Protocol Synopsis

Protocol Number: IST-06

Title: 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

Short Title (if applicable): Dose-Ranging Phase 2b Study of MBS2320 in Participants with Methotrexate-Refractory RA

Sponsor: Modern Biosciences Ltd
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Study Phase: 2b

Study Sites: approximately 45 to 55 sites globally

Indication: Rheumatoid arthritis

Rationale: The current treatment regimen for rheumatoid arthritis (RA) consists of initial treatment with non-steroidal anti-inflammatory drugs (NSAIDs), low-dose glucocorticoids, and non-biologic disease-modifying anti-rheumatic drugs (DMARDs) such as the immunosuppressant, methotrexate (MTX). Second and third-line therapy is increasingly focused on the biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), the most commonly used of which are anti-tumour necrosis factor (TNF) α agents such as adalimumab, infliximab, and etanercept and the Janus kinase (JAK) inhibitors such as tofacitinib, baricitinib, and upadacitinib. These agents have demonstrated their efficacy in reducing the signs and symptoms of disease and the inhibition of progression of

structural damage, but a high failure rate necessitates switching between agents. Furthermore, bDMARDs are associated with rare but serious side effects, including opportunistic infections such as tuberculosis (TB), invasive fungal infections, and malignancies such as lymphoma and tsDMARDs are associated with increased infections and cardiovascular events. In addition, neither the bDMARDs nor the tsDMARDs directly address the mechanism of structural damage; thus, the disability stemming from bone and joint destruction remains the most debilitating feature of the disease.

There is, therefore, scope for a new DMARD with a novel mechanism of action, greater safety, and a mode of action that not only prevents the inflammatory component of RA, but also provides a directly protective effect on bone.

MBS2320 is being developed for the once daily oral therapy of RA. Based on the non-clinical and clinical data generated to date, it is anticipated that MBS2320 can have a direct impact on structural damage in RA, in contrast to the current standard of care, and a reduced propensity for adverse events (AEs) arising from immunosuppression.

Objectives and Estimands:

Objectives	Estimand Description (Including Endpoint)
Primary Objective 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 RA on stable background MTX who have had an inadequate response to MTX alone, with confirmed intra-articular synovitis on baseline MRI.	**Primary Endpoint:** Composite clinical response (Success/Failure) at Week 12 defined as: • Achieving clinical response according to the criteria for ACR20: o ≥20% improvement in 68-TJC; o ≥20% improvement in 66-SJC; and o ≥20% improvement in at least 3 of the 5 following parameters: ▪ Physician's global assessment of disease activity ▪ Participant's global assessment of disease activity ▪ Participant's assessment of arthritis pain ▪ HAQ-DI

Objectives	Estimand Description (Including Endpoint)
	▪ hsCRP o Not discontinuing treatment due to tolerability issues or lack of efficacy; and o Not requiring any increase in RA medications - either in background medication dose (MTX) or any further alternative RA treatment or procedure. **Primary Estimand 1**: Difference in percentage of patients with moderate to severe active RA and a previous inadequate response to MTX alone, with confirmed intra-articular synovitis on baseline MRI, who would have a successful composite clinical response after 12 weeks of treatment with MBS2320 (5 mg, 20 mg, or 40 mg once daily) compared to placebo (each on top of stable background RA medication of weekly MTX). A successful composite clinical response is defined as achieving clinical response according to the criteria for ACR20 without discontinuing treatment due to tolerability issues or lack of efficacy or requiring any increase in RA medications, but irrespective of any interruptions required for treatment related reasons.
Key Secondary Objectives To evaluate the efficacy of MBS2320 (5 mg once daily, 20 mg once daily, and 40 mg once daily) compared with placebo on other clinical endpoints in participants with active RA on stable background MTX who have had an inadequate response to MTX alone, with confirmed intra-articular synovitis on baseline MRI.	**Endpoint:** Change in RAMRIS scores (synovitis, bone oedema, and bone erosion scores, measured with MRI) from baseline to Week 12. **Estimand 2A:** Difference in mean change from baseline in each RAMRIS score (synovitis, bone oedema, and bone erosion scores, measured with MRI), in patients with moderate to severe active RA and a previous inadequate response to MTX alone, with confirmed intra-articular synovitis on **Estimand 2B:** Difference in mean change from baseline in each RAMRIS score (synovitis, bone oedema, and bone erosion scores, measured with MRI), in patients with moderate to severe active RA and a previous inadequate response to MTX alone, with confirmed intra-articular synovitis on

Objectives	Estimand Description (Including Endpoint)	
	baseline MRI, assessed after 12 weeks of treatment with MBS2320 (5 mg, 20 mg, or 40 mg once daily) compared to placebo (each on top of stable background RA medication of weekly MTX), as though no increase in any RA medication and no treatment discontinuation or interruption for any reason.	baseline MRI, assessed after 12 weeks of treatment with MBS2320 (5 mg, 20 mg, or 40 mg once daily) compared to placebo (each on top of stable background RA medication of weekly MTX), irrespective of treatment discontinuation or interruption due to tolerability issues or lack of efficacy, and as though no increase in any other RA medication.
	Endpoint: Change in DAS28-hsCRP from baseline to Weeks 4, 8, and 12.	
	Estimand 3A: Difference in mean change from baseline in DAS28-hsCRP in patients with moderate to severe active RA with a previous inadequate response to MTX alone, with confirmed intra-articular synovitis on baseline MRI, after each of 4, 8, and 12 weeks of treatment with MBS2320 (5 mg, 20 mg, or 40 mg once daily) compared to placebo (each on top of stable background RA medication of weekly MTX), as though no increase in any RA medication and no treatment	**Estimand 3B:** Difference in mean change from baseline in DAS28-hsCRP in patients with moderate to severe active RA with a previous inadequate response to MTX alone, with confirmed intra-articular synovitis on baseline MRI, after each of 4, 8, and 12 weeks of treatment with MBS2320 (5 mg, 20 mg, or 40 mg once daily) compared to placebo (each on top of stable background RA medication of weekly MTX), irrespective of treatment discontinuation or interruption due to

Objectives	Estimand Description (Including Endpoint)	
	discontinuation or interruption for any reason.	tolerability issues or lack of efficacy, and as though no increase in any other RA medication.
	Endpoint: Composite clinical response (Success/Failure) at Weeks 4 and 8 defined as achieving clinical response according to the criteria for ACR20 without discontinuing treatment due to tolerability issues or lack of efficacy or requiring any increase in RA medications.	
	Estimand 4: Difference in percentage of patients with moderate to severe active RA with a previous inadequate response to MTX alone, with confirmed intra-articular synovitis on baseline MRI, who would have a successful composite clinical response after each of 4 and 8 weeks of treatment with MBS2320 (5 mg, 20 mg, or 40 mg once daily) compared to placebo (each on top of stable background RA medication of weekly MTX). A successful composite clinical response is defined as achieving clinical response according to the criteria for ACR20 without discontinuing treatment due to tolerability issues or lack of efficacy or requiring any increase in RA medications, but irrespective of any interruptions required for treatment related reasons.	
Other Secondary Objectives	**Endpoints**	
To evaluate the efficacy of MBS2320 (5 mg once daily, 20 mg once daily, and 40 mg once daily) compared with placebo on other clinical endpoints in participants with active RA on stable background MTX who have had an inadequate response to MTX alone, with confirmed	1. Percentage of participants achieving clinical response according to the criteria for ACR50 at Weeks 4, 8, and 12; 2. Percentage of participants achieving clinical response according to the criteria for ACR70 at Weeks 4, 8, and 12; 3. Change in hsCRP level compared to baseline at Weeks 4, 8, and 12; 4. Change in TJC (68 joints) compared to baseline at Weeks 4, 8, and 12;	

Objectives	Estimand Description (Including Endpoint)
intra-articular synovitis on baseline MRI.	5. Change in SJC (66 joints) compared to baseline at Weeks 4, 8, and 12; 6. Change in participant's assessment of arthritis pain (as measured on a 0 to 100 mm VAS) compared to baseline at Weeks 4, 8, and 12; 7. Change in participant's global assessment of disease activity (as measured on a 0 to 100 mm VAS) compared to baseline at Weeks 4, 8, and 12; 8. Change in physician's global assessment of disease activity (as measured on 0 to 100 mm VAS) compared to baseline at Weeks 4, 8, and 12; 9. Change in participant's global impression of change (as measured on a 7-point scale) compared to baseline at Weeks 4, 8, and 12; 10. Change in participant's global assessment of health (as measured on 0 to 100 mm VAS) compared to baseline at Weeks 4, 8, and 12; 11. Change in EULAR RAID score compared to baseline at Weeks 4, 8, and 12; 12. DAS28-hsCRP remission (i.e. DAS28-hsCRP <2.6) rate at Weeks 4, 8, and 12; 13. DAS28-hsCRP low disease activity rate (i.e. DAS28-hsCRP <3.2) at Weeks 4, 8, and 12; 14. EULAR response rate at Weeks 4, 8, and 12; 15. SDAI remission (i.e. SDAI score ≤3.3) rate at Weeks 4, 8, and 12; 16. CDAI remission (i.e. CDAI score ≤2.8) rate at Weeks 4, 8, and 12; 17. Change in fatigue score (FACIT-F) (as measured on a 5-point scale) compared to baseline at Weeks 4, 8, and 12; 18. Change in HAQ-DI scores compared to baseline at Weeks 4, 8, and 12; 19. Change in EQ-5D scores compared to baseline at Weeks 4, 8, and 12; 20. Change in CARLOS from baseline to Week 12.

Objectives	Estimand Description (Including Endpoint)
To evaluate the safety and tolerability of select MBS2320 doses (5 mg once daily, 20 mg once daily, and 40 mg once daily) compared with placebo in participants with active RA on stable background MTX who have had an inadequate response to MTX alone.	Incidence of TEAEs.
To evaluate steady-state plasma concentrations of MBS2320 and MBS2473.	MBS2320 and MBS2473 plasma concentrations (pre-dose at Weeks 4 and 12) and 3 (±1) hours postdose following last dose at Week 12 and at the EOS.
Exploratory Objectives	**Endpoints**
To evaluate the exploratory endpoints after treatment with MBS2320 (5 mg once daily, 20 mg once daily, and 40 mg once daily) and placebo in participants with active RA on stable background MTX who have had an inadequate response to MTX alone, with confirmed intra-articular synovitis on baseline MRI.	1. Change in exploratory biomarkers (which may include but will not be limited to: inflammatory cytokines, metabolites, and biomarkers of bone turnover) compared to baseline at Week 12; 2. Change in peripheral blood leucocyte phenotype (which may include but will not be limited to: flow cytometry, gene expression, and/or protein levels) compared to baseline at Weeks 4 and 12; 3. Change in ACPA levels from screening to Week 12; 4. Change in rheumatoid factor compared to baseline at Week 12. Other exploratory endpoints will be defined in the SAP.

ACPA=anti-citrullinated protein antibody; ACR20=American College of Rheumatology 20% response; ACR50=American College of Rheumatology 50% response; ACR70=American College of Rheumatology 70% response; CARLOS=cartilage loss; CDAI=clinical disease activity index; DAS28=disease activity score 28 joints; EOS=end of study; EQ-5D=EuroQoL-5 dimensions; EULAR=European League Against Rheumatism; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI=Health Assessment Questionnaire-Disability Index; hsCRP=high-sensitivity C-reactive protein; MRI=magnetic resonance imaging; MTX=methotrexate; RA=rheumatoid arthritis; RAID=Rheumatoid Arthritis Impact of Disease; RAMRIS=rheumatoid arthritis MRI scoring system; SAP=statistical analysis plan; SDAI=simplified disease activity index; SJC=swollen joint count; TEAE=treatment-emergent adverse event; TJC=tender joint count; VAS=visual analogue scale.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

Each participant must meet all the following criteria to be enrolled in this study:

1. Between 18 and 75 years of age, inclusive.
2. Diagnosed with RA based on either the 1987-revised American College of Rheumatology (ACR) classification criteria or the 2010 ACR/ European League Against Rheumatism (EULAR) criteria for ≥3 months prior to screening.
3. Has active RA as defined by the following minimum disease activity criteria:
    - ≥6 swollen joints (based on 66 joint counts) at screening and baseline visits.
    - ≥6 tender joints (based on 68 joint counts) at screening and baseline visits.
    - High-sensitivity C-reactive protein (hsCRP) > upper limit of normal reference range (ULN) at screening. One repeat assessment is acceptable for C-reactive protein per Investigator's discretion if all other eligibility criteria are met.
4. Considered to be inadequately responding to oral or parenteral MTX therapy for ≥3 months and <10 years prior to screening and to be tolerating a dose of 15 to 25 mg per week for at least 56 days prior to baseline visit. Participants should also be on a stable dose of folic acid (or equivalent) for at least 56 days prior to baseline visit. Participants should continue with their stable doses of MTX and folic acid throughout the study.
5. Except for MTX, must have discontinued all oral DMARDs prior to baseline visit as specified below or for at least 5 half-lives of a drug, whichever is longer:
    - ≥4 weeks prior to baseline visit for minocycline, D-penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, oral or parenteral gold formulations.

- ≥8 weeks prior to baseline visit for leflunomide (if no elimination procedure was followed or adhere to a washout procedure i.e. 11 days washout with cholestyramine or 30 days washout with activated charcoal) and for oral cyclosporine.
- ≥24 weeks prior to the baseline visit for cyclophosphamide.

6. Negative test for TB by QuantiFERON-TB Gold In-Tube test. Indeterminate results may be repeated and if negative or still indeterminate, participant may be included in the study if they have no clinical symptoms of TB, have had no known exposure to TB, and have had a negative chest X-ray within previous 3 months.
7. If participants are taking NSAIDs or acetaminophen for stable medical conditions, they should be receiving these medications at a stable dose for at least 4 weeks prior to baseline visit and the doses of the medications should be kept stable throughout the study. If participants are taking non-steroidal anti-inflammatory drugs, acetaminophen, tramadol, codeine, hydrocodone, and propoxyphene on a need basis, these drugs should not be taken 24 hours prior to any study visit.
8. If participants are taking oral corticosteroids (equivalent to prednisolone ≤10 mg), or inhaled corticosteroids, they should be receiving these medications at a stable dose for at least 4 weeks prior to baseline visit for stable medical conditions. The doses of the medications should be kept stable throughout the study. Oral and inhaled corticosteroids taken as needed are allowed but may not be taken 24 hours prior to any study visit.
9. Willing to provide written informed consent to participate in the study and to abide by the study restrictions.

Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

Medical Conditions:

1. Abnormality in heart rate or blood pressure at screening that in the opinion of the Investigator increases the risk of participating in the study.
2. Abnormality in the 12-lead electrocardiogram (ECG) at screening that in the opinion of the Investigator increases the risk of participating in the study.
    - Specific exclusion criteria are participants with QT interval corrected for heart rate using Fridericia's formula (QTcF) of >450 ms (males) or >460 ms (females) and participants with PR interval of >220 ms at screening (1 repeat assessment is allowed).
3. Significant history of drug allergy, including to MBS2320 or excipients, as determined by the Investigator.
4. Allergic reaction, anaphylaxis, or other reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis or leukopenia) to sulphonamides drugs.
5. Any clinically significant neurological, gastrointestinal (GI), renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, haematological, ophthalmic, or other major disorder which in the opinion of the Investigator would put the participant at risk by participating in the study (except for RA or disorders associated with RA that, in the Investigator’s opinion, do not constitute a risk when taking the investigational product (IP) and would not interfere with the study objectives).
6. Any current malignancy or a history of malignancy within 5 years prior to screening, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma *in situ*.
7. Any other inflammatory or arthritic disease in addition to RA that may interfere with the study (such as fibromyalgia, polymyalgia rheumatica, giant-cell arteritis, reactive arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis).

8. Active infection that is clinically significant, in the Investigator's opinion, or any infection requiring hospitalisation or treatment with intravenous antimicrobials ≤60 days of screening, or any infection requiring oral antimicrobial therapy ≤2 weeks of the baseline visit.
9. Clinically significant features of arthroses that could interfere with study assessments and objectives.
10. History of alcoholic hepatitis or non-alcoholic steatohepatitis.
11. History of opportunistic, chronic, or recurrent infections.

Prior/Concomitant Therapy

12. A live virus vaccination within the 90 days prior to baseline visit (1 year for Bacillus Calmette-Guerin vaccination) or intend to receive a live virus vaccination during the study or within 28 days after study completion.
13. Prior exposure to any JAK inhibitor, investigational or approved, (e.g. tofacitinib, baricitinib, upadacitinib, filgotinib).
14. Prior exposure to any biologic RA therapy, investigational or approved, (e.g. abatacept, rituximab, anakinra or tocilizumab, anti-TNFα agents [including, but not limited to, infliximab, adalimumab, golimumab, and biosimilars thereof]) or any approved or investigational monoclonal antibody or recombinant protein therapy
15. Prosorba column treatment within 60 days prior to baseline visit.
16. Current or expected need of other immunosuppressant medications including >10 mg oral prednisolone/day or equivalent corticosteroid therapy (see inclusion criterion 8). Use of MTX as described in Inclusion Criteria 4 is permitted.
17. Any intravenous, intramuscular, or intra-articular corticosteroids within 30 days prior to baseline visit or expected to require parenteral corticosteroid through the study.
18. High potency opiates including (but not limited to): oxycodone, oxymorphone, fentanyl, levorphanol, buprenorphine, methadone, hydromorphone, and morphine within 4 weeks prior to baseline visit.

19. Oral bisphosphonates within 6 months prior to baseline visit or once-a-year intravenous bisphosphonates within 1 year prior to baseline visit.
20. Any prior use of denosumab.
21. Use of strong cytochrome P450 3A4 inhibitors/inducers within 30 days or 5 half-lives, whichever is longer, prior to baseline visit.
22. Use of uridine 5'-diphospho-glucuronosyltransferase family 2 member B7 inhibitors within 30 days or 5 half-lives, whichever is longer, prior to baseline visit.
23. Systemically administered carbonic anhydrase inhibitors within 30 days or 5 half-lives, whichever is longer, prior to baseline visit.
24. Any prior use of cytotoxic agents for indications other than RA (including, but not limited to, chlorambucil, nitrogen mustard, or other alkylating agents).

Prior/Concurrent Clinical Study Experience

25. Participation in another clinical study (including attending follow-up visits) or receipt of any investigational drug of chemical or biologic nature within a minimum of 90 days or 5 half-lives of the drug (whichever is longer) prior to baseline visit.
26. Previously received MBS2320.

Diagnostic Assessments

27. Chest X-ray within 90 days prior to baseline visit that shows an abnormality suggestive of malignancy, current infection, or old inactive TB.
28. Screening laboratory values meeting the following criteria:
    - Serum aspartate aminotransferase or alanine aminotransferase >1.2 × ULN OR total bilirubin >1.5 × ULN;
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula ≤60 mL/min/1.73 m²;
    - Total white blood cell count <3,000/µL;
    - Absolute neutrophil count <1,500/µL;

- Platelet count <100,000/µL;
- Absolute lymphocyte count <800/µL;
- Haemoglobin <9 gm/dL.

Note: One repeat assessment is acceptable (not including any laboratory findings that in the Investigator's opinion are consistent with a diagnosis of RA).

29. Positive serology results for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb), hepatitis C (HCV) antibody with positive confirmatory test for HCV (eg polymerase chain reaction [PCR]), or human immunodeficiency virus (HIV) antibody at the screening visit.

    Note: Participants with a positive HBcAb and a negative HBsAg can be included in this study if hepatitis B surface antibody (HBsAb) is positive (considered immune after a natural infection). Participants with negative confirmatory test for HCV can be included in this clinical study.

Other Exclusions

30. Female who is pregnant or breastfeeding.
31. Non-sterilized male participants who:
    - do not agree to use appropriate contraception (e.g. a condom with spermicidal foam/gel/film/cream) with their partners of childbearing potential or partners sterilised by tubal ligation.
    - do not agree to refrain from donating sperm from the time of the first dose until 90 days after the final dosing occasion.
32. Female participants of childbearing potential who do not agree to use a highly effective method of birth control (e.g. contraceptive measure with a failure rate of <1% per year) in conjunction with male contraception (i.e. a condom with spermicidal foam/gel/film/cream) from the time of the first dose until 90 days after the final dosing occasion.
33. Donated blood in the 90 days prior to screening.

34. Significant history of alcoholism or drug/chemical abuse within 1 year prior to screening, as determined by the Investigator.
35. Surgery for RA (e.g. synovectomy, arthroplasty) within 90 days prior to baseline visit, previous joint replacement surgery, or surgery for RA planned during the study.
36. History of other major surgery (requiring regional block or general anaesthesia) within 3 months prior to baseline or planned surgery during the study.
37. Prior GI surgeries or any GI procedures/conditions that may cause concerns with absorption of the IP.
38. Risk factors for severe coronavirus disease 2019, which in the opinion of the Investigator would put the participant at risk by participating in the study.

Study Design:

This is a randomised, double-blind, multicentre, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and tolerability of MBS2320 with background MTX in participants with moderate to severe RA who have had an inadequate response to MTX alone.

Approximately 224 participants will be enrolled in 4 cohorts (56 participants each) across approximately 45 to 55 sites globally. Participants will be randomly assigned in 1:1:1:1 ratio to receive 1 of 3 doses of MBS2320 (5 mg, 20 mg, or 40 mg) or placebo.

The study will include 3 periods: 1) Screening Period (up to 4 weeks); 2) Treatment Period (12 weeks); and 3) Follow-up Period (6 weeks).

All prospective participants will sign and date the informed consent form (ICF) prior to any study assessments or procedures. Potential participants will be assessed as per the eligibility criteria at screening. After completing all screening assessments, participants who meet all the inclusion criteria and none of the exclusion criteria will proceed to the Treatment Period.

On Day 1 (Baseline Visit), participants will have to visit the study site having fasted for at least an 8-hour period to allow for the collection of exploratory biomarker samples in the

fasted state. After confirming a participant's eligibility, they will be randomly assigned to receive either MBS2320 (5 mg, 20 mg, or 40 mg) or placebo. Dosing will be once daily. All participants will be administered their first dose of IP with food and a glass of water at the study site.

Following administration of first dose of MBS2320 or placebo and before leaving the site, each participant will be given a card to carry at all times in case of an emergency outside the site. The card gives details of the study number, start and end date of the participant's involvement in the study, participant details, name of the relevant study physician, and the address and telephone number of the site. Participants may destroy this card 4 weeks after they have completed the study.

Investigational product, sufficient to last until the next visit will be dispensed to the participant. Participants will be instructed to self-administer the IP once daily in the morning, with food. If participant does not take a dose of IP within +12 hours of their regular dosing time, then the dose of IP should be skipped, and the participant should be instructed to take the IP at the next regularly scheduled time.

Participants will have to visit the study site at Week 4 (Day 28±3 days), Week 8 (Day 56±3 days), and Week 12 (Day 84±3 days) for study assessments. Participants will be instructed NOT to take their morning dose of IP at home every time they attend a study visit on Visits 3, 4, and 5. At Week 12 visit, the participants will arrive at the study site having fasted for at least an 8-hour period to allow for the collection of exploratory biomarker samples in the fasted state.

The Week 12 visit will constitute the End-of-Treatment (EOT) Visit. Participants will complete a 6-week Follow-up Period after the last dose of IP. The Week 18 visit will constitute the End-of-Study (EOS) Visit.

The maximum duration of study participation for a participant will be 22 weeks (approximately 154 days), which consists of a Screening Period of up to 4 weeks (28 days), Treatment Period of 12 weeks (84 days), and a Follow-up Period of 6 weeks (42 days).

The start of the study is defined as the date the first participant signs the ICF. The end of the study is defined as the date of the last participant's last assessment (scheduled or unscheduled).

Duration of Treatment: 12 weeks

Efficacy Assessments:

Swollen/Tender Joint Count

An assessment of 66 joints for swelling and 68 joints for tenderness will be made by the independent Joint Assessor. Joints will be assessed and classified as swollen/not swollen and tender/not tender (by pressure and joint manipulation) on physical examination. Joint prosthesis, arthrodesis, or fused joints will not be taken into consideration for swelling or tenderness. Confirmation of the joints to be assessed for swelling and tenderness will be provided to the participating sites.

The assessment of swollen and tender joints will also be used for the ACR clinical response assessment and the 28-joint count required for the DAS28-hsCRP, simplified disease activity index (SDAI), and clinical disease activity index (CDAI) scores.

Participant's Global Assessment of Disease Activity

The participant's overall assessment of their current disease activity will be measured on a visual analogue scale (VAS). The left-hand extreme of the line should be described as "very well" (no arthritis symptoms) and the right-hand extreme as "very poor" (maximum arthritis disease activity).

Physician's Global Assessment of Disease Activity

The physician's assessment of the participant's current disease activity will be measured on a VAS. The left-hand extreme of the line should be described as "no arthritis activity" and the right-hand extreme as "extremely active arthritis". This should be completed by the identified experienced Investigator.

Participant's Assessment of Arthritis Pain

The participant's assessment of their current level of arthritis pain will be measured on a VAS. The left-hand extreme of the line should be described as "no pain" and the right-hand extreme as "worst possible pain".

Participant's Global Assessment of Health

The participant will rate their general health within the context of their RA and how they are doing on a VAS. The left-hand extreme of the line should be described as "very well" and the right-hand extreme as "extremely bad".

Participant's Global Impression of Change Scale

The participant's assessment of the change (if any) in activity, limitations, symptoms, emotions, and overall quality of life (QoL) related to their condition will be assessed using a 7-point scale, where 1 = No change (or condition has got worse) and 7 = A great deal better, and a considerable improvement that has made all the difference.

European League Against Rheumatism RA Impact of Disease

The participant's assessment of disease impact with respect to pain, functional disability assessment, fatigue, sleep, physical well-being, emotional well-being, and coping will each be assessed using a 10-point scale, where higher values indicate worse status.

Health Assessment Questionnaire - Disability Index

The Stanford Health Assessment Questionnaire - Disability Index (HAQ-DI) is a participant-completed questionnaire specific for RA. It consists of 20 questions referring to 8 component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. The questionnaire will be provided in validated translation into the local languages at the participating sites and will be scored based on the instructions from the Stanford University Medical Center.

EuroQoL 5-Dimension

EuroQoL 5-Dimension (EQ-5D) is an instrument that evaluates the generic QoL. The EQ-5D consists of 1 question for each of the 5 dimensions that include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D questionnaire also includes a VAS (EQ VAS), by which participants can report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status).

Functional Assessment of Chronic Illness Therapy-Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale will be used to assess fatigue. This is a 13-item questionnaire, in which participants are requested to score each question on a 0-4 scale. The FACIT-F assessment was originally developed for chronic illnesses and is now validated for patients with RA.

High-Sensitivity C-Reactive Protein

Blood samples for hsCRP analysis will be taken by venepuncture or cannulation.

Results from the same hsCRP samples will be used for both efficacy (ACR clinical response and DAS28-hsCRP and SDAI scores) and PD assessments.
Note: Participants, Investigators, and the Sponsor will be kept blinded to the results of the hsCRP results from randomisation to EOS.

Magnetic Resonance Imaging

All enrolled participants will have the magnetic resonance imaging (MRI) scans to capture images of their worst affected hand and wrist performed at the Week 0 (Day 1/Baseline Visit) and Week 12 visit.

All images will be sent to an independent blinded central MRI reading facility for review and scoring. Two independent readers will assess bone erosion, bone oedema (osteitis), and synovitis by means of the Outcome Measures in Rheumatology Clinical Trials group

semi-quantitative RA-MRI scoring system (RAMRIS). Cartilage loss (CARLOS) determined by MRI will be assessed using a previously validated 9-point CARLOS scale.

Safety Assessments:

Safety variables will include assessment of concomitant medications, physical examination findings, ophthalmological assessments including slit-lamp examination, vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), chest X-ray, ECG tracings, clinical laboratory test results (haematology, serum chemistry, urinalysis, and pregnancy test), weight, body mass index, and reporting of AEs.

Pharmacokinetic Assessments

Blood samples (approximately 2 mL per time point) for the determination of plasma concentrations of MBS2320 and MBS2473 will be taken at the following time points:

- Pre-dose at Weeks 4 and 12,
- 3 (±1) hours postdose following last dose at Week 12, and
- At EOS visit.

The actual date and time (24-hour clock time) of each sampling as well as the time and date of the last dose immediately prior to sampling will be recorded.

Pharmacodynamic and Biomarker Assessments

Anti-Citrullinated Peptide Antibody

Blood samples for anti-citrullinated peptide antibody (ACPA) analysis will be taken at screening and at Week 12 (EOT) visit.

Rheumatoid Factor

Blood samples for rheumatoid factor analysis will be taken at screening and at Week 12 (EOT) visit.

Peripheral Blood Leucocyte Phenotype

Blood samples for evaluating peripheral blood leucocyte phenotype will be taken on Day 1 and at Week 4 and Week 12 (EOT) visits but may be subject to change based on the ongoing review of the data.

Analysis will include but will not be limited to flow cytometry and/or protein levels.

Gene Expression

Blood samples for gene expression analysis will be taken on Day 1 and at Week 4 and Week 12.

Exploratory Biomarkers

Blood samples for exploratory analysis will be taken on Day 1 and at Week 12 (EOT) visit but may be subject to change based on the ongoing review of the data.

Exploratory analysis will include but will not be limited to inflammatory cytokines, metabolites, and biomarkers of bone turnover.

Pharmacogenomic Assessments

A blood sample for pharmacogenomics analysis will be taken on Day 1.

Details of Applicable Monitoring Committee:

Not applicable.

Investigational Product, Dosage, and Route of Administration:

The IP will be presented in a capsule formulation containing immediate release powder of active drug (MBS2320) or placebo. All capsules will be identical in size and colour (opaque white) and contain MBS2320 at unit doses of 5 mg, 20 mg, or 40 mg, or placebo. The excipients used in MBS2320 comprise standard compendial pharmaceutical excipients: sorbitol, sodium lauryl sulphate, and magnesium stearate. On each dosing occasion, participants will swallow 1 capsule whole with food and a glass of water (approximately 250 mL). Participants will be instructed to contact the Investigator in case they experience emesis after dosing. Any episode of emesis after dosing will be reported as an AE and is to be managed with anti-emetics, as advised by the Investigator. The IP dose should not be repeated if emesis occurs after dosing and the participant should be instructed to take the IP at the next regularly scheduled time.

Sample Size:

This study has been powered assuming that 180 participants (approximately 45 per treatment arm) with confirmed IA synovitis at baseline provide an ACR20 composite clinical endpoint at Week 12; this would provide 80% power to detect a difference between placebo (assuming 35% response) versus MBS2320 (assuming 65% response) using a two-sided 5% significance level. Thus, it is anticipated that approximately 224 participants will be randomized which allows for a loss of 20% which may be due to unconfirmed IA synovitis, treatment discontinuation due to reasons unrelated to tolerability or worsening disease or for an unknown reason (loss to follow up without prior related intercurrent events). Note that participants who either discontinue treatment due to tolerability issues or require further treatment or increases in RA medication due to worsening disease do provide an ACR20 composite clinical endpoint (treatment failure) even if they do not provide study data at Week 12.

Statistical Methods:

The following analysis sets will be used in the statistical analyses.

Enrolled Set	The enrolled set will consist of all participants who sign the ICF.
Safety Set	The safety set will consist of all participants who receive at least 1 dose of MBS2320 or placebo. All analyses using the safety set will group participants according to the treatment they actually receive.
Full Analysis Set (FAS)	The FAS will consist of all randomised participants whether or not they experienced significant protocol deviations affecting evaluation of the endpoints. All analyses using the FAS will group participants according to the randomised treatment.
Modified Full Analysis Set (mFAS)	The mFAS will consist of all randomised and eligible participants with confirmed intra-articular synovitis on baseline MRI in FAS (grouped according to randomised treatment). The mFAS applies analysis flags to censor data after certain intercurrent events: Flag P: Censors data after discontinuation or interruption of treatment for unrelated reasons (i.e. due to logistical issues or AEs due to an unrelated medical condition not considered to be due to treatment or the underlying RA disease) and resulting in >20% reduction in treatment administered during the approximately 4-week period since last visit. If treatment is resumed following an interruption, then subsequent data may be included provided at least 80% of treatment is taken during the previous 4-week period. This will be particularly useful for targeting Estimands 1 and 4. Flag A: Censors data after discontinuation or interruption of treatment for any reason or any increase in RA medications and will be particularly useful for targeting hypothetical estimands (Estimands 2A and 3A). Only interruptions resulting in >20% reduction in treatment administered during the approximately 4-week period since last visit are considered relevant; for shorter interruptions, all resulting data are selected. If treatment is resumed following an interruption, then subsequent data may be included provided at least 80% of treatment is taken during the previous 4-week period. Flag B: Censors data after discontinuation of treatment for unrelated reasons or any increase in RA medications and will be particularly useful for targeting the 'partially' hypothetical estimands (Estimands 2B and 3B). Interruptions for unrelated reasons are handled in the same way as Flag P.

Pharmacokinetics (PK) Set	The PK set will consist of all participants who receive at least 1 dose of MBS2320 and have at least 1 evaluable PK concentration. Analyses using the PK population will group participants according to treatment received.

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarised using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions will be described in the statistical analysis plan (SAP). All statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% (2-sided) confidence intervals (CIs), unless indicated otherwise.

Analysis of Primary Efficacy Endpoint

Main Estimation of Primary Efficacy Estimand 1

The primary efficacy estimand is the absolute difference between each of the 3 different doses of MBS2320 and placebo in the percentage of participants who would achieve successful composite clinical response at Week 12 (which assumes failure for those who have any increase in RA medications or treatment discontinuation due to lack of efficacy or tolerability issues). The primary efficacy estimand will be estimated using a logistic regression model and the delta method, with the stratification factors and treatment as factors using the mFAS (Flag P). Missing data will not be imputed and are assumed missing completely at random (MCAR).

Sensitivity Analysis of Primary Efficacy Estimand 1

In the sensitivity analysis of the primary efficacy estimand, multiple imputation (MI) assuming missingness at random (MAR) will be used to impute any missing component of the composite clinical response at Weeks 4, 8, and 12, and then to derive the composite

outcomes. The logistic model will be fitted to each multiply imputed data set and the estimates of difference in percentages and standard error (SE) from the delta method will be pooled using Rubin's method. The overall difference of each dose relative to placebo will be presented with *P* value.

Also, in order to further study the successful composite clinical response profile across active doses, an additional sensitivity analysis will be conducted for studying the dose response relationship among the 3 MBS2320 doses and placebo dose. A logistic model will be fitted to multiply imputed data sets with dose in mg as a continuous variable to assess the trend across dose, including placebo as zero dose (i.e. placebo=0 mg dose level and dose levels of 5 mg, 20 mg, and 40 mg). The slope with CI and *P* value will be pooled using Rubin's method.

Analysis of Key Secondary Efficacy Endpoints

Main Estimation of Secondary Efficacy Estimand 2A

The first key secondary efficacy estimand (Estimand 2A) is based on the difference in mean change in Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) score from baseline to Week 12, as though no increase in any other RA medication and no treatment discontinuation for any reason, in patients with MBS2320 (5 mg, 20 mg, or 40 mg once daily) compared to placebo.

All assessments after any of the intercurrent events will be censored. An MI model will be used to impute any missing (or censored) score at Week 12 assuming MAR. The RAMRIS score and change from baseline in RAMRIS score will be derived on each multiply imputed data set and analysed using analysis of covariance (ANCOVA) with fixed effect terms for treatment and stratification factors, and baseline RAMRIS score as covariate. Rubin's method will be used to pool results so that the differences in mean change in RAMRIS score can be presented with 95% CI and *P* value.

Estimation of Supportive Efficacy Estimand 2B

Estimand 2B is defined as the difference in mean change in RAMRIS score from baseline to Week 12 in patients with MBS2320 (5 mg, 20 mg, or 40 mg once daily) compared to

placebo, irrespective of treatment discontinuation or interruption due to tolerability issues or lack of efficacy and as though no increase in any other RA medication. Data after all intercurrent events except discontinuation or interruption of treatment due to tolerability issues or lack of efficacy will be censored. Data missing for reasons unrelated to treatment (e.g. participant not willing to undergo MRI scan) will be imputed under the MAR assumption.

A reference-based multiply imputation model will be used to impute missing data after discontinuation of treatment due to related reasons (tolerability issues or lack of efficacy). As for Estimand 2A, the change from baseline in RAMRIS score will be derived on each multiply imputed data set and analysed using ANCOVA, and Rubin's method will be used to pool results.

Main Estimation of Secondary Efficacy Estimand 3A

A mixed model for repeated measures (MMRM) will be fitted to change from baseline at Weeks 4, 8, and 12 as the dependent variable and including fixed effects for DAS28-hsCRP baseline covariate, treatment, visit, treatment by visit interaction, and the stratification factors. An unstructured covariance will be used to model the covariances over time on participants. The least squares mean change from baseline in DAS28-hsCRP and differences relative to placebo with 95% CI and *P* value will presented at each time point.

Missing data are assumed to be MAR in the MMRM, which is well suited to estimate this type of hypothetical estimand.

Main Estimation of Secondary Efficacy Estimand 3B

Similar estimation (via MMRM) as described for Estimand 3A will be conducted for Estimand 3B. Note that this requires participants who discontinue treatment to return at Week 12 for assessment. Missing data are assumed to be MAR, which is unlikely to hold in the case of dropouts following discontinuation of treatment.

A sensitivity analysis will be conducted for Estimand 3B, using a reference-based MI model to impute missing data after discontinuation due to related reasons. The change from baseline

in DAS28-hsCRP will be derived on each multiply imputed data set and analysed using MMRM, and Rubin's method will be used to pool results.

Main Estimation of Secondary Efficacy Estimand 4

The estimation of Estimand 4 is similar to that described for Estimand 1. A logistic model will be fitted to successful composite clinical response at each of Weeks 4 and 8 including the stratification factors and treatment (qualitative) as factors; missing data will not be imputed and assumed MCAR.

In a sensitivity analysis, an MI model will be used to impute any missing components of the composite clinical response at Weeks 4, 8, and 12. Logistic model will be fitted to each multiply imputed data set and Rubin's method use to pool results. The overall difference of each dose relative to placebo will be presented with *P* value, at each time point.

Additional sensitivity analysis of the successful composite clinical response at Weeks 4, 8, and 12 will be performed using Logistic Generalized Linear Mixed Model with fixed effects for treatment, visit, treatment by visit interaction, and the stratification factors. More details will be provided in the SAP.

Analyses of Other Efficacy and Exploratory Endpoints

The other efficacy endpoints will be analysed descriptively, based on the mFAS (Flag B), except for ordinal endpoints (e.g. ACR50 & ACR70) which will be analysed based on mFAS (Flag P). Sensitivity analysis may be undertaken; details will be provided in the SAP.

The exploratory efficacy endpoints will be analysed descriptively, based on the mFAS (with no flags applied) and the mFAS (Flag A). Sensitivity analysis may be undertaken; details will be provided in the SAP.

Analysis of Pharmacokinetic Endpoints

MBS2320 and MBS2473 plasma concentrations will be determined in pre-dose samples at Weeks 4 and 12, postdose samples collected 3 (±1) hours following last dose at Week 12, and at EOS.

Plasma concentration of MBS2320 and MBS2473 (where applicable) will be determined for each sample, excluding placebo controls.

All MBS2320 and MBS2473 plasma concentration data will be listed by participant and visit/sampling time point and summarised by administered treatment.

SAS® software Version 9.4 or higher (SAS Institute, Inc, Cary, North Carolina) will be utilised for the generation of any tables, listings, and figures.

Analyses of Safety

The incidence of treatment-emergent AEs for the safety population will be summarised by treatment group. Adverse events will be coded using the Medical Dictionary for Regulatory Activities to classify events under primary system organ class and preferred term. Adverse event data will be presented in incidence tables. Adverse events will also be summarised by severity, seriousness, and relationship to IP for each treatment group. Data will also be listed in data listings.

The incidence of laboratory abnormalities by type, frequency, and severity will be summarised by treatment groups. Change from baseline in continuous laboratory variables will be summarised by visit and treatment groups.

All other safety variables (including vital signs and ECGs) will be summarised by treatment group and visit.

Other Analyses

Summary statistical analyses will be provided for demographics, medical history, and physical examination, and ophthalmological assessments at baseline.

Version and Date of Protocol: Version 2.0, 12 January 2023