



Clinical trial results:

A randomized, doubleblind, placebo-controlled multicenter trial to evaluate the safety and efficacy of rituximab (Mabthera) in subjects with new onset myasthenia gravis; the RINOMAX study

Summary

EudraCT number	2015-005749-30
Trial protocol	SE
Global end of trial date	22 November 2021

Results information

Result version number	v1 (current)
This version publication date	29 April 2022
First version publication date	29 April 2022

Trial information

Trial identification

Sponsor protocol code	2015-00887
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02950155
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	Neuroimmunology Unit CMM L8;4 Visionsgatan 18, Stockholm, Sweden, 17176
Public contact	Fredrik Piehl, Karolinska Institutet, +46 736718101, fredrik.piehl@ki.se
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2021
Global end of trial reached?	Yes
Global end of trial date	22 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if rituximab is more effective than placebo to achieve minimal disease manifestations defined as a QMG score ≤ 4 and a daily dose of prednisolone of ≤ 10 mg/d at week 16, with no need of rescue treatment procedure(s) during study weeks 9 to 16.

Protection of trial subjects:

Worsening in MG symptoms would first be addressed by optimising the acetylcholine esterase inhibitor dose, but if not enough, by raising corticosteroids or starting rescue-treatment

Background therapy:

Acetylcholine esterase inhibitors without limits. Intravenous immunoglobulins and/or plasma exchange allowed during run-in phase. Prednisolone ≤ 40 mg/day also allowed, but tapered to ≤ 10 mg/day during run-in phase.

Evidence for comparator:

The objective of the study was to address any possible benefit of rituximab added to standard of care, which justified the use of placebo as a comparator

Actual start date of recruitment	20 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	17

From 65 to 84 years	29
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Specialized care with recruitment from 7 Swedish region based community samples, i.e. regional community-based catchment areas for five Swedish university clinics and two larger regional neurology clinics. Screening occurred between October 20th, 2016, and March 2nd, 2020

Pre-assignment

Screening details:

87 potentially eligible patients were screened, out of which 47 were enrolled. Reasons for not being included: not fulfilling inclusion criteria, 10; having exclusion criteria, 21; not providing consent, 6; not stated, 4.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Randomization and preparation of blinded study drug were performed by a central pharmacy, Apoteket Produktion & Laboratorier (APL; Stockholm, Sweden) and shipped to study centers in identical liquid containers to preserve masking. Patients, investigators and all study personnel were blinded throughout the study duration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

intravenous infusion of 500 mg of rituximab dissolved in sodiumchloride to 2 mg rituximab/ml

Arm type	Active comparator
Investigational medicinal product name	Mabthera (rituximab)
Investigational medicinal product code	L01FA01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

500 mg rituximab dissolved in sodiumchloride to a final concentration of 2 mg/ml

Investigational medicinal product name	Sodiumchloride
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Sodiumchloride 9mg/ml

Arm title	Placebo
Arm description: -	
Arm type	Placebo

Investigational medicinal product name	Sodiumchloride
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Sodiumchloride 9mg/ml, 250 ml

Number of subjects in period 1	Rituximab	Placebo
Started	25	22
Completed	25	22

Baseline characteristics

Reporting groups

Reporting group title	Rituximab
Reporting group description: intravenous infusion of 500 mg of rituximab dissolved in sodiumchloride to 2 mg rituximab/ml	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Rituximab	Placebo	Total
Number of subjects	25	22	47
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	67.4 ± 13.4	58.0 ± 18.6	-
Gender categorical Units: Subjects			
Female	7	7	14
Male	18	15	33
Body mass index Units: kg/m2 arithmetic mean standard deviation	27.5 ± 3.7	27.6 ± 5.7	-

Subject analysis sets

Subject analysis set title	Full data set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects that fulfilled inclusion- and exclusion criteria and consented to participate (n=47), all received study drug and were included in the data set	

Reporting group values	Full data set		
Number of subjects	47		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	63.0 ± 16.6		
Gender categorical Units: Subjects			
Female	14		
Male	33		

Body mass index			
Units: kg/m ²			
arithmetic mean			
standard deviation	±		

End points

End points reporting groups

Reporting group title	Rituximab
Reporting group description: intravenous infusion of 500 mg of rituximab dissolved in sodiumchloride to 2 mg rituximab/ml	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full data set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects that fulfilled inclusion- and exclusion criteria and consented to participate (n=47), all received study drug and were included in the data set	

Primary: Minimal disease manifestation at week 16

End point title	Minimal disease manifestation at week 16
End point description: minimal disease manifestations defined as a QMG score ≤ 4 and a daily dose of prednisolone of ≤ 10 mg/d at week 16	
End point type	Primary
End point timeframe: week 16	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24 ^[1]	21 ^[2]		
Units: subjects	17	6		

Notes:

[1] - missing value 1

[2] - missing value 1

Statistical analyses

Statistical analysis title	Primary outcome, minimal disease manifestations
Statistical analysis description: Difference in proportions fulfilling criteria for minimal disease manifestations was analyzed on an intention-to-treat basis with Fisher's exact test and $\alpha=0.05$	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	2.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	5.11

Secondary: Change in QMG, week 24

End point title	Change in QMG, week 24
End point description:	
Subjects receiving rescue treatment was censored at time of treatment	
QMG, Quantitative Myasthenia Gravis score	
End point type	Secondary
End point timeframe:	
week 24	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23 ^[3]	13 ^[4]		
Units: change in score points				
arithmetic mean (standard deviation)	-6.9 (± 5.6)	-5.8 (± 4.6)		

Notes:

[3] - 2 censored

[4] - 9 censored

Statistical analyses

Statistical analysis title	Change in QMG, week 24
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	2.1

Secondary: Change in MG-ADL, week 16

End point title	Change in MG-ADL, week 16
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End point description:	
MG-ADL, Myasthenia Gravis Activities of Daily Living score	
End point type	Secondary
End point timeframe:	
week 16	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23 ^[5]	13 ^[6]		
Units: change in score points				
arithmetic mean (standard deviation)	-1.7 (± 2.5)	-0.5 (± 3.6)		

Notes:

[5] - 2 censored

[6] - 9 censored

Statistical analyses

Statistical analysis title	Change in MG-ADL, week 16
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	0.8

Secondary: Change in MG-QoL, week 16

End point title	Change in MG-QoL, week 16
End point description:	
MG-QoL, Myasthenia Gravis Quality of Life questionnaire	
End point type	Secondary
End point timeframe:	
week 16	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[7]	15 ^[8]		
Units: change in score points				
arithmetic mean (standard deviation)	-9.2 (± 9.2)	-7.0 (± 9.3)		

Notes:

[7] - 3 censored

[8] - 7 censored

Statistical analyses

Statistical analysis title	Change in MG-QoL, week 16
Statistical analysis description:	
Subjects receiving rescue treatment was censored at time of treatment	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	3.8

Secondary: Change in QMG, week 24 (post-hoc)

End point title	Change in QMG, week 24 (post-hoc)
End point description:	
QMG, Quantitative Myasthenia Gravis score	
Intention-to-treat analysis for secondary endpoints using worst rank imputation for those receiving rescue therapy	
End point type	Secondary
End point timeframe:	
week 24	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24 ^[9]	21 ^[10]		
Units: change in score points				
arithmetic mean (standard deviation)	-6.5 (± 5.9)	-2.0 (± 6.0)		

Notes:

[9] - missing data 1

Statistical analyses

Statistical analysis title	Change in QMG, week 24
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	45
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.04
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	-1

Secondary: Change in MG-ADL, week 16 (post-hoc)

End point title	Change in MG-ADL, week 16 (post-hoc)
End point description:	
End point type	Secondary
End point timeframe:	
week 16	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23 ^[11]	21 ^[12]		
Units: change in score points				
arithmetic mean (standard deviation)	-1.3 (± 3.2)	2.0 (± 5.0)		

Notes:

[11] - missing data 2

[12] - missing data 1

Statistical analyses

Statistical analysis title	Change in MG-ADL, week 16
Comparison groups	Rituximab v Placebo

Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.03
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	-0.8

Secondary: Change in MG-QoL, week 16 (post-hoc)

End point title	Change in MG-QoL, week 16 (post-hoc)
End point description:	
MG-QoL, Myasthenia Gravis Quality of Life questionnaire Intention-to-treat analysis for secondary endpoints using worst rank imputation for those receiving rescue therapy	
End point type	Secondary
End point timeframe:	
week 16	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23 ^[13]	21 ^[14]		
Units: change in score points				
arithmetic mean (standard deviation)	-8.4 (± 10.2)	-2.1 (± 11.1)		

Notes:

[13] - missing data 2

[14] - missing data 1

Statistical analyses

Statistical analysis title	Change in MG-QoL, week 16
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.06
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-6.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	-0.1

Other pre-specified: Minimal disease manifestations week 24

End point title	Minimal disease manifestations week 24
End point description: Minimal disease manifestation, prednisolone $\leq$ 10 mg daily and no rescue therapy at week 24	
End point type	Other pre-specified
End point timeframe: week 24	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	21 ^[15]		
Units: subjects	18	8		

Notes:

[15] - missing data 1

Statistical analyses

Statistical analysis title	Minimal disease manifestations week 24
Comparison groups	Placebo v Rituximab
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	3.44

Other pre-specified: Rescue treatment before 24 weeks

End point title	Rescue treatment before 24 weeks
End point description: Rescue treatment given weeks 9-24	
End point type	Other pre-specified

End point timeframe:

Weeks 9-24

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	22		
Units: subjects	1	8		

Statistical analyses

Statistical analysis title	Rescue treatment before 24 weeks
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.81

Other pre-specified: Antibody titers week 24

End point title	Antibody titers week 24
End point description:	serum acetylcholine receptor (AChR+) antibody titers at week 24
End point type	Other pre-specified
End point timeframe:	week 24

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16 ^[16]	19		
Units: nmol/L				
arithmetic mean (standard deviation)	14.1 (± 21.8)	118.8 (± 228.5)		

Notes:

[16] - 2 subjects AChR negative, several missing data

Statistical analyses

Statistical analysis title	Antibody titer
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Point estimate	-104.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-205.3
upper limit	-4.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From administration of study drug to week 48

Assessment type	Systematic
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Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	CT
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Reporting groups

Reporting group title	active treatment
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Reporting group description: -

Reporting group title	placebo
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Reporting group description: -

Serious adverse events	active treatment	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)	4 / 22 (18.18%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thymoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: In context of myocardial infarction and anoxic myocardial dysfunction with MG respiratory crisis in in the active and placebo treatment arms, respectively		

subjects affected / exposed	1 / 25 (4.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Subileus			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Vertebral compression fracture			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	active treatment	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 25 (84.00%)	17 / 22 (77.27%)	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 25 (8.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Fever of unknown cause			
subjects affected / exposed	2 / 25 (8.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 25 (8.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	3 / 25 (12.00%)	2 / 22 (9.09%)	
occurrences (all)	3	2	
Eye disorders			
Conjunctivitis viral			
subjects affected / exposed	2 / 25 (8.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	5 / 25 (20.00%)	2 / 22 (9.09%)	
occurrences (all)	5	2	
Dry mouth			
subjects affected / exposed	2 / 25 (8.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Nausea			

subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	2 / 22 (9.09%) 2	
Rectal bleeding subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 22 (0.00%) 0	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	4 / 22 (18.18%) 4	
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 22 (4.55%) 1	
Renal stone subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	2 / 22 (9.09%) 2	
Musculoskeletal and connective tissue disorders Muscle cramps subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5	1 / 22 (4.55%) 1	
Musculoskeletal pain subjects affected / exposed occurrences (all)	10 / 25 (40.00%) 10	4 / 22 (18.18%) 4	
Infections and infestations Upper respiratory infection subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 7	10 / 22 (45.45%) 10	
Urinary tract infection bacterial subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	0 / 22 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2017	Prolonging the inclusion period to end of q4 2020
26 October 2018	change of PI at trial site
26 April 2021	Clarifying open label treatment with rituximab at any time between baseline and 24 weeks as rescue therapy, extending the time window for efficacy evaluation visits from +/- 7 to +/- 21 days and changes in the statistical analysis plan, this comprised changing from using linear regression for analyses of change in secondary outcomes, to the use of Mann-Whitneys U-test for the analysis of differences in change, but still using linear regression to establish 95% CIs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Imbalances in some baseline characteristics, censoring of subjects receiving rescue treatment affected affected per-protocol secondary outcome analyses

Notes: