Clinical trial results:
Randomized, double-blind, placebo-controlled, multicenter Phase 2 trial assessing the effect of IMU-838 on disease activity, as measured by magnetic resonance imaging (MRI), as well as safety and tolerability in patients with relapsing-remitting multiple sclerosis (RRMS)

Summary

EudraCT number	2018-001896-19
Trial protocol	BG DE RO
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	28 January 2023
First version publication date	28 January 2023

Trial information

Trial identification

Sponsor protocol code	P2-IMU-838-MS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03846219
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Immunic AG
Sponsor organisation address	Lochhamer Schlag 21, Graefelfing, Germany, 82166
Public contact	Chief Medical Officer, Immunic AG, +49 892500 79464, andreas.muehler@immunic.de
Scientific contact	Chief Medical Officer, Immunic AG, +49 892500 79464, andreas.muehler@immunic.de

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	Interim
Date of interim/final analysis	30 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 April 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Cohort 1 (i.e. the main trial):
Primary
• To evaluate the efficacy of 45 mg/day IMU-838 in the treatment of RRMS based on MRI assessments

Cohort 2 (i.e. the sub-trial):
Primary
• To obtain more efficacy and safety data of IMU-838 in patients with RRMS and to allow pharmacodynamic modelling of the dose response

Protection of trial subjects:

The trial was conducted in a manner consistent with all applicable regulatory authority and independent ethics committee regulations (e.g. International Council for Harmonisation [ICH] Guideline for Good Clinical Practice [GCP, CPMP/ICH/135/95], the Declaration of Helsinki [in its currently acknowledged version] as well as in keeping with applicable local law(s) and regulation(s).
Before any clinical trial-related activities were performed, the investigator (or authorized designee) reviewed the informed consent form and explained the study to the patient. The investigator ensured that the patient was fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical trial.
Further risk minimisation procedures included:
• specific inclusion and exclusion criteria which ensured that patients who presented with characteristics that may have increased the risk for an adverse outcome were excluded
• close monitoring for red blood cells in urine
• regular monitoring of liver enzymes
• a 1-week initiation dose at half-dose level.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	9 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Bulgaria: 67
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Ukraine: 168
Worldwide total number of subjects	269
EEA total number of subjects	101

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)	269
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 2 parts (Cohort 1 and Cohort 2). Recruitment for Cohort 1 started in January 2019 and ended September 2019; recruitment for Cohort 2 started November 2020 and ended December 2020.

Pre-assignment

Screening details:

In Cohort 1, 284 patients were screened, and 210 patients were randomised. All randomised patients were treated, except for 1 patient who withdrew consent.
In Cohort 2, 70 patients were screened. As 10 patients were not eligible and 1 patient withdraw withdrew consent before randomization, 59 patients were randomised and treated.

Period 1

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

Blinding implementation details:

Trial participants, treating and evaluating physicians (performed all standardised neurological examinations for the Expanded Disability Status Scale [EDSS], central magnetic resonance imaging (MRI) readers, and all other personnel directly involved in trial conduct were blinded to treatment assignments. The evaluating physician was also blinded to any clinical outcome or treatment change.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (MT): 30 mg IMU-838

Arm description:

Patients received once-daily oral doses of 30 mg IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the main treatment period (24 weeks), patients received once-daily oral doses of 30 mg IMU-838 (2 tablets of 15 mg) with an initiation dosing scheme of half the dose (1 tablet per day) during the first 7 days. Tablets were taken once daily in the morning in fasted state (no food after midnight, unrestricted intake of water was always allowed) and taken with one glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets were to be taken, these were to be taken at the same time.

Arm title	Cohort 1 (MT): 45 mg IMU-838

Arm description:

Patients received once-daily oral doses of 45 mg IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the main treatment period (24 weeks), patients received once-daily oral doses of 45 mg IMU-838 (2 tablets of 22.5 mg) with an initiation dosing scheme of half the dose (1 tablet per day) during the first 7 days. Tablets were taken once daily in the morning in fasted state (no food after midnight, unrestricted intake of water was always allowed) and taken with one glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets were to be taken, these were to be taken at the same time.

Arm title	Cohort 1 (MT): placebo

Arm description:

Patients received once-daily oral doses of 2 tablets of placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the main treatment period (24 weeks), patients received once-daily oral doses of placebo (2 tablets) with an initiation dosing scheme of half the dose (1 tablet per day) during the first 7 days. Tablets were taken once daily in the morning in fasted state (no food after midnight, unrestricted intake of water was always allowed) and taken with one glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets were to be taken, these were to be taken at the same time.

Arm title	Cohort 2 (MT): 10 mg IMU-838

Arm description:

Patients received once-daily oral doses of 10 mg IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the main treatment period (24 weeks), patients received once-daily oral doses of 10 mg IMU-838 (2 tablets of 5 mg) with an initiation dosing scheme of half the dose (1 tablet per day) during the first 7 days. Tablets were taken once daily in the morning in fasted state (no food after midnight, unrestricted intake of water was always allowed) and taken with one glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets were to be taken, these were to be taken at the same time.

Arm title	Cohort 2 (MT): placebo

Arm description:

Patients received once-daily oral doses of 2 tablets of placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the main treatment period (24 weeks), patients received once-daily oral doses of placebo (2 tablets) with an initiation dosing scheme of half the dose (1 tablet per day) during the first 7 days. Tablets were taken once daily in the morning in fasted state (no food after midnight, unrestricted intake of water was always allowed) and taken with one glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets were to be taken, these were to be taken at the same time.

Number of subjects in period 1[1]	Cohort 1 (MT): 30 mg IMU-838	Cohort 1 (MT): 45 mg IMU-838	Cohort 1 (MT): placebo
Started	71	69	69
Completed	69	65	64
Not completed	2	4	5
Consent withdrawn by subject	2	2	2
Adverse event, non-fatal	-	-	2
Fulfilled hepatoxicity stopping rules	-	2	1

Number of subjects in period 1[1]	Cohort 2 (MT): 10 mg IMU-838	Cohort 2 (MT): placebo
Started	47	12
Completed	45	11
Not completed	2	1
Consent withdrawn by subject	2	1
Adverse event, non-fatal	-	-
Fulfilled hepatoxicity stopping rules	-	-

Notes:

[1] - 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: 1 patient in Cohort 1 was randomised and enrolled, but not treated. Thus, this patient was not included in any analysis and is not reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (MT): 30 mg IMU-838
Reporting group description:	
Patients received once-daily oral doses of 30 mg IMU-838.	
Reporting group title	Cohort 1 (MT): 45 mg IMU-838
Reporting group description:	
Patients received once-daily oral doses of 45 mg IMU-838.	
Reporting group title	Cohort 1 (MT): placebo
Reporting group description:	
Patients received once-daily oral doses of 2 tablets of placebo.	
Reporting group title	Cohort 2 (MT): 10 mg IMU-838
Reporting group description:	
Patients received once-daily oral doses of 10 mg IMU-838.	
Reporting group title	Cohort 2 (MT): placebo
Reporting group description:	
Patients received once-daily oral doses of 2 tablets of placebo.	

Reporting group values	Cohort 1 (MT): 30 mg IMU-838	Cohort 1 (MT): 45 mg IMU-838	Cohort 1 (MT): placebo
Number of subjects	71	69	69
Age categorical Units: Subjects			
Age continuous Units: years			
median	38.0	36.0	37.0
full range (min-max)	18 to 55	21 to 51	21 to 55
Gender categorical Units: Subjects			
Female	40	50	46
Male	31	19	23

Reporting group values	Cohort 2 (MT): 10 mg IMU-838	Cohort 2 (MT): placebo	Total
Number of subjects	47	12	268
Age categorical Units: Subjects			
Age continuous Units: years			
median	37.0	36.5	
full range (min-max)	20 to 54	21 to 54	-
Gender categorical Units: Subjects			
Female	34	8	178
Male	13	4	90

End points

End points reporting groups

Reporting group title	Cohort 1 (MT): 30 mg IMU-838
Reporting group description:	
Patients received once-daily oral doses of 30 mg IMU-838.	
Reporting group title	Cohort 1 (MT): 45 mg IMU-838
Reporting group description:	
Patients received once-daily oral doses of 45 mg IMU-838.	
Reporting group title	Cohort 1 (MT): placebo
Reporting group description:	
Patients received once-daily oral doses of 2 tablets of placebo.	
Reporting group title	Cohort 2 (MT): 10 mg IMU-838
Reporting group description:	
Patients received once-daily oral doses of 10 mg IMU-838.	
Reporting group title	Cohort 2 (MT): placebo
Reporting group description:	
Patients received once-daily oral doses of 2 tablets of placebo.	
Subject analysis set title	Cohort 1 (MT): 30 mg IMU-838 (1.5 Tesla)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients received once-daily oral doses of 30 mg IMU-838. Only patients who were investigated using 1.5 Tesla MRI were included.	
Subject analysis set title	Cohort 1 (MT): 45 mg IMU-838 (1.5 Tesla)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients received once-daily oral doses of 45 mg IMU-838. Only patients who were investigated using 1.5 Tesla MRI were included.	
Subject analysis set title	Cohort 1+2 (MT): placebo (1.5 Tesla)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients who received once-daily oral doses of placebo in Cohorts 1 and 2 were combined. From Cohort 1 only patients who were investigated using 1.5 Tesla MRI and who were from the same sites that contributed to the Cohort 2 placebo were included.	

Primary: Difference between 45 mg/day IMU-838 and placebo in the cumulative number of combined unique active (CUA) MRI lesions

End point title	Difference between 45 mg/day IMU-838 and placebo in the cumulative number of combined unique active (CUA) MRI lesions[1]
End point description:	
MRI scans were assessed centrally and adhered to a standardized MRI protocol. Estimates were adjusted for baseline volume of T2 lesions, MRI field strength (1.5 or 3.0 Tesla), and baseline number of gadolinium enhancing (Gd+) lesions (0, ≥1) using a generalized linear model with a negative binomial distribution and a logarithmic link function. Log transformation of time from first investigational medicinal product (IMP) dose to date of last MRI assessment was used as offset term. Mainly due to the differing number of patients with 3.0 Tesla MRI examinations in each treatment arm, the statistical adjustments (to ensure comparability) for each individual comparison differed and hence the adjusted mean cumulative number of CUA MRI lesions in each arm (e.g. placebo) differed depending on the comparison (45 mg IMU-838 vs placebo or 30 mg IMU-838 vs placebo).	
End point type	Primary
End point timeframe:	
Up to Week 24.	

Notes:

[1] - 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: The pre-specified primary end point included only the comparison between 45 mg IMU-838 and placebo. The comparison of 30 mg IMU-838 with placebo was defined as key secondary end point.

End point values	Cohort 1 (MT): 45 mg IMU-838	Cohort 1 (MT): placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	69		
Units: Lesions				
arithmetic mean (confidence interval 95%)	2.4 (1.1 to 4.9)	6.3 (2.8 to 13.9)		

Statistical analyses

Statistical analysis title	Rate ratio

Statistical analysis description:

A generalized linear model with a negative binomial distribution and logarithmic link function was used to compare 45 mg IMU-838 with placebo. Log transformation of time from first IMP dose to date of last MRI assessment was used as offset term. H0: cumulative number of CUA MRI lesions up to Week 24 with 45 mg IMU-838 equal to or higher than that with placebo.

Comparison groups	Cohort 1 (MT): 45 mg IMU-838 v Cohort 1 (MT): placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [2]
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.64

Notes:

[2] - A one-sided alpha level of 0.1 was used.

Secondary: Difference between 30 mg/day IMU-838 and placebo in the CUA MRI lesions

End point title	Difference between 30 mg/day IMU-838 and placebo in the CUA MRI lesions[3]

End point description:

This was defined as key-secondary end point. MRI scans were assessed centrally and adhered to a standardised MRI protocol. Estimates were adjusted for baseline volume of T2 lesions, MRI field strength (1.5 or 3.0 Tesla), and baseline number of Gd+ lesions (0, ≥1) using a generalized linear model with a negative binomial distribution and a logarithmic link function. Log transformation of time from first IMP dose to date of last MRI assessment was used as offset term. Mainly due to the differing number of patients with 3.0 Tesla MRI examinations in each treatment arm, the statistical adjustments (to ensure comparability) for each individual comparison differed and hence the adjusted mean cumulative number of CUA MRI lesions in each arm (e.g. placebo) differed depending on the comparison (45 mg IMU-838 vs placebo or 30 mg IMU-838 vs placebo).

End point type	Secondary

End point timeframe:

Up to Week 24.

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: This key secondary end point included only the comparison between 30 mg IMU-838 and placebo. The comparison of 45 mg IMU-838 with placebo was defined as primary end point.

End point values	Cohort 1 (MT): 30 mg IMU-838	Cohort 1 (MT): placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: Lesions				
arithmetic mean (confidence interval 95%)	4.0 (2.2 to 7.2)	13.2 (6.6 to 26.4)		

Statistical analyses

Statistical analysis title	Rate ratio

Statistical analysis description:

A generalized linear model with a negative binomial distribution and logarithmic link function was used. Log transformation of time from first IMP dose to date of last MRI assessment was used as offset term.

Comparison groups	Cohort 1 (MT): placebo v Cohort 1 (MT): 30 mg IMU-838
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Generalized linear model
Parameter estimate	Rate ratio
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.53

Notes:

[4] - A hierarchical testing procedure with a one-sided alpha level of 0.1 was used.

Secondary: Between-treatment differences in the cumulative number of CUA MRI lesions

End point title	Between-treatment differences in the cumulative number of CUA MRI lesions[5]

End point description:

The cumulative number of CUA lesions was compared between 10 mg IMU-838 (from Cohort 2), 30 mg IMU-838 (from Cohort 1, only patients with 1.5 Tesla MRI examinations [for Cohort 1, 1.5 and 3.0 Tesla MRI examinations were allowed while in Cohort 2 only 1.5 Tesla MRI examinations were allowed]), 45 mg IMU-838 (from Cohort 1, only patients with 1.5 Tesla MRI examinations), and placebo (patients were combined from Cohorts 1 and 2, only patients with 1.5 Tesla MRI examinations). This endpoint was of primary interest.
MRI scans were assessed centrally and adhered to a standardised MRI protocol. Estimates were adjusted for baseline volume of T2 lesions and baseline number of Gd+ lesions (0, ≥1) using a generalized linear model with a negative binomial distribution and a logarithmic link function. Log transformation of time from first IMP dose to date of last MRI assessment was used as offset term.

End point type	Secondary

End point timeframe:

Up to Week 24.

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: To analyse this end point only patients with 1.5 Tesla MRI examinations were used excluding few patients from the arms defined in the baseline period. In addition, patients from Cohort 1 and Cohort 2 who received placebo were combined.

End point values	Cohort 2 (MT): 10 mg IMU-838	Cohort 1 (MT): 30 mg IMU-838 (1.5 Tesla)	Cohort 1 (MT): 45 mg IMU-838 (1.5 Tesla)	Cohort 1+2 (MT): placebo (1.5 Tesla)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46[6]	65	66	71
Units: Lesion				
arithmetic mean (confidence interval 95%)	5.9 (3.8 to 9.0)	1.4 (0.9 to 2.1)	1.7 (1.1 to 2.5)	5.8 (4.1 to 8.2)

Notes:

[6] - Value for 1 patient missing.

Statistical analyses

No statistical analyses for this end point

Secondary: Between-treatment differences in the cumulative number of new Gd+ lesions

End point title	Between-treatment differences in the cumulative number of new Gd+ lesions[7]

End point description:

The cumulative number of new Gd+ lesions was compared between 10 mg IMU-838 (from Cohort 2), 30 mg IMU-838 (from Cohort 1, only patients with 1.5 Tesla MRI examinations [for Cohort 1, 1.5 and 3.0 Tesla MRI examinations were allowed while in Cohort 2 only 1.5 Tesla MRI examinations were allowed]), 45 mg IMU-838 (from Cohort 1, only patients with 1.5 Tesla MRI examinations), and placebo (patients were combined from Cohorts 1 and 2, only patients with 1.5 Tesla MRI examinations). This end point was of primary interest.
MRI scans were assessed centrally and adhered to a standardised MRI protocol. Estimates were adjusted for baseline volume of T2 lesions and baseline number of Gd+ lesions (0, ≥1) using a generalized linear model with a negative binomial distribution and a logarithmic link function. Log transformation of time from first IMP dose to date of last MRI assessment was used as offset term.

End point type	Secondary

End point timeframe:

Up to Week 24.

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: To analyse this end point only patients with 1.5 Tesla MRI examinations were used excluding few patients from the arms defined in the baseline period. In addition, patients from Cohort 1 and Cohort 2 who received placebo were combined.

End point values	Cohort 2 (MT): 10 mg IMU-838	Cohort 1 (MT): 30 mg IMU-838 (1.5 Tesla)	Cohort 1 (MT): 45 mg IMU-838 (1.5 Tesla)	Cohort 1+2 (MT): placebo (1.5 Tesla)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	65	66	71
Units: Lesion				
arithmetic mean (confidence interval 95%)	4.0 (2.6 to 6.2)	1.0 (0.7 to 1.6)	1.2 (0.8 to 1.8)	4.6 (3.2 to 6.5)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to Week 24.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Cohort 1 (MT): 30 mg IMU-838
Reporting group description: Patients received once-daily oral doses of 30 mg IMU-838.	
Reporting group title	Cohort 1 (MT): 45 mg IMU-838
Reporting group description: Patients received once-daily oral doses of 45 mg IMU-838.	
Reporting group title	Cohort 1 (MT): placebo
Reporting group description: Patients received once-daily oral doses of 2 tablets of placebo.	
Reporting group title	Cohort 2 (MT): 10 mg IMU-838
Reporting group description: Patients received once-daily oral doses of 10 mg IMU-838.	
Reporting group title	Cohort 2 (MT): placebo
Reporting group description: Patients received once-daily oral doses of placebo.	

Serious adverse events	Cohort 1 (MT): 30 mg IMU-838	Cohort 1 (MT): 45 mg IMU-838	Cohort 1 (MT): placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 71 (2.82%)	0 / 69 (0.00%)	1 / 69 (1.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Open fracture			

subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2 (MT): 10 mg IMU-838	Cohort 2 (MT): placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 47 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Open fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			

subjects affected / exposed	0 / 47 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1 (MT): 30 mg IMU-838	Cohort 1 (MT): 45 mg IMU-838	Cohort 1 (MT): placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 71 (8.45%)	7 / 69 (10.14%)	8 / 69 (11.59%)
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	4 / 69 (5.80%)	4 / 69 (5.80%)
occurrences (all)	3	5	4
Infections and infestations			
Corona virus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 71 (4.23%)	5 / 69 (7.25%)	3 / 69 (4.35%)
occurrences (all)	5	7	4
Respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort 2 (MT): 10 mg IMU-838	Cohort 2 (MT): placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 47 (10.64%)	5 / 12 (41.67%)	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 47 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Infections and infestations			
Corona virus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 47 (8.51%)	3 / 12 (25.00%)	
occurrences (all)	4	3	
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 47 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 47 (2.13%)	1 / 12 (8.33%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2019	• 'Time to relapse at time of final analysis of main part' added as secondary efficacy endpoint. • 'Time to treatment discontinuation for any reason' and 'rate of treatment discontinuations up to Week 24' added as secondary safety endpoints. • Analysis of lymphocytes and estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration) added to the screening laboratory. • New malignancies were defined as important medical events that were to be reported as SAEs. • A positive HIV antigen /antibody test at Screening was to be followed up by further HIV testing based on NAAT. • The Week 24 MRI could be repeated if the initial MRI was not at least partially assessable.
28 August 2020	• A Cohort 2 sub-trial was added with the objective to obtain more data for pharmacodynamic modelling of IMU-838 by evaluating a lower IMU-838 dose in the presumed effective dose range, i.e. 10 mg/day IMU-838. • Added that special care must be taken if ibuprofen is used as concomitant medication and whenever possible therapeutic alternatives should be used. • Added that serum samples collected at Baseline, stored but not used for the primary analysis ("B-sample"), may be used in future research to evaluate other MS related serum markers (e.g. Epstein-Barr Virus) and address MS-related research questions that may arise after trial completion.
30 September 2021	• Added that patients in the extended treatment (ET) period may be transferred to a separate long-term follow-up trial or to commercial vidofludimus calcium (if applicable and patients have access). In this case the EMPhASIS trial will only be closed once all remaining patients in the extended treatment period have been transferred to the follow-up trial or commercial vidofludimus calcium. • The visit schedule in the ET period was changed from a 12-week schedule to a 24-week schedule. • Dosing in the ET period was switched from 45 mg IMU-838 to 30 mg IMU 838 (30 mg patients continue unchanged). • Because of a new manufacturing process, a revised IMU-838 formulation, i.e. IMU 838-RC, was introduced. • The procedure how compliance will be assessed during ET clarified. • The possibility to do safety interim analyses during the open-label part of the extended treatment period was included. • Sections on prohibited medication and restricted medications rewritten to adjust to revised recommendations given in the current investigator's brochure and to reduce redundancy with exclusion criteria. • New reasons for withdrawal, trial termination, and closing a centre were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35698927