizures >0pct																
Age Group	20 mg/kg	0.4814 2-5 years	5	2	15	4	1.5000	0.3840	5.8596	0.6126	0.5455	0.0652	4.5619	0.1333	-0.3509	0.6176
		6-12 years	11	2	15	5	0.5455	0.1288	2.3103	0.6576	2.2500	0.3465	14.6108	-0.1515	-0.4815	0.1784
		13-18 years	6	0	11	1	-	-	-	1.0000	-	-	-	-0.0909	-0.2608	0.0790
Sex	20 mg/kg	0.4135 F	12	3	21	5	1.0500	0.3029	3.6403	1.0000	0.9375	0.1804	4.8715	0.0119	-0.2934	0.3172
		M	10	1	20	5	0.4000	0.0537	2.9805	0.6328	3.0000	0.3006	29.9400	-0.1500	-0.4157	0.1157
Region	20 mg/kg	0.0241 REST OF THE WORLD	9	4	13	3	1.9259	0.5616	6.6041	0.3762	0.3750	0.0594	2.3661	0.2137	-0.1836	0.6110
		USA	13	0	28	7	1.3333	1.0766	1.6512	0.0765	-	-	-	-0.2500	-0.4104	-0.0896
Valproate Use	20 mg/kg	0.7298 N	10	1	21	4	0.5250	0.0671	4.1103	1.0000	2.1176	0.2049	21.8854	-0.0905	-0.3410	0.1601
		Y	12	3	20	6	0.8333	0.2543	2.7305	1.0000	1.2857	0.2546	6.4919	-0.0500	-0.3668	0.2668
Stiripentol Use	20 mg/kg	0.0071 N	11	0	29	9	1.4500	1.1359	1.8510	0.0433	-	-	-	-0.3103	-0.4787	-0.1420
		Y	11	4	12	1	4.3636	0.5715	33.3199	0.1550	0.1591	0.0146	1.7318	0.2803	-0.0441	0.6047
Baseline Convulsive Seizure Frequency	20 mg/kg	0.4403 <=8.0	9	1	10	0	0.8889	0.7056	1.1199	0.4737	-	-	-	0.1111	-0.0942	0.3164
		>8.0 to <=25.0	8	2	13	5	0.6500	0.1630	2.5921	0.6557	1.8750	0.2663	13.2023	-0.1346	-0.5346	0.2654
		>25.0	5	1	18	5	0.7200	0.1072	4.8367	1.0000	1.5385	0.1365	17.3343	-0.0778	-0.4849	0.3293
Current AEDs	20 mg/kg	0.8933 <3	6	1	16	4	0.6667	0.0920	4.8298	1.0000	1.6667	0.1472	18.8744	-0.0833	-0.4493	0.2826
		>=3	16	3	25	6	0.7813	0.2271	2.6881	1.0000	1.3684	0.2890	6.4804	-0.0525	-0.3067	0.2017
Prior AEDs	20 mg/kg	0.1052 <4	9	3	20	4	1.6667	0.4664	5.9559	0.6424	0.5000	0.0854	2.9257	0.1333	-0.2210	0.4877
		>=4	13	1	21	6	0.2692	0.0364	1.9910	0.2100	4.8000	0.5064	45.4948	-0.2088	-0.4503	0.0327
SCN1A Mutation-Positive	20 mg/kg	0.8105 Truncation Variants	13	3	19	5	0.8769	0.2524	3.0468	1.0000	1.1905	0.2297	6.1703	-0.0324	-0.3351	0.2704

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Missense Variants	8	1	19	4	0.5938	0.0780	4.5193	1.0000	1.8667	0.1749	19.9255	-0.0855	-0.3790	0.2079
No Known Mutation	1	0	3	1	1.5000	0.6739	3.3388	1.0000	-	-	-	-0.3333	-0.8668	0.2001

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc: GWEP1332B - Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
All Data			40 / 59	1.175 [-17.5%] / 0.709 [29.1%]	1.657 [-65.7%]	(1.170, 2.347)	0.0049
Age Group	0.5227	2-5 years	14 / 17	1.274 [-27.4%] / 0.638 [36.2%]	1.998 [-99.8%]	(1.085, 3.680)	0.0266
		6-12 years	15 / 24	1.200 [-20.0%] / 0.675 [32.5%]	1.778 [-77.8%]	(1.008, 3.134)	0.0467
		13-18 years	11 / 18	1.026 [-2.6%] / 0.850 [15.0%]	1.208 [-20.8%]	(0.617, 2.364)	0.5778
Sex	0.2664	Female	18 / 32	1.095 [-9.5%] / 0.811 [18.9%]	1.350 [-35.0%]	(0.810, 2.249)	0.2460
		Male	22 / 27	1.245 [-24.5%] / 0.620 [38.0%]	2.007 [-100.7%]	(1.236, 3.260)	0.0053
Region	0.2233	USA	23 / 37	1.459 [-45.9%] / 0.747 [25.3%]	1.953 [-95.3%]	(1.259, 3.029)	0.0032
		Rest of the World	17 / 22	0.835 [16.5%] / 0.659 [34.1%]	1.267 [-26.7%]	(0.733, 2.188)	0.3930
Valproic Acid Use	0.4796	Not Currently Taking	15 / 27	1.040 [-4.0%] / 0.733 [26.7%]	1.419 [-41.9%]	(0.815, 2.469)	0.2133
		Currently Taking	25 / 32	1.273 [-27.3%] / 0.694 [30.6%]	1.834 [-83.4%]	(1.161, 2.897)	0.0099
Stiripentol Use	0.2076	Not Currently Taking	17 / 38	2.019 [-101.9%] / 0.895 [10.5%]	2.255 [-125.5%]	(1.495, 3.402)	0.0002
		Currently Taking	23 / 21	0.729 [27.1%] / 0.479 [52.1%]	1.523 [-52.3%]	(0.966, 2.403)	0.0699
Baseline Convulsive Seizure Frequency	0.3302	<=7	14 / 20	1.241 [-24.1%] / 0.706 [29.4%]	1.758 [-75.8%]	(1.008, 3.065)	0.0469
		>7 to <=21	16 / 16	0.966 [3.4%] / 0.796 [20.4%]	1.214 [-21.4%]	(0.653, 2.258)	0.5355
		>21	10 / 23	1.737 [-73.7%] / 0.680 [32.0%]	2.556 [-155.6%]	(1.170, 5.586)	0.0192
Number of concurrent AEDs	0.6139	<3	12 / 19	1.505 [-50.5%] / 0.816 [18.4%]	1.844 [-84.4%]	(1.032, 3.296)	0.0392
		>=3	28 / 40	1.023 [-2.3%] / 0.666 [33.4%]	1.536 [-53.6%]	(1.011, 2.335)	0.0445

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

01-NOV-2023 13:19

Page 1 of 2

C:\SASData\elypcd\CBD\PhaseII\GWEP1332 Dravet\Reporting\Part B\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1332B LSF1 NBR (subgroup s).sas

Adhoc: GWEP1332B Negative Binomial Regression Effect Modification Analysis of Longest Total Seizure Free Interval Count during Baseline and Treatment Period (ITT Analysis Set, Patients Taking CBD - CBZ + All Placebos)

Factor	Inte- raction P-value	Factor Level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	P-value
Number of prior AEDs	0.7285	<4	21 / 27	1.204 [-20.4%] / 0.683 [31.7%]	1.762 [-76.2%]	(1.076, 2.886)	0.0249
		>=4	19 / 32	1.142 [-14.2%] / 0.733 [26.7%]	1.557 [-55.7%]	(0.942, 2.574)	0.0832
SCN1A Mutation	0.1182	Truncation Variants	25 / 27	0.919 [8.1%] / 0.679 [32.1%]	1.353 [-35.3%]	(0.842, 2.174)	0.2090
		No Known Mutation	3 / 3	1.268 [-26.8%] / 1.027 [-2.7%]	1.235 [-23.5%]	(0.293, 5.198)	0.7714
		Missense Variants	12 / 29	2.072 [-107.2%] / 0.717 [28.3%]	2.891 [-189.1%]	(1.625, 5.142)	0.0004

Total seizures include all seizure types combined.

Treatment period is defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.

01-NOV-2023 13:19

Page 2 of 2

C:\SASData\elypdc\CBD\PhaseII\GWEP1332 Dravet\Reporting\Part B\Market Access\20231019 Germany HTA CBD-CBZ vs all PBO\GWEP1332B LSF1 NBR (subgroup s).sas

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B CGIC Responder [VMI, MI, SI] (subgroups) (ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction	Factor Level	Active		Placebo		Relative Risk [2]			p-value	Odds Ratio			Risk Difference		
					n (event)	N (total)	n (event)	N (total)	Relative	95% Lower	95% Upper		Odds Ratio	95% Lower	95% Upper	Risk	95% Lower	95% Upper
End of Treatment	Age Group	20 mg/kg	0.6704	2-5 years	12	10	16	7	1.9048	1.0344	3.5073	0.0540	0.1556	0.0254	0.9517	0.3958	0.0740	0.7176
6-12 years				14	9	23	8	1.8482	0.9341	3.6567	0.1014	0.2963	0.0738	1.1893	0.2950	-0.0226	0.6127	
13-18 years				11	5	18	5	1.6364	0.6099	4.3901	0.4320	0.4615	0.0958	2.2237	0.1768	-0.1830	0.5365	
Last Visit (LOCF)	Age Group	20 mg/kg	0.8391	2-5 years	13	10	16	7	1.7582	0.9361	3.3024	0.1297	0.2333	0.0460	1.1848	0.3317	-0.0022	0.6657
6-12 years				15	9	24	8	1.8000	0.8933	3.6270	0.1837	0.3333	0.0876	1.2691	0.2667	-0.0448	0.5782	
13-18 years				11	5	18	5	1.6364	0.6099	4.3901	0.4320	0.4615	0.0958	2.2237	0.1768	-0.1830	0.5365	
End of Treatment	Sex	20 mg/kg	0.7307	F	17	12	30	13	1.6290	0.9767	2.7167	0.1273	0.3186	0.0896	1.1332	0.2725	-0.0074	0.5525
Last Visit (LOCF)				M	20	12	27	7	2.3143	1.1140	4.8078	0.0343	0.2333	0.0674	0.8075	0.3407	0.0698	0.6117
Last Visit (LOCF)	Sex	20 mg/kg	0.9720	F	17	12	31	13	1.6833	1.0053	2.8186	0.0750	0.3009	0.0850	1.0650	0.2865	0.0089	0.5642
End of Treatment				M	22	12	27	7	2.1039	1.0008	4.4228	0.0758	0.2917	0.0877	0.9704	0.2862	0.0205	0.5519
End of Treatment	Region	20 mg/kg	0.8619	REST OF THE WORLD	16	9	21	5	2.3625	0.9812	5.6883	0.0857	0.2431	0.0594	0.9941	0.3244	0.0206	0.6282
Last Visit (LOCF)				USA	21	15	36	15	1.7143	1.0695	2.7477	0.0531	0.2857	0.0900	0.9074	0.2976	0.0461	0.5491
Last Visit (LOCF)	Region	20 mg/kg	0.8808	REST OF THE WORLD	17	9	21	5	2.2235	0.9161	5.3967	0.0943	0.2778	0.0696	1.1085	0.2913	-0.0078	0.5904
End of Treatment				USA	22	15	37	15	1.6818	1.0371	2.7274	0.0596	0.3182	0.1047	0.9670	0.2764	0.0256	0.5272
End of Treatment	Valproate Use	20 mg/kg	0.5770	N	14	8	26	9	1.6508	0.8228	3.3121	0.1978	0.3971	0.1048	1.5037	0.2253	-0.0920	0.5425
Last Visit (LOCF)				Y	23	16	31	11	1.9605	1.1354	3.3852	0.0267	0.2406	0.0759	0.7625	0.3408	0.0884	0.5933
Last Visit (LOCF)	Valproate Use	20 mg/kg	0.5948	N	15	8	27	9	1.6000	0.7841	3.2648	0.3256	0.4375	0.1202	1.5925	0.2000	-0.1088	0.5088
End of Treatment				Y	24	16	31	11	1.8788	1.0812	3.2648	0.0306	0.2750	0.0894	0.8455	0.3118	0.0590	0.5647
End of Treatment	Stiripentol Use	20 mg/kg	0.4826	N	15	13	37	16	2.0042	1.3180	3.0476	0.0055	0.1172	0.0231	0.5950	0.4342	0.1996	0.6689
Last Visit (LOCF)				Y	22	11	20	4	2.5000	0.9467	6.6017	0.0577	0.2500	0.0630	0.9917	0.3000	0.0273	0.5727
Last Visit (LOCF)	Stiripentol Use	20 mg/kg	0.6275	N	16	13	38	16	1.9297	1.2417	2.9990	0.0154	0.1678	0.0409	0.6881	0.3914	0.1440	0.6389
End of Treatment				Y	23	11	20	4	2.3913	0.9020	6.3393	0.1074	0.2727	0.0695	1.0705	0.2783	0.0092	0.5473
End of Treatment	Baseline Convulsive Seizure Frequency	20 mg/kg	0.2550	<=8.0	13	10	20	8	1.9231	1.0409	3.5528	0.0724	0.2000	0.0416	0.9613	0.3692	0.0553	0.6832
Last Visit (LOCF)				>8.0 to <=25.0	16	11	15	4	2.5781	1.0462	6.3531	0.0320	0.1653	0.0348	0.7849	0.4208	0.1020	0.7397
End of Treatment				>25.0	8	3	22	8	1.0313	0.3603	2.9517	1.0000	0.9524	0.1785	5.0811	0.0114	-0.3797	0.4025
Last Visit (LOCF)	Baseline Convulsive Seizure Frequency	20 mg/kg	0.2341	<=8.0	14	10	20	8	1.7857	0.9503	3.3554	0.0921	0.2667	0.0617	1.1535	0.3143	-0.0052	0.6338
End of Treatment				>8.0 to <=25.0	16	11	15	4	2.5781	1.0462	6.3531	0.0320	0.1653	0.0348	0.7849	0.4208	0.1020	0.7397
Last Visit (LOCF)				>25.0	9	3	23	8	0.9583	0.3254	2.8225	1.0000	1.0667	0.2090	5.4443	-0.0145	-0.3788	0.3498
End of Treatment	Current AEDs	20 mg/kg	0.9142	<3	12	9	18	8	1.6875	0.9159	3.1092	0.1414	0.2667	0.0536	1.3256	0.3056	-0.0302	0.6413
Last Visit (LOCF)				>=3	25	15	39	12	1.9500	1.1036	3.4456	0.0370	0.2963	0.1037	0.8468	0.2923	0.0518	0.5328

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Current AEDs	20 mg/kg	0.6911 <3 >=3	12	9	19	8	1.7813	0.9580	3.3120	0.1378	0.2424	0.0493	1.1920	0.3289	-0.0017	0.6596	
			27	15	39	12	1.8056	1.0118	3.2221	0.0738	0.3556	0.1283	0.9852	0.2479	0.0110	0.4847	
End of Treatment																	
Prior AEDs	20 mg/kg	0.9557 <4 >=4	19	13	26	10	1.7789	1.0018	3.1589	0.0712	0.2885	0.0827	1.0058	0.2996	0.0191	0.5800	
			18	11	31	10	1.8944	1.0097	3.5546	0.0734	0.3030	0.0903	1.0166	0.2885	0.0096	0.5675	
Last Visit (LOCF)																	
Prior AEDs	20 mg/kg	0.9835 <4 >=4	20	13	26	10	1.6900	0.9434	3.0273	0.1362	0.3365	0.1002	1.1306	0.2654	-0.0151	0.5459	
			19	11	32	10	1.8526	0.9757	3.5177	0.0815	0.3306	0.1018	1.0739	0.2664	-0.0076	0.5404	
End of Treatment																	
SCN1A Mutation-Positive	20 mg/kg	0.9004 Truncation Variants	24	15	26	9	1.8056	0.9786	3.3312	0.0882	0.3176	0.1000	1.0090	0.2788	0.0125	0.5452	
			Missense Variants	10	7	29	10	2.0300	1.0648	3.8700	0.0711	0.2256	0.0477	1.0672	0.3552	0.0226	0.6877
			No Known Mutation	3	2	2	1	1.3333	0.2691	6.6061	1.0000	0.5000	0.0128	19.5624	0.1667	-0.7078	1.0000
Last Visit (LOCF)																	
SCN1A Mutation-Positive	20 mg/kg	0.9733 Truncation Variants	25	15	26	9	1.7333	0.9346	3.2147	0.0950	0.3529	0.1132	1.1004	0.2538	-0.0113	0.5190	
			Missense Variants	11	7	29	10	1.8455	0.9427	3.6127	0.1530	0.3008	0.0707	1.2790	0.2915	-0.0412	0.6243
			No Known Mutation	3	2	3	1	2.0000	0.3342	11.9693	1.0000	0.2500	0.0084	7.4519	0.3333	-0.4211	1.0000

LOCF = last observation carried forward; MI = much improved; VMI = very much improved; SI = slightly improved.

End of treatment = The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF page (Visit 8: Day 99).

Last visit = Last visit is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

Adhoc Table: GWEP1332B CGIC Responder [VMI, MI] (subgroups) (ITT Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)	Odds Ratio			Risk Difference		
					N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI		Odds Ratio	95% Lower CI	95% Upper CI	Risk Difference	95% Lower CI	95% Upper CI
End of Treatment	Age Group	20 mg/kg	0.4239	2-5 years	12	6	16	3	2.6667	0.8306	8.5612	0.1139	0.2308	0.0426	1.2508	0.3125	-0.0290	0.6540
6-12 years				14	5	23	2	4.1071	0.9172	18.3923	0.0801	0.1714	0.0279	1.0541	0.2702	-0.0060	0.5463	
13-18 years				11	2	18	3	1.0909	0.2149	5.5366	1.0000	0.9000	0.1254	6.4589	0.0152	-0.2705	0.3008	
Last Visit (LOCF)	Age Group	20 mg/kg	0.4660	2-5 years	13	6	16	3	2.4615	0.7587	7.9861	0.2256	0.2692	0.0510	1.4200	0.2740	-0.0576	0.6057
6-12 years				15	5	24	2	4.0000	0.8858	18.0636	0.0846	0.1818	0.0300	1.1023	0.2500	-0.0129	0.5129	
13-18 years				11	2	18	3	1.0909	0.2149	5.5366	1.0000	0.9000	0.1254	6.4589	0.0152	-0.2705	0.3008	
End of Treatment	Sex	20 mg/kg	0.1414	F	17	5	30	6	1.4706	0.5266	4.1065	0.4933	0.6000	0.1518	2.3714	0.0941	-0.1655	0.3537
M				20	8	27	2	5.4000	1.2825	22.7361	0.0111	0.1200	0.0220	0.6539	0.3259	0.0896	0.5623	
Last Visit (LOCF)	Sex	20 mg/kg	0.1948	F	17	5	31	6	1.5196	0.5431	4.2519	0.4856	0.5760	0.1461	2.2712	0.1006	-0.1568	0.3580
M				22	8	27	2	4.9091	1.1589	20.7948	0.0289	0.1400	0.0260	0.7526	0.2896	0.0656	0.5135	
End of Treatment	Region	20 mg/kg	0.8802	REST OF THE WORLD	16	3	21	1	3.9375	0.4506	34.4065	0.2962	0.2167	0.0203	2.3142	0.1399	-0.0720	0.3517
USA				21	10	36	7	2.4490	1.0981	5.4615	0.0364	0.2655	0.0808	0.8722	0.2817	0.0321	0.5314	
Last Visit (LOCF)	Region	20 mg/kg	0.8921	REST OF THE WORLD	17	3	21	1	3.7059	0.4227	32.4882	0.3068	0.2333	0.0219	2.4811	0.1289	-0.0740	0.3317
USA				22	10	37	7	2.4026	1.0699	5.3955	0.0399	0.2800	0.0865	0.9069	0.2654	0.0220	0.5087	
End of Treatment	Valproate Use	20 mg/kg	0.4723	N	14	5	26	5	1.8571	0.6462	5.3373	0.2779	0.4286	0.0990	1.8547	0.1648	-0.1283	0.4580
Y				23	8	31	3	3.5942	1.0693	12.0812	0.0389	0.2009	0.0463	0.8717	0.2511	0.0303	0.4718	
Last Visit (LOCF)	Valproate Use	20 mg/kg	0.4721	N	15	5	27	5	1.8000	0.6194	5.2313	0.4508	0.4545	0.1069	1.9330	0.1481	-0.1318	0.4281
Y				24	8	31	3	3.4444	1.0218	11.6110	0.0428	0.2143	0.0497	0.9247	0.2366	0.0212	0.4520	
End of Treatment	Stiripental Use	20 mg/kg	0.7527	N	15	9	37	7	3.1714	1.4470	6.9507	0.0069	0.1556	0.0415	0.5826	0.4108	0.1326	0.6890
Y				22	4	20	1	3.6364	0.4426	29.8732	0.3465	0.2368	0.0241	2.3252	0.1318	-0.0555	0.3192	
Last Visit (LOCF)	Stiripental Use	20 mg/kg	0.7898	N	16	9	38	7	3.0536	1.3769	6.7722	0.0091	0.1756	0.0486	0.6341	0.3783	0.1058	0.6508
Y				23	4	20	1	3.4783	0.4226	28.6259	0.3508	0.2500	0.0255	2.4483	0.1239	-0.0581	0.3059	

Dossier zur Nutzenbewertung - Modul 4A Anhang 4G

End of Treatment																
Baseline Convulsive Seizure Frequency	20 mg/kg	0.8306 <=8.0	13	5	20	2	3.8462	0.8723	16.9591	0.0838	0.1778	0.0283	1.1185	0.2846	-0.0107	0.5800
		>8.0 to <=25.0	16	5	15	2	2.3438	0.5331	10.3044	0.3944	0.3385	0.0545	2.1012	0.1792	-0.1057	0.4641
		>25.0	8	3	22	4	2.0625	0.5854	7.2667	0.3446	0.3704	0.0615	2.2298	0.1932	-0.1790	0.5654
Last Visit (LOCF)																
Baseline Convulsive Seizure Frequency	20 mg/kg	0.8396 <=8.0	14	5	20	2	3.5714	0.8042	15.8598	0.0969	0.2000	0.0323	1.2401	0.2571	-0.0262	0.5405
		>8.0 to <=25.0	16	5	15	2	2.3438	0.5331	10.3044	0.3944	0.3385	0.0545	2.1012	0.1792	-0.1057	0.4641
		>25.0	9	3	23	4	1.9167	0.5311	6.9167	0.3702	0.4211	0.0727	2.4374	0.1594	-0.1853	0.5042
End of Treatment																
Current AEDs	20 mg/kg	0.1090 <3	12	8	18	3	4.0000	1.3212	12.1103	0.0086	0.1000	0.0178	0.5615	0.5000	0.1825	0.8175
		>=3	25	5	39	5	1.5600	0.5023	4.8453	0.4940	0.5882	0.1514	2.2852	0.0718	-0.1169	0.2605
Last Visit (LOCF)																
Current AEDs	20 mg/kg	0.0788 <3	12	8	19	3	4.2222	1.3876	12.8479	0.0070	0.0938	0.0168	0.5240	0.5088	0.1957	0.8219
		>=3	27	5	39	5	1.4444	0.4627	4.5089	0.7286	0.6471	0.1676	2.4975	0.0570	-0.1232	0.2372
End of Treatment																
Prior AEDs	20 mg/kg	0.2813 <4	19	6	26	5	1.6421	0.5869	4.5945	0.4851	0.5159	0.1306	2.0376	0.1235	-0.1347	0.3816
		>=4	18	7	31	3	4.0185	1.1847	13.6312	0.0255	0.1684	0.0368	0.7712	0.2921	0.0440	0.5402
Last Visit (LOCF)																
Prior AEDs	20 mg/kg	0.2685 <4	20	6	26	5	1.5600	0.5548	4.3862	0.4935	0.5556	0.1417	2.1775	0.1077	-0.1439	0.3593
		>=4	19	7	32	3	3.9298	1.1514	13.4128	0.0278	0.1773	0.0392	0.8032	0.2747	0.0354	0.5139
End of Treatment																
SCN1A Mutation-Positive	20 mg/kg	0.6851 Truncation Variants	24	7	26	4	1.8958	0.6336	5.6730	0.3139	0.4416	0.1109	1.7585	0.1378	-0.0909	0.3665
		Missense Variants	10	4	29	3	3.8667	1.0401	14.3751	0.0569	0.1731	0.0304	0.9864	0.2966	-0.0267	0.6198
		No Known Mutation	3	2	2	1	1.3333	0.2691	6.6061	1.0000	0.5000	0.0128	19.5624	0.1667	-0.7078	1.0000
Last Visit (LOCF)																
SCN1A Mutation-Positive	20 mg/kg	0.7434 Truncation Variants	25	7	26	4	1.8200	0.6064	5.4620	0.3238	0.4675	0.1179	1.8535	0.1262	-0.0979	0.3502
		Missense Variants	11	4	29	3	3.5152	0.9331	13.2423	0.0755	0.2019	0.0364	1.1208	0.2602	-0.0449	0.5653
		No Known Mutation	3	2	3	1	2.0000	0.3342	11.9693	1.0000	0.2500	0.0084	7.4519	0.3333	-0.4211	1.0000

LOCF = last observation carried forward; MI = much improved; VMI = very much improved; SI = slightly improved.

End of treatment = The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF page (Visit 8: Day 99).

Last visit = Last visit is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] Results are not reported (-) when the event count in one study arm is 0.

Adhoc Table: GWEP1332B Any AE (subgroups) (Safety Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	
Age Group	20 mg/kg	0.8131	2-5 years		14	14	17	13	1.2889	0.9714	1.7101	0.1075
				6-12 years	15	15	24	19	1.2420	0.9907	1.5570	0.1359
				13-18 years	11	10	18	12	1.3300	0.9019	1.9613	0.2021
Sex	20 mg/kg	0.2033	F		18	17	32	26	1.1470	0.9258	1.4210	0.3978
				M	22	22	27	18	1.4806	1.1276	1.9441	0.0025
Region	20 mg/kg	0.3077	REST OF THE WORLD		17	17	22	14	1.5421	1.1170	2.1290	0.0056
				USA	23	22	37	30	1.1680	0.9674	1.4103	0.1377
Valproate Use	20 mg/kg	0.5925	N		15	14	27	18	1.3716	1.0073	1.8677	0.0679
				Y	25	25	32	26	1.2213	1.0229	1.4583	0.0299
Stiripentol Use	20 mg/kg	0.7336	N		17	17	38	29	1.2853	1.0582	1.5612	0.0444
				Y	23	22	21	15	1.3306	0.9960	1.7777	0.0420
Baseline Convulsive Seizure Frequency	20 mg/kg	0.7767	<=8.0		14	13	20	14	1.3265	0.9617	1.8297	0.1978
				>8.0 to <=25.0	16	16	16	15	1.0667	0.9399	1.2105	1.0000
				>25.0	10	10	23	15	1.5333	1.1377	2.0666	0.0715
Current AEDs	20 mg/kg	0.9931	<3		12	12	19	15	1.2407	0.9567	1.6090	0.1389
				>=3	28	27	40	29	1.3179	1.0692	1.6246	0.0112
Prior AEDs	20 mg/kg	0.9005	<4		21	21	27	23	1.1644	0.9783	1.3859	0.1210
				>=4	19	18	32	21	1.4198	1.0741	1.8766	0.0201
SCN1A Mutation-Positive	20 mg/kg	0.8169	Truncation Variants		25	24	27	22	1.1726	0.9540	1.4414	0.1928
				Missense Variants	12	12	29	20	1.4071	1.0777	1.8373	0.0392
				No Known Mutation	3	3	3	2	1.4000	0.6016	3.2580	1.0000

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc Table: GWEP1332B Maximal AE mild (subgroups) (Safety Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction		Active		Placebo		Relative Risk [2]			p-value (vs. Placebo)
			p-value [1]	Factor Level	N (total)	n (event)	N (total)	n (event)	Relative Risk	95% Lower CI	95% Upper CI	
Age Group	20 mg/kg	0.7150	2-5 years	14	7	17	11	0.7727	0.4113	1.4517	0.4809	
			6-12 years	15	5	24	15	0.5333	0.2445	1.1633	0.1053	
			13-18 years	11	5	18	10	0.8182	0.3796	1.7635	0.7104	
Sex	20 mg/kg	0.7391	F	18	8	32	21	0.6772	0.3814	1.2025	0.2324	
			M	22	9	27	15	0.7364	0.4021	1.3485	0.3931	
Region	20 mg/kg	0.9179	REST OF THE WORLD	17	6	22	12	0.6471	0.3062	1.3673	0.3340	
			USA	23	11	37	24	0.7373	0.4525	1.2015	0.2817	
Valproate Use	20 mg/kg	0.0184	N	15	10	27	15	1.2000	0.7338	1.9623	0.5306	
			Y	25	7	32	21	0.4267	0.2169	0.8395	0.0074	
Stiripentol Use	20 mg/kg	0.6547	N	17	8	38	23	0.7775	0.4415	1.3691	0.3908	
			Y	23	9	21	13	0.6321	0.3434	1.1636	0.2271	
Baseline Convulsive Seizure Frequency	20 mg/kg	0.6426	<=8.0	14	6	20	11	0.7792	0.3781	1.6060	0.7283	
			>8.0 to <=25.0	16	9	16	13	0.6923	0.4232	1.1324	0.2524	
			>25.0	10	2	23	12	0.3833	0.1045	1.4064	0.1312	
Current AEDs	20 mg/kg	0.3838	<3	12	7	19	12	0.9236	0.5126	1.6641	1.0000	
			>=3	28	10	40	24	0.5952	0.3408	1.0396	0.0837	
Prior AEDs	20 mg/kg	0.4790	<4	21	10	27	20	0.6429	0.3895	1.0610	0.0773	
			>=4	19	7	32	16	0.7368	0.3721	1.4590	0.3984	
SCN1A Mutation-Positive	20 mg/kg	0.7348	Truncation Variants	25	13	27	18	0.7800	0.4917	1.2374	0.3972	
			Missense Variants	12	3	29	16	0.4531	0.1612	1.2736	0.0977	
			No Known Mutation	3	1	3	2	0.5000	0.0835	2.9923	1.0000	

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.

Adhoc Table: GWEP1332B Maximal AE moderate (Safety Analysis Set, Patients Taking CBD + Clobazam vs. All Placebos)

Analysis	Factor	Treatment	Interaction p-value [1]	Factor Level	Active		Placebo		Relative Risk	Relative Risk [2]		p-value (vs. Placebo)
					N (total)	n (event)	N (total)	n (event)		95% Lower CI	95% Upper CI	
Age Group	20 mg/kg	0.7002	2-5 years	14	4	17	0	10.8000	0.6308	184.8979	0.0318	
				15	7	24	4	2.6042	0.9716	6.9801	0.0685	
				11	4	18	2	2.8500	0.7266	11.1791	0.1638	
Sex	20 mg/kg	0.4167	F	18	6	32	4	2.6667	0.8652	8.2195	0.1381	
				22	9	27	2	5.5227	1.3282	22.9631	0.0071	
Region	20 mg/kg	0.2503	REST OF THE WORLD	17	7	22	1	9.0588	1.2292	66.7632	0.0125	
				23	8	37	5	2.5739	0.9576	6.9184	0.0627	
Valproate Use	20 mg/kg	0.2614	N	15	2	27	2	1.8000	0.2815	11.5114	0.6080	
				25	13	32	4	4.1600	1.5442	11.2072	0.0028	
Stiripentol Use	20 mg/kg	0.5122	N	17	7	38	5	3.1294	1.1570	8.4641	0.0330	
				23	8	21	1	7.3043	0.9956	53.5910	0.0227	
Baseline Convulsive Seizure Frequency	20 mg/kg	0.8802	<=8.0	14	5	20	2	3.5714	0.8042	15.8598	0.0969	
				16	6	16	1	6.0000	0.8117	44.3512	0.0829	
				10	4	23	3	3.0667	0.8359	11.2511	0.1605	
Current AEDs	20 mg/kg	0.8665	<3	12	5	19	2	3.9583	0.9083	17.2498	0.0776	
				28	10	40	4	3.5714	1.2446	10.2486	0.0146	
Prior AEDs	20 mg/kg	0.5559	<4	21	6	27	1	7.7143	1.0043	59.2534	0.0335	
				19	9	32	5	3.0316	1.1910	7.7166	0.0227	
SCN1A Mutation-Positive	20 mg/kg	0.7769	Truncation Variants	25	8	27	3	2.6154	0.8495	8.0521	0.0928	
				12	5	29	3	3.6264	1.1238	11.7019	0.0345	
				3	2	3	0	5.0000	0.3355	74.5196	0.4000	

Adverse events (AE) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Multiple entries for an individual under each system organ class/preferred term are only counted once. A TEAE is defined as an AE with a start date on or after the first dose of investigational medicinal product.

Table includes results for TEAEs where there are 10 or more subjects in at least one study arm within a subgroup.

[1] P-value from a test of interaction based upon a Breslow-Day test of homogeneity.

[2] When TEAE counts in both groups are non-zero, p-values are from Fisher's Exact tests. When the TEAE count in either subgroup is 0, relative risks and 95 % confidence intervals are calculated after adding 0.5 to the count in both groups, p-values are from Fisher's Exact tests based on the original data. Results are not reported (-) when the TEAE count in both groups is 0.