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

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 (addresed 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

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	58.7	58.2	
standard deviation	± 11.5	± 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	77.8	77.4	
standard deviation	± 13.4	± 13.8	
Height Units: cm			
arithmetic mean	172.4	172.2	
standard deviation	± 9.2	± 9.6	
Body mass index Units: kg/m2			
arithmetic mean	26.1	26.1	
standard deviation	± 3.7	± 3.8	
Leukocyte count Units: 10^9 cells/ L			
arithmetic mean	11.8	11.5	
standard deviation	± 5.2	± 5.4	
Haematocrit Units: percent			
arithmetic mean	45.1	45.1	
standard deviation	± 4.0	± 4.1	
Platelet count Units: 10^9 cells/L			
arithmetic mean	457.9	448.8	
standard deviation	± 186.5	± 182.0	
Spleen size			
Four subject had missing observation.			
Units: cm			
arithmetic mean	14.1	14.2	
standard deviation	± 3.2	± 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	

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 occured 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

End point description:

Time to response among patients who achieved corresponding molecular 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	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

End point description:

Range of median absolute values of haematocrit.

End point type	Secondary

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

End point description:

Range of median differences from baseline in haematocrit.

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: 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%

End point description:

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

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	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

End point description:

Range of median absolute platelets values.

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: 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

End point description:

Range of median differences from baseline in platelets.

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: 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

End point description:

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

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	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

End point description:

Range of median absolute luekocytes values.

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: 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

End point description:

Range of median differences from baseline in leukocytes.

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: 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

End point description:

Range of percentage of patients with leukocytes less than or equal to 10 x 10^9 cells/ L.

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	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

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

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

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

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 >= 30%

End point title	Spleen evaluation - reduction >= 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 lesast 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

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

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

End point description:

Range of mean Cmax values. Minimal mean Cmax occured for 50-80 µg dose level, maximal mean Cmax occured 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

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)

End point description:

Range of mean AUC(0-t) values. Minimal mean AUC(0-t) occured for 50-80 µg dose level, maximal mean AUC(0-t) occured 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

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

End point description:

Range of mean AUC(0-t) values per day. Minimal mean AUC(0-t) per day occured for 50-80 µg dose level, maximal mean AUC(0-t) per day occured 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

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

End point description:

Range of mean Ct values. Minimal mean Ct occured for 50-80 µg dose level, maximal mean Ct occured 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

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

End point description:

Range of mean λz values. Minimal mean λz occured for 450 µg dose level, maximal mean λz occured 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 R^2

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 occured for 50-80 µg, 100 µg and 450 µg dose level, maximal mean R^2 occured 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

End point description:

Range of mean AUCextra values. Minimal mean AUCextra occured for 50-80 µg dose level, maximal mean AUCextra occured 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

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)

End point description:

Range of mean AUCextra (% from AUCinf) values. Minimal mean AUCextra occured for 360 µg dose level, maximal mean AUCextra occured 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

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)

End point description:

Range of mean AUC(0–inf) values. Minimal mean AUC(0–inf) occured for 50-80 µg dose level, maximal mean AUC(0–inf) occured 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

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

End point description:

Range of mean t½ values. Minimal mean t½ occured for 360 µg dose level, maximal mean t½ occured 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

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Overall

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	3 / 51 (5.88%)		
occurrences (all)	6		
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Endodontic procedure			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Meniscus operation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Skin neoplasm excision			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Synovectomy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tooth extraction			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Chest discomfort			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	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	1 / 51 (1.96%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pruritus genital			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	6		
Dysphonia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Dyspnoea exertional			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	5		
Emphysema			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	5		
Increased upper airway secretion			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	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	6 / 51 (11.76%)		
occurrences (all)	6		
Stress			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Anti-thyroid antibody positive			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	6		
Antinuclear antibody positive			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Arthroscopy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Body temperature increased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Cardiac murmur			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Coombs direct test positive			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	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 occurrences (all)	4 / 51 (7.84%) 4			
Atrioventricular block subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1			
Bradycardia subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 2			
Cardiac failure subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1			
Cardiovascular disorder subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1			
Cardiovascular insufficiency subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1			
Dilatation ventricular subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1			
Left ventricular hypertrophy subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1			
Tachycardia subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 3			
Nervous system disorders Aura subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1			
Balance disorder subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 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 occurrences (all)	2 / 51 (3.92%) 2		
Haemorrhagic diathesis subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Leukopenia subjects affected / exposed occurrences (all)	9 / 51 (17.65%) 16		
Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Neutropenia subjects affected / exposed occurrences (all)	8 / 51 (15.69%) 15		
Pancytopenia subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Splenic infarction subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Spontaneous haematoma subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 9		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Deafness transitory subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 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	1 / 51 (1.96%)			
occurrences (all)	1			
Panophthalmitis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences (all)	1			
Retinal artery occlusion				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences (all)	1			
Scintillating scotoma				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences (all)	1			
Visual acuity reduced				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences (all)	1			
Visual impairment				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences (all)	1			
Gastrointestinal disorders				
Abdominal distension				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences (all)	1			
Abdominal pain				
subjects affected / exposed	4 / 51 (7.84%)			
occurrences (all)	4			
Abdominal pain lower				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences (all)	1			
Abdominal pain upper				
subjects affected / exposed	6 / 51 (11.76%)			
occurrences (all)	7			
Chapped lips				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences (all)	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 occurrences (all)	1 / 51 (1.96%) 1		
Tooth abscess subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 5		
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 7		
Viral infection subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Wound infection subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Metabolism and nutrition disorders Abnormal loss of weight subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Decreased appetite subjects affected / exposed occurrences (all)	9 / 51 (17.65%) 10		
Dyslipidaemia subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Folate deficiency subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 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 thrombocythyaemia. 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: 1. 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. 2. Study flow chart The assessment time pints 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). 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. 4. 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. ophthalmogist investigations, endoscopy, computed tomography etc.) must be shceduled if an organ specific toxicity of AOP2014 will be suspected. The findings, if clinically relevat 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 eacht 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 drugsaftey 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