Clinical trial results:
An Open-label, One-arm, Proof of Concept Trial to Evaluate the Safety of ATX-MS-1467 (MSC2358825A) and its Effect on Immune Tolerance in Subjects with Relapsing Multiple Sclerosis

Summary

EudraCT number	2013-002916-28
Trial protocol	LV
Global end of trial date	11 April 2016

Results information

Result version number	v1 (current)
This version publication date	17 March 2017
First version publication date	17 March 2017

Trial information

Trial identification

Sponsor protocol code	EMR200166-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01973491
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center Merck KGaA, Merck KGaA, +49 615172 5200 , service@merckgroup.com
Scientific contact	Communication Center Merck KGaA, Merck KGaA, +49 615172 5200 , service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	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	11 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2016
Global end of trial reached?	Yes
Global end of trial date	11 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate the effects of ATX-MS-1467 administered intradermally, titrated to a dose of 800 microgram (mcg) every 2 weeks (biweekly), for a total period of 20 weeks on 1.5T MRI parameters compared to a Baseline Control Period off treatment in subjects with relapsing Multiple Sclerosis.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Russian Federation: 36
Worldwide total number of subjects	37
EEA total number of subjects	1

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)	37
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

37 subjects were enrolled in the study and entered the 8-week Baseline Control Period. Following completion of the Baseline Control Period, eligible subjects entered the 4-week Titration Period followed by a 16-week Treatment Period.

Period 1

Period 1 title	Baseline Control Period (8 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ATX-MS-1467

Arm description:

Subjects received ATX-MS-1467 50 mcg, 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period followed by biweekly dose of ATX-MS-1467 800 mcg for 16 weeks during the treatment period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	ATX-MS-1467
Started	37
Completed	19
Not completed	18
Consent withdrawn by subject	1
Did not meet Eligibility Criteria	17

Period 2

Period 2 title	Titration Period (4 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ATX-MS-1467

Arm description:

Subjects received ATX-MS-1467 50 mcg, 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period followed by biweekly dose of ATX-MS-1467 800 mcg for 16 weeks during the treatment period.

Arm type	Experimental
Investigational medicinal product name	ATX-MS-1467
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received intradermal injection of ATX-MS-1467 50 mcg, 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period.

Number of subjects in period 2	ATX-MS-1467
Started	19
Completed	19

Period 3

Period 3 title	Treatment Period (16 Weeks)
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ATX-MS-1467

Arm description:

Subjects received ATX-MS-1467 50 mcg, 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period followed by biweekly dose of ATX-MS-1467 800 mcg for 16 weeks during the treatment period.

Arm type	Experimental
Investigational medicinal product name	ATX-MS-1467
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received biweekly intradermal injection of ATX-MS-1467 800 mcg for 16 weeks during the treatment period.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: All analysis in the study were carried out for the subjects who received the study drug during the Treatment Period.

Number of subjects in period 3[2]	ATX-MS-1467
Started	19
Completed	18
Not completed	1
Adverse Event	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline Characteristics were to be presented for the subjects who received study treatment. Therefore, out of 37 subjects enrolled in the study, 19 subjects who received treatment were included in the Baseline Characteristics section.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period (16 Weeks)
Reporting group description:	
Subjects received ATX-MS-1467 50 mcg, 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period followed by biweekly dose of ATX-MS-1467 800 mcg for 16 weeks during the treatment period. The Safety (SAF) Analysis Set included all subjects who received at least 1 dose of investigational medicinal product (IMP).	

Reporting group values	Treatment Period (16 Weeks)	Total	
Number of subjects	19	19	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	27.1		
standard deviation	± 5.45	-	
Gender categorical			
Units: Subjects			
Female	15	15	
Male	4	4	

End points

End points reporting groups

Reporting group title	ATX-MS-1467

Reporting group description:

Subjects received ATX-MS-1467 50 mcg, 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period followed by biweekly dose of ATX-MS-1467 800 mcg for 16 weeks during the treatment period.

Reporting group title	ATX-MS-1467

Reporting group description:

Subjects received ATX-MS-1467 50 mcg, 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period followed by biweekly dose of ATX-MS-1467 800 mcg for 16 weeks during the treatment period.

Reporting group title	ATX-MS-1467

Reporting group description:

Subjects received ATX-MS-1467 50 mcg, 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period followed by biweekly dose of ATX-MS-1467 800 mcg for 16 weeks during the treatment period.

Primary: Change From Baseline in the Average Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) Over On-treatment Scans

End point title	Change From Baseline in the Average Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) Over On-treatment Scans[1]

End point description:

T1 CELs were measured using Magnetic Resonance Imaging (MRI) scans. Baseline value was calculated as the average number of T1 CELs during the 3 visits in the Baseline Control Period (Weeks -8, -4 and 0) and On-treatment value was calculated as the average number of T1 CELs during the 3 visits in the treatment period (Weeks 12, 16 and 20). The change from baseline in average number of T1 CELs was reported. The modified intention-to-treat (mITT) analysis set included all enrolled subjects who received at least 1 dose of IMP and had 2 or more MRI scans during the Baseline Control Period and planned on-treatment visits (Weeks 12, 16, and 20) or end of treatment visit provided it occurred within 28 days of the last dose of IMP.

End point type	Primary

End point timeframe:

Baseline (Weeks -8, -4 and 0), Treatment Period (Weeks 12, 16 and 20)

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: Only descriptive statistics were planned for this endpoint.

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: lesions				
arithmetic mean (standard deviation)				
Baseline	7.4 (± 7.62)			
Change Over Treatment Period	-2.4 (± 4.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs)

End point title	Total Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs)

End point description:

The number of T1 CELs were measured using MRI scans. mITT analysis set included all enrolled subjects who received at least 1 dose of IMP and had 2 or more MRI scans during the Baseline Control Period and planned on-treatment visits (Weeks 12, 16, and 20) or end of treatment visit provided it occurred within 28 days of the last dose of IMP. Here, "n" signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Weeks 12, 16, 20, 24, 28 and 36

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: lesions				
arithmetic mean (standard deviation)				
Week 12 (n = 18)	3.1 (± 3.92)			
Week 16 (n= 19)	4.6 (± 6.26)			
Week 20 (n= 18)	5.6 (± 9.55)			
Week 24 (n= 18)	4.9 (± 11.07)			
Week 28 (n= 17)	2.6 (± 3.28)			
Week 36 (n= 17)	2.2 (± 2.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) at Weeks 12, 16, 20, 24, 28 and 36

End point title	Change From Baseline in Total Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) at Weeks 12, 16, 20, 24, 28 and 36

End point description:

T1 CELs were measured using MRI scans. Baseline was calculated as the average number of T1 CELs during the 3 visits in the Baseline Control Period (Weeks -8, -4 and 0). mITT analysis set included all enrolled subjects who received at least 1 dose of IMP and had 2 or more MRI scans during the Baseline Control Period and planned on-treatment visits (Weeks 12, 16, and 20) or end of treatment visit provided it occurred within 28 days of the last dose of IMP. Here, "n " signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline (Weeks -8, -4 and 0), Weeks 12, 16, 20, 24, 28 and 36

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: lesions				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 18)	-3 (± 4.9)			
Change at Week 16 (n= 19)	-2.8 (± 5.2)			
Change at Week 20 (n= 18)	-1.6 (± 5.11)			
Change at Week 24 (n= 18)	-2.2 (± 7.1)			
Change at Week 28 (n= 17)	-4.2 (± 7.06)			
Change at Week 36 (n = 17)	-4.6 (± 6.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Volume of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) at Weeks 12, 16, 20, 24, 28 and 36

End point title	Change From Baseline in Total Volume of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) at Weeks 12, 16, 20, 24, 28 and 36

End point description:

T1 CELs were measured using MRI scans. Baseline was calculated as the average number of T1 CELs during the 3 visits in the Baseline Control Period (Weeks -8, -4 and 0). mITT analysis set included all enrolled subjects who received at least 1 dose of IMP and had 2 or more MRI scans during the Baseline Control Period and planned on-treatment visits (Weeks 12, 16, and 20) or end of treatment visit provided it occurred within 28 days of the last dose of IMP. Here, "n" signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline (Weeks -8, -4, 0), Weeks 12, 16, 20, 24, 28 and 36

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: milliliter				
arithmetic mean (standard deviation)				
Baseline	0.838 (± 1.0151)			
Change at Week 12 (n = 18)	-0.321 (± 0.5618)			
Change at Week 16 (n = 19)	-0.316 (± 0.7184)			
Change at Week 20 (n = 18)	-0.225 (± 0.7845)			

Change at Week 24 (n = 18)	-0.333 (± 0.8622)			
Change at Week 28 (n = 17)	-0.454 (± 0.9403)			
Change at Week 36 (n = 17)	-0.579 (± 0.8807)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of New or Newly Enlarging Time Constant 2 (T2) Lesions

End point title	Total Number of New or Newly Enlarging Time Constant 2 (T2) Lesions

End point description:

T2 lesions were measured using MRI scans. mITT analysis set included all enrolled subjects who received at least 1 dose of IMP and had 2 or more MRI scans during the Baseline Control Period and planned on-treatment visits (Weeks 12, 16, and 20) or end of treatment visit provided it occurred within 28 days of the last dose of IMP. Here, "n" signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Weeks 12, 16, 20, 24, 28 and 36

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: lesions				
arithmetic mean (standard deviation)				
Week 12 (n= 18)	14.7 (± 20.69)			
Week 16 (n= 19)	4.5 (± 6.16)			
Week 20 (n= 18)	5.4 (± 10.07)			
Week 24 (n= 18)	4.9 (± 8.27)			
Week 28 (n= 17)	2.6 (± 3.28)			
Week 36 (n= 17)	4.2 (± 3.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 0 in Total Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) at Weeks 12, 16, 20, 24, 28 and 36

End point title	Change From Week 0 in Total Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) at Weeks 12, 16, 20, 24, 28 and 36

End point description:

T1 CELs were measured using MRI scans. mITT analysis set included all enrolled subjects who received

at least 1 dose of IMP and had 2 or more MRI scans during the Baseline Control Period and planned on-treatment visits (Weeks 12, 16, and 20) or end of treatment visit provided it occurred within 28 days of the last dose of IMP. Here, "Number of subjects analyzed" signifies those subjects who were evaluable for this outcome measure and "n" signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Week 0, 12, 16, 20, 24, 28 and 36

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: lesions				
arithmetic mean (standard deviation)				
Week 0 (n = 18)	7.2 (± 6.71)			
Change at Week 12 (n = 17)	-3.4 (± 6.67)			
Change at Week 16 (n = 18)	-2.3 (± 7.03)			
Change at Week 20 (n = 17)	-0.9 (± 8.57)			
Change at Week 24 (n = 17)	-1.5 (± 10.87)			
Change at Week 28 (n = 16)	-3.1 (± 5.04)			
Change at Week 36 (n = 16)	-3.5 (± 4.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 0 in Total Volume of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) at Weeks 12, 16, 20, 24, 28 and 36

End point title	Change From Week 0 in Total Volume of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) at Weeks 12, 16, 20, 24, 28 and 36

End point description:

T1 CELs were measured using MRI scans. mITT analysis set included all enrolled subjects who received at least 1 dose of IMP and had 2 or more MRI scans during the Baseline Control Period and planned on-treatment visits (Weeks 12, 16, and 20) or end of treatment visit provided it occurred within 28 days of the last dose of IMP. Here, "Number of subjects analyzed" signifies those subjects who were evaluable for this outcome measure and "n" signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Weeks 0, 12, 16, 20, 24, 28 and 36

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: milliliter				
arithmetic mean (standard deviation)				
Week 0 (n = 18)	0.815 (± 0.8121)			
Change at Week 12 (n = 17)	-0.42 (± 0.752)			
Change at Week 16 (n = 18)	-0.264 (± 0.7737)			
Change at Week 20 (n = 17)	-0.157 (± 0.9839)			
Change at Week 24 (n = 17)	-0.271 (± 1.4318)			
Change at Week 28 (n = 16)	-0.341 (± 0.4541)			
Change at Week 36 (n = 16)	-0.473 (± 0.5914)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Annualized Relapse Rate

End point title	Mean Annualized Relapse Rate

End point description:

Relapse was defined as new, worsening or recurrent neurological symptoms attributed to multiple sclerosis that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. These new or worsening symptoms should be noted by the subject and must be accompanied by at least one of the following: An increase of greater than or equal to (>=) 1 grade in >=2 functional scales of the Expanded Disability Status Scale (EDSS) or an increase of >=2 grades in 1 functional scale of the EDSS or an increase of >= 0.5 or an increase of >=1.0 in EDSS if the previous EDSS was 0. Annualized Relapse Rate was calculated as = 365.25 x (Number of relapses during Treatment Period) per (Number of days on treatment during Treatment Period). Analysis population included subset of mITT analysis set who had relapse.

End point type	Secondary

End point timeframe:

Week 20

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: relapse per year				
arithmetic mean (standard deviation)	2.6 (± 0.011)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Relapse

End point title	Time to First Relapse

End point description:

Relapse was defined as new, worsening or recurrent neurological symptoms attributed to multiple sclerosis that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. These new or worsening symptoms should be noted by the subject and must be accompanied by at least one of the following: An increase of greater than or equal to (>=) 1 grade in >=2 functional scales of the Expanded Disability Status Scale (EDSS) or an increase of >=2 grades in 1 functional scale of the EDSS or an increase of >= 0.5 or an increase of >=1.0 in EDSS if the previous EDSS was 0. Time to first relapse was defined as the time in days from the date of first dose of study treatment to the date of first multiple sclerosis relapse. The miTT analysis set was evaluable. Here, "99999" indicated data not available as very few subjects had relapse during the study.

End point type	Secondary

End point timeframe:

Baseline up to Week 36

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Expanded Disability Status Scale (EDSS) Score at Week 20

End point title	Change From Baseline in Total Expanded Disability Status Scale (EDSS) Score at Week 20

End point description:

EDSS is an ordinal scale in half-point increments that qualifies disability in subjects with Multiple Sclerosis. It consists of 8 ordinal rating scales assessing seven functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as any other neurological findings due to Multiple Sclerosis. Total EDSS score ranges from 0 (normal neurological examination) to 10 (death due to MS). Baseline was defined as the last measurement taken prior to the first dose of study drug (Week 0). mITT analysis set included all enrolled subjects who received at least 1 dose of IMP and had 2 or more MRI scans during the Baseline Control Period and planned on-treatment visits (Weeks 12, 16, and 20) or end of treatment visit provided it occurred within 28 days of the last dose of IMP. Here, "n" signifies those subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 20

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (Week 0) (n= 19) Change at Week 20 (n = 18)	2.32 (± 0.803) -0.11 (± 0.916)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Multiple Sclerosis Functional Composite (MSFC) Score at Week 20

End point title	Change From Baseline in Total Multiple Sclerosis Functional Composite (MSFC) Score at Week 20

End point description:

The MSFC is a multidimensional clinical outcome measure which consists of three sub-tests; Timed 25-Foot Walk, 9-Hole Peg Test and Paced Auditory Serial Addition Test-3(PASAT-3). The Timed 25-Foot Walk is a quantitative measure of lower extremity function. The 9-Hole Peg Test is a quantitative measure of upper extremity (arm and hand) function. The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. Standardized results (Z-scores) of these sub-tests and the overall MSFC Z-score as an average of these three Z-scores was calculated. Higher Z-scores reflect better neurological function and a positive change from baseline indicates improvement. An increase in score indicates an improvement (range -3 to +3). Baseline was defined as the last measurement taken prior to the first dose of study drug (Week 0). The mITT analysis set was evaluable. Here, "n" signifies those subjects who were eva

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 20

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Z-score				
arithmetic mean (standard deviation)				
Baseline (Week 0) (n = 19) Change at Week 20 (n = 18)	0.001 (± 0.7215) 0.187 (± 0.4321)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Death, TEAEs Leading to Discontinuation

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Death, TEAEs Leading to Discontinuation

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a subject which does not necessarily have a causal relationship with the study drug. An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug or worsening of pre-existing medical condition, whether or not related to study drug. A serious adverse event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Treatment-emergent adverse events are defined as any AE with a start date on or after the date of first dose and within 28 days after the date of last dose in the current study. TEAEs include both Serious TEAEs and non-serious TEAEs.Safety Set.

End point type	Secondary

End point timeframe:

Baseline up to Week 25

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: subjects				
TEAEs	15			
Serious TEAEs	0			
TEAEs Leading to Death	0			
TEAEs Leading to Discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing Injection Site Reactions (ISRs)

End point title	Number of Subjects Experiencing Injection Site Reactions (ISRs)

End point description:

Treatment-emergent ISRs were defined as any ISR with a start date on or after the date of first dose and within 7 days after the date of last dose in the current study. Injection site reactions were identified as erythema, induration, pruritus, nodules and/or cysts, ecchymosis, pain and local edema. The SAF Analysis Set included all subjects who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 22

End point values	ATX-MS-1467			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: subjects	7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Week 25	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	ATX-MS-1467
Reporting group description: Subjects received ATX-MS-1467 50 microgram (mcg), 200 mcg and 800 mcg on Day 1, Day 15 and Day 29 respectively during the titration period followed by biweekly dose of ATX-MS-1467 800 mcg for 16 weeks during the treatment period.	

Serious adverse events	ATX-MS-1467		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	ATX-MS-1467		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Monocyte count decreased			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Monocyte percentage decreased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Neutrophil count increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Reticulocyte count decreased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Weight decreased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Fibroadenoma of breast subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 4		
Blood and lymphatic system disorders Eosinophilia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Neutrophilia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	5 / 19 (26.32%) 5		
Injection site haemorrhage subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

Injection site induration subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Injection site pruritus subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2 2 / 19 (10.53%) 2 2 / 19 (10.53%) 2		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Enterocolitis subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 2 / 19 (10.53%) 2 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Diffuse alopecia subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 2 / 19 (10.53%) 2		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Cervicitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vaginitis gardnerella			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2014	1) Removed the requirement for purified protein derivative skin test at Visit 1 (Screening) as part of the inclusion criteria. 2) Clarified the timeframe between the optional lumbar puncture at Visit 4 and Visit 5, and timing of Visit 15 lumbar puncture. 3) Deleted the laboratory parameter "cholinesterase".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported