Clinical trial results:
A two-part placebo-controlled study to evaluate the safety, tolerability and preliminary efficacy of BVS857 in patients with spinal and bulbar muscular atrophy (SBMA)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2013-002608-15
Trial protocol	IT DK DE
Global end of trial date	13 April 2016

Results information

Result version number	v1 (current)
This version publication date	11 July 2018
First version publication date	11 July 2018

Trial information

Trial identification

Sponsor protocol code	CBVS857X2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02024932
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	13 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of BVS857 in patients with SBMA

To evaluate the preliminary efficacy of BVS857 on thigh muscle volume (TMV) by MRI in patients with SBMA after 12 weeks of dosing (Part B only)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	37
EEA total number of subjects	25

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	28
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 2 parts, Part A and Part B. In Part A, Cohort 1 participants received open-label BVS857. Cohort 2 participants were randomized to double-blind BVS857 or double-blind placebo in a 2:1 ratio.

Pre-assignment

Screening details:

In Part B, Cohort 3 was not enrolled. Cohort 4 participants received open-label BVS857. Cohort 5 participants were randomized to double-blind BVS857 or double-blind placebo in a ratio of 18:10.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BVS857 Part A Open label (Cohort 1)

Arm description:

Participants received single doses of 0.01 mg/kg BVS857 intravenously (i.v.) on day 1, 0.01 mg/kg BVS857 subcutaneously (s.c.) on day 15, 0.03 mg/kg BVS857 s.c. on day 29, 0.06 mg/kg BVS857 s.c. on day 43 and 0.10 mg/kg BVS857 s.c. on day 57.

Arm type	Experimental
Investigational medicinal product name	BVS857
Investigational medicinal product code	BVS857
Other name	
Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Participants received single doses of 0.01 mg/kg BVS857 intravenously (i.v.) on day 1, 0.01 mg/kg BVS857 subcutaneously (s.c.) on day 15, 0.03 mg/kg BVS857 s.c. on day 29, 0.06 mg/kg BVS857 s.c. on day 43 and 0.10 mg/kg BVS857 s.c. on day 57.

Arm title	BVS857 Part A double blind (Cohort 2)

Arm description:

Participants received single doses of 0.03 mg/kg BVS857 i.v. on day 1, 0.03 mg/kg BVS857 s.c. on day 15, 0.06 mg/kg BVS857 s.c. on day 29, 0.10 mg/kg BVS857 s.c. on day 43 and 0.10 mg/kg BVS857 s.c. on day 57. (BVS857 concentrations differed on days 43 and 57.)

Arm type	Experimental
Investigational medicinal product name	BVS857
Investigational medicinal product code	BVS857
Other name	
Pharmaceutical forms	Solution for injection, Solution for infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Participants received single doses of 0.03 mg/kg BVS857 i.v. on day 1, 0.03 mg/kg BVS857 s.c. on day 15, 0.06 mg/kg BVS857 s.c. on day 29, 0.10 mg/kg BVS857 s.c. on day 43 and 0.10 mg/kg BVS857 s.c. on day 57. (BVS857 concentrations differed on days 43 and 57.)

Arm title	Placebo Part A double blind (Cohort 2)

Arm description:

Participants received single doses of matching placebo i.v. on day 1 and matching placebo s.c. on days 15, 29, 43 and 57.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Participants received single doses of matching placebo i.v. on day 1 and matching placebo s.c. on days 15, 29, 43 and 57.

Arm title	BVS857 Part B open-label (Cohort 4)

Arm description:

Participants received 0.1 mg/kg BVS857 i.v. weekly for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BVS857
Investigational medicinal product code	BVS857
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 0.1 mg/kg BVS857 i.v. weekly for 12 weeks.

Arm title	BVS857 Part B double blind (Cohort 5)

Arm description:

Participants received 0.06 mg/kg (maximum 6 mg) BVS857 i.v. weekly for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BVS857
Investigational medicinal product code	BVS857
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 0.06 mg/kg (maximum 6 mg) BVS857 i.v. weekly for 12 weeks.

Arm title	Placebo Part B double blind (Cohort 5)

Arm description:

Participants received matching placebo i.v. to BVS857 weekly for 12 weeks.

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

Dosage and administration details:

Participants received matching placebo i.v. to BVS857 weekly for 12 weeks.

Number of subjects in period 1	BVS857 Part A Open label (Cohort 1)	BVS857 Part A double blind (Cohort 2)	Placebo Part A double blind (Cohort 2)
Started	2	4	2
Safety analysis set	2	4	2
Pharmacokinetic (PK) analysis set	2	4	0 [1]
Pharmacodynamic (PD) analysis set	2	4	2
Completed	0	1	2
Not completed	2	3	0
Adverse event, non-fatal	2	3	-
Abnormal laboratory value	-	-	-

Number of subjects in period 1	BVS857 Part B open-label (Cohort 4)	BVS857 Part B double blind (Cohort 5)	Placebo Part B double blind (Cohort 5)
Started	2	18	9
Safety analysis set	2	18	9
Pharmacokinetic (PK) analysis set	2	18	0 [2]
Pharmacodynamic (PD) analysis set	2	18	9
Completed	0	16	9
Not completed	2	2	0
Adverse event, non-fatal	-	2	-
Abnormal laboratory value	2	-	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: PK analysis does not apply to placebo participants.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: PK analysis does not apply to placebo participants.

Baseline characteristics

Reporting groups	
Reporting group title	BVS857 Part A Open label (Cohort 1)
Reporting group description:	
Participants received single doses of 0.01 mg/kg BVS857 intravenously (i.v.) on day 1, 0.01 mg/kg BVS857 subcutaneously (s.c.) on day 15, 0.03 mg/kg BVS857 s.c. on day 29, 0.06 mg/kg BVS857 s.c. on day 43 and 0.10 mg/kg BVS857 s.c. on day 57.	
Reporting group title	BVS857 Part A double blind (Cohort 2)
Reporting group description:	
Participants received single doses of 0.03 mg/kg BVS857 i.v. on day 1, 0.03 mg/kg BVS857 s.c. on day 15, 0.06 mg/kg BVS857 s.c. on day 29, 0.10 mg/kg BVS857 s.c. on day 43 and 0.10 mg/kg BVS857 s.c. on day 57. (BVS857 concentrations differed on days 43 and 57.)	
Reporting group title	Placebo Part A double blind (Cohort 2)
Reporting group description:	
Participants received single doses of matching placebo i.v. on day 1 and matching placebo s.c. on days 15, 29, 43 and 57.	
Reporting group title	BVS857 Part B open-label (Cohort 4)
Reporting group description:	
Participants received 0.1 mg/kg BVS857 i.v. weekly for 12 weeks.	
Reporting group title	BVS857 Part B double blind (Cohort 5)
Reporting group description:	
Participants received 0.06 mg/kg (maximum 6 mg) BVS857 i.v. weekly for 12 weeks.	
Reporting group title	Placebo Part B double blind (Cohort 5)
Reporting group description:	
Participants received matching placebo i.v. to BVS857 weekly for 12 weeks.	

Reporting group values	BVS857 Part A Open label (Cohort 1)	BVS857 Part A double blind (Cohort 2)	Placebo Part A double blind (Cohort 2)
Number of subjects	2	4	2
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	3	1
From 65-84 years	1	1	1
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	67	56	59.5
standard deviation	± 5.66	± 12.33	± 7.78
Gender Categorical Units: Subjects			
Male	2	4	2

Reporting group values	BVS857 Part B open-label (Cohort 4)	BVS857 Part B double blind (Cohort 5)	Placebo Part B double blind (Cohort 5)
Number of subjects	2	18	9
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	12	9
From 65-84 years	0	6	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	41.5	57	54
standard deviation	± 4.95	± 55.5	± 5.94
Gender Categorical			
Units: Subjects			
Male	2	18	9

Reporting group values	Total		
Number of subjects	37		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	28		
From 65-84 years	9		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Gender Categorical			
Units: Subjects			
Male	37		

End points

End points reporting groups

Reporting group title	BVS857 Part A Open label (Cohort 1)
Reporting group description:	
Participants received single doses of 0.01 mg/kg BVS857 intravenously (i.v.) on day 1, 0.01 mg/kg BVS857 subcutaneously (s.c.) on day 15, 0.03 mg/kg BVS857 s.c. on day 29, 0.06 mg/kg BVS857 s.c. on day 43 and 0.10 mg/kg BVS857 s.c. on day 57.	
Reporting group title	BVS857 Part A double blind (Cohort 2)
Reporting group description:	
Participants received single doses of 0.03 mg/kg BVS857 i.v. on day 1, 0.03 mg/kg BVS857 s.c. on day 15, 0.06 mg/kg BVS857 s.c. on day 29, 0.10 mg/kg BVS857 s.c. on day 43 and 0.10 mg/kg BVS857 s.c. on day 57. (BVS857 concentrations differed on days 43 and 57.)	
Reporting group title	Placebo Part A double blind (Cohort 2)
Reporting group description:	
Participants received single doses of matching placebo i.v. on day 1 and matching placebo s.c. on days 15, 29, 43 and 57.	
Reporting group title	BVS857 Part B open-label (Cohort 4)
Reporting group description:	
Participants received 0.1 mg/kg BVS857 i.v. weekly for 12 weeks.	
Reporting group title	BVS857 Part B double blind (Cohort 5)
Reporting group description:	
Participants received 0.06 mg/kg (maximum 6 mg) BVS857 i.v. weekly for 12 weeks.	
Reporting group title	Placebo Part B double blind (Cohort 5)
Reporting group description:	
Participants received matching placebo i.v. to BVS857 weekly for 12 weeks.	

Primary: Number of patients with adverse events (AEs), serious adverse events (SAEs) and deaths as a measure of safety and tolerability

End point title	Number of patients with adverse events (AEs), serious adverse events (SAEs) and deaths as a measure of safety and tolerability[1]
End point description:	
Safety was monitored throughout the study.	
End point type	Primary
End point timeframe:	
After 78 days in Part A and after 85 days in Part B.	

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: Descriptive summary statistics only were reported for this end point.

End point values	BVS857 Part A Open label (Cohort 1)	BVS857 Part A double blind (Cohort 2)	Placebo Part A double blind (Cohort 2)	BVS857 Part B open-label (Cohort 4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	4	2	2
Units: Participants				
Non-serious AEs	2	4	2	1
SAEs	0	0	0	0
Deaths	0	0	0	0

End point values	BVS857 Part B double blind (Cohort 5)	Placebo Part B double blind (Cohort 5)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	9		
Units: Participants				
Non-serious AEs	17	8		
SAEs	0	0		
Deaths	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of mild, moderate and severe adverse events as a measure of safety and tolerability

End point title	Number of mild, moderate and severe adverse events as a measure of safety and tolerability[2]

End point description:

Safety was monitored throughout the study.

End point type	Primary

End point timeframe:

After 78 days in Part A and after 85 days in Part B.

Notes:

[2] - 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: Descriptive summary statistics only were reported for this end point.

End point values	BVS857 Part A Open label (Cohort 1)	BVS857 Part A double blind (Cohort 2)	Placebo Part A double blind (Cohort 2)	BVS857 Part B open-label (Cohort 4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	4	2	2
Units: Participants				
Mild	1	2	2	0
Moderate	1	2	0	0
Severe	0	0	0	0

End point values	BVS857 Part B double blind (Cohort 5)	Placebo Part B double blind (Cohort 5)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	9		
Units: Participants				
Mild	5	4		
Moderate	11	3		

Severe	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Mean percent change from baseline in thigh muscle volume in Part B, Cohort 5

End point title	Mean percent change from baseline in thigh muscle volume in Part B, Cohort 5[3]

End point description:

Thigh muscle volume was assessed by magnetic resonance imaging (MRI). Change from baseline was calculated from the ratio of the post-baseline mean value to the baseline mean value: [(Day 85/baseline) - 1)] x 100. A positive change from baseline indicates improvement.

End point type	Primary

End point timeframe:

Baseline, Day 85

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part B double blind (Cohort 5)	Placebo Part B double blind (Cohort 5)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	9		
Units: Percent change				
geometric mean (standard deviation)	0 (± 2.42)	-3.4 (± 4.79)		

Statistical analyses

Statistical analysis title	Change from BL in TMV in Part B, Cohort 5
Comparison groups	BVS857 Part B double blind (Cohort 5) v Placebo Part B double blind (Cohort 5)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0164
Method	ANCOVA
Parameter estimate	Geo-mean ratio
Point estimate	1.037

Confidence interval	
level	90 %
sides	2-sided
lower limit	1.009
upper limit	1.065

Secondary: Mean change from baseline in score on the adult myopathy assessment tool (AMAT) in Part B, Cohort 5

End point title	Mean change from baseline in score on the adult myopathy assessment tool (AMAT) in Part B, Cohort 5[4]

End point description:

The AMAT rated physical function and muscle endurance, with higher scores indicating better performance. The tool includes 7 timed functional tasks rated on a scale from 0 - 21 and 6 endurance tasks rated on a scale from 0 - 24. The range for the total score was from 0 (worst) to 45 (best). A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Day 85

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All arms do not apply to this end point.

End point values	BVS857 Part B double blind (Cohort 5)	Placebo Part B double blind (Cohort 5)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	9		
Units: score on a scale				
arithmetic mean (standard deviation)	1 (± 4.2)	2.3 (± 1.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in total lean body mass (LBM) in Part B, Cohort 5

End point title	Mean change from baseline in total lean body mass (LBM) in Part B, Cohort 5[5]

End point description:

LBM was assessed by dual-energy X-ray (DXA) absorptiometry. A positive change from baseline indicate improvement.

End point type	Secondary

End point timeframe:

Baseline, Day 85

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All arms do not apply to this end point.

End point values	BVS857 Part B double blind (Cohort 5)	Placebo Part B double blind (Cohort 5)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: kilograms				
arithmetic mean (standard deviation)	0.77 (± 1.556)	0.16 (± 1.199)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: Observed maximum concentration following drug administration (Cmax) in Part A, Cohort 1

End point title	Plasma Pharmacokinetics (PK) of BVS857: Observed maximum concentration following drug administration (Cmax) in Part A, Cohort 1[6]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1, 15, 29, 43: pre-dose, 1, 4, 12, 24, 48, 168 hours post-dose. Day 57: pre-dose, 1, 4, 12, 24, 48, 168, 504 hours post-dose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All arms do not apply to this end point.

End point values	BVS857 Part A Open label (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.01 mg/kg BVS857 s.c.	184 (± 6.36)			
Day 15, 0.01 mg/kg BVS857 s.c.	34.6 (± 48.9)			
Day 29, 0.03 mg/kg BVS857 s.c.	83.1 (± 20.3)			
Day 43, 0.06 mg/kg BVS857 s.c.	74.2 (± 16.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: Observed maximum concentration following drug administration (Cmax) in Part A, Cohort 2

End point title	Plasma Pharmacokinetics (PK) of BVS857: Observed maximum concentration following drug administration (Cmax) in Part A, Cohort 2[7]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1, 15

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A double blind (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.03 mg/kg BVS857 i.v. (n=4)	393 (± 30.1)			
Day 15, 0.03 mg/kg BVS857 s.c. (n=3)	77.3 (± 46.5)			
Day 29, 0.06 mg/kg BVS857 s.c. (n=2)	113 (± 2.12)			
Day 43, 0.10 mg/kg BVS857 s.c. (n=3)	191 (± 19.2)			
Day 57, 0.10 mg/kg BVS857 s.c. (n=1)	232 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: Time to reach the maximum concentration after drug administration (Tmax) in Part A, Cohort 1

End point title	Plasma Pharmacokinetics (PK) of BVS857: Time to reach the maximum concentration after drug administration (Tmax) in Part A, Cohort 1[8]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1, 15, 29, 43: pre-dose, 1, 4, 12, 24, 48, 168 hours post-dose. Day 57: pre-dose, 1, 4, 12, 24, 48, 168, 504 hours post-dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A Open label (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: hours				
arithmetic mean (standard deviation)				
Day 1, 0.01 mg/kg BVS857 i.v. (n=2)	4.04 (± 0.0566)			

Day 15, 0.01 mg/kg BVS857 s.c. (n=1)	12.1 (± 9999)			
Day 29, 0.03 mg/kg BVS857 s.c.(n=2)	18.1 (± 8.41)			
Day 43, 0.06 mg/kg BVS857 s.c. (n=2)	36 (± 16.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: Time to reach the maximum concentration after drug administration (Tmax) in Part A, Cohort 2

End point title	Plasma Pharmacokinetics (PK) of BVS857: Time to reach the maximum concentration after drug administration (Tmax) in Part A, Cohort 2[9]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Day 1, 15

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A double blind (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: hours				
arithmetic mean (standard deviation)				
Day 1, 0.03 mg/kg BVS857 i.v. (n=4)	2.53 (± 1.7)			
Day 15, 0.03 mg/kg BVS857 s.c.(n=3)	24.1 (± 0.1)			
Day 29, 0.06 mg/kg BVS857 s.c. (n=2)	24 (± 0)			
Day 43, 0.10 mg/kg BVS857 s.c. (n=3)	24 (± 0.2)			
Day 57, 0.10 mg/kg BVS857 s.c. (n=1)	48 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) in Part A, Cohort 1

End point title	Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) in Part A, Cohort 1[10]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1, 15, 29, 43: pre-dose, 1, 4, 12, 24, 48, 168 hours post-dose. Day 57: pre-dose, 1, 4, 12, 24, 48, 168, 504 hours post-dose

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A Open label (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.01 mg/kg BVS857 i.v.(n=2)	4630 (± 1200)			
Day 15, 0.01 mg/kg BVS857 s.c. (n=2)	1060 (± 1500)			
Day 29, 0.03 mg/kg BVS857 s.c.(n=2)	2720 (± 870)			
Day 43, 0.06 mg/kg BVS857 s.c.(n=2)	5310 (± 4720)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) in Part A, Cohort 2

End point title	Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) in Part A, Cohort 2[11]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1, 15

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A double blind (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: H*ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.03 mg/kg BVS857 i.v.(n=4)	9850 (± 4480)			
Day 15, 0.03 mg/kg BVS857 s.c. (n=3)	6480 (± 5850)			
Day 29, 0.06 mg/kg BVS857 s.c. (n=2)	7340 (± 5610)			

Day 43, 0.10 mg/kg BVS857 s.c. (n=3) Day 57, 0.10 mg/kg BVS857 s.c. (n=1)	14400 (± 3320) 28400 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: The area under the plasma concentration-time curve from zero to 48 hours (AUC0_48h) in Part A, Cohort 1

End point title	Plasma Pharmacokinetics (PK) of BVS857: The area under the plasma concentration-time curve from zero to 48 hours (AUC0_48h) in Part A, Cohort 1[12]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1, 15, 29, 43: pre-dose, 1, 4, 12, 24, 48, 168 hours post-dose. Day 57: pre-dose, 1, 4, 12, 24, 48, 168, 504 hours post-dose

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A Open label (Cohort 1)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.01 mg/kg BVS857 i.v.(n=2) Day 15, 0.01 mg/kg BVS857 s.c. (n=1) Day 29, 0.03 mg/kg BVS857 s.c. (n=2) Day 43, 0.06 mg/kg BVS857 s.c. (n=2)	4620 (± 1200) 2120 (± 9999) 2720 (± 870) 2210 (± 339)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: The area under the plasma concentration-time curve from zero to 48 hours (AUC0_48h) in Part A, Cohort 2

End point title	Plasma Pharmacokinetics (PK) of BVS857: The area under the plasma concentration-time curve from zero to 48 hours (AUC0_48h) in Part A, Cohort 2[13]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1, 15

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A double blind (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.03 mg/kg BVS857 i.v. (n=4)	7980 (± 1710)			
Day 15, 0.03 mg/kg BVS857 s.c. (n=3)	2640 (± 1500)			
Day 29, 0.06 mg/kg BVS857 s.c. (n=2)	3880 (± 735)			
Day 43, 0.10 mg/kg BVS857 s.c. (n=3)	6390 (± 925)			
Day 57, 0.10 mg/kg BVS857 s.c. (n=1)	7360 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: Observed maximum concentration following drug administration (Cmax) in Part B, Cohort 4

End point title	Plasma Pharmacokinetics (PK) of BVS857: Observed maximum concentration following drug administration (Cmax) in Part B, Cohort 4[14]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1: pre-dose, 1, 4, 24, 48 hours post-dose

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part B open-label (Cohort 4)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng/mL				
arithmetic mean (standard deviation)	2490 (± 799)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: Observed maximum concentration following drug administration (Cmax) in Part B, Cohort 5

End point title	Plasma Pharmacokinetics (PK) of BVS857: Observed maximum concentration following drug administration (Cmax) in Part B, Cohort 5[15]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1 and 36: pre-dose, 1, 4, 24, 48 hours post-dose. Day 78: pre-dose, 1, 4, 24, 48, 168 hours post-dose.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part B double blind (Cohort 5)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.06 mg/kg BVS857 i.v. (n=18)	854 (± 669)			
Day 36, 0.06 mg/kg BVS857 i.v. (n=16)	790 (± 184)			
Day 78, 0.06 mg/kg BVS857 i.v. (n=16)	712 (± 218)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: Time to reach the maximum concentration after drug administration (Tmax) in Part B, Cohort 4

End point title	Plasma Pharmacokinetics (PK) of BVS857: Time to reach the maximum concentration after drug administration (Tmax) in Part B, Cohort 4[16]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1: pre-dose, 1, 4, 24, 48 hours post-dose

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part B open-label (Cohort 4)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: hours				
arithmetic mean (standard deviation)	1.08 (± 0.0707)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: Time to reach the maximum concentration after drug administration (Tmax) in Part B, Cohort 5

End point title	Plasma Pharmacokinetics (PK) of BVS857: Time to reach the maximum concentration after drug administration (Tmax) in Part B, Cohort 5[17]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Days 1 and 36: pre-dose, 1, 4, 24, 48 hours post-dose. Day 78: pre-dose, 1, 4, 24, 48, 168 hours post-dose.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part B double blind (Cohort 5)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: hours				
arithmetic mean (standard deviation)				
Day 1, 0.06 mg/kg BVS857 i.v. (n=18)	2.39 (± 1.54)			
Day 36, 0.06 mg/kg BVS857 i.v. (n=16)	1.73 (± 1.2)			
Day 78, 0.06 mg/kg BVS857 i.v. (n=16)	1.49 (± 1.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) in Part B, Cohort 5

End point title	Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) in Part B, Cohort 5

	[18]

End point description:

Serum samples were obtained for PK assessment.

End point type	Secondary

End point timeframe:

Day 36: pre-dose, 1, 4, 24, 48 hours post-dose. Day 78: pre-dose, 1, 4, 24, 48, 168 hours post-dose.

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part B double blind (Cohort 5)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 36, 0.06 mg/kg BVS857 i.v. (n=1) Day 78, 0.06 mg/kg BVS857 i.v. (n=15)	13100 (± 9999) 28000 (± 13500)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857:The area under the plasma concentration-time curve from zero to 48 hours (AUC0_48h) in Part B, Cohort 4

End point title	Plasma Pharmacokinetics (PK) of BVS857:The area under the plasma concentration-time curve from zero to 48 hours (AUC0_48h) in Part B, Cohort 4[19]

End point description:

Serum samples were obtained for the PK assessment.

End point type	Secondary

End point timeframe:

Days 1: pre-dose, 1, 4, 24, 48 hours post-dose

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part B open-label (Cohort 4)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: H*ng/mL				
arithmetic mean (standard deviation)	40600 (± 1270)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857:The area under the plasma concentration-time curve from zero to 48 hours (AUC0_48h) in Part B, Cohort 5

End point title	Plasma Pharmacokinetics (PK) of BVS857:The area under the plasma concentration-time curve from zero to 48 hours (AUC0_48h) in Part B, Cohort 5[20]

End point description:

End point type	Secondary

End point timeframe:

Days 1 and 36: pre-dose, 1, 4, 24, 48 hours post-dose. Day 78: pre-dose, 1, 4, 24, 48, 168 hours post-dose.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part B double blind (Cohort 5)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.06 mg/kg BVS857 i.v. (n=18)	19400 (± 4160)			
Day 36, 0.06 mg/kg BVS857 i.v.(n=16)	19600 (± 5240)			
Day 78, 0.06 mg/kg BVS857 i.v. (n=16)	18100 (± 5850)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to the end of the dosing interval tau (AUCtau)

End point title	Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to the end of the dosing interval tau (AUCtau)[21]

End point description:

Serum samples were obtained for PK assessment. This PK parameter was not analyzed in either Part A

or Part B because there were insufficient data points after Cmax. Therefore, this parameter could not be calculated.

End point type	Secondary

End point timeframe:

Part A: days 1, 15, 29, 43: pre-dose, 1, 4, 12, 24, 48, 168 hours post-dose. Day 57: pre-dose, 1, 4, 12, 24, 48, 168, 504 hours post-dose. Part B: days 1 and 36: pre-dose, 1, 4, 24, 48 hours post-dose. Day 78: pre-dose, 1, 4, 24, 48, 168 hours post-dose.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A Open label (Cohort 1)	BVS857 Part A double blind (Cohort 2)	BVS857 Part B open-label (Cohort 4)	BVS857 Part B double blind (Cohort 5)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[22]	0[23]	0[24]	0[25]
Units: ng*h/mL				

Notes:

[22] - This PK parameter was not analyzed.

[23] - This PK parameter was not analyzed.

[24] - This PK parameter was not analyzed.

[25] - This PK parameter was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: The terminal elimination half-life (T1/2)

End point title	Plasma Pharmacokinetics (PK) of BVS857: The terminal elimination half-life (T1/2)[26]

End point description:

Serum samples were obtained for PK assessment. This PK parameter was not analyzed in either Part A or Part B because there were insufficient data points after Cmax. Therefore, this parameter could not be calculated.

End point type	Secondary

End point timeframe:

Part A: days 1, 15, 29, 43: pre-dose, 1, 4, 12, 24, 48, 168 hours post-dose. Day 57: pre-dose, 1, 4, 12, 24, 48, 168, 504 hours post-dose. Part B: days 1 and 36: pre-dose, 1, 4, 24, 48 hours post-dose. Day 78: pre-dose, 1, 4, 24, 48, 168 hours post-dose.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A Open label (Cohort 1)	BVS857 Part A double blind (Cohort 2)	BVS857 Part B open-label (Cohort 4)	BVS857 Part B double blind (Cohort 5)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[27]	0[28]	0[29]	0[30]
Units: ng*h/mL				

Notes:

[27] - This PK parameter was not analyzed.

[28] - This PK parameter was not analyzed.

[29] - This PK parameter was not analyzed.

[30] - This PK parameter was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to infinity (AUCinf)

End point title	Plasma Pharmacokinetics (PK) of BVS857: The area under the serum concentration-time curve from time zero to infinity (AUCinf)[31]

End point description:

Serum samples were obtained for PK assessment. This PK parameter was not analyzed in either Part A or Part B because there were insufficient data points after Cmax. Therefore, this parameter could not be calculated.

End point type	Secondary

End point timeframe:

Part A: days 1, 15, 29, 43: pre-dose, 1, 4, 12, 24, 48, 168 hours post-dose. Day 57: pre-dose, 1, 4, 12, 24, 48, 168, 504 hours post-dose. Part B: days 1 and 36: pre-dose, 1, 4, 24, 48 hours post-dose. Day 78: pre-dose, 1, 4, 24, 48, 168 hours post-dose.

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A Open label (Cohort 1)	BVS857 Part A double blind (Cohort 2)	BVS857 Part B open-label (Cohort 4)	BVS857 Part B double blind (Cohort 5)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[32]	0[33]	0[34]	0[35]
Units: hour				

Notes:

[32] - This PK parameter was not analyzed.

[33] - This PK parameter was not analyzed.

[34] - This PK parameter was not analyzed.

[35] - This PK parameter was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Compare dose normalized log-transformed AUCinf following IV and SC administrations

End point title	Compare dose normalized log-transformed AUCinf following IV

	and SC administrations[36]

End point description:

Serum samples were obtained for PK assessment. This PK parameter was not analyzed in either Part A or Part B because there were insufficient data points after Cmax. Therefore, this parameter could not be calculated.

End point type	Secondary

End point timeframe:

In Part A: days 1 and 15, pre-dose, 1, 4, 12, 24, 48, 168 hours post-dose.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this end point.

End point values	BVS857 Part A Open label (Cohort 1)	BVS857 Part A double blind (Cohort 2)	BVS857 Part B open-label (Cohort 4)	BVS857 Part B double blind (Cohort 5)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[37]	0[38]	0[39]	0[40]
Units: ng*h/mL				

Notes:

[37] - This PK parameter was not analyzed.

[38] - This PK parameter was not analyzed.

[39] - This PK parameter was not analyzed.

[40] - This PK parameter was not analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Study Part 1: BVS857 (cohort 1)
Reporting group description:	
Study Part 1: BVS857 (cohort 1)	
Reporting group title	Study Part 1: Placebo (cohort 2)
Reporting group description:	
Study Part 1: Placebo (cohort 2)	
Reporting group title	Study Part 1: BVS857 (cohort 2)
Reporting group description:	
Study Part 1: BVS857 (cohort 2)	
Reporting group title	Study Part 2: BVS857 0.1 mg/kg i.v. (cohort 4)
Reporting group description:	
Study Part 2: BVS857 0.1 mg/kg i.v. (cohort 4)	
Reporting group title	Study Part 2: BVS857 0.06 mg/kg i.v. (cohort 5)
Reporting group description:	
Study Part 2: BVS857 0.06 mg/kg i.v. (cohort 5)	
Reporting group title	Study Part 2: Placebo (cohort 5)
Reporting group description:	
Study Part 2: Placebo (cohort 5)	

Serious adverse events	Study Part 1: BVS857 (cohort 1)	Study Part 1: Placebo (cohort 2)	Study Part 1: BVS857 (cohort 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Study Part 2: BVS857 0.1 mg/kg i.v. (cohort 4)	Study Part 2: BVS857 0.06 mg/kg i.v. (cohort 5)	Study Part 2: Placebo (cohort 5)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Study Part 1: BVS857 (cohort 1)	Study Part 1: Placebo (cohort 2)	Study Part 1: BVS857 (cohort 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	2 / 2 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Seborrhoeic keratosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Administration site hypersensitivity			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Catheter site extravasation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Fatigue			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infusion site erythema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infusion site pruritus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	3 / 4 (75.00%)
occurrences (all)	2	0	5
Injection site rash			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injection site swelling			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Malaise			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Puncture site pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Therapeutic response unexpected			
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Respiratory, thoracic and mediastinal disorders			

Bronchospasm			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Choking			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Panic attack			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood potassium increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Neutralising antibodies positive			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Fall			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Fibula fracture			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Road traffic accident			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Somnolence			

subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Eustachian tube dysfunction			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Eye disorders			
Eyelid haematoma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Glaucoma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ocular discomfort			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Scleral hyperaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gingival pain			

subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Lip disorder			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Lip oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Periodontal disease			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sensitivity of teeth			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Erythema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin discolouration			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin irritation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Exostosis of jaw			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Myalgia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 2 (100.00%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Study Part 2: BVS857 0.1 mg/kg i.v. (cohort 4)	Study Part 2: BVS857 0.06 mg/kg i.v. (cohort 5)	Study Part 2: Placebo (cohort 5)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	17 / 18 (94.44%)	8 / 9 (88.89%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic keratosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

Vascular disorders			
Flushing			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Administration site hypersensitivity			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Catheter site extravasation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 2 (0.00%)	2 / 18 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Feeling hot			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Infusion site erythema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Infusion site pruritus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	4	0
Injection site erythema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injection site rash			

subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Puncture site pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 18 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Therapeutic response unexpected			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Choking			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Upper respiratory tract congestion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Panic attack			

subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Investigations			
Blood potassium increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood pressure increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Neutralising antibodies positive			
subjects affected / exposed	0 / 2 (0.00%)	2 / 18 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Weight increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Fibula fracture			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	1 / 2 (50.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Carotid artery stenosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	2 / 18 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	11	0
Headache			
subjects affected / exposed	0 / 2 (0.00%)	3 / 18 (16.67%)	1 / 9 (11.11%)
occurrences (all)	0	4	1
Hypoaesthesia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 18 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Presyncope			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Eustachian tube dysfunction			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eyelid haematoma			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Glaucoma			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ocular discomfort			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	8	0
Scleral hyperaemia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gingival pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lip disorder			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Lip oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Oesophagitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Paraesthesia oral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	3	0

Periodontal disease			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Sensitivity of teeth			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Skin discolouration			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Back pain			

subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Exostosis of jaw			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Joint stiffness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 2 (0.00%)	2 / 18 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Myalgia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Spinal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 18 (5.56%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 2 (0.00%)	0 / 18 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	4 / 18 (22.22%)	1 / 9 (11.11%)
occurrences (all)	0	5	1

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 18 (0.00%) 0	1 / 9 (11.11%) 1
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 18 (5.56%) 1	0 / 9 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2013	The purpose of this amendment was to address FDA comments regarding temporary and permanent dosing discontinuation due to adverse events. The amendment redefined the conditions leading to temporary discontinuation of study treatment. The amendment also stipulated permanent dosing discontinuation due to elevated liver function tests
19 August 2014	The purpose of this amendment was to address clinical issues that had come to light upon analysis of data from the first 2 patients enrolled in the trial. As per protocol, these patients were dosed open-label (BVS857 s.c.). Both patients experienced a mild injection site skin reaction subsequent to the 0.06 mg/kg s.c. dose, triggering patient discontinuation. This amendment stipulated modifications in the dosing regimen in Part A and clarified that patients had to be withdrawn in the event of severe or persistent and recurrent infusion- and injection-site skin reactions. It was also determined that the 0.01 mg/kg dose (both i.v. and s.c.) was associated with very low PK exposure levels, and this dose was therefore to be eliminated. The third planned interim analysis in Part B was clarified to state that early futility was the primary purpose of this analysis, and that it was to be performed when approximately18 patients had completed the study, instead of 12, in order to provide sufficient power for the statistical test based on the futility criterion at the interim analysis. Moreover, the criterion for claiming the preliminary efficacy of BVS857 at the end of the study was also clarified and the statistical tests were adjusted to it. Plans for development of BVS857 include application to selected central nervous system (CNS) disorders. Therefore, determination of BVS857's CNS penetration was explored via an optional lumbar puncture with cerebrospinal fluid examination of PK at baseline and Visit 19 in Part B.
06 February 2015	This amendment was to allow the use of i.v. administration route for Part B in the event that (1) the s.c. route did not provide sufficient exposure to trigger the expected PD effect and/or did not show clear dose proportionality of exposure, or (2) the planned s.c. dosing schemes resulted in severe or recurrent injection site reactions. If Part B was performed using i.v. route of administration under this amendment, the first two patients were to receive 12 weekly i.v. doses of open-label BVS857 0.1 mg/kg. A safety review was to be performed after the first two patients had completed 3 weekly doses of open-label i.v. BVS857 prior to proceeding with the rest of the planned randomized cohort. BVS857 0.1 mg/kg i.v. was expected to be safe based on the following: 1) established single MTD of 0.1 mg/kg i.v. in healthy volunteers (including insulin resistant patients), which was not expected to accumulate upon weekly dosing. 2) SBMA patients had lower circulating IGF-1 compared to healthy volunteers, allowing for a wider margin for supplementation. 3) Based on simulations, total IGF-1-like activity following BVS857 0.1 mg/kg weekly i.v. for 12 weeks was not expected to exceed the established exposure cap (400 ng/mL).
31 March 2015	The purpose of this amendment was to make administrative updates to clarify sample numbering and appropriate QMT equipment. AMAT, DXA and TMV assessments at week 6 were added to the exploratory objectives following request for clarification from German radiation agency (BfS).

20 July 2015	The purpose of this amendment was to decrease the i.v. dose to be used in Cohort 5 of Part B. Following the review of safety data of Cohort 4 (first two patients in Part B dosed open-label) after the first 3 i.v. doses, a study stopping rule was met, with both patients having a total IGF-1-like activity greater than 400 ng/mL after the first dose. Accordingly, the dose for Cohort 5 was lowered as follows: 1) Patients with baseline body weight ≤ 100 kg were to receive BVS857 or placebo at 0.06 mg/kg i.v. weekly (i.e., lowered by 40%). The total dose was capped at 6 mg (i.e., patients with baseline body weight >100 kg were to receive 6 mg i.v. weekly). 2) PK and IGF-1 analysis were reviewed in an ongoing manner by an unblinded PK bioanalyst and blinded pharmacokineticist for the first 48 hours of Week 1 in each patient. Patients who had total IGF-1-like activity ≥ 400 ng/mL or Cmax ≥ 2.3 µg/mL would have their weekly doses reduced to 0.05 mg/kg i.v. weekly (5 mg maximum; i.e., further reduction by 17%) as soon as this was determined, and at the latest in time for the Week 6 dose. The dose could be further reduced to 0.04 mg/kg i.v. weekly (4 mg maximum dose) if a patient continued to reach these criteria following the dose reduction. Due to the absence of AEs associated with total IGF-1-like activity ≥ 400 ng/mL, planned dose reduction by 40% (from 0.1 mg/kg to 0.06 g/kg), and planned ongoing review of PK and IGF-1 data with online changes to dose levels, the criteria surrounding total IGF-1-like activity and Cmax levels were shifted from Study Stopping Rules to instructions for ermitted Dose Adjustments for Cohort 5.
09 November 2015	The purpose of this amendment was to add two follow-up visits to the end of the treatment period, at 4 and 8 weeks after the last dose, to assess whether efficacy, if any, was sustained after weekly doses over 12 weeks. This amendment provided valuable information for possible future dosing regimens.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: