## Dossier zur Nutzenbewertung gemäß § 35a SGB V

Tezepelumab (Tezspire®)

AstraZeneca GmbH

## Modul 4 A – Anhang 4-G-11

Add-on-Erhaltungstherapie bei Erwachsenen und Jugendlichen ab 12 Jahren mit schwerem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus eines weiteren Arzneimittels zur Erhaltungstherapie unzureichend kontrolliert ist

Ergänzende Ergebnisse Studien NAVIGATOR, PATHWAY, DRI12544, QUEST Indirekte Vergleiche auf Basis randomisierter kontrollierter Studien

Stand: 11.11.2022

MT1IE_ILIDI: AAER during 24 weeks treatment period - indirect comparison with pooled QR - pooled NP set, DITTL	_
MT1IE_ILIN2: AAER during 24 weeks treatment period -complete follow-up period as offset - pooled NP set, DITTL	_
NT1IE_ILIN2: AAER during 24 weeks treatment period -complete follow-up period as offset - NAVIGATOR, DITTL	_
PT3IE_ILIN2: AAER during 24 weeks treatment period -complete follow-up period as offset - PATHWAY, DITTL	_
MT1IE_ILIND: AAER during 24 weeks treatment period by subgroups relevant for ITC - complete follow-up period as offset - pooled NP set, DITTL	_
MT1IES_ILIDI: Severe AAER during 24 weeks treatment period - indirect comparison with pooled QR - pooled NP set, DITTL	_
MT1IES_ILIN2: Severe AAER during 24 weeks treatment period -complete follow-up period as offset - pooled NP set, DITTL	_
NT1IES_ILIN2: Severe AAER during 24 weeks treatment period -complete follow-up period as offset - NAVIGATOR, DITTL	_
PT3IES_ILIN2: Severe AAER during 24 weeks treatment period -complete follow-up period as offset - PATHWAY, DITTL	_
MT1IES_ILIND: Severe AAER during 24 weeks treatment period by subgroups relevant for ITC - complete follow-up period as offset - pooled NP set, DITTL	_
MT1IE_ICIDI: AAER during 24 weeks treatment period - indirect comparison with pooled QR - pooled NP set, DITTL - patients without OCS medications	_
MT1IES_ICIDI: Severe AAER during 24 weeks treatment period - indirect comparison with pooled QR - pooled NP set, DITTL - patients without OCS medications	-
MT1IA_SLII0: Incidence of TEAEs during 24 weeks treatment period - pooled NP set, DSAFL	_
NT1IA_SLII0: Incidence of TEAEs during 24 weeks treatment period - NAVIGATOR, DSAFL	_
PT3IA_SLII0: Incidence of TEAEs during 24 weeks treatment period - PATHWAY, DSAFL	_
MT1IA_SLIDI: Incidence of TEAEs during 24 weeks treatment period - indirect comparison with pooled QC - pooled NP set, DSAFL	_
MT1IA_SLIID: Incidence of TEAEs during 24 weeks treatment period by subgroups relevant for ITC - pooled NP set, DSAFL	_
MT1IAN_SLII0: Incidence of non-severe TEAEs during 24 weeks treatment period - pooled NP set, DSAFL	_
NT1IAN_SLII0: Incidence of non-severe TEAEs during 24 weeks treatment period - NAVIGATOR, DSAFL	_
PT3IAN_SLII0: Incidence of non-severe TEAEs during 24 weeks treatment period - PATHWAY, DSAFL	_
MT1IAC_SLII0: Incidence of severe TEAEs during 24 weeks treatment period - pooled NP set, DSAFL	_
NT1IAC_SLII0: Incidence of severe TEAEs during 24 weeks treatment period - NAVIGATOR, DSAFL	_
PT3IAC_SLII0: Incidence of severe TEAEs during 24 weeks treatment period - PATHWAY, DSAFL	_
MT1IAS_SLII0: Incidence of serious TEAEs during 24 weeks treatment period - pooled NP set, DSAFL	_
NT1IAS_SLII0: Incidence of serious TEAEs during 24 weeks treatment period - NAVIGATOR, DSAFL	_
PT3IAS_SLII0: Incidence of serious TEAEs during 24 weeks treatment period - PATHWAY, DSAFL	_
MT1IAS_SLIDI: Incidence of serious TEAEs during 24 weeks treatment period - indirect comparison with pooled QC - pooled NP set, DSAFL	_
MT1IAS_SLIID: Incidence of serious TEAEs during 24 weeks treatment period by subgroups relevant for ITC - pooled NP set, DSAFL	_
MT1IAT_SLII0: Incidence of TEAEs leading to study drug discontinuation during 24 weeks treatment period - pooled NP set, DSAFL	_
NT1IAT_SLII0: Incidence of TEAEs leading to study drug discontinuation during 24 weeks treatment period - NAVIGATOR, DSAFL	_

PT3IAT_SLII0: Incidence of TEAEs leading to study drug discontinuation during 24 weeks treatment period - PATHWAY, DSAFL	. 33
MT1IAD_SLII0: Incidence of fatal TEAEs during 24 weeks treatment period - pooled NP set, DSAFL	. 34
NT1IAD_SLII0: Incidence of fatal TEAEs during 24 weeks treatment period - NAVIGATOR, DSAFL	35
PT3IAD_SLII0: Incidence of fatal TEAEs during 24 weeks treatment period - PATHWAY, DSAFL	36
MT1IA_SCIDI: Incidence of TEAEs during 24 weeks treatment period - indirect comparison with pooled QR - pooled NP set, DSAFL - patients without OCS medi-	
cations	37
MT1IAS_SCIDI: Incidence of serious TEAEs during 24 weeks treatment period - indirect comparison with pooled QR - pooled NP set, DSAFL - patients without	
OCS medications	38

Value Dossier Analysis: Meta\_analysis, NAVIGATOR, QUEST, DRI12544

Data Cut Date: ITC

Program Name: I\_aaer\_a.sas Run Date: 11MAY2022:07:55:57

Page 1 of 1

Table MT1IE\_ILIDI: AAER during 24 weeks treatment period - indirect comparison with pooled QR  $_{\rm DITTL}$ 

		Indire	ect comparison (Buc	her)
Variable	Study	Risk Ratio	95% CI	p-value
AAER during 24 weeks treatment period	Pooled NP	0.432	(0.346, 0.539)	<0.001 *
	Pooled QR	0.470	(0.330, 0.650)	<0.01 *
	Pooled NP/Pooled QR	0.919	(0.620, 1.361)	0.672

Note: DITTL = Dossier Label Intent-to-Treat Set.

CI = confidence interval. Pooled NP = Pooled NAVIGATOR (adult)/PATHWAY. Pooled QR = pooled QUEST/DRI12522.

AAER = annual asthma exacerbation rates.

Source tables: MT1IE\_ILIN2, IT1E\_ILMN0.

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Table MT1IE\_ILIN2: AAER during 24 weeks treatment period -complete follow-up period as offset

Page 1 of 1

Program Name: M\_indirect\_a.sas

Run Date: 09MAY2022:14:52:25

AAER during 24	weeks tr	eatment	period		Adjı	sted rates		Rate ratio		
Treatment	N	nev	Time at risk (years)	Crude rate	Estimate	95% CI	Estimate	95% CI	p-value	
Tezepelumab	446 436	182 410	218.9 214 1	0.83	0.83	(0.70, 0.99) (1.68, 2.21)	0.432	(0.346, 0.539)	<0.001	*

Source Data: aaer, created on: 27APR2022

MT1IE\_ILIN2

Note: DITTL = Dossier Label Intent-to-Treat Set.

N = total number of patients in analysis set. nev = number of events within considered period. NE = not evaluable. 95% CI = 95% confidence interval coming from a negative binomial model.

A negative binomial model was applied with factors treatment. The logarithm of follow-up time (including duration of exacerbations) was used as offset. No additional factors were considered to achieve robust results across all analyses.

Value Dossier Analysis: D5180C00007

Data Cut Date: 290ct2020

Table NT1IE\_ILIN2: AAER during 24 weeks treatment period -complete follow-up period as offset DITTL

Page 1 of 1

Program Name: N\_indirect\_a.sas

Run Date: 09MAY2022:14:44:22

AAER during 24	weeks tr	eatment	period		Adjı	sted rates		Rate ratio		
Treatment	N	nev	Time at risk (years)	Crude rate	Estimate	95% CI	Estimate	95% CI	p-value	
Tezepelumab	395	182	194.6	0.94	0.93	(0.78, 1.11)	0.463	(0.370, 0.580)	<0.001	*
Placebo	391	386	192.2	2.01	2.02	(1.75. 2.32)		, , ,		

NT1IE\_ILIN2 5

Note: DITTL = Dossier Label Intent-to-Treat Set.

N = total number of patients in analysis set. nev = number of events within considered period. NE = not evaluable. 95% CI = 95% confidence interval coming from a negative binomial model.

A negative binomial model was applied with factors treatment. The logarithm of follow-up time (including duration of exacerbations) was used as offset. No additional factors were considered to achieve robust results across all analyses.

Source Data: aaer, created on: 27APR2022

Value Dossier Analysis: CD-RI-MEDI9929-1146

Data Cut Date: 06JUN2017

Program Name: P\_indirect\_a.sas Run Date: 09MAY2022:14:48:38

Page 1 of 1

Table PT3IE\_ILIN2: AAER during 24 weeks treatment period -complete follow-up period as offset DITTL

AAER during 24	weeks to	reatment	period		Adjı	usted rates		Rate ratio		
Treatment	N	nev	Time at risk (years)	Crude rate	Estimate	95% CI	Estimate	95% CI	p-value	
Tezepelumab	66	7	31.3	0.22	0.22	(0.10, 0.49)	0.204	(0.084, 0.497)	<0.001	*
Placebo	65	35	31.9	1.10	1.09	(0.72, 1.67)		,		

Note: DITTL = Dossier Label Intent-to-Treat Set.

N = total number of patients in analysis set. nev = number of events within considered period. NE = not evaluable. 95% CI = 95% confidence interval coming from a negative binomial model.

A negative binomial model was applied with factors treatment. The logarithm of follow-up time (including duration of exacerbations) was used as offset. No additional factors were considered to achieve robust results across all analyses.

Page 1 of 1 Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146 Program Name: M\_indirect\_add.sas

Data Cut Date: Meta\_analysis Run Date: 31AUG2022:11:18:37

Table MT1IE\_ILIND: AAER during 24 weeks treatment period by subgroups relevant for ITC - complete follow-up period as offset DTTTT

AAER during 24 week	s treatment period					Adjı	isted rates		Rate ratio	
Subgroup	Treatment	N	nev	Time at risk (years)	Crude rate	Estimate	95% CI	Estimate	95% CI	p-value
OCS at baseline	Tezepelumab									0.205
Yes	Tezepelumab	55	37	27.0	1.37	1.37	(0.90, 2.08)	0.600	(0.344, 1.045)	0.071
Yes	Placebo	55	61	26.6	2.29	2.28	(1.58, 3.29)			
No	Tezepelumab	391	145	191.8	0.76	0.75	(0.62, 0.91)	0.403	(0.316, 0.514)	<0.001 *
No	Placebo	381	349	187.5	1.86	1.87	(1.61, 2.17)			

MT1IE ILIND

Note: DITTL = Dossier Label Intent-to-Treat Set.

N = total number of patients in analysis set. nev = number of events within considered period. NE = not evaluable.

<sup>95%</sup> CI = 95% confidence interval coming from a negative binomial model.

A negative binomial model was applied with factors treatment. The logarithm of follow-up time (including duration of exacerbations) was used as offset. No additional factors were considered to achieve robust results across all analyses. Source Data: aaer, created on: 27APR2022

Page 1 of 1 Value Dossier Analysis: Meta\_analysis, NAVIGATOR, QUEST, DRI12544 Program Name: I\_aaer\_a.sas Run Date: 11MAY2022:07:55:57

Data Cut Date: ITC

Table MT1IES\_ILIDI: Severe AAER during 24 weeks treatment period - indirect comparison with pooled QR DITTL

		Indire	ct comparison (Buc	her)
Variable	Study	Risk Ratio	95% CI	p-value
Severe AAER during 24 weeks treatment period	Pooled NP	0.228	(0.118, 0.440)	<0.001 *
	Pooled QR	0.560	(0.230, 1.370)	0.210
	Pooled NP/Pooled QR	0.408	(0.134, 1.237)	0.113

Note: DITTL = Dossier Label Intent-to-Treat Set.

CI = confidence interval. Pooled NP = Pooled NAVIGATOR (adult)/PATHWAY. Pooled QR = pooled QUEST/DRI12522.

AAER = annual asthma exacerbation rates.

Source tables: MT1IES\_ILIN2, IT1ES\_ILMN0.

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Page 1 of 1
Program Name: M\_indirect\_a.sas
Run Date: 09MAY2022:14:52:25

Table MT1IES\_ILIN2: Severe AAER during 24 weeks treatment period -complete follow-up period as offset DITTL

Severe AAER du	ring 24 v	weeks tr	eatment period		Adjı	ısted rates	_	Rate ratio		
Treatment	N	nev	Time at risk (years)	Crude rate	Estimate	95% CI	Estimate	95% CI	p-value	
Tezepelumab	446	15	218.9	0.07	0.07	(0.04, 0.12)	0.228	(0.118, 0.440)	<0.001	*
Placebo	436	64	214.1	0.30	0.30	(0.21, 0.42)				

Note: DITTL = Dossier Label Intent-to-Treat Set.

MT1IES\_ILIN2 9

N = total number of patients in analysis set. nev = number of events within considered period. NE = not evaluable.

<sup>95%</sup> CI = 95% confidence interval coming from a negative binomial model.

A negative binomial model was applied with factors treatment. The logarithm of follow-up time (including duration of exacerbations) was used as offset. No additional factors were considered to achieve robust results across all analyses.

Source Data: aaer, created on: 27APR2022

Value Dossier Analysis: D5180C00007

Data Cut Date: 290ct2020

follow-up period as offset

Page 1 of 1

Program Name: N\_indirect\_a.sas

Run Date: 09MAY2022:14:44:22

Table NT1IES\_ILIN2: Severe AAER during 24 weeks treatment period -complete follow-up period as offset DITTL

Severe AAER du	ring 24 v	weeks tr	eatment period		Adjı	ısted rates	_	Rate ratio	
Treatment	N	nev	Time at risk (years)	Crude rate	Estimate	95% CI	Estimate	95% CI	p-value
Tezepelumab	395	12	194.6	0.06	0.06	(0.03, 0.11)	0.197	(0.096, 0.404)	<0.001 *
Placebo	391	60	192.2	0.31	0.31	(0.22, 0.45)			

Note: DITTL = Dossier Label Intent-to-Treat Set.

NT1IES\_ILIN2 10

N = total number of patients in analysis set. nev = number of events within considered period. NE = not evaluable.

<sup>95%</sup> CI = 95% confidence interval coming from a negative binomial model.

A negative binomial model was applied with factors treatment. The logarithm of follow-up time (including duration of exacerbations) was used as offset. No additional factors were considered to achieve robust results across all analyses.

Source Data: aaer, created on: 27APR2022

Value Dossier Analysis: CD-RI-MEDI9929-1146

Data Cut Date: 06JUN2017

Page 1 of 1
Program Name: P\_indirect\_a.sas
Run Date: 09MAY2022:14:48:38

Table PT3IES\_ILIN2: Severe AAER during 24 weeks treatment period -complete follow-up period as offset DITTL

Severe AAER du	ring 24 v	weeks tr	eatment period		Adjı	usted rates		Rate ratio	
Treatment	N	nev	Time at risk (vears)	Crude rate	Estimate	95% CI	Estimate	95% CI	p-value
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Tezepelumab	66	3	31.3	0.10	0.10	(0.03, 0.31)	0.507	(0.115, 2.230)	0.369
Placebo	65	6	31.9	0.19	0.19	(0.08, 0.45)			

Note: DITTL = Dossier Label Intent-to-Treat Set.

PT3IES\_ILIN2 11

N = total number of patients in analysis set. nev = number of events within considered period. NE = not evaluable. 95% CI = 95% confidence interval coming from a negative binomial model.

A negative binomial model was applied with factors treatment. The logarithm of follow-up time (including duration of exacerbations) was used as offset. No additional factors were considered to achieve robust results across all analyses.

Source Data: aaer, created on: 27APR2022

Page 1 of 1 Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146 Program Name: M\_indirect\_add.sas Run Date: 31AUG2022:11:18:37

Data Cut Date: Meta\_analysis

Table MT1IES\_ILIND: Severe AAER during 24 weeks treatment period by subgroups relevant for ITC - complete follow-up period as offset DITTL

Severe AAER during	24 weeks treatment	period				Adjı	usted rates		Rate ratio	
Subgroup	Treatment	N	nev	Time at risk (years)	Crude rate	Estimate	95% CI	Estimate	95% CI	p-value
OCS at baseline	Tezepelumab									0.300
Yes	Tezepelumab	55	1	27.0	0.04	0.04	(0.01, 0.27)	0.083	(0.010, 0.679)	0.020 *
Yes	Placebo	55	12	26.6	0.45	0.45	(0.23, 0.88)			
No	Tezepelumab	391	14	191.8	0.07	0.07	(0.04, 0.13)	0.261	(0.128, 0.532)	<0.001 *
No	Placebo	381	52	187 5	0.28	0.28	(0 19 0 41)			

12 MT1IES ILIND

Note: DITTL = Dossier Label Intent-to-Treat Set.

N = total number of patients in analysis set. nev = number of events within considered period. NE = not evaluable. 95% CI = 95% confidence interval coming from a negative binomial model.

A negative binomial model was applied with factors treatment. The logarithm of follow-up time (including duration of exacerbations) was used as offset. No additional factors were considered to achieve robust results across all analyses. Source Data: aaer, created on: 27APR2022

Value Dossier Analysis: Meta\_analysis, NAVIGATOR, QUEST, DRI12544

Data Cut Date: ITC

Page 1 of 1 Program Name: I\_aaer\_add.sas

Run Date: 30MAY2022:07:00:27

Table MT1IE ICIDI: AAER during 24 weeks treatment period - indirect comparison with pooled QR DITTL - patients without OCS medications

		Indire	ct comparison (Buc	her)
Variable	Study	Risk Ratio	95% CI	p-value
AAER during 24 weeks treatment period	Pooled NP	0.403	(0.316, 0.514)	<0.001 *
	Pooled QR	0.470	(0.330, 0.650)	<0.01 *
	Pooled NP/Pooled QR	0.858	(0.572, 1.286)	0.459

Note: DITTL - patients without OCS medications = Dossier Label Intent-to-Treat Set - patients without OCS medications. CI = confidence interval. Pooled NP = Pooled NAVIGATOR (adult)/PATHWAY. Pooled QR = pooled QUEST/DRI12522. AAER = annual asthma exacerbation rates.

Source tables: MT1IE\_ILIND, IT1IE\_ILMN0.

Value Dossier Analysis: Meta\_analysis, NAVIGATOR, QUEST, DRI12544

Data Cut Date: ITC

Page 1 of 1
Program Name: I\_aaer\_add.sas
Run Date: 30MAY2022:07:00:27

Table MT1IES\_ICIDI: Severe AAER during 24 weeks treatment period - indirect comparison with pooled QR DITTL - patients without OCS medications

		Indire	ct comparison (Buc	her)	
Variable	Study	Risk Ratio	95% CI	p-value	
Severe AAER during 24 weeks treatment period	Pooled NP	0.261	(0.128, 0.532)	<0.001	*
	Pooled QR	0.560	(0.230, 1.370)	0.210	
	Pooled NP/Pooled QR	0.467	(0.149, 1.463)	0.191	

Note: DITTL - patients without OCS medications = Dossier Label Intent-to-Treat Set - patients without OCS medications.
CI = confidence interval. Pooled NP = Pooled NAVIGATOR (adult)/PATHWAY. Pooled QR = pooled QUEST/DRI12522.
AAER = annual asthma exacerbation rates.

AAER = annual asthma exacerbation rates. Source tables: MT1IES\_ILIND, IT1IES\_ILMN0.

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Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Page 1 of 1
Program Name: M\_indirect\_a.sas
Run Date: 09MAY2022:14:52:25

Table MT1IA\_SLII0: Incidence of TEAEs during 24 weeks treatment period  $_{\rm DSAFL}$ 

	Tezepelumab		Placebo		_			
		n (%)		n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
TEAEs during 24 weeks treatment period	446	290 (65.0)	436	303 (69.5)	0.936	0.816	-4.5	0.173
*		[60.4, 69.4]		[64.9, 73.8]	[0.853, 1.026]	[0.616, 1.082]	[-10.9, 1.9]	l

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method). p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell. TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Source Data: aae, created on: 26APR2022

Value Dossier Analysis: D5180C00007

Data Cut Date: 290ct2020

Page 1 of 1
Program Name: N\_indirect\_a.sas
Run Date: 09MAY2022:14:44:22

Table NT11A\_SLII0: Incidence of TEAEs during 24 weeks treatment period  $$\operatorname{DSAFL}$$ 

	T	ezepelumab		Placebo	_			
	N	n (%) [95 % CI]	N	n (%) [95 % CI]		OR [95 % CI]	RD [95 % CI]	p-value
TEAEs during 24 weeks treatment period	395	260 (65.8) [60.9, 70.5]	391	279 (71.4) [66.6, 75.8]	0.922 [0.839, 1.014]	0.773 [0.572, 1.046]	-5.5 [-12.3, 1.2]	0.107

Note: DSAFL = Dossier Label Safety Set.

 $<sup>{\</sup>tt N}$  = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method). p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: CD-RI-MEDI9929-1146

Data Cut Date: 06JUN2017

Page 1 of 1 Program Name: P\_indirect\_a.sas

Run Date: 09MAY2022:14:48:38

Table PT3IA\_SLIIO: Incidence of TEAEs during 24 weeks treatment period DSAFL

		Tezepelumab		Placebo	_			
		n (%)	_	n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
TEAEs during 24 weeks treatment period	66	37 (56.1)	65	37 (56.9)	0.985	0.966	-0.9	1.000
1		[43.3, 68.3]		[44.0, 69.2]	[0.729, 1.330]	[0.484, 1.927]	[-19.4, 17.6	]

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: Meta\_analysis, NAVIGATOR, QUEST, DRI12544

Data Cut Date: ITC

Page 1 of 1
Program Name: I\_aae\_a.sas
Run Date: 11MAY2022:07:54:53

Table MT1IA\_SLIDI: Incidence of TEAEs during 24 weeks treatment period - indirect comparison with pooled QC  $_{
m DSAFL}$ 

		Indir	rect comparison (Buc	her)
		Relative Ris	k	
Variable	Study	Ratio	95% CI	p-value
TEAEs during 24 weeks treatment period	Pooled NP	0.936	(0.853, 1.026)	0.173
	Pooled QR	1.100	(0.990, 1.220)	0.060
	Pooled NP/Pooled OR	0.851	(0.740.0.977)	0.022 *

Note: DSAFL = Dossier Label Safety Set.

CI = confidence interval. Pooled NP = Pooled NAVIGATOR (adult)/PATHWAY. Pooled QR = pooled QUEST/DRI12522.

TEAE = treatment emergent adverse event.

Source tables: MT1IA\_SLIIO, IT1IA\_SLMIO

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Table MT1IA\_SLIID: Incidence of TEAEs during 24 weeks treatment period by subgroups relevant for ITC DSAFL

		Tezepelumab		Placebo	<u></u>			
TEAEs during 24 weeks treatment		n (%)		n (%)	RR	OR	RD	
period	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
OCS at baseline								0.309
Yes	55	46 (83.6)	55	45 (81.8)	1.022	1.136	1.8	1.000
		[71.2, 92.2]		[69.1, 90.9]	[0.862, 1.213]	[0.422, 3.056]	[-14.1, 17.8	3]
No	391	244 (62.4)	381	258 (67.7)	0.922	0.791	-5.3	0.131
		[57.4, 67.2]		[62.8, 72.4]	[0.831, 1.022]	[0.588, 1.065]	[-12.3, 1.7]	]

Source Data: aae, created on: 26APR2022

Page 1 of 1

Program Name: MTlaae\_IID.sas

Run Date: 31AUG2022:11:20:49

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Page 1 of 1 Program Name: M\_indirect\_a.sas Run Date: 09MAY2022:14:52:25

Table MT1IAN\_SLII0: Incidence of non-severe TEAEs during 24 weeks treatment period DSAFL

	1	Tezepelumab		Placebo	_			
		n (%)		n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
Non-severe TEAEs during 24 weeks treatment period	446	285 (63.9) [59.3, 68.4]	436	295 (67.7) [63.0, 72.0]	0.944 [0.859. 1.039]	0.846 [0.640, 1.118]	-3.8 [-10.2. 2.7]	0.256

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: D5180C00007

Data Cut Date: 290ct2020

Page 1 of 1 Program Name: N\_indirect\_a.sas Run Date: 09MAY2022:14:44:22

Table NT1IAN\_SLII0: Incidence of non-severe TEAEs during 24 weeks treatment period DSAFL

		Гezepelumab		Placebo	_			
		n (%)	_	n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
Non-severe TEAEs during 24 weeks treatment	395	256 (64.8)	391	273 (69.8)	0.928	0.796	-5.0	0.149
period		[59.9, 69.5]		[65.0, 74.3]	[0.842, 1.023]	[0.590, 1.073]	[-11.8, 1.8]	]

Note: DSAFL = Dossier Label Safety Set.

21 NT1IAN SLII0

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method). p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Source Data: aae, created on: 26APR2022

Value Dossier Analysis: CD-RI-MEDI9929-1146

Data Cut Date: 06JUN2017

Page 1 of 1
Program Name: P\_indirect\_a.sas
Run Date: 09MAY2022:14:48:38

Table PT3IAN\_SLII0: Incidence of non-severe TEAEs during 24 weeks treatment period  ${ t DSAFL}$ 

		Tezepelumab		Placebo	_			
		n (%)		n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
Non-severe TEAEs during 24 weeks treatment	66	36 (54.5)	65	35 (53.8)	1.013	1.029	0.7	1.000
period		[41.8, 66.9]		[41.0, 66.3]	[0.739, 1.388]	[0.517, 2.045]	[-17.9, 19.3	]

Note: DSAFL = Dossier Label Safety Set.
N = total number of patients in analysis set

 $<sup>{\</sup>tt N}$  = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method). p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Page 1 of 1
Program Name: M\_indirect\_a.sas
Run Date: 09MAY2022:14:52:25

Table MT1IAC\_SLII0: Incidence of severe TEAEs during 24 weeks treatment period  $_{\rm DSAFL}$ 

	T	ezepelumab		Placebo	_				
		n (%)		n (%)	RR	OR	RD		
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-valu	1e
Severe TEAEs during 24 weeks treatment period	446	30 (6.7)	436	47 (10.8)	0.624	0.597	-4.1	0.042	*
		[4.6, 9.5]		[8.0, 14.1]	[0.402, 0.967]	[0.370, 0.963]	[-8.0, -0.1]	1	

Source Data: aae, created on: 26APR2022

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

95% CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: D5180C00007

Data Cut Date: 290ct2020

Page 1 of 1 Program Name: N\_indirect\_a.sas Run Date: 09MAY2022:14:44:22

Table NT1IAC SLIIO: Incidence of severe TEAEs during 24 weeks treatment period DSAFL

	T	ezepelumab		Placebo					
		n (%)		n (%)	RR	OR	RD		
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-valu	ıe_
Severe TEAEs during 24 weeks treatment period	395	20 (5.1) [3.1, 7.7]	391	36 (9.2) [6.5, 12.5]	0.550 [0.324, 0.933]	0.526 [0.299, 0.926]	-4.1 [-8.00.3	0.026	*

Note: DSAFL = Dossier Label Safety Set.

Source Data: aae, created on: 26APR2022

NT1IAC SLII0 24

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell. TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: CD-RI-MEDI9929-1146

Data Cut Date: 06JUN2017

Page 1 of 1 Program Name: P\_indirect\_a.sas Run Date: 09MAY2022:14:48:38

Table PT3IAC SLIIO: Incidence of severe TEAEs during 24 weeks treatment period DSAFL

	T	Tezepelumab		Placebo	_			
		n (%)		n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
Severe TEAEs during 24 weeks treatment period	66	10 (15.2)	65	12 (18.5)	0.821	0.789	-3.3	0.647
•		[7.5, 26.1]		[9.9, 30.0]	[0.381, 1.766]	[0.314, 1.978]	[-17.6, 11.0	]

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method). p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Page 1 of 1
Program Name: M\_indirect\_a.sas
Run Date: 09MAY2022:14:52:25

Table MT1IAS\_SLII0: Incidence of serious TEAEs during 24 weeks treatment period  $_{\rm DSAFL}$ 

	T	ezepelumab		Placebo					
		n (%)		n (%)	RR	OR	RD		
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-valu	16
Serious TEAEs during 24 weeks treatment period	446	25 (5.6) [3.7, 8.2]	436	49 (11.2) [8.4, 14.6]	0.499 [0.314, 0.793]	0.469 [0.284, 0.774]	-5.6 [-9.5, -1.8]	0.003	*

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell. TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Source Data: aae, created on: 26APR2022

Value Dossier Analysis: D5180C00007

Data Cut Date: 290ct2020

Page 1 of 1
Program Name: N\_indirect\_a.sas
Run Date: 09MAY2022:14:44:22

Table NT1IAS\_SLII0: Incidence of serious TEAEs during 24 weeks treatment period  $$\operatorname{DSAFL}$$ 

	T	ezepelumab		Placebo					
		n (%)		n (%)	RR	OR	RD		
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-valu	ιe
Serious TEAEs during 24 weeks treatment period	395	19 (4.8)	391	43 (11.0)	0.437	0.409	-6.2	0.001	*
		[2.9, 7.4]		[8.1, 14.5]	[0.260, 0.737]				

Note: DSAFL = Dossier Label Safety Set.

Source Data: AAE, created on: 26APR2022

NT1IAS\_SLII0 27

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: CD-RI-MEDI9929-1146

Data Cut Date: 06JUN2017

Page 1 of 1
Program Name: P\_indirect\_a.sas
Run Date: 09MAY2022:14:48:38

Table PT3IAS\_SLII0: Incidence of serious TEAEs during 24 weeks treatment period  $$\operatorname{DSAFL}$$ 

		Tezepelumab		Placebo	_			
		n (%)		n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
Serious TEAEs during 24 weeks treatment period	66	6 (9.1)	65	7 (10.8)	0.844	0.829	-1.7	0.778
		[3.4, 18.7]		[4.4, 20.9]	[0.300, 2.377]	[0.263, 2.613]	[-13.4, 10.1]	]

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell. TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Source Data: aae, created on: 26APR2022

Value Dossier Analysis: Meta\_analysis, NAVIGATOR, QUEST, DRI12544

Data Cut Date: ITC

Program Name: I\_aae\_a.sas Run Date: 11MAY2022:07:54:53

Page 1 of 1

Table MT1IAS\_SLIDI: Incidence of serious TEAEs during 24 weeks treatment period - indirect comparison with pooled QC  $_{
m DSAFL}$ 

		Indirec	t comparison (Bucl	her)
		Relative Risk		
Variable	Study	Ratio	95% CI	p-value
Serious TEAEs during 24 weeks treatment period	Pooled NP	0.499	(0.314, 0.793)	0.003 *
	Pooled QR	0.790	(0.400, 1.580)	0.510
	Pooled NP/Pooled OR	0.631	(0.274. 1.453)	0.280

Note: DSAFL = Dossier Label Safety Set.

CI = confidence interval. Pooled NP = Pooled NAVIGATOR (adult)/PATHWAY. Pooled QR = pooled QUEST/DRI12522.

TEAE = treatment emergent adverse event.

Source tables: MT1IAS\_SLIIO, IT1IAS\_SLMIO

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Page 1 of 1
Program Name: MTlaae\_IID.sas
Run Date: 31AUG2022:11:20:49

Table MT1IAS\_SLIID: Incidence of serious TEAEs during 24 weeks treatment period by subgroups relevant for ITC DSAFL

	T	'ezepelumab		Placebo				
Serious TEAEs during 24 weeks treatment period	N	n (%) [95 % CI]	N	n (%) [95 % CI]	RR [95 % CI]	OR [95 % CI]	RD [95 % CI]	p-value
OCS at baseline								0.690
Yes	55	6 (10.9) [4.1, 22.2]	55	14 (25.5) [14.7, 39.0]	0.429 [0.178, 1.034]	0.359 [0.126, 1.017]	-14.5 [-30.5, 1.4	0.082 ]
No	391	19 (4.9) [3.0, 7.5]	381	35 (9.2) [6.5, 12.5]	0.529 [0.308, 0.908]	0.505 [0.283, 0.899]	-4.3 [-8.2, -0.5	0.023 *

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Source Data: aae, created on: 26APR2022

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Page 1 of 1
Program Name: M\_indirect\_a.sas
Run Date: 09MAY2022:14:52:25

Table MT1IAT\_SLII0: Incidence of TEAEs leading to study drug discontinuation during 24 weeks treatment period DSAFL

	T	ezepelumab		Placebo			
		n (%)		n (%)	RR	OR	RD
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI] p-value
TEAEs leading to study drug discontinuation	446	8 (1.8)	436	15 (3.4)	0.521	0.513	-1.6 0.142
during 24 weeks treatment period		[0.8, 3.5]		[1.9, 5.6]	[0.223, 1.217]	[0.215, 1.222]	1 [-4.0, 0.7]

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Source Data: aae, created on: 26APR2022

Value Dossier Analysis: D5180C00007

Data Cut Date: 290ct2020

Page 1 of 1
Program Name: N\_indirect\_a.sas
Run Date: 09MAY2022:14:44:22

Table NT1IAT\_SLII0: Incidence of TEAEs leading to study drug discontinuation during 24 weeks treatment period  $_{
m DSAFL}$ 

	T	ezepelumab		Placebo			
		n (%)	_	n (%)	RR	OR	RD
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI] p-value
TEAEs leading to study drug discontinuation	395	7 (1.8)	391	15 (3.8)	0.462	0.452	-2.1 0.087
during 24 weeks treatment period		[0.7, 3.6]		[2.2, 6.2]	[0.190, 1.121]	[0.182, 1.122]	] [-4.6, 0.5]

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: CD-RI-MEDI9929-1146

Data Cut Date: 06JUN2017

Page 1 of 1
Program Name: P\_indirect\_a.sas
Run Date: 09MAY2022:14:48:38

Table PT3IAT\_SLII0: Incidence of TEAEs leading to study drug discontinuation during 24 weeks treatment period DSAFL

	T	'ezepelumab		Placebo	_			
		n (%)		n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI]	p-value
TEAEs leading to study drug discontinuation	66	1 (1.5)	65	0 (0.0)	2.955 +	3.000 +	1.5	1.000
during 24 weeks treatment period		[0.0, 8.2]		[0.0, 5.5]	[0.123, 71.242]	[0.120, 75.000]	[-3.0, 6.0]	1

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: D5180C00007, CD-RI-MEDI9929-1146

Data Cut Date: Meta\_analysis

Program Name: M\_indirect\_a.sas Run Date: 09MAY2022:14:52:25

Page 1 of 1

Table MT1IAD\_SLII0: Incidence of fatal TEAEs during 24 weeks treatment period  $$\operatorname{DSAFL}$$ 

	T	Tezepelumab		Placebo	_			
		n (%)	- '	n (%)	RR	OR	RD	
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI] p-value	е
Fatal TEAEs during 24 weeks treatment period	446	0 (0.0)	436	2 (0.5)	0.196 +	0.195 +	-0.5 0.244	
		[0.0, 0.8]		[0.1, 1.6]	[0.009, 4.061][	[0.009, 4.066]	[-1.3, 0.4]	

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: D5180C00007

Data Cut Date: 290ct2020

Table NT1IAD\_SLIIO: Incidence of fatal TEAEs during 24 weeks treatment period DSAFL

Page 1 of 1

Program Name: N\_indirect\_a.sas

Run Date: 09MAY2022:14:44:22

	Т	ezepelumab	Placebo		_		
	N	n (%) [95 % CI]	N	n (%) [95 % CI]		OR [95 % CI]	RD [95 % CI] p-value
Fatal TEAEs during 24 weeks treatment period	395	0 (0.0)	391	2 (0.5)	0.198 +	0.197 +	-0.5 0.247
•		[0.0, 0.9]		[0.1, 1.8]	[0.010, 4.111]	0.009, 4.116	] [-1.5, 0.5]

Source Data: aae, created on: 26APR2022

NT1IAD\_SLII0 35

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell.

TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Value Dossier Analysis: CD-RI-MEDI9929-1146

Data Cut Date: 06JUN2017

Page 1 of 1
Program Name: P\_indirect\_a.sas
Run Date: 09MAY2022:14:48:38

Table PT3IAD\_SLII0: Incidence of fatal TEAEs during 24 weeks treatment period  $$\operatorname{DSAFL}$$ 

	T	ezepelumab		Placebo			
		n (%)		n (%)	RR	OR	RD
	N	[95 % CI]	N	[95 % CI]	[95 % CI]	[95 % CI]	[95 % CI] p-value
Fatal TEAEs during 24 weeks treatment period	66	0 (0.0) [0.0, 5.4]	65	0 (0.0) [0.0, 5.5]			

Note: DSAFL = Dossier Label Safety Set.

N = total number of patients in analysis set. n = number of patients with events.

<sup>95%</sup> CI = 95% confidence interval (percentages: Clopper-Pearson, RR/OR: Wald, RD: Newcombe method).

p-value = exact test of Fisher. \* = significant treatment effect. + = adding of + 0.5 to each cell. TEAE = treatment emergent adverse event. RR = relative risk. OR = odds ratio. RD = risk difference.

Source Data: aae, created on: 26APR2022

Value Dossier Analysis: Meta\_analysis, NAVIGATOR, QUEST, DRI12544

Data Cut Date: ITC

Program Name: I\_aae\_add.sas Run Date: 30MAY2022:04:23:55

Page 1 of 1

Table MT1IA\_SCIDI: Incidence of TEAEs during 24 weeks treatment period - indirect comparison with pooled QR DSAFL - patients without OCS medications

		Indirect comparison (Bucher)				
Variable	Relative Risk					
	Study	Ratio	95% CI	p-value		
TEAEs during 24 weeks treatment period	Pooled NP	0.922	(0.831, 1.022)	0.131		
	Pooled QR	1.100	(0.990, 1.220)	0.060		
	Pooled NP/Pooled OR	0.838	(0.724, 0.970)	0.018 *		

Note: DSAFL - patients without OCS medications = Dossier Label Safety Set - patients without OCS medications. CI = confidence interval. Pooled NP = Pooled NAVIGATOR (adult)/PATHWAY. Pooled QR = pooled QUEST/DRI12522. TEAE = treatment emergent adverse event.

Source tables: MT1IA\_SLIID, IT1IA\_SLMI0

Value Dossier Analysis: Meta\_analysis, NAVIGATOR, QUEST, DRI12544

Data Cut Date: ITC

Page 1 of 1
Program Name: I\_aae\_add.sas
Run Date: 30MAY2022:04:23:55

Table MT1IAS\_SCIDI: Incidence of serious TEAEs during 24 weeks treatment period - indirect comparison with pooled QR DSAFL - patients without OCS medications

		Indirect comparison (Bucher)			
	Relative Risk				
Variable	Study	Ratio	95% CI	p-value	
Serious TEAEs during 24 weeks treatment period	Pooled NP	0.529	(0.308, 0.908)	0.023 *	
	Pooled QR	0.790	(0.400, 1.580)	0.510	
	Pooled NP/Pooled QR	0.670	(0.278, 1.613)	0.371	

Note: DSAFL - patients without OCS medications = Dossier Label Safety Set - patients without OCS medications. CI = confidence interval. Pooled NP = Pooled NAVIGATOR (adult)/PATHWAY. Pooled QR = pooled QUEST/DRI12522. TEAE = treatment emergent adverse event.

Source tables: MT1IAS\_SLIID, IT1IAS\_SLMI0