



## Clinical trial results:

### A Multicenter, Multinational, Open-Label Extension Study of Recombinant Human N-acetylgalactosamine 4-sulfatase (rhASB) in Patients with Mucopolysaccharidosis VI

#### Summary

EudraCT number	2004-000642-21
Trial protocol	IE
Global end of trial date	29 September 2006

#### Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

#### Trial information

##### Trial identification

Sponsor protocol code	ASB-03-06
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00104234
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc.
Sponsor organisation address	105 Digital Drive, Novato, United States, CA 94949
Public contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com

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?	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	01 June 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2006
Global end of trial reached?	Yes
Global end of trial date	29 September 2006
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the long-term efficacy and safety of rhASB treatment in patients with mucopolysaccharidosis VI (MPS VI).

Protection of trial subjects:

This clinical study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S.federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2004
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 Kingdom: 6
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	39
EEA total number of subjects	25

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)	23

Adolescents (12-17 years)	8
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This is a Multicenter and Multinational Study conducted in 6 countries.

### Pre-assignment

Screening details:

Of the 39 subjects enrolled to study, 38 subjects remained on treatment through the end of the study.

### Period 1

Period 1 title	Entire Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	rhASB/rhASB
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Arm description:

Patients received rhASB in the double-blind study (ASB-03-05, NCT00067470) and continued to receive rhASB in the extension study (ASB-03-06)

Arm type	Experimental
Investigational medicinal product name	rhASB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will receive IV infusions of rhASB at a dose of 1.0 mg/kg diluted to a volume of 250 mL with sterile 0.9% sodium chloride. The solution will be administered intravenously over approximately a 4-hour period once a week for the duration of the study.

<b>Arm title</b>	Placebo/rhASB
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Arm description:

Patients received placebo in the double-blind study (ASB-03-05, NCT00067470) then received rhASB in the extension study (ASB-03-06)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will receive IV infusions of Placebo/rhASB at a dose of 1.0 mg/kg diluted to a volume of 250 mL with sterile 0.9% sodium chloride. The solution will be administered intravenously over approximately a 4-hour period once a week for the duration of the study.

<b>Number of subjects in period 1</b>	rhASB/rhASB	Placebo/rhASB
Started	19	20
Completed	19	19
Not completed	0	1
Consent withdrawn by subject	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	rhASB/rhASB
Reporting group description:	
Patients received rhASB in the double-blind study (ASB-03-05, NCT00067470) and continued to receive rhASB in the extension study (ASB-03-06)	
Reporting group title	Placebo/rhASB
Reporting group description:	
Patients received placebo in the double-blind study (ASB-03-05, NCT00067470) then received rhASB in the extension study (ASB-03-06)	

Reporting group values	rhASB/rhASB	Placebo/rhASB	Total
Number of subjects	19	20	39
Age categorical			
Units: Subjects			

Age continuous			
Demographic and baseline characteristics were recorded at baseline in the double-blind study, ASB-03-05			
Units: years			
arithmetic mean	13.7	10.7	
standard deviation	± 6.47	± 4.35	-
Gender categorical			
Demographic and baseline characteristics were recorded at baseline in the double-blind study, ASB-03-05			
Units: Subjects			
Female	12	14	26
Male	7	6	13
Race/Ethnicity			
Demographic and baseline characteristics were recorded at baseline in the double-blind study, ASB-03-05			
Units: Subjects			
White, non-Hispanic	15	9	24
Hispanic	1	3	4
Black	1	2	3
Asian	1	1	2
Indigenous	1	1	2
Other	0	4	4
Region of Enrollment			
Demographic and baseline characteristics were recorded at baseline in the double-blind study, ASB-03-05			
Units: Subjects			
United States	2	4	6
Germany	4	4	8
United Kingdom	3	3	6
Brazil	4	4	8
France	2	3	5
Portugal	4	2	6

## End points

### End points reporting groups

Reporting group title	rhASB/rhASB
Reporting group description: Patients received rhASB in the double-blind study (ASB-03-05, NCT00067470) and continued to receive rhASB in the extension study (ASB-03-06)	
Reporting group title	Placebo/rhASB
Reporting group description: Patients received placebo in the double-blind study (ASB-03-05, NCT00067470) then received rhASB in the extension study (ASB-03-06)	
Subject analysis set title	All Participants
Subject analysis set type	Full analysis
Subject analysis set description: rhASB/rhASB and placebo/rhASB groups were combined for the analysis, representing 72 weeks of rhASB treatment in each group.	

### Primary: 12-Minute Walk Test

End point title	12-Minute Walk Test
End point description: Mean change in meters walked in 12 minutes. Mean change is the mean difference between the 12-Minute Walk Test at 96 weeks and that measured before first ever treatment with rhASB. For the rhASB/rhASB group, mean change is calculated for Week 96 – Baseline. For the placebo/rhASB group, mean change is calculated for Week 96 – Week 24.  The efficacy analysis included all subjects who continued in the extension study (ASB-03-06) except the 1 subject from the rhASB/rhASB group and 1 subject from the placebo/rhASB group who missed the Week 96 measurement.	
End point type	Primary
End point timeframe: Baseline of ASB-03-05 through week 96 of ASB-03-06	

End point values	rhASB/rhASB	Placebo/rhASB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: meters				
arithmetic mean (standard deviation)	187 (± 187)	118 (± 127)		

### Statistical analyses

Statistical analysis title	rhASB-treated patients Vs placebo-treated patients
Comparison groups	rhASB/rhASB v Placebo/rhASB

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Repeated measures model

### Secondary: 3-Minute Stair Climb

End point title	3-Minute Stair Climb
End point description:	
Mean change in number of stairs climbed per minute in 3 minutes. Mean change is the mean difference between the 3-Minute Stair Climb at 96 weeks and that measured before first ever treatment with rhASB. Mean change is calculated for Week 96 – Baseline for the rhASB/rhASB group and for Week 96 – Week 24 for the placebo/rhASB group.	
The efficacy analysis included all subjects who continued in the extension study (ASB-03-06) except 1 subject from the placebo/rhASB group who missed the Week 96 measurement.	
End point type	Secondary
End point timeframe:	
Baseline ASB-03-05 through week 96 of ASB-03-06	

End point values	rhASB/rhASB	Placebo/rhASB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	18		
Units: stairs/min				
arithmetic mean (standard deviation)	13.1 (± 16.1)	11.1 (± 10.0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Urinary Glycosaminoglycans (GAG) Level

End point title	Change in Urinary Glycosaminoglycans (GAG) Level
End point description:	
Mean change in urinary GAG level for the first 72 weeks of rhASB treatment. For the rhASB/rhASB group, mean change was calculated for Week 72 -Baseline. For the placebo/rhASB, mean change was calculated for Week 96 - Week 24.	
rhASB/rhASB and placebo/rhASB groups were combined for the analysis, representing 72 weeks of rhASB treatment in each group.	
End point type	Secondary
End point timeframe:	
72 weeks	

<b>End point values</b>	All Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: microgram/mg creatinine				
arithmetic mean (standard deviation)	-231 (± 91)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to week 249 (Entire Study)

Adverse event reporting additional description:

rhASB/rhASB and placebo/rhASB groups were combined for analysis.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	6.1
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### Reporting groups

Reporting group title	All Participants
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Reporting group description:

rhASB/rhASB and placebo/rhASB groups were combined for analysis

Serious adverse events	All Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 38 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post traumatic headache			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			

Hip deformity			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Mitral valve stenosis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical myelopathy			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Convulsion			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Corneal lesion			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Tracheal stenosis			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopneumopathy			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia staphylococcal			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mastoiditis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Corneal abscess			
subjects affected / exposed	1 / 38 (2.63%)		
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 %

<b>Non-serious adverse events</b>	All Participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Poor venous access			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Haematoma			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Hyperaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	24 / 38 (63.16%)		
occurrences (all)	24		
Fatigue			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Influenza like illness			

subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Hernia pain			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Infusion site pain			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Rigors			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 38 (73.68%)		
occurrences (all)	28		
Pharyngolaryngeal pain			
subjects affected / exposed	13 / 38 (34.21%)		
occurrences (all)	13		
Rhinorrhoea			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Bronchospasm			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Dyspnoea			

subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Nasal congestion			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Pulmonary hypertention			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Rhinitis			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Wheezing			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Asthma			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Restrictive pulmonary disease			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Apnoea			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Increased bronchial secretion			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Oropharyngeal swelling			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Tachypnoea			

subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Upper respiratory tract congestion subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Psychiatric disorders Abnormal behaviour subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Anxiety subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Investigations Neutrophil count increased subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3		
QRS axis abnormal subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Cardiac murmur subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Oxygen saturation decreased subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Injury, poisoning and procedural complications Post procedural pain subjects affected / exposed occurrences (all)	10 / 38 (26.32%) 10		
Head injury subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 4		
Procedural site reaction			

subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3		
Excoriation subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Fall subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Joint injury subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Cardiac disorders Cardiac valve disease subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5		
Atrial hypertrophy subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Cardiac failure subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Cyanosis subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Dilatation atrial subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	27 / 38 (71.05%) 27		
Dizziness subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5		
Paraesthesia			

subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Hyperreflexia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Hypoaesthesia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Tremor			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Cervical myelopathy			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Leukopenia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	13 / 38 (34.21%)		
occurrences (all)	13		
Hypoacusis			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Otorrhoea			

subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Cerumen impaction			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Eye irritation			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Eye pain			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Eye redness			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Visual acuity reduced			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Eyelid oedema			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Glaucoma			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Keratoconjunctivitis sicca			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	21 / 38 (55.26%)		
occurrences (all)	21		
Vomiting			

subjects affected / exposed	18 / 38 (47.37%)		
occurrences (all)	18		
Abdominal pain			
subjects affected / exposed	15 / 38 (39.47%)		
occurrences (all)	15		
Nausea			
subjects affected / exposed	11 / 38 (28.95%)		
occurrences (all)	11		
Abdominal pain upper			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Toothache			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Inguinal hernia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Mouth ulceration			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Rash papular			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Urticaria			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Prurigo			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Acne			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Exanthem			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Face oedema			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Pityriasis rosea			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Rash erythematous			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 38 (50.00%)		
occurrences (all)	19		
Pain in extremity			
subjects affected / exposed	18 / 38 (47.37%)		
occurrences (all)	18		
Back pain			
subjects affected / exposed	15 / 38 (39.47%)		
occurrences (all)	15		
Bone pain			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Joint stiffness			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Hip deformity			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Groin pain			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Intervertebral disc disorder			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Joint contracture			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Kyphoscoliosis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Infections and infestations			
Ear infection			
subjects affected / exposed	17 / 38 (44.74%)		
occurrences (all)	17		
Nasopharyngitis			
subjects affected / exposed	16 / 38 (42.11%)		
occurrences (all)	16		
Upper respiratory tract infection			
subjects affected / exposed	15 / 38 (39.47%)		
occurrences (all)	15		
Gastroenteritis			
subjects affected / exposed	12 / 38 (31.58%)		
occurrences (all)	12		
Bronchitis			
subjects affected / exposed	9 / 38 (23.68%)		
occurrences (all)	9		
Otitis externa			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Influenza			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Otitis media acute			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Sinusitis			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		

Hordeolum			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Pharyngitis			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Laryngitis			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Dental caries			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Respiratory tract infection			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Tinea pedis			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Varicella			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Bronchopneumonia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Fungal infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

Furuncle			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Subcutaneous abscess			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Iron deficiency			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2005	<ol style="list-style-type: none"><li>1. Update the address for BioMarin Pharmaceutical Inc.</li><li>2. Change the name of the Medical Monitor</li><li>3. Update the Clinical Studies Section with current data</li><li>4. Change the description of the scale for assessing joint pain, joint stiffness, and physical energy from an analogue scale to a Semantic Differential-type scale</li><li>5. Update SAE reporting sections</li><li>6. Update the job title for Jean Masonek</li><li>7. Administrative changes to correct minor inconsistencies.</li></ol>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported