



Clinical trial results:

An open-label, prospective, multicentre, phase I/II dose escalation study to determine the maximum tolerated dose and to assess the safety and efficacy of P1101, PEG-Proline-Interferon alpha-2b for patients with Polycythaemia vera (PV).

Summary

EudraCT number	2010-018768-18
Trial protocol	AT
Global end of trial date	25 January 2018

Results information

Result version number	v1 (current)
This version publication date	23 October 2019
First version publication date	23 October 2019

Trial information

Trial identification

Sponsor protocol code	P11012010
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01193699
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AOP Orphan Pharmaceuticals AG
Sponsor organisation address	Wilhelminenstraße 91/II f, Wien, Austria,
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2018
Global end of trial reached?	Yes
Global end of trial date	25 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Identification of the maximum tolerated dose (MTD) of the investigational medicinal product (addressed to Stage 1).

The determination of standard safety and tolerability of AOP2014 in patients with PV, including an exploratory analysis of efficacy and biomarker modulation; and determination of PK parameters (addressed to Stage 2).

Protection of trial subjects:

Patients in part A/dose escalation part were reviewed for each dose cohort by the sponsor and the coordinating investigator prior to allowing a new dose cohort to be recruited. All patients in part A were additionally reviewed case by case by the coordinating investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2010
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	Austria: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	34
From 65 to 84 years	17

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Total of 51 patients were enrolled in 6 centres in Austria. Twenty-five patients were enrolled for Stage 1 of the study and continued in Stage 2. An additional 26 patients were directly enrolled into Stage 2.

Pre-assignment

Screening details:

At the time of screening for the Stage 1 part of the study, 10/25 (40.0 %) patients were undergoing treatment with HU and one patient was a newly-diagnosed PV case. At the time of screening for the Stage 2, 17/51 (33.3%) patients were undergoing treatment with HU and a minority 8/51 (15.7%) were newly-diagnosed disease cases.

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	AOP2014
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Pegylated-Proline-Interferon α-2b (AOP2014)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose levels escalation up to 540 µg.

Number of subjects in period 1	AOP2014
Started	51
Completed	25
Not completed	26
Adverse event, serious fatal	3
Consent withdrawn by subject	2
Adverse event, non-fatal	18
Treatment cycle delayed for more than 4 weeks	1
Increased antibodies TgAK, TtO-AK at Screening	1
Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	51	51	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	34	34	
From 65-84 years	17	17	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	58.7		
standard deviation	± 11.5	-	
Gender categorical			
Units: Subjects			
Female	20	20	
Male	31	31	
Ethnic origin			
Units: Subjects			
Caucasian	50	50	
Asian	1	1	
Spleen size - frequencies			
Enlarged spleen size means > 13 cm for males and > 12 cm for females.			
Units: Subjects			
Normal	19	19	
Enlarged	28	28	
Missing	4	4	
Weight			
Units: kg			
arithmetic mean	77.8		
standard deviation	± 13.4	-	
Height			
Units: cm			
arithmetic mean	172.4		
standard deviation	± 9.2	-	
Body mass index			
Units: kg/m2			

arithmetic mean	26.1		
standard deviation	± 3.7	-	
Leukocyte count			
Units: 10 ⁹ cells/ L			
arithmetic mean	11.8		
standard deviation	± 5.2	-	
Haematocrit			
Units: percent			
arithmetic mean	45.1		
standard deviation	± 4.0	-	
Platelet count			
Units: 10 ⁹ cells/L			
arithmetic mean	457.9		
standard deviation	± 186.5	-	
Spleen size			
Four subject had missing observation.			
Units: cm			
arithmetic mean	14.1		
standard deviation	± 3.2	-	
Phlebotomies			
Number of phlebotomies performed in the last 3 months prior to screening.			
Units: Number of phlebotomies			
median	1.0		
full range (min-max)	0 to 8	-	

Subject analysis sets

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety set includes all patients who took at least one dose of study medication. This set is used for safety analysis.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full analysis set includes all treated patients without major violations of eligibility criteria. This set is used for efficacy analyses.

Reporting group values	Safety set	Full analysis set	
Number of subjects	51	46	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	34	32	
From 65-84 years	17	14	
85 years and over	0	0	

Age continuous Units: years arithmetic mean standard deviation	58.7 ± 11.5	58.2 ± 11.3	
Gender categorical Units: Subjects			
Female	20	20	
Male	31	26	
Ethnic origin Units: Subjects			
Caucasian	50	45	
Asian	1	1	
Spleen size - frequencies			
Enlarged spleen size means > 13 cm for males and > 12 cm for females.			
Units: Subjects			
Normal	19	17	
Enlarged	28	25	
Missing	4	4	
Weight Units: kg arithmetic mean standard deviation	77.8 ± 13.4	77.4 ± 13.8	
Height Units: cm arithmetic mean standard deviation	172.4 ± 9.2	172.2 ± 9.6	
Body mass index Units: kg/m2 arithmetic mean standard deviation	26.1 ± 3.7	26.1 ± 3.8	
Leukocyte count Units: 10 ⁹ cells/ L arithmetic mean standard deviation	11.8 ± 5.2	11.5 ± 5.4	
Haematocrit Units: percent arithmetic mean standard deviation	45.1 ± 4.0	45.1 ± 4.1	
Platelet count Units: 10 ⁹ cells/L arithmetic mean standard deviation	457.9 ± 186.5	448.8 ± 182.0	
Spleen size			
Four subject had missing observation.			
Units: cm arithmetic mean standard deviation	14.1 ± 3.2	14.2 ± 3.4	
Phlebotomies			
Number of phlebotomies performed in the last 3 months prior to screening.			
Units: Number of phlebotomies median	1.0	1.0	

full range (min-max)	0 to 8	0 to 8	
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End points

End points reporting groups

Reporting group title	AOP2014
Reporting group description:	-
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety set includes all patients who took at least one dose of study medication. This set is used for safety analysis.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full analysis set includes all treated patients without major violations of eligibility criteria. This set is used for efficacy analyses.	

Primary: Maximum tolerated dose

End point title	Maximum tolerated dose ^[1]
End point description:	
Maximum tolerated dose (MTD) of AOP2014 was identified during the Stage 1 of the study, consisting of 25 patients. Dose reduction occurred only for 1 patient. A total of 37 treatment-emergent adverse events were recorded for 17 patients. The MTD is the result of the standard 3 + 3 dose escalation process, it is defined as the highest dose at which there is at most one patient out of 6 patients with a dose limiting toxicity (DLT). No DLTs were observed during the study.	
End point type	Primary
End point timeframe:	
Duration of Stage 1 of the study.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses have been specified for this primary end point

End point values	AOP2014			
Subject group type	Reporting group			
Number of subjects analysed	25 ^[2]			
Units: µg				
number (not applicable)	540			

Notes:

[2] - Only patients from Stage 1 of the study were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Haematological response

End point title	Haematological response
End point description:	
Best individual response.	
End point type	Secondary
End point timeframe:	
Duration of Stage 2 of the study.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	42 ^[3]			
Units: patients				
Complete	27			
Partial	14			
None	1			

Notes:

[3] - Four patients had missing observations.

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular response

End point title	Molecular response
End point description:	
Best individual response.	
End point type	Secondary
End point timeframe:	
Duration of Stage 2 of the study.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	42 ^[4]			
Units: patients				
Complete	12			
Partial	19			
None	11			

Notes:

[4] - Four patients had missing observations.

Statistical analyses

No statistical analyses for this end point

Secondary: Haematological response with derived spleen size criterion

End point title	Haematological response with derived spleen size criterion
End point description:	
Best individual response.	
End point type	Secondary
End point timeframe:	
Duration of Stage 2 of the study.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	41 ^[5]			
Units: patients				
Complete	27			
Partial	13			
None	1			

Notes:

[5] - Five patients had missing observations.

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of haematological responders

End point title	Rate of haematological responders
End point description:	
Best individual response.	
End point type	Secondary
End point timeframe:	
Duration of Stage 2 of the study.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	42 ^[6]			
Units: Percentage of patients				
number (not applicable)				
Complete	64.3			
Partial	33.3			
Non	2.4			

Notes:

[6] - Four patients had missing observations.

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of molecular response

End point title	Rate of molecular response
End point description:	
Best individual response.	
End point type	Secondary

End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	42 ^[7]			
Units: Percentage of patients				
number (not applicable)				
Complete	28.6			
Partial	45.2			
Non	26.2			

Notes:

[7] - Four patients had missing observations.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to achieve haematological response

End point title	Time to achieve haematological response
End point description:	
Time to response among patients who achieved corresponding haematological response.	
End point type	Secondary
End point timeframe:	
Duration of Stage 2 of the study.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	41 ^[8]			
Units: Weeks				
median (inter-quartile range (Q1-Q3))				
Complete haematological response	34 (10 to 96)			
Any haematological response	10 (10 to 20)			
Best individual haematological response	10 (10 to 63)			

Notes:

[8] - Number of subjects with any haematological response.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to achieve molecular response

End point title	Time to achieve molecular response
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End point description:

Time to response among patients who achieved corresponding molecular response.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	31 ^[9]			
Units: Weeks				
median (inter-quartile range (Q1-Q3))				
Complete molecular response	82 (44 to 115)			
Any molecular response	34 (18 to 55)			
Best individual molecular response	45 (20 to 97)			

Notes:

[9] - Number of patients with any molecular response.

Statistical analyses

No statistical analyses for this end point

Secondary: Haematocrit evaluation - absolute values

End point title	Haematocrit evaluation - absolute values
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End point description:

Range of median absolute values of haematocrit.

End point type	Secondary
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End point timeframe:

During the Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percent				
number (not applicable)				
Minimal median	40.2			
Maximal median	46.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Haematocrit evaluation - differences from baseline

End point title	Haematocrit evaluation - differences from baseline
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End point description:

Range of median differences from baseline in haematocrit.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percent				
number (not applicable)				
Minimal median	-7.5			
Maximal median	3.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Haematocrit evaluation - haematocrit <45%

End point title	Haematocrit evaluation - haematocrit <45%
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End point description:

Range of percentage of patients with haematocrit values less than 45%.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Percentage of patients				
number (not applicable)				
Minimal percentage	33.3			
Maximal percentage	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet evaluation - absolute values

End point title	Platelet evaluation - absolute values
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End point description:

Range of median absolute platelets values.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: 10 ⁹ / L				
number (not applicable)				
Minimal median	144.0			
Maximal median	456.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet evaluation - differences from baseline

End point title	Platelet evaluation - differences from baseline
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End point description:

Range of median differences from baseline in platelets.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: 10 ⁹ /L				
number (not applicable)				
Minimal median	-344.0			
Maximal median	169.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet evaluation - platelet ≤ 400

End point title	Platelet evaluation - platelet ≤ 400
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End point description:

Range of percentage of patients with platelets less than or equal to $400 \times 10^9/L$.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Percentage of patients				
number (not applicable)				
Minimal percentage	50.0			
Maximal percentage	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Leukocyte evaluation - absolute values

End point title	Leukocyte evaluation - absolute values
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End point description:

Range of median absolute leukocytes values.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: 10^9 cells/L				
number (not applicable)				
Minimal median	4.00			
Maximal median	13.67			

Statistical analyses

No statistical analyses for this end point

Secondary: Leukocyte evaluation - differences from baseline

End point title	Leukocyte evaluation - differences from baseline
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End point description:

Range of median differences from baseline in leukocytes.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: 10 ⁹ cells/L				
number (not applicable)				
Minimal median	-11.30			
Maximal median	2.27			

Statistical analyses

No statistical analyses for this end point

Secondary: Leukocyte evaluation - leukocytes ≤10

End point title	Leukocyte evaluation - leukocytes ≤10
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End point description:

Range of percentage of patients with leukocytes less than or equal to 10 x 10⁹ cells/ L.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Percentage of patients				
number (not applicable)				
Minimal percentage	33.3			
Maximal percentage	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Spleen evaluation - absolute values

End point title	Spleen evaluation - absolute values
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End point description:

Range of the median absolute spleen sizes at visits for which data were available for at least 10 patients.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: cm				
number (not applicable)				
Minimal median	11.7			
Maximal median	13.95			

Statistical analyses

No statistical analyses for this end point

Secondary: Spleen evaluation - differences from baseline

End point title	Spleen evaluation - differences from baseline
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End point description:

Range of median differences from baseline in spleen size at visits for which data were available for at least 10 patients.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: cm				
number (not applicable)				
Minimal median	-2.00			
Maximal median	0.50			

Statistical analyses

No statistical analyses for this end point

Secondary: Spleen evaluation - reduction $\geq 30\%$

End point title Spleen evaluation - reduction $\geq 30\%$

End point description:

Range of percentage of patients with spleen size reductions greater than or equal to 30% at visits for which data were available for at least 10 patients.

End point type Secondary

End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Percentage of patients				
number (not applicable)				
Minimal percentage	0			
Maximal percentage	17.7			

Statistical analyses

No statistical analyses for this end point

Secondary: JAK-2 evaluation - absolute values

End point title JAK-2 evaluation - absolute values

End point description:

Range of median absolute JAK-2 values at visits for which data were available for at least 10 patients.

End point type Secondary

End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percentage				
number (not applicable)				
Minimal median	3.8			
Maximal median	38.5			

Statistical analyses

No statistical analyses for this end point

Secondary: JAK-2 - differences from baseline

End point title	JAK-2 - differences from baseline
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End point description:

Range of median differences from baseline in JAK-2 values for visits at which data were available for at least 10 patients.

End point type	Secondary
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End point timeframe:

Duration of Stage 2 of the study.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Percentage				
number (not applicable)				
Minimal median	-40.3			
Maximal median	3.5			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean Cmax

End point title	PK profiles within 14 days between IMPs - mean Cmax
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End point description:

Range of mean Cmax values. Minimal mean Cmax occurred for 50-80 µg dose level, maximal mean Cmax occurred for 450 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
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End point timeframe:

Duration of 14-day period between two IMP administrations.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	19 ^[10]			
Units: pg/ml				
number (not applicable)				
Minimal mean Cmax	2393.3			
Maximal mean Cmax	48640			

Notes:

[10] - Only subjects with available PK data.

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean AUC(0-t)

End point title	PK profiles within 14 days between IMPs - mean AUC(0-t)
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End point description:

Range of mean AUC(0-t) values. Minimal mean AUC(0-t) occurred for 50-80 µg dose level, maximal mean AUC(0-t) occurred for 450 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
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End point timeframe:

Duration of 14-day period between two IMP administrations.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: pg*h/mL				
number (not applicable)				
Minimal mean	28546.7			
Maximal mean	552570			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean AUC(0-t) per day

End point title	PK profiles within 14 days between IMPs - mean AUC(0-t) per day
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End point description:

Range of mean AUC(0-t) values per day. Minimal mean AUC(0-t) per day occurred for 50-80 µg dose level, maximal mean AUC(0-t) per day occurred for 450 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
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End point timeframe:

Duration of 14-day period between two IMP administration

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: pg*h/mL				
number (not applicable)				
Minimal mean	2074.8			
Maximal mean	38713.9			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean Ct

End point title	PK profiles within 14 days between IMPs - mean Ct
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End point description:

Range of mean Ct values. Minimal mean Ct occurred for 50-80 µg dose level, maximal mean Ct occurred for 450 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
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End point timeframe:

Duration of 14-day period between two IMP administrations.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: pg/mL				
number (not applicable)				
Minimal mean	1596.7			
Maximal mean	25440			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean λz

End point title	PK profiles within 14 days between IMPs - mean λz
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End point description:

Range of mean λz values. Minimal mean λz occurred for 450 µg dose level, maximal mean λz occurred for 360 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ

concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
End point timeframe:	
Duration of 14-day period between two IMP administrations.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: ratio				
number (not applicable)				
Minimal mean	0.088			
Maximal mean	0.116			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean R²

End point title	PK profiles within 14 days between IMPs - mean R ²
End point description:	
Range of mean R ² values. Minimal mean R ² occurred for 50-80 µg, 100 µg and 450 µg dose level, maximal mean R ² occurred for 150 µg, 180 µg, 300 µg, 360 µg and 540 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.	
End point type	Secondary
End point timeframe:	
Duration of 14-day period between two IMP administrations.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: ratio				
number (not applicable)				
Minimal mean	0.9			
Maximal mean	1.0			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean AUCextra

End point title	PK profiles within 14 days between IMPs - mean AUCextra
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End point description:

Range of mean AUCextra values. Minimal mean AUCextra occurred for 50-80 µg dose level, maximal mean AUCextra occurred for 450 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
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End point timeframe:

Duration of 14-day period between two IMP administrations.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: pg*h/mL				
number (not applicable)				
Minimal mean	21384			
Maximal mean	291605.5			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean AUCextra (% from AUCinf)

End point title	PK profiles within 14 days between IMPs - mean AUCextra (% from AUCinf)
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End point description:

Range of mean AUCextra (% from AUCinf) values. Minimal mean AUCextra occurred for 360 µg dose level, maximal mean AUCextra occurred for 50-80 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
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End point timeframe:

Duration of 14-day period between two IMP administrations.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percentage				
number (not applicable)				
Minimal mean	26.8			
Maximal mean	40.3			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean AUC(0-inf)

End point title	PK profiles within 14 days between IMPs - mean AUC(0-inf)
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End point description:

Range of mean AUC(0-inf) values. Minimal mean AUC(0-inf) occurred for 50-80 µg dose level, maximal mean AUC(0-inf) occurred for 450 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
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End point timeframe:

Duration of 14-day period between two IMP administrations.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: pg*h/mL				
number (not applicable)				
Minimal mean	49930.6			
Maximal mean	844175.5			

Statistical analyses

No statistical analyses for this end point

Secondary: PK profiles within 14 days between IMPs - mean t½

End point title	PK profiles within 14 days between IMPs - mean t½
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End point description:

Range of mean t½ values. Minimal mean t½ occurred for 360 µg dose level, maximal mean t½ occurred for 150 µg dose level. Of the 21 patients who had available data, 2 patients were excluded due to BLQ concentrations. Total of 19 patients were included in the analysis of PK profiles.

End point type	Secondary
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End point timeframe:

Duration of 14-day period between two IMP administrations.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: days				
number (not applicable)				
Minimal mean	6			
Maximal mean	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of Stage 1 and Stage 2 of the study.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Overall
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Reporting group description: -

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 51 (54.90%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Glioblastoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hypertensive crisis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute stress disorder			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adjustment disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Completed suicide			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Depression			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Anti-thyroid antibody positive			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Antinuclear antibody increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Clavicle fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye injury			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dementia with Lewy bodies			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Splenic infarction			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Eye disorders			
Diplopia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis haemorrhagic			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis norovirus			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pilonidal cyst			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Sepsis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 51 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
5q minus syndrome			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Basal cell carcinoma			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Colon adenoma			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Haemangioma of liver			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Lipoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Myelofibrosis			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Neoplasm prostate			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Prostate cancer			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Squamous cell carcinoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Thyroid neoplasm			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Aortic dilatation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blood pressure fluctuation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cardiovascular disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Circulatory collapse			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Erythromelalgia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	5		

Haematoma			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	8		
Hypertensive crisis			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Microangiopathy			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Peripheral artery stenosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Raynaud's phenomenon			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Thrombophlebitis superficial			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Umbilical haematoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		

Varicose vein subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 6		
Surgical and medical procedures			
Cataract operation subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Endodontic procedure subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Meniscus operation subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Skin neoplasm excision subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Synovectomy subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Tooth extraction subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
General disorders and administration site conditions			
Application site pruritus subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Asthenia subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3		
Chest discomfort subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 2		
Chest pain subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4		
Chills			

subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	12		
Crying			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Early satiety			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	23 / 51 (45.10%)		
occurrences (all)	42		
Feeling abnormal			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Feeling cold			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Feeling hot			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Gait disturbance			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	3		
General physical health deterioration			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	10		
Inflammation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	14 / 51 (27.45%)		
occurrences (all)	32		
Injection site erythema			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	5		
Injection site irritation			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Injection site reaction			
subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	20		
Malaise			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	8		
Pain			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Performance status decreased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	12 / 51 (23.53%)		
occurrences (all)	35		
Sensitivity to weather change			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Immune system disorders			
Basedow's disease			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

Seasonal allergy subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Pruritus genital subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Vaginal haemorrhage subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 6		
Dysphonia subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Dyspnoea subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 3		
Dyspnoea exertional subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 5		
Emphysema subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Epistaxis subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 5		
Increased upper airway secretion subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Nasal congestion			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Nasal crusting			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Pulmonary embolism			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Apathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Depressed mood			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

Depression			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	7		
Depressive symptom			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Disorientation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hallucination			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	6		
Irritability			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Listless			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Mental disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Mood altered			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Nervousness			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Psychiatric symptom			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

Sleep disorder subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 6		
Stress subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Anti-thyroid antibody positive subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 6		
Antinuclear antibody positive subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Arthroscopy subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Body temperature increased subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 3		
Cardiac murmur subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Coombs direct test positive subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
DNA antibody positive			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	5		
Haemoglobin decreased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Platelet count increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Transaminases increased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Contusion			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Foot fracture			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Foreign body			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Meniscus injury			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Muscle injury			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Neck injury			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Procedural headache			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Radius fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rib fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Toxicity to various agents			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

Atrial fibrillation			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Atrioventricular block			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Bradycardia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Cardiac failure			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cardiovascular disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cardiovascular insufficiency			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dilatation ventricular			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Left ventricular hypertrophy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Nervous system disorders			
Aura			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Carotid arteriosclerosis			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Carpal tunnel syndrome			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Cervicobrachial syndrome			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cranial nerve disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	11 / 51 (21.57%)		
occurrences (all)	18		
Dysaesthesia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Head discomfort			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	15 / 51 (29.41%)		
occurrences (all)	30		
Hypoaesthesia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Mental impairment			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Neurological symptom			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Paraesthesia			

subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	5		
Parkinson's disease			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Parkinsonism			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Polyneuropathy			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Restless legs syndrome			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Sensory disturbance			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Sensory integrative dysfunction			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	8		
Vascular encephalopathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Haemorrhagic diathesis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	16		
Lymphadenopathy			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	15		
Pancytopenia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Splenic infarction			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Spontaneous haematoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	9		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Deafness transitory			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
External ear disorder			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Sudden hearing loss			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Vertigo			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	7		
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cataract			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	5		
Dry eye			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Eye irritation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Macular fibrosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Ocular discomfort			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	4		

Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Panophthalmitis subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Retinal artery occlusion subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Scintillating scotoma subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Visual impairment subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Abdominal pain subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4		
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 7		
Chapped lips subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Chronic gastritis			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	17 / 51 (33.33%)		
occurrences (all)	29		
Diverticulum			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Faeces discoloured			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Faeces soft			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Frequent bowel movements			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastric disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Gastric polyps			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastritis erosive			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Gingival bleeding			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Hiatus hernia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Irritable bowel syndrome			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Large intestine polyp			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	14 / 51 (27.45%)		
occurrences (all)	17		
Odynophagia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Oral discomfort			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Painful defaecation			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pancreatic steatosis			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Saliva discolouration			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tongue coated			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Hepatomegaly			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hepatotoxicity			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	9		
Blister			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Erythema multiforme			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	10		
Hyperkeratosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Nail dystrophy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	10		
Photosensitivity reaction			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	23 / 51 (45.10%)		
occurrences (all)	37		
Psoriasis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Rash			

subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	9		
Rash generalised			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Rash papular			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Skin hyperpigmentation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Renal and urinary disorders			
Bladder irritation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cystitis haemorrhagic			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	4		

Nocturia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Polyuria			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Renal cyst			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Urinary retention			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hyperthyroidism			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Hypothyroidism			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 51 (45.10%)		
occurrences (all)	45		
Arthritis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	3		
Arthropathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	13 / 51 (25.49%)		
occurrences (all)	17		
Bone pain			

subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Bursitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Exostosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	11		
Muscular weakness			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	7		
Musculoskeletal stiffness			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Myalgia			

subjects affected / exposed	10 / 51 (19.61%)		
occurrences (all)	13		
Osteoarthritis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	15		
Rheumatoid arthritis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Sjogren's syndrome			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Bacteriuria			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Chronic sinusitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	5		

Cystitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	4		
Erysipelas			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Fungal skin infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Gastroenteritis viral			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Haematoma infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Helicobacter gastritis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Localised infection			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		

Nasopharyngitis			
subjects affected / exposed	21 / 51 (41.18%)		
occurrences (all)	28		
Oesophageal candidiasis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Onychomycosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Oral herpes			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Paronychia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	11		
Sinusitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tinea pedis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

Tonsillitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	7		
Viral infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	10		
Dyslipidaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Folate deficiency			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gout			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Hyperuricaemia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Polydipsia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2010	Version 2 to version 3: The preparation of the IMP was facilitated due to the possibility of now omitting the dilution step. IMP can now be drawn directly from IMP-vial into syringe to be administered subcutaneously thereafter.
29 April 2011	Version 3 to version 4: The protocol amendment took mainly place because of the implementation of an intensive PK/PD blood sampling scheme.
07 June 2011	Version 4 to version 5: The clinical investigators pointed out that hydroxyurea (HU) usage, as defined in the protocol amendment (4.0, 29.04.11) might be hazardous, since a gradual discontinuation with HU (e.g. 1000 mg until screening, decrease to 500 mg until shortly prior 1st administration of study medication) prevents abrupt potential thrombocythaemia. For this reason the amendment to protocol 5.0 (07.06.11) is to be complied with immediately by all sites.
13 December 2011	Version 5 to version 6: Study length The study length was prolonged from 1 to 3 years. The dose finding phase was completed with 25 patients. Further 25 patients are planned to be enrolled. The doses to be administered will invariably be in the range investigated so far (50-540mcg). The therapy is to be continued as long as the investigator considers it reasonable and the patient benefits from the therapy, respectively. Study flow chart The assessment time points for JAK-2 analysis and immunogenicity were extended; ultrasonography has a time frame of +/- 10 days (originally +/- 3 days) now; the original time frame for the study medication administration (+/- 3 days) was changed to -3/+1 day. The study flow chart was adapted to the extended study length (year 2-3). Dosing scheme of study medication including Hydroxyurea switch therapy In the dose finding stage of the study the 3+3 escalation design was predetermined. For the treatment of additional 25 patients a new scheme was established in cooperation with the participating investigators. Phlebotomies The hematocrit value for resuce phlebotomy was reduced from ≥50% to 45% according to the currently effective therapy standards in Austria.
28 December 2012	Version 7 to 8: After at least 1-year participation in the study plus available disease response (either partial or complete) it is allowed for every patient to extend the once every 2 weeks IMP dosage scheme to a once every 4 weeks interval. This is to accommodate the patient with more convenience and reflects the common practice of myeloproliferative neoplasms treatment with interferons.

30 September 2013	Version 8 to version 9: The planned duration of 3 years will be prolonged for another 3 years. The examinations during the prolonged 3 years period, starting with visit 75 (week 148) has to follow the assessment schemes of visit 75 (week 148) has to follow the assessment schemes of visit 27 (week 52) till visit 74 (week 146), as specified in the protocol.
26 March 2014	Version 9 to version 10: In order to reduce injections of IMP in patients a strength of 500 µg/mL AOP2014 has been developed. The regime of dose is for patients getting 180 µg/mL or 500 µg/mL IMP AOP2014 the same. Two strengths of IMP AOP2014 will be used: 500 µg/mL and 180 µg/mL IMP AOP2014. At every visit of patients it will be documented if the patient will be administered 180 µg/mL or 500 µg/mL IMP AOP2014 in order to investigate separate assessments of both strengths.
01 April 2014	Version 10 to version 11: In depth specialist examinations (E.g. ophthalmologist investigations, endoscopy, computed tomography etc.) must be scheduled if an organ specific toxicity of AOP2014 will be suspected. The findings, if clinically relevant and abnormal, will be recorded on the AE page of the CRF.
31 March 2015	Version 11 to version 12: 1. Three additional PK samples will be drawn for each patient who has switched to the once every 4 weeks treatment scheme in order to obtain pharmacokinetic information under the new, 4 week cycle, condition. After completion of these 3 samples no additional PK sampling procedures will occur for the rest of the study duration. 2. Bone Marrow Biopsies will be taken to monitor the changes in the bone marrow following treatment with AOP2014. 3. The drugsafety processing has been outsourced to an external service provider, therefore contact details regarding SAE reporting have been updated.
14 September 2016	Version 12 to version 13: 1. Study prolongation of 18 months and appropriate insertion of a new Study Flowchart (Table 5). 2. Continuation of treatment beyond visit 147 till visit 164. 3. Insertion of section "4.7.6. End of treatment visit/Premature discontinuation visit" showing an overview about all assessments during this visit (according to flow chart e). 4. Harmonization and improvement of wording throughout the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported