Clinical trial results:
A randomised, double-blind, placebo-controlled, dose-ranging Phase 2b study to investigate the efficacy and safety of MBS2320 with background methotrexate (MTX) in participants with moderate to severe active rheumatoid arthritis (RA) who have had an inadequate response to MTX alone

Summary

EudraCT number	2020-005496-13
Trial protocol	CZ PL BG
Global end of trial date	28 December 2023

Results information

Result version number	v1 (current)
This version publication date	03 April 2025
First version publication date	03 April 2025

Trial information

Trial identification

Sponsor protocol code	IST-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05460832
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Modern Biosciences Ltd.
Sponsor organisation address	2nd Floor, 3 Pancras Square, London, United Kingdom, N1C 4AG
Public contact	ist06@istesso.co.uk, Modern Biosciences Ltd., +44 207 444 0066, ist06@istesso.co.uk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2023
Global end of trial reached?	Yes
Global end of trial date	28 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of MBS2320 (5 mg once daily, 20 mg once daily, and 40 mg once daily) compared with placebo in participants with active Rheumatoid arthritis (RA) on stable background Methotrexate (MTX) who have had an inadequate response to MTX alone, with confirmed intra-articular (IA) synovitis on baseline magnetic resonance imaging (MRI)

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations. The investigator was responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or as otherwise specified by the IEC. The investigator promptly supplied the sponsor or its designee, the IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

Background therapy:

Participants had to be on a stable once-weekly MTX dose regimen (15 to 25 mg per week, either as an oral or parenteral dose) for at least 56 days prior to the baseline visit. Participants also had to be on a stable dose of folic acid (or equivalent) for at least 56 days prior to the baseline visit. The investigator monitored for MTX toxicity for the duration of the study and adjusted the dose according to current clinical guidelines. Participants continued their prescribed dosing regimen of MTX and folic acid (or equivalent) throughout the study. Participants were permitted to use oral corticosteroid background therapy for RA as prescribed by a physician, unless otherwise excluded (see below), as long as the doses were stable for at least 4 weeks prior to the baseline visit and the daily dose did not exceed 10 mg prednisolone (or equivalent). Participants were also permitted to use oral or topical (but not both) NSAID background therapy for RA or therapies for other conditions as prescribed by a physician, unless otherwise excluded (see below), as long as the doses were stable for at least 4 weeks prior to the baseline visit. Short-term (up to 7 total days) of NSAIDs or analgesics for other indications (e.g. headaches) were permitted during the study.

Evidence for comparator:

This study is placebo-controlled and placebo is used for comparator.

Actual start date of recruitment	25 July 2022
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Bosnia and Herzegovina: 8

Country: Number of subjects enrolled	Chile: 60
Country: Number of subjects enrolled	Guatemala: 30
Country: Number of subjects enrolled	Mexico: 80
Country: Number of subjects enrolled	Serbia: 16
Worldwide total number of subjects	248
EEA total number of subjects	54

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)	209
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 224 participants were planned to be enrolled into the 4 treatment groups (56 participants per group).

Pre-assignment

Screening details:

In total 414 participants were screened - 154 failed to meet inclusion/exclusion criteria and 12 withdrew consent during screening period.Remaining 248 participants were randomised and received at least one dose of either MBS2320 (186 participants: 62 randomised to 5 mg, 63 randomised to 20 mg and 61 randomised to 40 mg) or placebo (62 participants

Period 1

Period 1 title	Treatment period (overall period)
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	MBS2320 5 mg

Arm description:

MBS2320 5 mg once daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	MBS2320
Investigational medicinal product code	
Other name	Leramistat
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MBS2320 5 mg once daily for 12 weeks used as an adjunct therapy to MTX (15 to 25 mg per week, either as an oral or parenteral dose)

Arm title	MBS2320 20 mg

Arm description:

MBS2320 20 mg once daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	MBS2320
Investigational medicinal product code	
Other name	Leramistat
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MBS2320 20 mg once daily for 12 weeks used as an adjunct therapy to MTX (15 to 25 mg per week, either as an oral or parenteral dose)

Arm title	MBS2320 40 mg

Arm description:

MBS2320 40 mg once daily for 12 weeks

Arm type	Experimental

Investigational medicinal product name	MBS2320
Investigational medicinal product code	
Other name	Leramistat
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MBS2320 40 mg once daily for 12 weeks used as an adjunct therapy to MTX (15 to 25 mg per week, either as an oral or parenteral dose)

Arm title	Placebo

Arm description:

Matching placebo capsules were provided containing the same excipients as the MBS2320 capsules but minus the active drug. The dosing instructions were the same as for MBS2320.

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

Dosage and administration details:

Placebo once daily for 12 weeks used as an adjunct therapy to MTX (15 to 25 mg per week, either as an oral or parenteral dose)

Number of subjects in period 1	MBS2320 5 mg	MBS2320 20 mg	MBS2320 40 mg
Started	62	63	61
Completed	61	54	57
Not completed	1	9	4
Withdrawal of Consent	-	1	3
Study terminated	-	1	1
Physician decision	1	1	-
Consent withdrawn by subject	-	2	-
Disease progression	-	1	-
Randomised by mistake	-	1	-
Adverse event, non-fatal	-	2	-
Lost to follow-up	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Placebo
Started	62
Completed	57
Not completed	5
Withdrawal of Consent	3
Study terminated	-
Physician decision	-

Consent withdrawn by subject	-
Disease progression	-
Randomised by mistake	-
Adverse event, non-fatal	-
Lost to follow-up	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	MBS2320 5 mg
Reporting group description:	
MBS2320 5 mg once daily for 12 weeks	
Reporting group title	MBS2320 20 mg
Reporting group description:	
MBS2320 20 mg once daily for 12 weeks	
Reporting group title	MBS2320 40 mg
Reporting group description:	
MBS2320 40 mg once daily for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Matching placebo capsules were provided containing the same excipients as the MBS2320 capsules but minus the active drug. The dosing instructions were the same as for MBS2320.	

Reporting group values	MBS2320 5 mg	MBS2320 20 mg	MBS2320 40 mg
Number of subjects	62	63	61
Age categorical Units: Subjects			
Adults (18-64 years)	49	54	54
From 65-84 years	13	9	7
Age continuous Units: years			
median	54.0	55.0	53.0
full range (min-max)	21.0 to 73.0	23.0 to 73.0	25.0 to 75.0
Gender categorical Units: Subjects			
Female	52	59	54
Male	10	4	7

Reporting group values	Placebo	Total	
Number of subjects	62	248	
Age categorical Units: Subjects			
Adults (18-64 years)	52	209	
From 65-84 years	10	39	
Age continuous Units: years			
median	55.5		
full range (min-max)	22.0 to 73.0	-	
Gender categorical Units: Subjects			
Female	48	213	
Male	14	35	

End points

End points reporting groups

Reporting group title	MBS2320 5 mg
Reporting group description: MBS2320 5 mg once daily for 12 weeks	
Reporting group title	MBS2320 20 mg
Reporting group description: MBS2320 20 mg once daily for 12 weeks	
Reporting group title	MBS2320 40 mg
Reporting group description: MBS2320 40 mg once daily for 12 weeks	
Reporting group title	Placebo
Reporting group description: Matching placebo capsules were provided containing the same excipients as the MBS2320 capsules but minus the active drug. The dosing instructions were the same as for MBS2320.	

Primary: ACR20 response at Week 12

End point title	ACR20 response at Week 12
End point description: Participants who achieved composite clinical response at week 12 according to the criteria for ACR20	
End point type	Primary
End point timeframe: 12 weeks	

End point values	MBS2320 5 mg	MBS2320 20 mg	MBS2320 40 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	63	61	62
Units: percent				
number (confidence interval 95%)				
Successful ACR20Ic CCR Rate (%)	49.2 (36.1 to 62.3)	42.4 (28.7 to 56.1)	54.7 (41.4 to 68.0)	48.4 (34.8 to 62.0)

Statistical analyses

Statistical analysis title	Logistic Regression model
Statistical analysis description: Logistic regression model included treatment and prognostic categorical factors: baseline use of corticosteroids for RA and qualitative screening ACPA.	
Comparison groups	MBS2320 5 mg v MBS2320 40 mg v MBS2320 20 mg v Placebo

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.963
Method	Regression, Logistic
Parameter estimate	Difference in ACR20Ic CCR Rate (%)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.3
upper limit	16

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The safety profile of MBS2320 in this 12-week study was favourable, with all doses assessed being generally well tolerated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	MBS2320 5 mg
Reporting group description: -	
Reporting group title	MBS2320 20 mg
Reporting group description: -	
Reporting group title	MBS2320 40 mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	MBS2320 5 mg	MBS2320 20 mg	MBS2320 40 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	2 / 61 (3.28%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 61 (1.64%)
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			
Abscess limb			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from	0		

adverse events			
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 62 (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: 5 %

Non-serious adverse events	MBS2320 5 mg	MBS2320 20 mg	MBS2320 40 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 62 (25.81%)	8 / 63 (12.70%)	13 / 61 (21.31%)
Investigations			
Blood bicarbonate decreased			
subjects affected / exposed	4 / 62 (6.45%)	4 / 63 (6.35%)	0 / 61 (0.00%)
occurrences (all)	4	4	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	4
Urinary tract infection			
subjects affected / exposed	4 / 62 (6.45%)	4 / 63 (6.35%)	0 / 61 (0.00%)
occurrences (all)	4	4	0
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	8 / 62 (12.90%)	0 / 63 (0.00%)	5 / 61 (8.20%)
occurrences (all)	8	0	5

Non-serious adverse events	Placebo		

Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 62 (6.45%)		
Investigations Blood bicarbonate decreased subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0 0 / 62 (0.00%) 0		
Metabolism and nutrition disorders Metabolic acidosis subjects affected / exposed occurrences (all)	0 / 62 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2021	Protocol Version 1.0 - Original protocol
12 January 2023	Protocol Version 2.0 - This amendment made the following changes: • Updated the objectives and estimands to include participants with confirmed condition of IA synovitis on baseline MRI. • Updated the primary endpoint to add that the successful composite clinical response at Weeks 4 and 8 according to the criteria for ACR20 were to be achieved without discontinuing treatment due to tolerability issues or lack of efficacy or requiring any increase in RA medications. • Endpoint descriptions have been modified: o Addition of DAS28-hsCRP <3.2 at Weeks 4, 8, and 12. o Addition of change in CARLOS from baseline to Week 12. o Change in ACPA levels from screening to Week 12. • Inclusion criteria updated to include: o Acceptance of one repeat assessment for CRP as per the investigator's discretion if all other eligibility criteria were met. o Updates to the conditions for discontinuation of oral DMARDs for ≥8 weeks prior to baseline visit to include oral cyclosporine. o Updates to the language in the criteria for participants taking NSAIDs or acetaminophen. • Exclusion criteria updated to include: o Clarification on the clinically significant features of arthroses that could interfere with study assessments and objectives. o Updates to the language on male and female contraception. o The exclusion due to major surgery for RA within 56 days prior to the baseline visit was deleted. o History of other major surgery timelines were changed from screening to baseline. • Study design was updated to change the study intervention dosage instructions at home during study visits 3, 4 and 5. • Efficacy assessments had the following minor changes: o VAS value for measuring disease activity, arthritis pain, and assessment of health removed. o Included that the CARLOS determined by MRI will be assessed using a previously validated 9-point CARLOS scale. • Sample size summary was modified. • Changes made to the statistical analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported