

Fremanezumab

Research questions:

1. Does any dose of Fremanezumab increase the risk of systemic infections?
2. Does any dose of Fremanezumab increase the risk of viral infections?
3. Does any dose of Fremanezumab increase the risk of bacterial infections?
4. Does any dose of Fremanezumab increase the risk of COVID-19 infection?
5. Does any dose of Fremanezumab increase the risk of urinary tract infections?
6. Does the clinical dose of Fremanezumab increase the risk of systemic infections?
7. Does the clinical dose of Fremanezumab increase the risk of viral infections?
8. Does the clinical dose of Fremanezumab increase the risk of bacterial infections?
9. Does the clinical dose of Fremanezumab increase the risk of COVID-19 infection?
10. Does the clinical dose of Fremanezumab increase the risk of urinary tract infections?
11. Does high dose Fremanezumab increase the risk of systemic infections?
12. Does high dose Fremanezumab increase the risk of viral infections?
13. Does high dose Fremanezumab increase the risk of bacterial infections?
14. Does Fremanezumab High Dose Increase the Risk of COVID-19 Infection?
15. Does high dose Fremanezumab increase the risk of urinary tract infections?

Fremanezumab dose	Statistics	Infection				
		Any	Viral	Bacterial	COVID-19	Urinary
Any	<i>p</i> -value	0.900	0.894	0.960	-	0.812
	RR	1.01	0.99	1.01		1.08
	Metaregression	-	-	-	-	-
Clinical	<i>p</i> -value	0.457	0.429	0.625	-	0.646
	RR	1.08	1.07	1.15		1.18
	Metaregression	-	-	-	-	-
High	<i>p</i> -value	0.855	0.602	0.650	-	0.345
	RR	0.99	0.95	1.12		1.37
	Metaregression	-	-	-	-	-

Ad. 1. Does any dose of Fremanezumab increase the risk of systemic infections ?

The meta-analysis included 7 studies (Table 1) that analyzed the side effects of migraine treatment in 4327 people aged 42.7 years (SD = 11.4). The information included in the publications included the year of publication, age of the placebo group (mean and standard deviation), gender structure in the placebo group (percentage of women) and the

number of patients in the group treated with Fremanezumab at any dose who had any infection (E1) or did not (E0) and the number of patients in the control group (placebo) who had any infection (C1) or did not (C0). Binary data in the form of a contingency table 2×2 allow for estimation of the side effect rate of treatment: RR (Risk Ratio).

Table 1 shows that no publication found a statistically significant association between Fremanezumab use and the occurrence of overall infection ($p > 0.05$). The combined effect also did not indicate a statistically significant association between treatment and side effect ($p = 0.900$).

Table. 1. Results of a meta-analysis of the effect of migraine treatment with any dose of Fremanezumab on the occurrence of any infection

Study	Fremanezumab		Placebo		p	RR [95% CI]
	Any infection	Lack of infection	Any infection	Lack of infection		
RCT1	84	497	39	255	0.633	1.09 [0.77; 1.55]
RCT2	53	508	28	249	0.760	0.93 [0.61; 1.44]
RCT3	18	156	9	80	0.953	1.02 [0.48; 2.18]
RCT4	85	670	49	326	0.375	0.86 [0.62; 1.20]
RCT5	107	271	52	139	0.787	1.04 [0.78; 1.38]
RCT6	26	166	13	91	0.801	1.08 [0.58; 2.02]
RCT7	54	185	23	94	0.531	1.15 [0.74; 1.78]
Total	427	2453	213	1234	0.900	1.01 [0.87; 1.17]

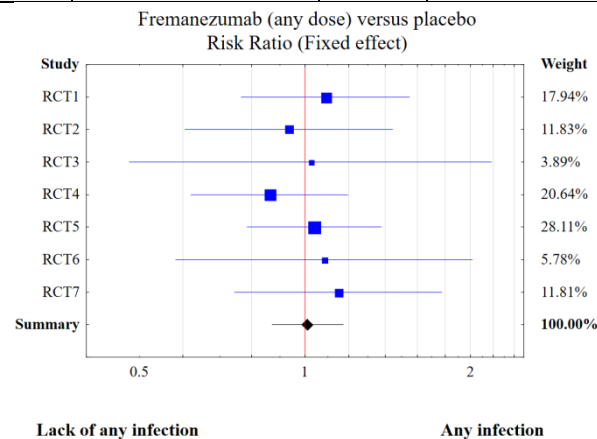


Figure 1. Forest plots of Risk Ratio of studies included in the meta-analysis and the summary results

The REML (Restricted Maximum Likelihood) method was used to estimate the variance between studies, and the test result ($Q = 1.62$, $df = 6$, $p = 0.951$, $I^2 = 0.00\%$) indicates low heterogeneity. The results are consistent, which increases the confidence in the overall results of the meta-analysis. In further analyses, it was assumed that if $I^2 < 25\%$, the fixed - effects model was adopted, and when $I^2 > 25\%$ - the random-effects model was adopted.

The tunnel plot and the trim-and-fill method were used to assess publication bias. The symmetry of the tunnel plot (all points representing studies included in the meta-analysis lie inside the funnel, Fig. 2) and the result of the formal regression test for funnel plot asymmetry (Egger's test: $t = 0.411$, $df = 5$, $p = 0.698$) indicate no significant influence of publication bias on the meta-analysis result. Additionally, the trim-and-fill technique was used to identify potentially missing studies due to possible publication bias. Three newly matched studies did not significantly affect the meta-analysis result.

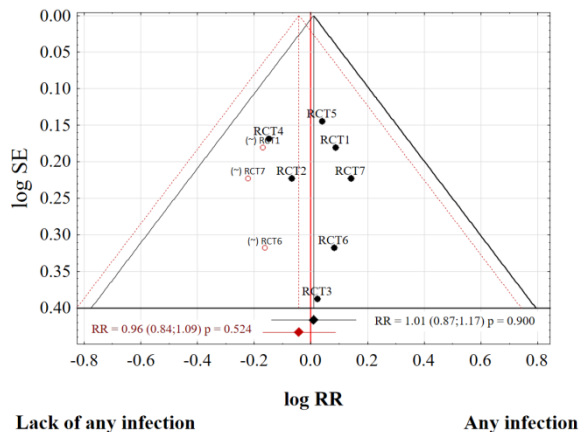


Figure 2. Tunnel plot for qualitative assessment of publication bias in meta-analysis.

L'Abbe and Galbraith plots (Fig.3) were used to visualize and analyze study results, including the assessment of heterogeneity and associations between variables. In the L'Abbe plot, the red line lying close to the diagonal (indicating no effect) confirms the agreement of study results with the pooled effect. In the Galbraith plot, points lying close to the central line (expected pooled effect, i.e. common RR) and within the red boundary lines (95% confidence limits) suggest low heterogeneity.

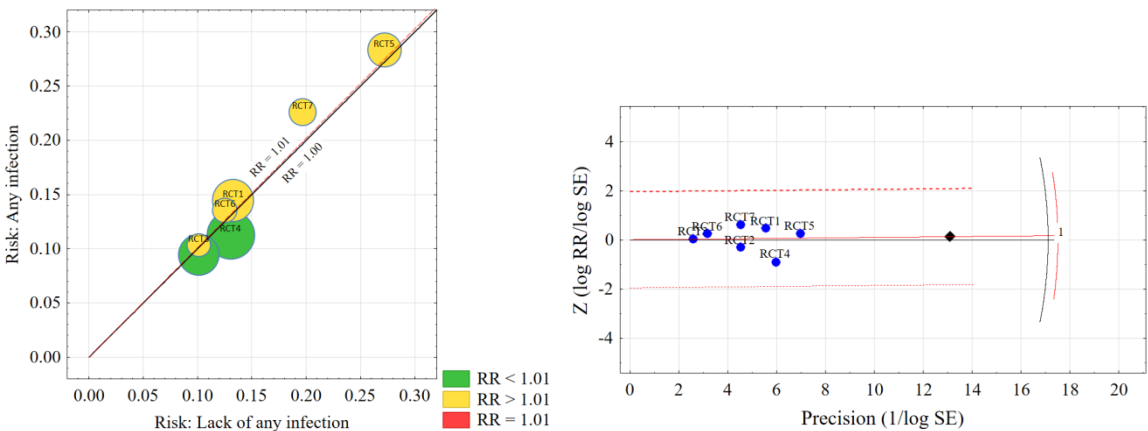


Figure 3. L'Abbe and Galbraith plot of RR for assessing heterogeneity and identifying outlier studies in meta-analysis

Sensitivity analysis was also performed (Fig. 4). Excluding any study from the meta-analysis did not significantly affect the RR value.

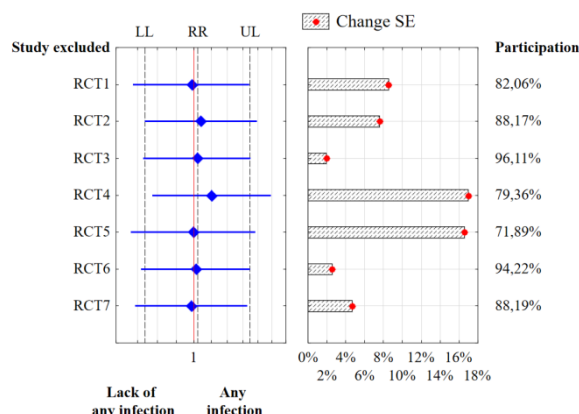


Figure 4. Sensitivity analysis of RR to exclusion of individual studies from meta-analysis

Meta-regression was used to verify the hypothesis whether the frequency of infections among patients treated with Fremanezumab was influenced by gender and age. Individual study effects (RR) and moderating variables: gender, age, sample size and year of publication were analyzed. The results are presented in Table 3.

Table. 2. Meta-regression results for log RR (fixed effect)

Parameter	<i>b</i>	SE _{<i>b</i>}	WITH	<i>p</i>
Constant	4.02	94.69	0.042	0.966
Female	-0.03	0.06	-0.521	0.602
Age	-0.01	0.05	-0.299	0.765
N	-0.00	0.00	-0.772	0.440
Year	-0.00	0.05	-0.007	0.995

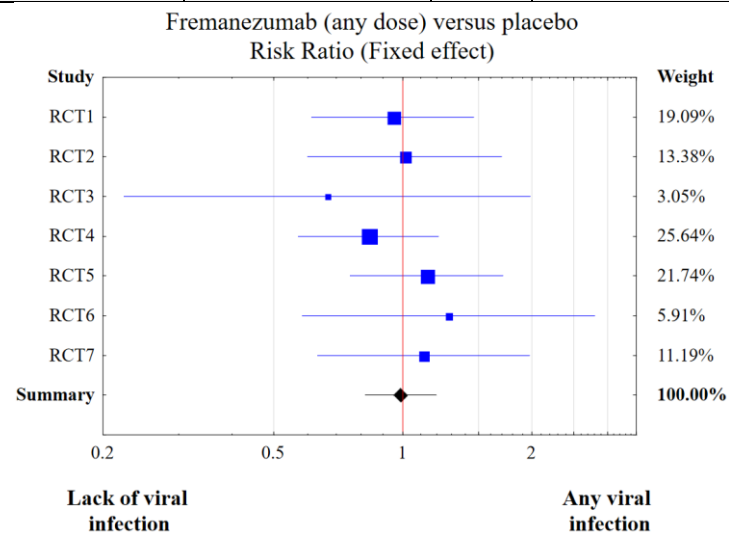
None of the four moderating variables included in the meta-regression had a significant impact on the overall effect of the meta-analysis ($p > 0.05$). In summary, it can be stated that any dose of Fremanezumab does not increase the risk of systemic infections.

Ad. 2. Does any dose of Fremanezumab increase the risk of viral infections?

The result of the homogeneity test ($Q = 2.39$, $df = 6$, $p = 0.881$, $I^2 = 0.00\%$) indicates low heterogeneity, therefore the fixed effects model was adopted. The result of the Egger asymmetry test ($t = 0.138$, $df = 5$, $p = 0.895$) indicates no significant influence of publication bias on the result of the meta-analysis. None of the four moderating variables (percentage of women, age, sample size and year of publication) included in the meta-regression had a significant influence on the summary effect of the meta-analysis ($p > 0.05$). Any dose of Fremanezumab does not increase the risk of viral infections.

Table. 3. Results of meta-analysis of the effect of migraine treatment with any dose of Fremanezumab on the occurrence of viral infections

Study	Fremanezumab		Placebo		<i>p</i>	RR [95% CI]
	Viral infection	Lack of infection	Viral infection	Lack of infection		
RCT1	66	515	35	259	0.812	0.95 [0.61; 1.47]
RCT2	47	514	23	254	0.971	1.01 [0.60; 1.70]
RCT3	8	166	6	83	0.466	0.67 [0.22; 1.98]
RCT4	84	671	49	326	0.341	0.83 [0.57; 1.21]
RCT5	96	282	44	147	0.537	1.14 [0.76; 1.71]
RCT6	23	169	10	94	0.538	1.28 [0.58; 2.80]
RCT7	47	192	21	96	0.699	1.12 [0.63; 1.98]
Summary	371	2509	188	1259	0.894	0.99 [0.82; 1.19]

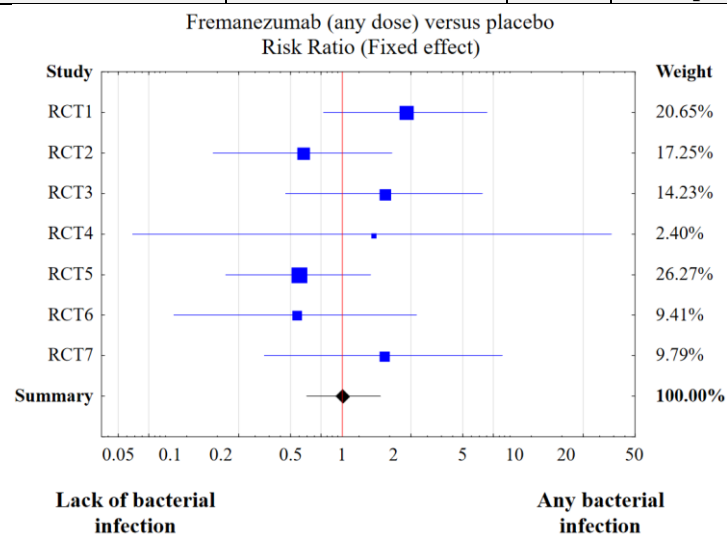


Ad.3. Does any dose of Fremanezumab increase the risk of bacterial infections?

The result of the homogeneity test ($Q = 6.21$, $df = 6$, $p = 0.400$, $I^2 = 3.43\%$) indicates low heterogeneity, therefore the fixed effects model was adopted. The result of the Egger asymmetry test ($t = 0.392$, $df = 5$, $p = 0.711$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. Any dose of Fremanezumab does not increase the risk of bacterial infections.

Table. 4. Results of meta-analysis of the effect of migraine treatment with any dose of Fremanezumab on the occurrence of bacterial infections

Study	Fremanezumab		Placebo		p	RR [95% CI]
	Bacterial infection	Lack of infection	Bacterial infection	Lack of infection		
RCT1	18	563	4	290	0.132	2.32 [0.78; 6.91]
RCT2	6	555	5	272	0.384	0.59 [0.18; 1.94]
RCT3	10	164	3	86	0.406	1.75 [0.47; 6.52]
RCT4	1	754	0	375	0.806	1.49 [0.06; 36.7]
RCT5	9	369	8	183	0.238	0.56 [0.21; 1.47]
RCT6	3	189	3	101	0.448	0.53 [0.11; 2.70]
RCT7	7	232	2	115	0.496	1.73 [0.35; 8.48]
Summary	54	2826	25	1422	0.960	1.01 [0.62; 1.66]



Ad.4. Does any dose of Fremanezumab increase the risk of COVID-19 infection?

There was no study so a meta-analysis cannot be performed.

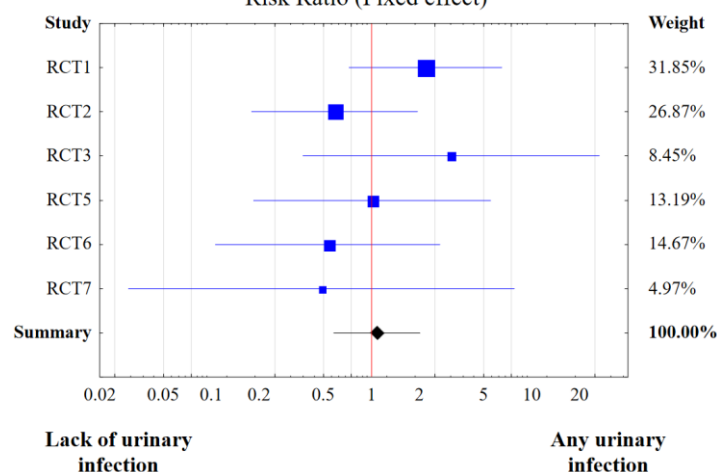
Ad.5. Does any dose of Fremanezumab increase the risk of urinary tract infections?

The result of the homogeneity test ($Q = 4.58$, $df = 5$, $p = 0.469$, $I^2 = 0.00\%$) indicates low heterogeneity, therefore the fixed effects model was adopted. The result of the Egger asymmetry test ($t = -0.324$, $df = 4$, $p = 0.762$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. Any dose of Fremanezumab does not increase the risk of urinary tract infections.

Table. 5. Results of a meta-analysis of the effect of migraine treatment with any dose of Fremanezumab on the occurrence of urinary infection

Study	Fremanezumab		Placebo		<i>p</i>	RR [95% CI]
	Urinary infection	Lack of infection	Urinary infection	Lack of infection		
RCT1	17	564	4	290	0.165	2.15 [0.73; 6.33]
RCT2	6	555	5	272	0.384	0.59 [0.18; 1.92]
RCT3	6	168	1	88	0.296	3.07 [0.38; 25.1]
RCT5	4	374	2	189	0.990	1.01 [0.19; 5.47]
RCT5	3	189	3	101	0.448	0.54 [0.11; 2.64]
RCT7	1	238	1	116	0.612	0.49 [0.03; 7.76]
Total	37	2088	16	1056	0.812	1.08 [0.58; 1.98]

Fremanezumab (any dose) versus placebo
Risk Ratio (Fixed effect)

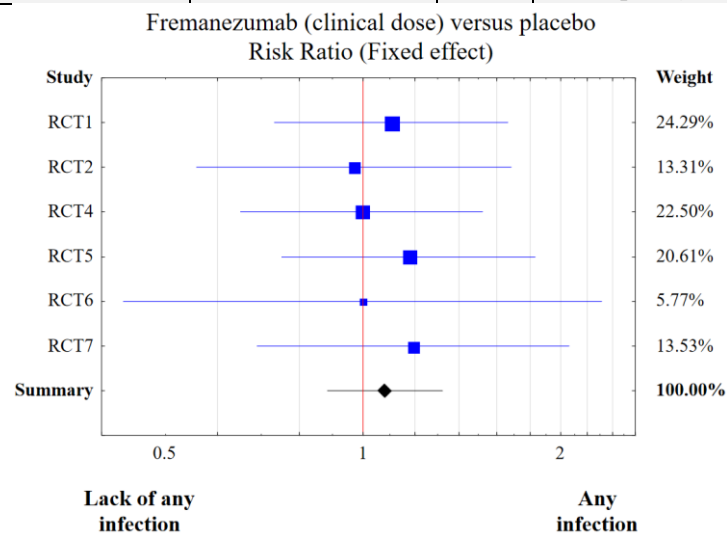


Ad. 6. Does the clinical dose of Fremanezumab increase the risk of systemic infections?

The result of the homogeneity test ($Q = 0.59$, $df = 5$, $p = 0.988$, $I^2 = 0.00\%$) indicates low heterogeneity. Therefore, the fixed effects model was adopted. The result of the Egger asymmetry test ($t = -0.434$, $df = 4$, $p = 0.687$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. The clinical dose of Fremanezumab does not increase the risk of any infections.

Table. 6. Results of a meta-analysis of the effect of migraine treatment with a clinical dose of Fremanezumab on the occurrence of any general infection

Study	Fremanezumab		Placebo		p	RR [95% CI]
	Any infection	Lack of infection	Any infection	Lack of infection		
RCT1	84	497	39	255	0.632	1.11 [0.73; 1.66]
RCT2	28	257	28	249	0.911	0.97 [0.56; 1.68]
RCT4	49	327	49	326	0.989	1.00 [0.65; 1.52]
RCT5	58	132	52	139	0.477	1.17 [0.75; 1.83]
RCT6	12	84	13	91	1.000	1.00 [0.43; 2.31]
RCT7	54	185	23	94	0.528	1.19 [0.69; 2.06]
Summary	285	1482	362	1767	0.457	1.08 [0.88; 1.32]

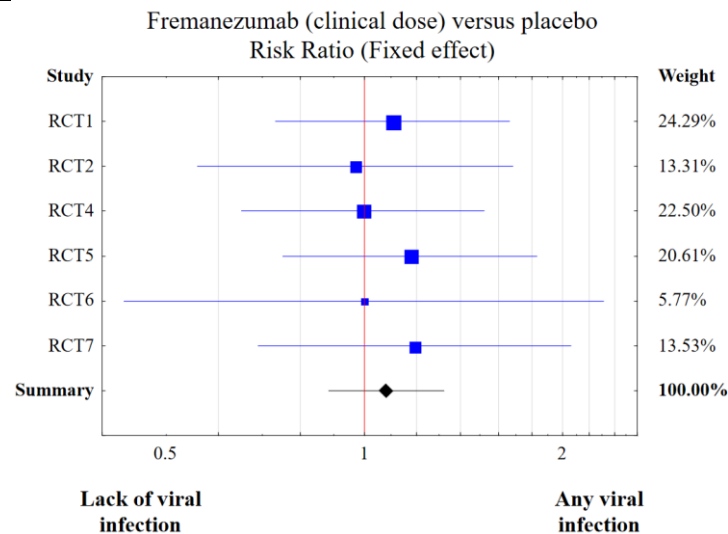


Ad. 7. Does the clinical dose of Fremanezumab increase the risk of viral infections?

The result of the homogeneity test ($Q = 0.59$, $df = 5$, $p = 0.988$, $I^2 = 0.00\%$) indicates low heterogeneity. Therefore, the fixed effects model was adopted. The result of the Egger asymmetry test ($t = -0.433$, $df = 4$, $p = 0.687$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. The clinical dose of Fremanezumab does not increase the risk of viral infections.

Table. 7. Results of a meta-analysis of the effect of migraine treatment with a clinical dose of Fremanezumab on the occurrence of any viral infection

Study	Fremanezumab		Placebo		<i>p</i>	RR [95% CI]
	Viral infection	Lack of infection	Viral infection	Lack of infection		
RCT1	66	515	35	259	0.633	1.09 [0.77; 1.55]
RCT2	25	260	23	254	0.911	0.97 [0.59; 1.60]
RCT4	48	328	49	326	0.989	1.00 [0.69; 1.44]
RCT5	50	140	44	147	0.478	1.12 [0.82; 1.54]
RCT6	12	84	10	94	1.000	1.00 [0.48; 2.08]
RCT7	47	192	21	96	0.531	1.15 [0.74; 1.78]
Total	248	1519	182	1176	0.429	1.07 [0.91; 1.26]



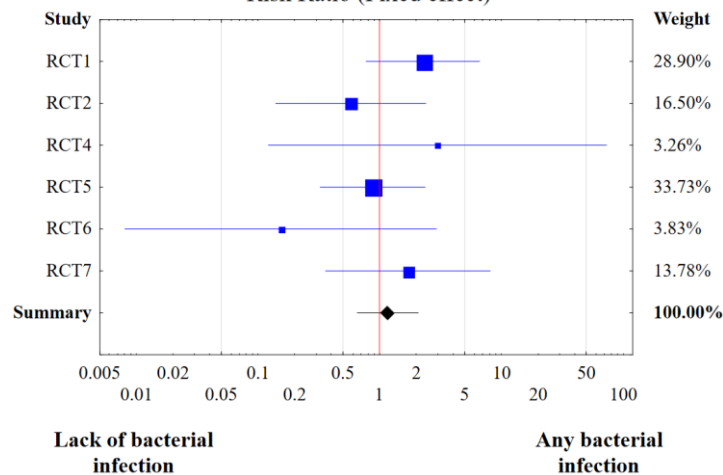
Ad. 8. Does the clinical dose of Fremanezumab increase the risk of bacterial infections?

The result of the homogeneity test ($Q = 5.08$, $df = 5$, $p = 0.406$, $I^2 = 1.60\%$) indicates low heterogeneity. Therefore, the fixed effects model was adopted. The result of the Egger asymmetry test ($t = -0.494$, $df = 4$, $p = 0.647$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. The clinical dose of Fremanezumab does not increase the risk of bacterial infections.

Table. 8. Results of a meta-analysis of the effect of migraine treatment with a clinical dose of Fremanezumab on the occurrence of any bacterial infection

Study	Fremanezumab		Placebo		p	RR [95% CI]
	Bacterial infection	Lack of infection	Bacterial infection	Lack of infection		
RCT1	18	563	4	290	0.133	2.28 [0.78; 6.67]
RCT2	3	282	5	272	0.457	0.58 [0.14; 2.42]
RCT4	1	375	0	375	0.502	2.99 [0.12; 73.2]
RCT5	7	183	8	183	0.800	0.88 [0.33; 2.38]
RCT6	0	96	3	101	0.215	0.15 [0.01; 2.96]
RCT7	7	232	2	115	0.498	1.71 [0.36; 8.12]
Summary	36	1731	22	1336	0.625	1.15 [0.65; 2.06]

Frenamezumab (clinical dose) versus placebo
Risk Ratio (Fixed effect)



Ad. 9. Does the clinical dose of Fremanezumab increase the risk of COVID-19 infection?

There were no studies so a meta-analysis cannot be conducted.

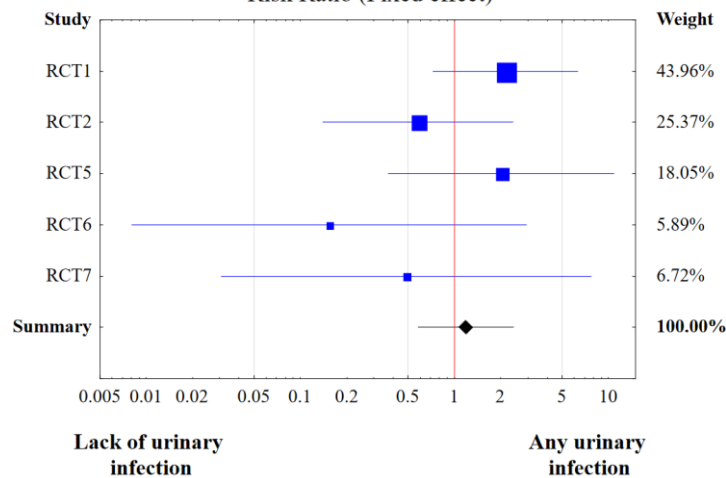
Ad.10. Does the clinical dose of Fremanezumab increase the risk of urinary tract infections?

The result of the homogeneity test ($Q = 4.726$, $df = 4$, $p = 0.317$, $I^2 = 15.37\%$) indicates low heterogeneity. Therefore, the fixed effects model was adopted. The result of the Egger asymmetry test ($t = -1.864$, $df = 3$, $p = 0.159$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. The clinical dose of Fremanezumab does not increase the risk of urinary tract infections.

Table. 9. Results of a meta-analysis of the effect of migraine treatment with any dose of Fremanezumab on the occurrence of urinary infection

Study	Fremanezumab		Placebo		<i>p</i>	RR [95% CI]
	Urinary infection	Lack of infection	Urinary infection	Lack of infection		
RCT1	17	564	4	290	0.165	2.15 [0.73; 6.33]
RCT2	3	282	5	272	0.457	0.58 [0.14; 2.42]
RCT5	4	186	2	189	0.417	2.01 [0.37; 10.9]
RCT6	0	96	3	101	0.215	0.15 [0.01; 2.96]
RCT7	1	238	1	116	0.612	0.49 [0.03; 7.76]
	25	1366	15	968	0.646	1.18 [0.58; 2.42]

Fremanezumab (clinical dose) versus placebo
Risk Ratio (Fixed effect)

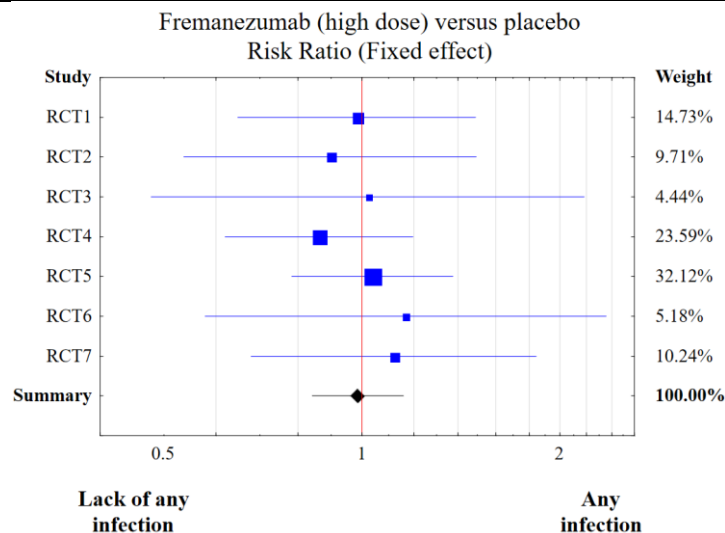


Ad. 11. Does a high dose of Fremanezumab increase the risk of systemic infections?

The result of the homogeneity test ($Q = 1.40$, $df = 6$, $p = 0.966$, $I^2 = 0.00\%$) indicates low heterogeneity. Therefore, the fixed effects model was adopted. The result of the Egger asymmetry test ($t = 0.664$, $df = 5$, $p = 0.536$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. High dose of Fremanezumab does not significantly increase the risk of general infections.

Table. 10. Results of a meta-analysis of the effect of high-dose Fremanezumab migraine treatment on the occurrence of systemic infection

Study	Fremanezumab		Placebo		p	RR [95% CI]
	Any infection	Lack of infection	Any infection	Lack of infection		
RCT1	38	253	39	255	0.941	0.98 [0.65; 1.49]
RCT2	25	251	28	249	0.675	0.90 [0.54; 1.50]
RCT3	18	156	9	80	0.953	1.02 [0.48; 2.18]
RCT4	85	670	49	326	0.375	0.86 [0.62; 1.20]
RCT5	107	271	52	139	0.787	1.04 [0.78; 1.38]
RCT6	14	82	13	91	0.667	1.17 [0.58; 2.35]
RCT7	26	92	23	94	0.654	1.12 [0.68; 1.85]
Summary	313	1775	213	1234	0.855	0.99 [0.84; 1.16]



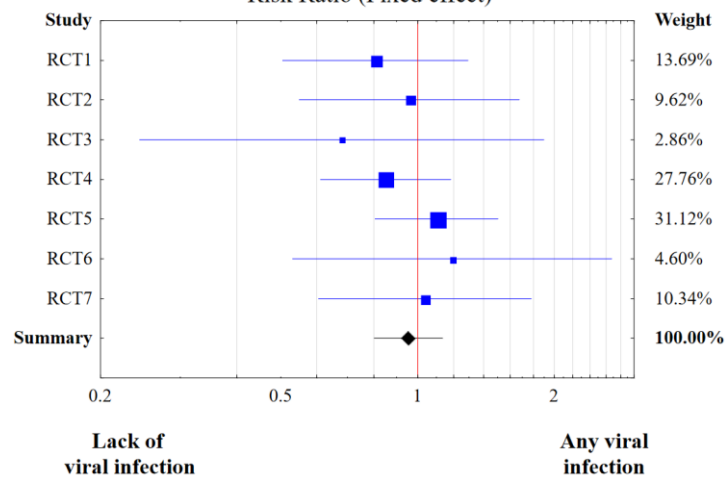
Ad. 12. Does a high dose of Fremanezumab increase the risk of viral infections?

The result of the homogeneity test ($Q = 2.56$, $df = 6$, $p = 0.862$, $I^2 = 0.00\%$) indicates low heterogeneity. Therefore, the fixed effects model was adopted. The result of the Egger asymmetry test ($t = -0.376$, $df = 5$, $p = 0.723$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. High dose of Fremanezumab does not significantly increase the risk of viral infections.

Table. 11. Results of a meta-analysis of the effect of high-dose Fremanezumab treatment for migraine on the incidence of viral infections

Study	Fremanezumab		Placebo		p	RR [95% CI]
	Viral infection	Lack of infection	Viral infection	Lack of infection		
RCT1	28	263	35	259	0.374	0.81 [0.51; 1.29]
RCT2	22	254	23	254	0.886	0.96 [0.55; 1.68]
RCT3	8	166	6	83	0.465	0.68 [0.24; 1.91]
RCT4	84	671	49	326	0.339	0.85 [0.61; 1.18]
RCT5	96	282	44	147	0.539	1.10 [0.81; 1.51]
RCT6	11	85	10	94	0.671	1.19 [0.53; 2.68]
RCT7	22	96	21	96	0.890	1.04 [0.61; 1.78]
Summary	271	1817	188	1259	0.602	0.95 [0.80; 1.14]

Fremanezumab (high dose) versus placebo
Risk Ratio (Fixed effect)

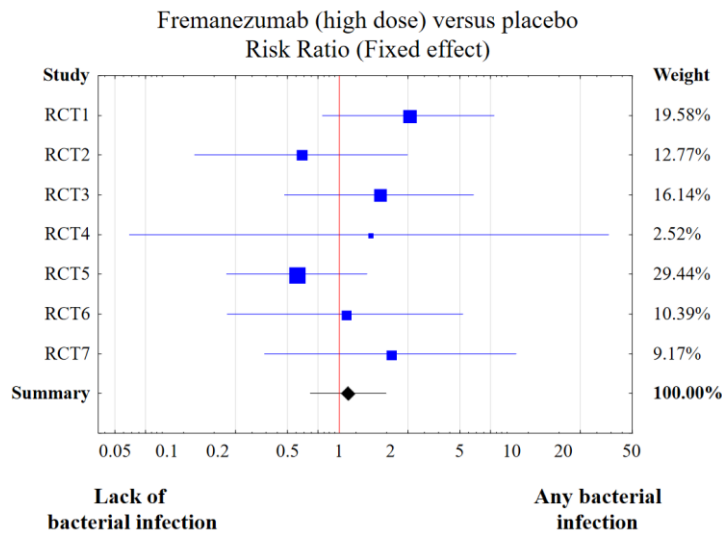


Ad. 13. Does a high dose of Fremanezumab increase the risk of bacterial infections?

The result of the homogeneity test ($Q = 5.58$, $df = 6$, $p = 0.472$, $I^2 = 0.00\%$) indicates low heterogeneity, therefore the fixed effects model was adopted. The result of the Egger asymmetry test ($t = 0.664$, $df = 5$, $p = 0.536$) indicates no significant influence of publication bias on the result of the meta-analysis. Meta-regression did not show a statistically significant influence of any of the variables. High dose of Fremanezumab does not increase the risk of bacterial infections.

Table. 12. Results of a meta-analysis of the effect of high-dose Fremanezumab treatment for migraine on the incidence of bacterial infections

Study	Fremanezumab		Placebo		p	RR [95% CI]
	Bacterial infection	Lack of infection	Bacterial infection	Lack of infection		
RCT1	10	281	4	290	0.114	2.53 [0.80; 7.96]
RCT2	3	273	5	272	0.484	0.60 [0.15; 2.50]
RCT3	10	164	3	86	0.408	1.70 [0.48; 6.04]
RCT4	1	754	0	375	0.806	1.49 [0.06; 36.5]
RCT5	9	369	8	183	0.237	0.57 [0.22; 1.45]
RCT6	3	93	3	101	0.921	1.08 [0.22; 5.24]
RCT7	4	114	2	115	0.424	1.98 [0.37; 10.6]
Summary	40	2048	25	1422	0.650	1.12 [0.68; 1.87]



Ad. 14. Does a high dose of Fremanezumab increase the risk of COVID-19 infection?

There were no studies so a meta-analysis cannot be conducted.

Ad.15. Does a high dose of Fremanezumab increase the risk of urinary tract infections?

The result of the homogeneity test ($Q = 3.20$, $df = 5$, $p = 0.669$, $I^2 = 0.00\%$) indicates low heterogeneity. Therefore, the fixed effects model was adopted. The result of the Egger asymmetry test ($t = -0.360$, $df = 4$, $p = 0.737$) indicates no significant influence of publication bias on the result of the meta-analysis. High dose of Fremanezumab does not increase the risk of urinary tract infections.

Table. 13. Results of a meta-analysis of the effect of migraine treatment with high-dose of Fremanezumab on the occurrence of urinary infection

Study	Fremanezumab		Placebo		<i>p</i>	RR [95% CI]
	Urinary infection	Lack of infection	Urinary infection	Lack of infection		
RCT1	10	281	4	290	0.114	2.53 [0.80; 7.96]
RCT2	3	273	5	272	0.484	0.60 [0.15; 2.50]
RCT3	6	168	1	88	0.296	3.07 [0.38; 25.1]
RCT5	4	374	2	189	0.990	1.01 [0.19; 5.47]
RCT6	3	93	3	101	0.921	1.08 [0.22; 5.24]
RCT7	1	117	1	116	0.995	0.99 [0.06; 15.7]
Summary	27	1306	16	1056	0.345	1.37 [0.71; 2.62]

