



Clinical trial results:

A long-term outcome study with the IL-1 receptor antagonist Anakinra/Kineret® in patients with Neonatal onset multisystem inflammatory disease (Nomid/Cinca syndrome)

Summary

EudraCT number	2013-000300-42
Trial protocol	Outside EU/EEA
Global end of trial date	16 August 2010

Results information

Result version number	v1 (current)
This version publication date	23 April 2016
First version publication date	23 April 2016

Trial information

Trial identification

Sponsor protocol code	03-AR-0298
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00069329
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Sponsor organisation address	10 Center Drive, Bethesda, United States, MD 20892
Public contact	NIH Clinical Center , National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 001 8004111222TTY8, prpl@mail.cc.nih.gov
Scientific contact	NIH Clinical Center , National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 001 8004111222TTY8, prpl@mail.cc.nih.gov

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001212-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
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	16 August 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2010
Global end of trial reached?	Yes
Global end of trial date	16 August 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Assess the change in the disease diary score after 3-4 months of open-label administration of anakinra/Kineret. This score is derived from the daily questionnaire filled out by the patient or patient's parent(s).
- Assess the change in SAA levels before and after 3-4 months of drug treatment
- Assess the change in SAA levels after drug withdrawal of 7 days
- Evaluate the safety of using anakinra/Kineret in patients with NOMID

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization/Good Clinical Practice (ICH/GCP) and applicable regulatory requirements and NIH guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2003
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	United States: 43
Worldwide total number of subjects	43
EEA total number of subjects	0

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)	13
Children (2-11 years)	18
Adolescents (12-17 years)	5

Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from a pool of genetically tested NOMID/CINCA patients at NIH, physicians who referred NOMID/CINCA patients to NIH, and by advertising at pediatric rheumatology meetings and via the parent organization for NOMID/CINCA. Given the rarity of the disease, the study comprised the major part of North American NOMID/CINCA patients.

Pre-assignment

Screening details:

The enrollment/observation phase lasted for up to 3 weeks to determine main baseline characteristics. If eligible, the patient was started on an open-label administration of Kineret at 1-2 mg/kg/day by s.c. injections.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Kineret
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Arm description:

Daily subcutaneous injection of Kineret. Starting dose of 1-2 mg/kg/day

Arm type	Experimental
Investigational medicinal product name	Kineret
Investigational medicinal product code	
Other name	Anakinra
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The initial dose of Kineret given was 1-2 mg/kg body weight per day. First evaluation of the clinical response was done 1-3 months after initiation. At intervals no less than 7 days, a patient who was not in clinical remission could continue to have his/her Kineret dose increased in increments between 0.5 and 1 mg/kg to a maximum dose of 10 mg/kg per day to achieve clinical remission.

Number of subjects in period 1	Kineret
Started	43
Completed	22
Not completed	21
Not reached Month 60	19
non-compliance and withdrawal of consent	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	43	43	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	13	13	
Children (2-11 years)	18	18	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	7	7	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	8.4		
full range (min-max)	0.7 to 46.3	-	
Gender categorical			
Units: Subjects			
Female	25	25	
Male	18	18	
Diagnosis			
Units: Subjects			
NOMID	36	36	
NOMID/MWS	7	7	
Mutation in exon 3 of CIAS1			
Units: Subjects			
Present	31	31	
Not present	10	10	
No data	2	2	
Age at diagnosis			
Units: years			
median	3.7		
full range (min-max)	0.1 to 46.3	-	
Time since diagnosis			
Units: years			
median	0.3		
full range (min-max)	0 to 20.9	-	

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: All enrolled patients who received at least one dose of study treatment were included in the safety population	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT population included all enrolled patients with pretreatment efficacy assessments	
Subject analysis set title	ITT diary population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The ITT diary population included all enrolled patients who had valid pretreatment diary data assessments.	
Subject analysis set title	Withdrawal population - withdrawn
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Subset of the ITT population for diary data, including patients who participated in the withdrawal period.	
Subject analysis set title	PK population
Subject analysis set type	Safety analysis
Subject analysis set description: Subset of the Safety population, in whom serum samples were taken for PK profiling at least once.	
Subject analysis set title	Withdrawal population - treatment group
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Subset of the ITT population for diary data, including patients who provided diary data during the period corresponding to the withdrawal period.	

Reporting group values	Safety population	ITT population	ITT diary population
Number of subjects	43	34	29
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	13	8	5
Children (2-11 years)	18	16	16
Adolescents (12-17 years)	5	4	2
Adults (18-64 years)	7	6	6
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	8.4	8.6	8.6
full range (min-max)	0.7 to 46.3	0.8 to 46.3	0.8 to 46.3
Gender categorical			
Units: Subjects			
Female	25	18	13
Male	18	16	16

Diagnosis			
Units: Subjects			
NOMID	36	28	23
NOMID/MWS	7	6	6
Mutation in exon 3 of CIAS1			
Units: Subjects			
Present	31	27	22
Not present	10	6	6
No data	2	1	1
Age at diagnosis			
Units: years			
median	3.7	4.6	5.1
full range (min-max)	0.1 to 46.3	0.1 to 46.3	0.1 to 46.3
Time since diagnosis			
Units: years			
median	0.3	0.5	0.5
full range (min-max)	0 to 20.9	0 to 17.1	0 to 17.1

Reporting group values	Withdrawal population - withdrawn	PK population	Withdrawal population - treatment group
Number of subjects	11	21	11
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	3
Children (2-11 years)	8	13	6
Adolescents (12-17 years)	0	4	1
Adults (18-64 years)	3	4	1
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	8.6	11.4	8.4
full range (min-max)	4.2 to 27.8	4.2 to 42.2	0.8 to 25.8
Gender categorical			
Units: Subjects			
Female	6	10	5
Male	5	11	6
Diagnosis			
Units: Subjects			
NOMID	11	20	8
NOMID/MWS	0	1	3
Mutation in exon 3 of CIAS1			
Units: Subjects			
Present	8	16	9
Not present	3	5	1
No data	0	0	1

Age at diagnosis			
Units: years			
median	4	7.8	6.5
full range (min-max)	0.6 to 27.3	0.6 to 42.2	0.1 to 25.8
Time since diagnosis			
Units: years			
median	3.5	1.3	0.3
full range (min-max)	0.3 to 17.1	0 to 17.1	0 to 6.8

End points

End points reporting groups

Reporting group title	Kineret
Reporting group description: Daily subcutaneous injection of Kineret. Starting dose of 1-2 mg/kg/day	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: All enrolled patients who received at least one dose of study treatment were included in the safety population	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT population included all enrolled patients with pretreatment efficacy assessments	
Subject analysis set title	ITT diary population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The ITT diary population included all enrolled patients who had valid pretreatment diary data assessments.	
Subject analysis set title	Withdrawal population - withdrawn
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Subset of the ITT population for diary data, including patients who participated in the withdrawal period.	
Subject analysis set title	PK population
Subject analysis set type	Safety analysis
Subject analysis set description: Subset of the Safety population, in whom serum samples were taken for PK profiling at least once.	
Subject analysis set title	Withdrawal population - treatment group
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Subset of the ITT population for diary data, including patients who provided diary data during the period corresponding to the withdrawal period.	

Primary: Change in DSSS (fever, rash, joint pain, vomiting, and headache) from baseline to Month 3-6

End point title	Change in DSSS (fever, rash, joint pain, vomiting, and headache) from baseline to Month 3-6
End point description: Diary Symptom Sum Score The severity of the main symptoms of the disease were scored on a scale from 0 (no symptoms) to 4 (highest severity) on a daily basis using a diary. Five key symptoms were included in the primary variable DSSS: fever, headache, rash, joint pain, and vomiting. Each of the diary variables was evaluated as a mean value for a period preceding the visits. The baseline value was the mean value of the 5-30 last days before the first dose of Kineret. For the subsequent visits, the mean value of the last 30 days with data before each visit was used as the response variable. Arithmetic mean is based on change from baseline to Month 3 and statistical analysis is based on change from baseline to Month 3-6.	
End point type	Primary
End point timeframe: From 30 days prior to Baseline and until the end of the study up to 3-6 months.	

End point values	Kineret	ITT diary population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	29	29		
Units: severity score				
arithmetic mean (standard deviation)	-3.8 (± 2.6)	-3.8 (± 2.6)		

Statistical analyses

Statistical analysis title	Change in DSSS from baseline to 3-6 months
Statistical analysis description:	
The change from baseline in DSSS was based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate.	
Comparison groups	Kineret v ITT diary population
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-3.2
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[1] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Primary: Change in SAA levels from baseline to Month 3-6

End point title	Change in SAA levels from baseline to Month 3-6
End point description:	
Arithmetic mean is based on change from baseline to Month 3 and statistical analysis is based on change from baseline to Month 3-6.	
End point type	Primary
End point timeframe:	
From baseline to month 3-6	

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	23	23		
Units: mg/L				
arithmetic mean (standard deviation)	-192 (± 197)	-192 (± 197)		

Attachments (see zip file)	SAA from baseline to Month 60/SAA from baseline to Month 60.
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Statistical analyses

Statistical analysis title	Change in SAA levels from baseline to Month 3-6
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Statistical analysis description:

The change from baseline in SAA was based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate.

Comparison groups	Kineret v ITT population
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-206
Confidence interval	
level	95 %
sides	2-sided
lower limit	-230
upper limit	-182
Variability estimate	Standard error of the mean
Dispersion value	12

Notes:

[2] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Primary: Change in SAA from Month 3 (before withdrawal) to end of withdrawal

End point title	Change in SAA from Month 3 (before withdrawal) to end of withdrawal
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End point description:

End point type	Primary
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End point timeframe:

From before to end of withdrawal period (up to 7 days)

End point values	Kineret	Withdrawal population - withdrawn		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: mg/L				
arithmetic mean (standard deviation)	352 (± 229)	352 (± 229)		

Statistical analyses

Statistical analysis title	Change from before to end of withdrawal period
Statistical analysis description:	
The change in SAA from before to end of withdrawal period was based on a repeated measures ANCOVA model including visit as a fixed factor and the before withdrawal value as a covariate.	
Comparison groups	Kineret v Withdrawal population - withdrawn
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from start of withdrawal
Point estimate	352
Confidence interval	
level	95 %
sides	2-sided
lower limit	240
upper limit	465
Variability estimate	Standard error of the mean
Dispersion value	50

Notes:

[3] - Analysis of change from before to end of withdrawal period within the group of patients that were withdrawn from treatment.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Change in DSSS from Month 3 (before withdrawal) to end of withdrawal

End point title	Change in DSSS from Month 3 (before withdrawal) to end of withdrawal
End point description:	
Change from before to end of withdrawal period in diary symptom sum score (DSSS).	
Diary Symptom Sum Score	
The severity of the main symptoms of the disease were scored on a scale from 0 (no symptoms) to 4 (highest severity) on a daily basis using a diary. Five key symptoms were included in the primary variable DSSS: fever, headache, rash, joint pain, and vomiting.	
End point type	Secondary
End point timeframe:	
from before to end of withdrawal period (up to 7 days)	

End point values	Withdrawal population - withdrawn	Withdrawal population - treatment group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: Severity score				
arithmetic mean (standard deviation)	4.6 (± 2.5)	0.1 (± 0.7)		

Statistical analyses

Statistical analysis title	Change from before to end of withdrawal period
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Statistical analysis description:

The change in DSSS from before to end of withdrawal period was based on a repeated measures ANCOVA model including visit, group and the interaction between visit and group as a fixed factors and the before withdrawal period value as a covariate.

Comparison groups	Withdrawal population - treatment group v Withdrawal population - withdrawn
Number of subjects included in analysis	22
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	5.6
Variability estimate	Standard error of the mean
Dispersion value	0.6

Secondary: Neutrophils - Change from baseline to Month 60

End point title	Neutrophils - Change from baseline to Month 60
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End point description:

End point type	Secondary
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End point timeframe:

From Baseline to Month 60

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: $\times 10^3/\mu\text{L}$				
arithmetic mean (standard deviation)	-7.9 (\pm 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: ALT - Change from baseline to Month 60

End point title	ALT - Change from baseline to Month 60
End point description:	
End point type	Secondary
End point timeframe:	
from baseline to Month 60	

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: U/L				
arithmetic mean (standard deviation)	20.8 (\pm 23.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hb - Change from baseline to Month 60

End point title	Hb - Change from baseline to Month 60
End point description:	
End point type	Secondary
End point timeframe:	
From baseline to Month 60	

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: g/dL				
arithmetic mean (standard deviation)	3.3 (\pm 1.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial opening pressure - Change from baseline to Month 60

End point title	Intracranial opening pressure - Change from baseline to Month 60
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End point description:

Intracranial opening pressure was measured with a normal value defined as less than 200 mm of water column.

End point type	Secondary
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End point timeframe:

From baseline to up to month 60

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	29	29		
Units: mm of water				
arithmetic mean (standard deviation)	-102 (\pm 72)	-102 (\pm 72)		

Statistical analyses

Statistical analysis title	Opening pressure - Change fr baseline to Month 60
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Statistical analysis description:

The change from baseline in intracranial opening pressure was based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate.

Comparison groups	Kineret v ITT population
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-123
upper limit	-43
Variability estimate	Standard error of the mean
Dispersion value	20

Notes:

[4] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Pleiocytois - change from baseline to Month 60

End point title	Pleiocytois - change from baseline to Month 60
End point description:	
Measured as change from baseline to up to Month 60 in CSF WBC adjusted cellularity	
End point type	Secondary
End point timeframe:	
From baseline up to month 60	

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	30		
Units: cells/ μ L				
arithmetic mean (standard deviation)	-24.7 (\pm 24)	-24.7 (\pm 24)		

Statistical analyses

Statistical analysis title	Pleiocytois - change from baseline to Month 60
Statistical analysis description:	
The change from baseline was based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate.	
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.0061
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-27.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.3
upper limit	-8.2

Variability estimate	Standard error of the mean
Dispersion value	9.8

Notes:

[5] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Total number of swollen joints - Change from baseline to Month 60

End point title	Total number of swollen joints - Change from baseline to Month 60
End point description:	
End point type	Secondary
End point timeframe:	
From baseline up to month 60	

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: Number of joints				
arithmetic mean (standard deviation)	-12.4 (± 11.9)	-12.4 (± 11.9)		

Statistical analyses

Statistical analysis title	Swollen joints - change from baseline to Month 60
Statistical analysis description:	
Estimated change from baseline based on repeated measures ANCOVA. Model includes visit (month) as a fixed factor and baseline as a covariate.	
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	-7.4
Variability estimate	Standard error of the mean
Dispersion value	0.9

Notes:

[6] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for

the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Total number of joints with loss of motion - Change from baseline to Month 60

End point title	Total number of joints with loss of motion - Change from baseline to Month 60
End point description:	
End point type	Secondary
End point timeframe:	
From baseline to Month 60	

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: Number of joints				
arithmetic mean (standard deviation)	-13.7 (\pm 10.3)	-13.7 (\pm 10.3)		

Statistical analyses

Statistical analysis title	Total number of joints with loss of motion
Statistical analysis description:	
the change from baseline was based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate.	
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	-8.8
Variability estimate	Standard error of the mean
Dispersion value	1.2

Secondary: Total number of joints with pain on motion - Change from baseline to Month 60

End point title	Total number of joints with pain on motion - Change from
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End point description:

End point type Secondary

End point timeframe:

From baseline to Month 60

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: Number of joints				
arithmetic mean (standard deviation)	-5.4 (± 9.2)	-5.4 (± 9.2)		

Statistical analyses

Statistical analysis title	Estimated change from baseline
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other ^[7]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	-4.4
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[7] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Change from baseline to Month 60 in bone mineral density in L1-L4

End point title Change from baseline to Month 60 in bone mineral density in L1-L4

End point description:

End point type Secondary

End point timeframe:

from baseline up to month 60

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	23	23		
Units: Z-score				
arithmetic mean (standard deviation)	0.9 (± 1.29)	0.9 (± 1.29)		

Statistical analyses

Statistical analysis title	L1-L4 - change from baseline to Month 60
Statistical analysis description: the change from baseline was based on a repeated measures analysis of covariance model including visit (month) as a fixed factor and baseline as a covariate	
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.48
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[8] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Bone mineral density in total hip area - Change from baseline to Month 60

End point title	Bone mineral density in total hip area - Change from baseline to Month 60
End point description:	
End point type	Secondary
End point timeframe: from baseline to Month 60	

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	23	23		
Units: Z-score				
arithmetic mean (standard deviation)	1.15 (± 1.48)	1.15 (± 1.48)		

Statistical analyses

Statistical analysis title	Bone mineral density in total hip area
Statistical analysis description:	
The change from baseline based in bone mineral density in total hip area was based on repeated measurement analysis of covariance model including visit (month) as a fixed factor and baseline as a covariate.	
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[9] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Childhood Health Assessment Questionnaire (CHAQ) overall score - Change from baseline to Month 60

End point title	Childhood Health Assessment Questionnaire (CHAQ) overall score - Change from baseline to Month 60
End point description:	
CHAQ - overall score, overall pain rating, overall global evaluation, subcategories for dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities	
End point type	Secondary
End point timeframe:	
From baseline up to month 60	

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: Score				
arithmetic mean (standard deviation)	-0.3 (± 0.43)	-0.3 (± 0.43)		

Statistical analyses

Statistical analysis title	CHAQ overall - change from baseline to Month 60
Statistical analysis description: the change from baseline was based on a repeated measures analysis of covariance model including visit (month) as a fixed factor and baseline as a covariate	
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other ^[10]
P-value	= 0.0367
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[10] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: CRP - Change from baseline to Month 60

End point title	CRP - Change from baseline to Month 60
End point description:	
End point type	Secondary
End point timeframe: From baseline to Month 60	

End point values	Kineret	Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	34	34		
Units: mg/L				
arithmetic mean (standard deviation)	-55 (\pm 37)	-55 (\pm 37)		

Statistical analyses

Statistical analysis title	CRP - Change from baseline to Month 60
Statistical analysis description:	
The change from baseline was based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate.	
Comparison groups	Kineret v Safety population
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other ^[11]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67
upper limit	-48
Variability estimate	Standard error of the mean
Dispersion value	5

Notes:

[11] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Total number of tender joints - Change from baseline to Month 60

End point title	Total number of tender joints - Change from baseline to Month 60
End point description:	
End point type	Secondary
End point timeframe:	
From baseline up to month 60	

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: Number of joints				
arithmetic mean (standard deviation)	-10.1 (± 13.7)	-10.1 (± 13.7)		

Statistical analyses

Statistical analysis title	Tender joints - change from baseline to Month 60
Statistical analysis description:	
Estimated change from baseline based on the repeated measures ANCOVA. Model includes visit (month) as a fixed factor and baseline as a covariate.	
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other ^[12]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	-6.9
Variability estimate	Standard error of the mean
Dispersion value	0.6

Notes:

[12] - Analysis of change from baseline within the Kineret treatment group.

Please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Secondary: Total number of warm joints - Change from baseline to Month 60

End point title	Total number of warm joints - Change from baseline to Month 60
End point description:	
End point type	Secondary
End point timeframe:	
From baseline to Month 60	

End point values	Kineret	ITT population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	14		
Units: Number of joints				
arithmetic mean (standard deviation)	-19.4 (± 14.1)	-19.4 (± 14.1)		

Statistical analyses

Statistical analysis title	Total number of warm joints
Comparison groups	Kineret v ITT population
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other ^[13]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean change from baseline
Point estimate	-14.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	-12.5
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[13] - Analysis of change from baseline within the Kineret treatment group

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs recorded from first dose of study medication up to the Month 60 visit, the last day of study medication, or the data cut-off date.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

Reporting group title	Overall Study
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Reporting group description: -

Serious adverse events	Overall Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 43 (32.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Catheterization cardiac			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Histiocytosis hematophagica			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Traumatic lumbar puncture			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Condition aggravated			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenitis bacterial			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis enteroviral			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 43 (93.02%)		
Investigations			
Weight increased			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	6		
Contusion			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 43 (48.84%)		
occurrences (all)	115		
Dizziness			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	10		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 43 (39.53%)		
occurrences (all)	51		
Fatigue			
subjects affected / exposed	10 / 43 (23.26%)		
occurrences (all)	27		
Injection site reaction			
subjects affected / exposed	8 / 43 (18.60%)		
occurrences (all)	12		
Chest pain			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	9		

Condition aggravated subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 6		
Malaise subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 18		
Pain subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 6		
Gait disturbance subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 5		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 7		
Vertigo subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3		
Eye disorders Ocular hyperaemia subjects affected / exposed occurrences (all)	12 / 43 (27.91%) 35		
Eye pain subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 4		
Conjunctivitis subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	10 / 43 (23.26%) 16		
Vomiting subjects affected / exposed occurrences (all)	7 / 43 (16.28%) 25		
Nausea			

subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	14		
Abdominal pain			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	11		
Abdominal pain upper			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	27		
Cough			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	19		
Nasal congestion			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	14		
Epistaxis			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	10		
Rhinorrhoea			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	6		
Sinus congestion			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Rhinitis allergic			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	14 / 43 (32.56%)		
occurrences (all)	51		
Exfoliative rash			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	5		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 43 (41.86%)		
occurrences (all)	133		
Pain in extremity			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	27		
Neck pain			
subjects affected / exposed	8 / 43 (18.60%)		
occurrences (all)	11		
Back pain			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	22		
Myalgia			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	7		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	17 / 43 (39.53%)		
occurrences (all)	48		
Nasopharyngitis			
subjects affected / exposed	15 / 43 (34.88%)		
occurrences (all)	40		
Sinusitis			
subjects affected / exposed	11 / 43 (25.58%)		
occurrences (all)	27		

Ear infection			
subjects affected / exposed	11 / 43 (25.58%)		
occurrences (all)	23		
Otitis media			
subjects affected / exposed	10 / 43 (23.26%)		
occurrences (all)	19		
Urinary tract infection			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	10		
Gastrointestinal viral infection			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	8		
Viral infection			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	8		
Gastroenteritis			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	6		
Bronchitis			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	6		
Pharyngitis			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Gastrointestinal infection			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Hordeolum			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Otitis externa			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2003	Main changes in study plan: Repeat lumbar punctures and extension of the open-label treatment period. Reason for change/Comment: No placebo available at the time of first patient reaching 3 months
23 December 2003	Main changes in study plan: The randomized double-blind withdrawal period, was replaced by an open-label withdrawal in all patients. Change in primary objective and definition of flare. Reason for change/Comment: Placebo could not be obtained so the withdrawal phase was changed to an open-label withdrawal of study drug in all patients. The withdrawal period reduced to 7 days to limit the untoward effects for the patients to a minimal period of time.
04 March 2004	Main changes in study plan: Move some tests from visit Month 3 to Month 6. Allow more flexibility in scheduling follow-up appointments. Reason for change/Comment: Due to the withdrawal of treatment early during the Month 3 visit it was not possible to do all the examinations before that and it was not of value to do the exams when off treatment (the intention was to study the drug effects)
15 June 2004	Main changes in study plan: The withdrawal phase was removed after completion of 11 patients. Reason for change/Comment: Because of the significance of the study drug treatment effects in the first 11 patients and the severity of their flares upon withdrawal, the withdrawal phase was removed.
12 November 2004	Main changes in study plan: Study prolonged and patients who complete the Month 12 evaluation were eligible for continued treatment for an additional year (visits at 18 and 24 months). Maximum allowed dose 3mg/kg/day Reason for change/Comment: To allow patients to continue treatment and for individual dosing above 2 mg/kg/day
10 March 2007	Main changes in study plan: An open-ended extension was added to the study and allowed for continued evaluation. Patients were to return to the NIH every 6 months for evaluation and had monthly visits to the local physician in between. The maximum dose allowed was increased to 5 mg/kg/day. The possibility to transfer eligible NOMID patients included in other research projects at the NIH to one protocol. The possibility to recruit more patients. PK sampling and method of calculation adjusted. Reason for change/Comment: The focus of the study was modified from short term effects to long term effects in organ disease manifestations to determine if treatment could prevent the occurrence or progression of organ damage. The primary objective did however not change. To allow for individual dosing above 3 mg/kg/day
11 June 2007	Main changes in study plan: Removal of age limit. Reason for change/Comment: The treatment outcome at this time point indicated slowed progression of organ damage. It was therefore of great interest to start treatment at the earliest age to evaluate whether organ damage could be completely prevented.

03 March 2009	Main changes in study plan: Other IL-1 receptor antagonist drugs were allowed as treatment in the study. (This allowance was removed in the September 10, 2010, amendment) Reason for change/Comment: To be able to evaluate the effects of other IL-1 blockers under the same investigational protocol
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported