Clinical trial results:
A Randomized, Multi-center, Blinded, Placebo-controlled Study With an Open-label Run-in Period to Evaluate the Efficacy, Safety, and Pharmacokinetics of Daily, Single, Subcutaneous Injections of r-metHuiL-1ra (Anakinra) in Polyarticular-Course Juvenile Rheumatoid Arthritis

Summary

EudraCT number	2015-002466-22
Trial protocol	Outside EU/EEA
Global end of trial date	11 November 2003

Results information

Result version number	v1 (current)
This version publication date	27 November 2016
First version publication date	27 November 2016

Trial information

Trial identification

Sponsor protocol code	990758

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00037648
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 3611

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Dr, Thousand Oaks, United States, CA 90049
Public contact	Terry Bevirt Therapeutic Area Planning & Operations Director Early Development , Amgen Inc., 001 805-447-0507, tbevirt@amgen.com
Scientific contact	Terry Bevirt Therapeutic Area Planning & Operations Director Early Development , Amgen Inc., 001 805-447-0507, tbevirt@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	21 December 2003
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2003
Global end of trial reached?	Yes
Global end of trial date	11 November 2003
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety of anakinra

Protection of trial subjects:

This study was conducted in compliance with principles of the Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 2000
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	Canada: 2
Country: Number of subjects enrolled	United States: 51
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	Costa Rica: 13
Worldwide total number of subjects	86
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)	0

Children (2-11 years)	43
Adolescents (12-17 years)	43
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Multicenter study conducted at 17 centers in the United States, Canada, Australia, New Zealand and Costa Rica

Pre-assignment

Screening details:

Screening up to 4 weeks prior to enrolment

Period 1

Period 1 title	Open label phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-label Kineret

Arm description: -

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

Dosage and administration details:

Subjects received a single dose of SC anakinra 1.0 mg/kg/day up to a maximum of 100 mg/day for 12 weeks

Number of subjects in period 1	Open-label Kineret
Started	86
Completed	50
Not completed	36
Consent withdrawn by subject	3
Adverse event, non-fatal	4
Administrative decision	1
Non-responders (protocol-specified criteria)	27
Protocol deviation	1

Period 2

Period 2 title	Blinded phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Kineret

Arm description:

16-week blinded, placebo-controlled phase with a 2-week follow-up visit

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

Dosage and administration details:

Subjects received a single dose of SC anakinra 1.0 mg/kg/day up to a maximum of 100 mg/day for 16 weeks

Arm title	Placebo

Arm description:

16-week blinded, placebo-controlled phase with a 2-week follow-up visit

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received daily SC blinded doses of placebo for 16 weeks.
Placebo was supplied in single-use vials, identical to anakinra.

Number of subjects in period 2	Kineret	Placebo
Started	25	25
Completed	19	12
Not completed	6	13
Disease flare	6	12
Administrative decision	-	1

Baseline characteristics

Reporting groups

Reporting group title	Open label phase

Reporting group description: -

Reporting group values	Open label phase	Total	
Number of subjects	86	86	
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)	0	0	
Children (2-11 years)	43	43	
Adolescents (12-17 years)	43	43	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	11.51		
standard deviation	± 3.88	-	
Gender categorical Units: Subjects			
Female	63	63	
Male	23	23	
Type of arthritis at onset Units: Subjects			
Pauciarticular	9	9	
Polyarticular	62	62	
Systemic	15	15	
Duration of JRA Units: years			
arithmetic mean	4.7		
standard deviation	± 3.7	-	

Subject analysis sets

Subject analysis set title	Kineret open-label phase
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least 1 dose of open-label study drug were considered evaluable for safety.

Subject analysis set title	Kineret double-blind phase
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects randomized to Kineret.

Subject analysis set title	Placebo double-blind phase
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomized to placebo.	
Subject analysis set title	Kineret double-blind phase - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of blinded study drug were considered evaluable for safety.	
Subject analysis set title	Placebo double-blind phase - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of blinded study drug were considered evaluable for safety.	

Reporting group values	Kineret open-label phase	Kineret double-blind phase	Placebo double-blind phase
Number of subjects	86	25	25
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)	43		
Adolescents (12-17 years)	43		
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	11.51		
standard deviation	± 3.88	±	±
Gender categorical			
Units: Subjects			
Female			
Male			
Type of arthritis at onset			
Units: Subjects			
Pauciarticular			
Polyarticular			
Systemic			
Duration of JRA			
Units: years			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Kineret double-blind phase - Safety	Placebo double-blind phase - Safety	
Number of subjects	25	25	
Age categorical			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			
Type of arthritis at onset Units: Subjects			
Pauciarticular Polyarticular Systemic			
Duration of JRA Units: years arithmetic mean standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Open-label Kineret
Reporting group description: -	
Reporting group title	Kineret
Reporting group description:	
16-week blinded, placebo-controlled phase with a 2-week follow-up visit	
Reporting group title	Placebo
Reporting group description:	
16-week blinded, placebo-controlled phase with a 2-week follow-up visit	
Subject analysis set title	Kineret open-label phase
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of open-label study drug were considered evaluable for safety.	
Subject analysis set title	Kineret double-blind phase
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomized to Kineret.	
Subject analysis set title	Placebo double-blind phase
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomized to placebo.	
Subject analysis set title	Kineret double-blind phase - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of blinded study drug were considered evaluable for safety.	
Subject analysis set title	Placebo double-blind phase - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of blinded study drug were considered evaluable for safety.	

Primary: Proportion of subjects with disease flares during the 16-week blinded phase

End point title	Proportion of subjects with disease flares during the 16-week blinded phase
End point description:	
Time to flare was also analysed and the difference between groups was not significant. For neither of the groups, a median time could be estimated.	

End point type	Primary
End point timeframe:	
From randomisation (week 12) to week 28 in the blinded phase	

End point values	Kineret double-blind phase	Placebo double-blind phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: Number of subjects				
Yes	4	9		
No	21	16		

Statistical analyses

Statistical analysis title	Proportion of subjects with disease flares
Comparison groups	Kineret double-blind phase v Placebo double-blind phase
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1963
Method	Fisher exact

Secondary: Change from week 12 assessments of CHAQ to week 28 (blinded phase)

End point title	Change from week 12 assessments of CHAQ to week 28 (blinded phase)

End point description:

CHAQ = Childhood Health Assessment Questionnaire

End point type	Secondary

End point timeframe:

From week 12 (randomisation) to week 28

End point values	Kineret double-blind phase	Placebo double-blind phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	11		
Units: score				
arithmetic mean (standard deviation)	-0.25 (± 0.48)	0.13 (± 0.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from week 12 assessments of number of active joints to week 28 (blinded phase)

End point title	Change from week 12 assessments of number of active joints

	to week 28 (blinded phase)

End point description:

End point type	Secondary

End point timeframe:

From week 12 (Randomisation) to week 28

End point values	Kineret double-blind phase	Placebo double-blind phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	11		
Units: Number of active joints				
arithmetic mean (standard deviation)	-0.35 (± 5.46)	-0.64 (± 4.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from week 12 assessments of number of joints with limitation of motion to week 28 (blinded phase)

End point title	Change from week 12 assessments of number of joints with limitation of motion to week 28 (blinded phase)

End point description:

End point type	Secondary

End point timeframe:

From week 12 (Randomisation) to week 28

End point values	Kineret double-blind phase	Placebo double-blind phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	11		
Units: Number of joints				
arithmetic mean (standard deviation)	-0.6 (± 5.21)	0.18 (± 4.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from week 12 assessments of physicians assessment of JRA disease activity to week 28 (blinded phase)

End point title	Change from week 12 assessments of physicians assessment of JRA disease activity to week 28 (blinded phase)

End point description:

End point type	Secondary

End point timeframe:

From week 12 (Randomisation) to week 28

End point values	Kineret double-blind phase	Placebo double-blind phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	11		
Units: score				
arithmetic mean (standard deviation)	3.35 (± 20.11)	9.27 (± 34.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from week 12 assessments of subject/parent assessment of JRA disease activity to week 28 (blinded phase)

End point title	Change from week 12 assessments of subject/parent assessment of JRA disease activity to week 28 (blinded phase)

End point description:

End point type	Secondary

End point timeframe:

From week 12 (Randomisation) to week 28

End point values	Kineret double-blind phase	Placebo double-blind phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	11		
Units: score				
arithmetic mean (standard deviation)	-6.55 (± 11.25)	1.36 (± 25.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: anti-Anakinra Antibodies

End point title	anti-Anakinra Antibodies

End point description:

Occurence of antibodies at any time during the open-label period

End point type	Secondary

End point timeframe:

From baseline to week 12 (open-label phase)

End point values	Kineret open-label phase			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: Subjects				
non-neutralising antibodies	48			
Neutralising antibodies	4			

Statistical analyses

No statistical analyses for this end point

Secondary: anti-Anakinra Antibodies - double-blind phase

End point title	anti-Anakinra Antibodies - double-blind phase

End point description:

Occurence of antibodies at any time during the double-blind period

End point type	Secondary

End point timeframe:

From week 12 (randomisation) to week 28

End point values	Kineret double-blind phase	Placebo double-blind phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	9		
Units: Subjects				
non-neutralising antibodies	13	4		
neutralising antibodies	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from week 12 in ESR to week 28 (blinded phase)

End point title	Change from week 12 in ESR to week 28 (blinded phase)

End point description:

ESR = Erythrocyte Sedimentation Rate

End point type	Secondary

End point timeframe:

From week 12 (randomisation) to week 28 (blinded phase)

End point values	Kineret double-blind phase	Placebo double-blind phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	15		
Units: mm/hr				
arithmetic mean (standard deviation)	-3.7 (± 11.23)	13.73 (± 22.52)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of enrolment until end of blinded phase	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Open-label Kineret
Reporting group description: -	
Reporting group title	Blinded phase - Kineret
Reporting group description: -	
Reporting group title	Blinded phase - Placebo
Reporting group description: -	

Serious adverse events	Open-label Kineret	Blinded phase - Kineret	Blinded phase - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 86 (3.49%)	0 / 25 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 86 (1.16%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 86 (1.16%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Open-label Kineret	Blinded phase - Kineret	Blinded phase - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 86 (93.02%)	17 / 25 (68.00%)	18 / 25 (72.00%)
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	3 / 86 (3.49%)	3 / 25 (12.00%)	0 / 25 (0.00%)
occurrences (all)	4	5	0
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 86 (22.09%)	6 / 25 (24.00%)	1 / 25 (4.00%)
occurrences (all)	36	10	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	31 / 86 (36.05%)	2 / 25 (8.00%)	1 / 25 (4.00%)
occurrences (all)	40	3	1
Injection site haemorrhage			
subjects affected / exposed	12 / 86 (13.95%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	18	1	4
Injection site inflammation			
subjects affected / exposed	8 / 86 (9.30%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	9	0	1
Injection site oedema			
subjects affected / exposed	9 / 86 (10.47%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	19	1	0
Injection site pruritus			
subjects affected / exposed	26 / 86 (30.23%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	36	2	1
Injection site pain			
subjects affected / exposed	29 / 86 (33.72%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	57	0	0
Injection site rash			
subjects affected / exposed	14 / 86 (16.28%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	19	0	0

Injection site reaction			
subjects affected / exposed	13 / 86 (15.12%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	14	2	0
Pain			
subjects affected / exposed	5 / 86 (5.81%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	9	0	7
Pyrexia			
subjects affected / exposed	14 / 86 (16.28%)	3 / 25 (12.00%)	2 / 25 (8.00%)
occurrences (all)	21	4	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 86 (17.44%)	3 / 25 (12.00%)	2 / 25 (8.00%)
occurrences (all)	19	5	2
Diarrhoea			
subjects affected / exposed	7 / 86 (8.14%)	3 / 25 (12.00%)	0 / 25 (0.00%)
occurrences (all)	7	3	0
Nausea			
subjects affected / exposed	7 / 86 (8.14%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	8	0	1
Vomiting			
subjects affected / exposed	6 / 86 (6.98%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	12	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 86 (5.81%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	5	1	0
Oropharyngeal pain			
subjects affected / exposed	5 / 86 (5.81%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	5	2	0
Upper respiratory tract congestion			
subjects affected / exposed	2 / 86 (2.33%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	2	2	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 86 (10.47%)	0 / 25 (0.00%)	3 / 25 (12.00%)
occurrences (all)	13	0	3

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 86 (12.79%)	1 / 25 (4.00%)	4 / 25 (16.00%)
occurrences (all)	21	1	6
Arthritis			
subjects affected / exposed	1 / 86 (1.16%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Back pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	2	0	3
Joint stiffness			
subjects affected / exposed	1 / 86 (1.16%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	1	0	2
Pain in extremity			
subjects affected / exposed	6 / 86 (6.98%)	3 / 25 (12.00%)	4 / 25 (16.00%)
occurrences (all)	6	3	5
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	20 / 86 (23.26%)	4 / 25 (16.00%)	5 / 25 (20.00%)
occurrences (all)	22	4	5
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 86 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2000	Amendment 1: • Increased sample size from 150 to 204 subjects in the open label phase and 50 to 68 subjects in the blinded phase • Revised inclusion and exclusion criteria • Clarified concomitant therapy use during the study • Included secondary objective of sustained response rate • General administrative changes and clarifications included typographical and spelling errors • Wording changed in Informed Consent document to lower the reading level score to a more appropriate level • Updated safety and efficacy profiles from recently completed IL-1ra studies
17 April 2000	Amendment 2: • Subject or parent pain assessment was included as a secondary objective • Maximum methotrexate dose was increased to 40 mg/wk • Eliminated 40 mg/mL study drug concentration • Clarified that subjects receiving methotrexate were to also receive folic acid or folinic acid • Clarified that subjects on stable doses of oral corticosteroids receive ≤ 10mg/day or 0.2 mg/kg/day of prednisone (whichever was less) • Added to exclusion criteria subjects known to be positive for hepatitis or HIV • Added to concomitant therapy that etanercept and infliximab be received 4 weeks prior to anakinra • Added to concomitant medication guidelines that subjects were allowed one intra-ocular corticosteroid injection in the case of uveitis

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.

CSP Amendment 3: CSP Amendment 3 (20Feb2004 post End of Trial). The objectives and statistical considerations of this protocol were changed to only evaluate the safety of anakinra in subjects with JRA.

Notes: