Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents with Erythropoietic Protoporphyria or X-Linked Protoporphyria

Summary

EudraCT number	2019-004226-16
Trial protocol	NO SE GB DE FI IT
Global end of trial date	26 July 2022

Results information

Result version number	v1 (current)
This version publication date	15 July 2023
First version publication date	15 July 2023

Trial information

Trial identification

Sponsor protocol code	MT-7117-G01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04402489
WHO universal trial number (UTN)	-
Other trial identifiers	jRCT: jRCT2080225355

Notes:

Sponsors

Sponsor organisation name	Mitsubishi Tanabe Pharma America (MTPA), Inc.
Sponsor organisation address	525 Washington Boulevard, Suite 1100, Jersey City, United States, 07310
Public contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd, regulatory@mt-pharma-eu.com
Scientific contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd, regulatory@mt-pharma-eu.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002850-PIP02-21
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	26 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of MT-7117 on time to onset and severity of first prodromal symptoms (burning, tingling, itching, or stinging) associated with sunlight exposure in adults and adolescents with Erythropoietic Protoporphyria (EPP)or X-Linked Protoporphyria (XLP).

Protection of trial subjects:

The study was conducted in accordance with the 2013 (Fortaleza) revision of the Declaration of Helsinki, Good Clinical Practice as required by the International Council for Harmonisation guidelines, applicable regional and local legislation, and standard operating procedures (SOPs) in place at MTPA. Clinical monitoring at the investigational site(s) was delegated to the Contract Research Organization (CRO), along with the responsibility to conform to the CRO's ethical standards and SOPs.
An external independent Data Monitoring Committee was established to perform regular review of safety data to ensure the ongoing safety of participating subjects until the last subject completed the Double blind extension period.
A subject was withdrawn from study if ANY of the following criteria were met:
1. The subject requests to voluntarily withdraw from further participation in study.
2. The subject is significantly noncompliant with the protocol.
3. Continuing in the study would be detrimental to the subject's safety in the opinion of the Investigator, e.g.,
a. The subject experiences intolerable AEs, SAEs, or AESIs.
b. The subject has clinically significant changes in safety parameters at any of the post-dose time points, as confirmed with a repeat assessment performed as soon as possible after the initial out-of-range result.
c. The subject experiences any clinically significant adverse findings from postbaseline nevi evaluation and adverse change is demonstrated histologically and confirmed by central pathologist. Visual evaluation of change will not be acceptable criteria for permanent discharge from treatment.
d. Development of any clinically significant liver dysfunction, as follows:
i. ALT or AST >8 × ULN.
ii. ALT or AST >5 × ULN for more than 2 weeks.
iii. Elevated total bilirubin >2 × ULN and ALT or AST >3 × ULN or
iv. Symptoms consistent with liver dysfunction (e.g., fatigue, nausea, vomiting, abdominal pain or tenderne

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2020
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	Norway: 3
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Sweden: 5

Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	United States: 93
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 8
Worldwide total number of subjects	184
EEA total number of subjects	46

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)	37
Adults (18-64 years)	138
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A sufficient number of subjects were screened to ensure the planned sample size was achieved. Each subject were screened according to the criteria. Only subjects eligible for the study were randomized.

Pre-assignment

Screening details:

Subjects attended the screening visit (Visit 1) up to 6 weeks before Randomization (Visit 2), to confirm eligibility, obtain pre-study safety assessments including nevi evaluation, and to receive instruction on how to use the electronic sunlight exposure diary (SED).

Period 1

Period 1 title	26 weeks Double-Blind Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	MT-7117 matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning

Arm title	MT-7117 low dose

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MT-7117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning. Subjects received 1 tablet of MT-7117 and 1 tablet of matching placebo.

Investigational medicinal product name	MT-7117 matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning. Subjects received 1 tablet of
MT-7117 and 1 tablet of matching placebo.

Arm title	MT-7117 high dose
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	MT-7117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning.

Number of subjects in period 1	placebo	MT-7117 low dose	MT-7117 high dose
Started	61	63	60
Completed	57	60	58
Not completed	4	3	2
Consent withdrawn by subject	3	2	2
Physician decision	1	-	-
Adverse event, non-fatal	-	1	-

Period 2

Period 2 title	26 Weeks Double-Blind Extention
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo -> low dose MT-7117
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	MT-7117 matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning. Subjects received 1 tablet of MT-7117 and 1 tablet of matching placebo.

Investigational medicinal product name	MT-7117
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning. Subjects received 1 tablet of MT-7117 and 1 tablet of matching placebo.

Arm title	Placebo -> high dose MT-7117

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MT-7117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning.

Arm title	MT-7117 low dose

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MT-7117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning. Subjects received 1 tablet of MT-7117 and 1 tablet of matching placebo.

Investigational medicinal product name	MT-7117 matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning. Subjects received 1 tablet of
MT-7117 and 1 tablet of matching placebo.

Arm title	MT-7117 high dose

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MT-7117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 2 tablets of investigational medicinal product (IMP) with or without food each morning.

Number of subjects in period 2[1]	Placebo -> low dose MT-7117	Placebo -> high dose MT-7117	MT-7117 low dose
Started	28	28	56
Completed	27	28	55
Not completed	1	0	1
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	-	1
Lost to follow-up	1	-	-

Number of subjects in period 2[1]	MT-7117 high dose
Started	55
Completed	52
Not completed	3
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Lost to follow-up	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects took the offer to participate in a 6-month extension which all participants were on active drug but were double-blinded to dose starting immediately after the end of DBT period. Subjects who received MT-7117 during the DBT period continued the DBE in the same treatment arm and remained blinded. Subjects who received placebo were randomized to receive MT-7117 low or high dose in 1:1 ratio for the DBE period.

Baseline characteristics

Reporting groups	
Reporting group title	placebo
Reporting group description: -	
Reporting group title	MT-7117 low dose
Reporting group description: -	
Reporting group title	MT-7117 high dose
Reporting group description: -	

Reporting group values	placebo	MT-7117 low dose	MT-7117 high dose
Number of subjects	61	63	60
Age categorical Units: Subjects			
Adolescents (12-17 years)	12	13	12
Adults 18-65	47	45	46
>65	2	5	2
Age continuous Units: years			
arithmetic mean	34.1	33.5	34.4
standard deviation	± 15.6	± 17.1	± 15.3
Gender categorical Units: Subjects			
Female	30	30	33
Male	31	33	27

Reporting group values	Total		
Number of subjects	184		
Age categorical Units: Subjects			
Adolescents (12-17 years)	37		
Adults 18-65	138		
>65	9		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	93		
Male	91		

Subject analysis sets	
Subject analysis set title	DBT ITT1 Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included all randomized subjects who received at least 1 dose of study medication with Baseline and post randomization- sunlight exposure diary assessments during the double-blind treatment period.

Subject analysis set title	DBT ITT1 MT-7117 low dose
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included all randomized subjects who received at least 1 dose of study medication with Baseline and post randomization- sunlight exposure diary assessments during the double-blind treatment period.

Subject analysis set title	DBT ITT1 MT-7117 high dose
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included all randomized subjects who received at least 1 dose of study medication with Baseline and post randomization- sunlight exposure diary assessments during the double-blind treatment period.

Reporting group values	DBT ITT1 Placebo	DBT ITT1 MT-7117 low dose	DBT ITT1 MT-7117 high dose
Number of subjects	60	63	60
Age categorical Units: Subjects			
Adolescents (12-17 years)	11	13	12
Adults 18-65	47	45	46
>65	2	5	2
Age continuous Units: years			
arithmetic mean	34.4	33.5	34.4
standard deviation	± 15.6	± 17.1	± 15.3
Gender categorical Units: Subjects			
Female	29	30	33
Male	31	33	27

End points

End points reporting groups

Reporting group title	placebo
Reporting group description: -	
Reporting group title	MT-7117 low dose
Reporting group description: -	
Reporting group title	MT-7117 high dose
Reporting group description: -	
Reporting group title	Placebo -> low dose MT-7117
Reporting group description: -	
Reporting group title	Placebo -> high dose MT-7117
Reporting group description: -	
Reporting group title	MT-7117 low dose
Reporting group description: -	
Reporting group title	MT-7117 high dose
Reporting group description: -	
Subject analysis set title	DBT ITT1 Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Included all randomized subjects who received at least 1 dose of study medication with Baseline and post randomization- sunlight exposure diary assessments during the double-blind treatment period.	
Subject analysis set title	DBT ITT1 MT-7117 low dose
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Included all randomized subjects who received at least 1 dose of study medication with Baseline and post randomization- sunlight exposure diary assessments during the double-blind treatment period.	
Subject analysis set title	DBT ITT1 MT-7117 high dose
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Included all randomized subjects who received at least 1 dose of study medication with Baseline and post randomization- sunlight exposure diary assessments during the double-blind treatment period.	

Primary: Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 26 (Visit 7)

End point title	Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 26 (Visit 7)
End point description:	
End point type	Primary
End point timeframe:	
Week 26 (Visit 7)	

End point values	DBT ITT1 Placebo	DBT ITT1 MT-7117 low dose	DBT ITT1 MT-7117 high dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60	63	60	
Units: minute				
least squares mean (standard error)				
Least Square Mean (SE)	20.59 (± 10.29)	30.39 (± 10.04)	43.29 (± 10.13)	

Statistical analyses

Statistical analysis title	Change from BL at Week 26 (DBT EOT) - lower dose
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 low dose
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.496
Method	mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference vs Placebo
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.52
upper limit	38.12
Variability estimate	Standard error of the mean
Dispersion value	14.35

Statistical analysis title	Change from BL at Week 26 (DBT EOT) - higher dose
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 high dose
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.116
Method	mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference vs Placebo
Point estimate	22.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.68
upper limit	51.09
Variability estimate	Standard error of the mean
Dispersion value	14.38

Secondary: Patient Global Impression of Change (PGIC) at Week 26

End point title	Patient Global Impression of Change (PGIC) at Week 26

End point description:

End point type	Secondary

End point timeframe:

Week 26

End point values	DBT ITT1 Placebo	DBT ITT1 MT-7117 low dose	DBT ITT1 MT-7117 high dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	56	59	56	
Units: point				
least squares mean (standard error)	3.25 (± 1.14)	2.41 (± 0.14)	1.82 (± 0.14)	

Statistical analyses

Statistical analysis title	Patient Global Impression of Change at week26
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 high dose
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference vs Placebo
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	-1.03
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Patient Global Impression of Change at week26
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 low dose
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference vs Placebo
Point estimate	-0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	-0.44
Variability estimate	Standard error of the mean
Dispersion value	0.2

Secondary: Total number of sunlight-induced pain events defined as prodrome symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during the 26-week double-blind treatment period.

End point title	Total number of sunlight-induced pain events defined as prodrome symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during the 26-week double-blind treatment period.

End point description:

End point type	Secondary

End point timeframe:

During the 26-week double-blind treatment period

End point values	DBT ITT1 Placebo	DBT ITT1 MT-7117 low dose	DBT ITT1 MT-7117 high dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60	63	60	
Units: pain rating				
geometric mean (standard deviation)	23.90 (± 30.93)	15.87 (± 22.05)	13.78 (± 18.70)	

Statistical analyses

Statistical analysis title	Total number of sunlight-induced pain events
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 low dose
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.199
Method	see analysis type comment
Parameter estimate	incidence rate ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.16

Notes:
[1] - Negative binomial regression model with log link was used.

Statistical analysis title	Total number of sunlight-induced pain events
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 high dose
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.006
Method	see analysis type comment
Parameter estimate	incidence rate ratio
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.84

Notes:
[2] - Negative binomial regression model with log link was used.

Secondary: Change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26

End point title	Change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26

End point description:

End point type	Secondary

End point timeframe:
week 26

End point values	DBT ITT1 Placebo	DBT ITT1 MT-7117 low dose	DBT ITT1 MT-7117 high dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	59	56	
Units: total score				
least squares mean (standard error)	-1.42 (± 0.18)	-1.56 (± 0.16)	-1.65 (± 0.17)	

Statistical analyses

Statistical analysis title	Change from Baseline for Total Score in Pain
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 low dose

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference vs Placebo
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.24

Statistical analysis title	Change from Baseline for Total Score in Pain
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 high dose
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.343
Method	mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference vs Placebo
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.25

Secondary: The percentage of subjects who are responders

End point title	The percentage of subjects who are responders

End point description:

The percentage of subjects who are responders based on average daily sunlight exposure time to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset defined by within-subject meaningful change of 66 minutes increase from baseline to Week 26

End point type	Secondary

End point timeframe:

week 26

End point values	DBT ITT1 Placebo	DBT ITT1 MT-7117 low dose	DBT ITT1 MT-7117 high dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60	63	60	
Units: responders				
Change from baseline ≥66 minutes	12	11	16	

Statistical analyses

Statistical analysis title	Responder Rate
Comparison groups	DBT ITT1 MT-7117 low dose v DBT ITT1 Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.642
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.805
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.323
upper limit	2.007

Statistical analysis title	Responder Rate
Comparison groups	DBT ITT1 MT-7117 high dose v DBT ITT1 Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.431
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.598
upper limit	3.336

Secondary: Change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

End point title	Change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

End point description:

End point type	Secondary
End point timeframe: week 26	

End point values	DBT ITT1 Placebo	DBT ITT1 MT-7117 low dose	DBT ITT1 MT-7117 high dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	59	56	
Units: total score				
least squares mean (standard error)	0.67 (± 0.36)	1.54 (± 0.32)	1.22 (± 0.33)	

Statistical analyses

Statistical analysis title	Change from Baseline for Total Score in Physical
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 low dose
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072
Method	mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference vs Placebo
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	1.82
Variability estimate	Standard error of the mean
Dispersion value	0.48

Statistical analysis title	Change from Baseline for Total Score in Physical
Comparison groups	DBT ITT1 Placebo v DBT ITT1 MT-7117 high dose
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.252
Method	mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference vs Placebo
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.51

Variability estimate	Standard error of the mean
Dispersion value	0.48

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screening to Follow up.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1
Reporting groups	
Reporting group title	SAF1 Placebo
Reporting group description: -	
Reporting group title	SAF1 MT-7117 low dose
Reporting group description: -	
Reporting group title	SAF1 MT-7117 high dose
Reporting group description: -	
Reporting group title	SAF2 Placebo -> MT-7117 low dose
Reporting group description: -	
Reporting group title	SAF2 Placebo -> MT-7117 high dose
Reporting group description: -	
Reporting group title	SAF2 MT-7117 low dose
Reporting group description: -	
Reporting group title	SAF2 MT-7117 high dose
Reporting group description: -	

Serious adverse events	SAF1 Placebo	SAF1 MT-7117 low dose	SAF1 MT-7117 high dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 61 (0.00%)	2 / 63 (3.17%)	2 / 60 (3.33%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic			

disorders			
Porphyria non-acute			
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Meningitis viral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SAF2 Placebo -> MT-7117 low dose	SAF2 Placebo -> MT-7117 high dose	SAF2 MT-7117 low dose
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	1 / 56 (1.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Porphyria non-acute			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholestasis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Meningitis viral			
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SAF2 MT-7117 high dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 54 (3.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 54 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Porphyria non-acute			
subjects affected / exposed	0 / 54 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 54 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 54 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 54 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 54 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Meningitis viral			
subjects affected / exposed	0 / 54 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	SAF1 Placebo	SAF1 MT-7117 low dose	SAF1 MT-7117 high dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 61 (65.57%)	44 / 63 (69.84%)	44 / 60 (73.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	6 / 63 (9.52%)	8 / 60 (13.33%)
occurrences (all)	0	0	0
Dysplastic naevus	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	4 / 63 (6.35%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	3 / 63 (4.76%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	5 / 61 (8.20%)	3 / 63 (4.76%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
SARS-CoV-2 test positive	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Weight decreased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Vaccination complication	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Post vaccination syndrome	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 61 (3.28%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

Cardiac disorders			
Sinus bradycardia	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	3 / 61 (4.92%)	8 / 63 (12.70%)	9 / 60 (15.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	4 / 61 (6.56%)	3 / 63 (4.76%)	3 / 60 (5.00%)
occurrences (all)	0	0	0
Pyrexia	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	2 / 63 (3.17%)	3 / 60 (5.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	4 / 61 (6.56%)	4 / 63 (6.35%)	16 / 60 (26.67%)
occurrences (all)	0	0	0
Diarrhoea	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	5 / 63 (7.94%)	8 / 60 (13.33%)
occurrences (all)	0	0	0
Abdominal pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	1 / 63 (1.59%)	4 / 60 (6.67%)
occurrences (all)	0	0	0
Abdominal discomfort	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	1 / 63 (1.59%)	3 / 60 (5.00%)
occurrences (all)	0	0	0
Pigmentation lip	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	3 / 63 (4.76%)	1 / 60 (1.67%)
occurrences (all)	0	0	0
Dyspepsia	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	1 / 63 (1.59%)	2 / 60 (3.33%)
occurrences (all)	0	0	0

Vomiting	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 61 (3.28%)	1 / 63 (1.59%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Abdominal pain upper	Additional description: Number of occurrences for each event were not reportedin this study.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Frequent bowel movements	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	1 / 63 (1.59%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin discolouration	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	5 / 63 (7.94%)	6 / 60 (10.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation	Additional description: Number of occurrences for each event were not reportedin this study.		
subjects affected / exposed	1 / 61 (1.64%)	2 / 63 (3.17%)	7 / 60 (11.67%)
occurrences (all)	0	0	0
Ephelides	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	3 / 63 (4.76%)	4 / 60 (6.67%)
occurrences (all)	0	0	0
Acne	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	1 / 63 (1.59%)	3 / 60 (5.00%)
occurrences (all)	0	0	0
Hair colour changes	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	1 / 63 (1.59%)	3 / 60 (5.00%)
occurrences (all)	0	0	0
Photosensitivity reaction	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	6 / 61 (9.84%)	1 / 63 (1.59%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Solar lentigo	Additional description: Number of occurrences for each event were not reported in this study.		

subjects affected / exposed	0 / 61 (0.00%)	1 / 63 (1.59%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Pigmentation disorder	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	3 / 63 (4.76%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 61 (3.28%)	5 / 63 (7.94%)	1 / 60 (1.67%)
occurrences (all)	0	0	0
Upper respiratory tract infection	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	5 / 61 (8.20%)	1 / 63 (1.59%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Nasopharyngitis	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 61 (1.64%)	1 / 63 (1.59%)	1 / 60 (1.67%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	0
Vitamin D deficiency	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Iron deficiency	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 61 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	SAF2 Placebo -> MT-7117 low dose	SAF2 Placebo -> MT-7117 high dose	SAF2 MT-7117 low dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 28 (75.00%)	20 / 28 (71.43%)	34 / 56 (60.71%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	4 / 28 (14.29%)	3 / 28 (10.71%)	3 / 56 (5.36%)
occurrences (all)	0	0	0
Dysplastic naevus	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	3 / 28 (10.71%)	1 / 28 (3.57%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Alanine aminotransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
SARS-CoV-2 test positive	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	3 / 56 (5.36%)
occurrences (all)	0	0	0
Weight decreased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	2 / 56 (3.57%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Vaccination complication	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Post vaccination syndrome	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus bradycardia	Additional description: Number of occurrences for each event were not reported in this study.		

subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 28 (7.14%)	3 / 28 (10.71%)	2 / 56 (3.57%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	2 / 56 (3.57%)
occurrences (all)	0	0	0
Pyrexia	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 28 (3.57%)	5 / 28 (17.86%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Diarrhoea	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Abdominal pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Pigmentation lip	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Dyspepsia	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Vomiting	Additional description: Number of occurrences for each event were not reported in this study.		

subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper	Additional description: Number of occurrences for each event were not reportedin this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Frequent bowel movements	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin discolouration	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation	Additional description: Number of occurrences for each event were not reportedin this study.		
subjects affected / exposed	2 / 28 (7.14%)	3 / 28 (10.71%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Ephelides	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Acne	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Hair colour changes	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Solar lentigo	Additional description: Number of occurrences for each event were not reported in this study.		

subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Pigmentation disorder	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	7 / 28 (25.00%)	8 / 28 (28.57%)	11 / 56 (19.64%)
occurrences (all)	0	0	0
Upper respiratory tract infection	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	4 / 56 (7.14%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	3 / 28 (10.71%)	1 / 28 (3.57%)	3 / 56 (5.36%)
occurrences (all)	0	0	0
Iron deficiency	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	4 / 56 (7.14%)
occurrences (all)	0	0	0

Non-serious adverse events	SAF2 MT-7117 high dose		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 54 (59.26%)		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Dysplastic naevus	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Investigations			
Aspartate aminotransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	0		
Alanine aminotransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
SARS-CoV-2 test positive	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	0		
Weight decreased	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Vaccination complication	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Post vaccination syndrome	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Cardiac disorders			
Sinus bradycardia	Additional description: Number of occurrences for each event were not reported in this study.		

subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Nervous system disorders			
Headache	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	0		
Pyrexia	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Diarrhoea	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	0		
Abdominal pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Abdominal discomfort	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	0		
Pigmentation lip	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	0		
Dyspepsia	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Vomiting	Additional description: Number of occurrences for each event were not reported in this study.		

subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Abdominal pain upper	Additional description: Number of occurrences for each event were not reportedin this study.		
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	0		
Frequent bowel movements	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Skin discolouration	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Skin hyperpigmentation	Additional description: Number of occurrences for each event were not reportedin this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Ephelides	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Acne	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Hair colour changes	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Photosensitivity reaction	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Solar lentigo	Additional description: Number of occurrences for each event were not reported in this study.		

subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Pigmentation disorder	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Infections and infestations			
COVID-19	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	10 / 54 (18.52%)		
occurrences (all)	0		
Upper respiratory tract infection	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Nasopharyngitis	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	0 / 54 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		
Iron deficiency	Additional description: Number of occurrences for each event were not reported in this study.		
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2020	Amendment 1 V2.0. The main changes were: -reflect inclusion of adolescents. - Sample size of the study was increased due to statistical considerations. - Secondary and Exploratory efficacy endpoints were amended. -Additional demographic information will be collected. -Description of the subgroup analyses was added. -Description of prohibited or precautionary concomitant medications was amended. -Approved prohibited concomitant medications were revised.
08 June 2021	Amendment 2 v3.0. The main changes were: - One exploratory objective to investigate the effect of mutations in MClR gene on efficacy was added. - Study methodology was updated to clarify the randomization rule for subjects with adolescents and better clarify the schedule of assessments. -The language in Number of planned subjects was revised correctly considering the stratification rule with subjects under 45 kg body weight. - Exclusion criteria 11 was revised to specify the criteria to exclude more than stage 3a Chronic Kidney Disease patients based on eGFR, and the equations for calculating eGFR for adolescents were specified. - The language in Risk: Benefit statement was updated to include the new findings of non-clinical findings (pre- and postnatal development study in rats) and COVID-19 pandemic.
25 October 2021	Amendment 3.0 v4.0. v4.0 was replaced by Amendment 3.1 v4.1 and approved as a part of v4.1 which was non-substatial amendment. The main changes were: - Sponsor's UK representative address was added' -Increased number of patients and sample size estimation. -Withdrawal of Individual Subjects section was updated. -QP certification revised to define UK and EU certification. -Adverse Events of Special Interest section was updated. -Management and Evaluation of Hepatic Adverse Events of Special Interest section was defined in more detail. -An external independent Data Monitoring Committee (iDMC) will be established.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported