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Phase 3, randomised, double-blind, placebo-controlled, 3-arm study to investigate the safety and efficacy of efimosfermin alfa in participants with biopsy-confirmed F2- or F3-stage metabolic dysfunction-associated steatohepatitis (MASH) (ZENITH-1)

Submission date
10/03/2026

Recruitment status
Recruiting

Registration date
30/07/2026

Overall study status
Ongoing

Last Edited
05/08/2026

Condition category
Nutritional, Metabolic, Endocrine

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This is a randomly allocated, double-blind, placebo-controlled, parallel-group, multicenter, 48-month study of the safety and efficacy of efimosfermin administered every 4weeks (Q4W) by subcutaneous (SC) injection in adult MASH participants with fibrosis that is consistent with stage F2 or F3. The total time of participation in the study, inclusive of Screening and safety follow-up, is approximately 52months.

The purpose of this study is to assess the safety and efficacy of monthly efimosfermin injection in the resolution of steatohepatitis and improvement of liver-related clinical outcome compared to placebo in individuals with MASH and biopsy-confirmed F2- or F3-stage fibrosis following a maximum treatment duration of 48months.

Who can participate?
Patients aged 18 years and over with MASH and biopsy-confirmed F2- or F3-stage fibrosis

What does the study involve?
Participants will be enrolled and randomly allocated 1:1:1 to receive 225mg efimosfermin, 300mg efimosfermin, or placebo Q4W by SC injection for a period of 48months, followed by a final follow-up safety assessment at Week 212 of the study. Total time of participation in the study, inclusive of a screening period of up to 3months and the final safety assessment, is approximately 52months. Since injection volumes for the 225-mg and 300-mg efimosfermin arms are 1.5mL and 2.0mL, respectively, additional measures will be implemented to preserve the study's blinding.
Criteria are established in this protocol for dose interruption, modification, discontinuation, and

resumption based on Investigator discretion and following consultation with the Study Medical Monitor (the Sponsor or designee) in specific circumstances.

What are the possible benefits and risks of participating?
Benefits not provided at time of registration

The most common (occurring in more than 1 in 10 people) side effects who took the study drug include nausea, vomiting, diarrhoea, injection site pain, redness, and rashes.
In previous studies with GSK6519754, nausea and vomiting were mild in severity and, most of the time, resolved without any treatment.
Some participants in other studies with GSK6519754 showed blood test results with high levels of liver proteins that required additional monitoring. There is a possible risk of gallbladder inflammation or symptoms of gallstones.
Changes in bone health (decreased bone density due to loss of minerals) have been seen in clinical studies with other drugs that work like GSK6519754. In human studies up to 24 weeks, no meaningful changes in bone tests have been seen.
GSK6519754 works in a way that is similar to a natural signal in the body that affects levels of some hormones, such as cortisol. Side effects suggesting changes in cortisol have not been seen in people taking efimosfermin to date.
As with other medications, efimosfermin may cause an immune or allergic reaction.
Severe allergic reactions are very rare, but life-threatening or fatal reactions can happen.

Where is the study run from?
King's College Hospital, London.

When is the study starting and how long is it expected to run for?
October 2025 to October 2031.

Who is funding the study?
GlaxoSmithKline

Who is the main contact?
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Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT07221227

Integrated Research Application System (IRAS)
1013369

Central Portfolio Management System (CPMS)
71373

Sponsor's protocol code number
301160

Study information

Scientific Title
A phase 3, randomized, double-blind, placebo-controlled, 3-arm study to investigate the safety and efficacy of efimosfermin alfa in participants with biopsy-confirmed F2- or F3-stage metabolic dysfunction-associated steatohepatitis (MASH) (ZENITH-1)

Acronym
ZENITH-1

Study objectives
Week 52 Analysis:
To determine the effect of 225 mg and 300 mg efimosfermin compared to placebo on histologic resolution of MASH and improvement in fibrosis after 52 weeks of Q4W SC injections.
To determine the effect of efimosfermin compared to placebo on histologic resolution of MASH and improvement in fibrosis after 52 weeks of treatment.

Month 48 Analysis:
To determine the time to a composite clinical outcome following treatment with 225 mg and 300 mg efimosfermin compared to placebo after up to 48 months of Q4W SC injections.
To determine the time to a composite clinical outcome following treatment with efimosfermin compared to placebo after up to 48 months of treatment.
To assess the effects of efimosfermin on safety and tolerability.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 01/06/2026, London Bridge Research Ethics Committee (2 Redman Place, Stratford, E20 1JQ, United Kingdom; -; londonbridge.rec@hra.nhs.uk), ref: 26/LO/0252

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Parallel

Purpose
Treatment

Study type(s)
Efficacy, Safety, Treatment, Other

Health condition(s) or problem(s) studied
Medical condition: Metabolic Dysfunction-Associated Steatohepatitis (MASH)
Medical condition in lay language: Metabolic Fatty Liver Inflamation
Therapeutic areas: Diseases [C] - Nutritional and Metabolic Diseases [C18]

Interventions
Overall Design Summary: This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, 48-month study of the safety and efficacy of efimosfermin administered every 4

weeks (Q4W) by subcutaneous (SC) injection in adult MASH participants with fibrosis that is consistent with stage F2 or F3. Patients will be randomized using a computerised system/ program. The total time of participation in the study, inclusive of Screening and safety follow-up, is approximately 52 months.

Brief Summary: The purpose of this study is to assess the safety and efficacy of monthly efimosfermin injection in the resolution of steatohepatitis and improvement of liver-related clinical outcome compared to placebo in individuals with MASH and biopsy-confirmed F2- or F3-stage fibrosis following a maximum treatment duration of 48 months.

Study Arms and Duration: Participants will be enrolled and randomized 1:1:1 to receive 225 mg efimosfermin, 300 mg efimosfermin, or placebo Q4W by SC injection for a period of 48 months, followed by a final follow-up safety assessment at Week 212 of the study. Total time of participation in the study, inclusive of a screening period of up to 3 months and the final safety assessment, is approximately 52 months. Since injection volumes for the 225-mg and 300-mg efimosfermin arms are 1.5 mL and 2.0 mL, respectively, additional measures will be implemented to preserve the study's blinding.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Efimosfermin alfa [EFIMOSFERMIN ALFA]

Primary outcome(s)
1. Composite clinical outcome measured using liver-related outcomes, comprising all-cause mortality; transplantation; occurrence of significant hepatic events (e.g., liver decompensation [Grade ≥ 2 ascites or Grade ≥ 2 encephalopathy requiring treatment, bleeding from varices or portal hypertensive gastropathy], histological or Non-invasive progression to cirrhosis; and increase in MELD (Model for End-Stage Liver Disease) score from a value of ≤ 12 to a value ≥ 15 due to liver condition) at month 48

2. Histologic resolution of MASH (Resolution of steatohepatitis on overall histopathological reading, with no worsening of fibrosis on the MASH CRN fibrosis score); improvement in liver fibrosis (improvement in fibrosis by at least 1 stage (MASH CRN fibrosis score) with no worsening of steatohepatitis, defined as no increase in any NAS component for ballooning, inflammation, or steatosis); improvement in liver fibrosis by at least 2 stages (improvement in fibrosis by 2 or more stages (MASH CRN fibrosis score) with no worsening of steatohepatitis, defined as no increase in any NAS component for ballooning, inflammation, or steatosis); and, histologic resolution of steatohepatitis (resolution of steatohepatitis on histopathological reading, with no worsening of MASH CRN fibrosis score; measured using centralised, blinded histopathological evaluation of liver biopsy samples using the MASH CRN fibrosis score and NAS scoring for ballooning, inflammation, and steatosis, at week 52 and month 48

Key secondary outcome(s)
1. Liver health measured using VCTE-LSM (vibration-controlled transient elastography- liver stiffness measurement) and CAP (controlled attenuation parameter) scores at baseline (day 1), week 52 and month 48

2. Stiffness of liver measured using MRE (magnetic resonance elastography) score at baseline (day 1), week 52 and month 48

3. Prognostic marker for disease progression measured using ELF (enhanced liver fibrosis) score at baseline (day 1), week 52 and month 48

4. Histologic resolution of MASH and improvement in fibrosis measured using the resolution of steatohepatitis on overall histopathological reading and improvement in liver fibrosis of ≥ 1 stage (MASH CRN fibrosis score) at week 52, improvement in fibrosis by ≥ 1 stage and no worsening of steatohepatitis (defined as no increase in NAS score for ballooning, inflammation, or steatosis) at month 48, improvement in fibrosis by ≥ 2 stages and no worsening of steatohepatitis (defined as no increase in NAS score for ballooning, inflammation, or steatosis) at week 52 and month 48, resolution of steatohepatitis reading and no worsening of MASH CRN score at week 52 and month 48

5. Liver health measured using the VCTE-LSM and CAP scores; the change from baseline to week 52 and month 48 in VCTE-LSM and CAP scores and the change from baseline in VCTE-LSM ≥ 30% at week 52 and month 48 at baseline, week 52 and month 48 6. The percentage of fat in the liver measured using the HFF (hepatic fat fraction) and ALT (alanin aminotransferase) normalization: change from baseline to week 52 and month 48 in HFF by MRI-PDFF (hepatic fat fraction) for all participants, change from baseline to week 52 and month 48 in ALT, AST (aspartate aminotransferase), and ALT/AST ratio ALT and HFF normalization at week 52 and month 48 and achieving HFF ≤ 5% at baseline, week 52 and month 48

6. Glycemic and metabolic biomarkers, including HbA1 (glycated hemoglobin) c for participants with T2DM (type 2 Diabetes Melitus) measured using standard methods at baseline (day 1), week 52 and month 48

7. Effects on lipids will be assessed via the change in fasting total cholesterol, LDL-C (low density lipoprotein C), HDL C (high density lipoprotein C), and fasting triglycerides measured using a lipid profile blood test at baseline (day 1), week 52 and month 48

8. Patient-reported outcomes measured using the CLDQ-NASH (Chronic Liver Disease Questionnaire- nonalcoholic steatohepatitis) domain and total scores at baseline, week 52 and month 48

9. Steady-state PK -pharmacokinetics of efimosfermin measured using a validated bioanalytical assay to quantify efimosfermin serum concentrations in participants with PK data following multiple doses at various time points up to up to month 48

Completion date
31/10/2031

Eligibility

Key inclusion criteria
1. Able and willing to understand and sign a written ICF that must be obtained prior to the initiation of study procedures
2. Age ≥ 18 and ≤ 75 years at enrollment
3. History or presence of 2 or more of the 5 components of metabolic syndrome per American Heart Association definition (Grundy et al, 2005):

3.1. Obesity/overweight (BMI ≥ 25 kg/m2 ; BMI ≥ 23 kg/m2 for Asian regions) or waist circumference of ≥ 40 inches (102 cm) for men and ≥ 35 inches (89 cm) for women
3.2. Increased triglycerides: ≥ 150 mg/dL (1.7 mmol/L) or taking medications to lower triglycerides
3.3. Reduced HDL cholesterol: males, ≤ 1.03 mmol/L (40 mg/dL); females, ≤ 1.29 mmol/L (50 mg /dL)
3.4. Elevated fasting glucose (≥100 mg/dL), or on drug treatment for elevated glucose
3.5. Hypertension
4. Magnetic resonance imaging (MRI)-derived proton density fat fraction (PDFF)≥ 8% for new or historical analysis submitted to the central reader ≤ 3 months before randomization
Note: MRI-PDFF assessment will be conducted at Screening if a historical value determined within 3 months prior to randomization is not available.
5. Vibration-controlled transient elastography (VCTE™)-liver stiffness measurement (LSM) ≥ 8.0 kPa and < 20 kPa with a controlled attenuation parameter (CAP™) score of ≥ 285 dB/m ≤ 3 months prior to randomization
6. Stable body weight for the past 6 months (change ≤ 5%)
7. Liver biopsy confirmation of MASH consistent with stage F2 or F3 fibrosis and a NAS score ≥ 4 confirmed by a central pathologist
7.1. If a historical liver biopsy was performed ≤ 6 months before Screening, the individual may proceed with Screening if the following conditions are confirmed:
7.1.1. The biopsy has been reviewed by a central pathologist and is consistent with the inclusion criteria.
7.1.2. No concomitant investigational drugs are being received.
Note: All previous investigational drugs used for MASH should have been discontinued ≥ 6 months before the historical liver biopsy and should not be used for the 6 months prior to Screening.
7.2. If a historical liver biopsy is unavailable, a liver biopsy can be performed at Screening if the following conditions are met:
7.2.1. The individual must meet all other inclusion-exclusion criteria for the study.
7.2.2. FibroScan-AST (FAST) value ≥ 0.35.
8. Females are eligible to participate if they are not pregnant or breastfeeding, and one of the following conditions applies:
8.1. Not a participant of childbearing potential (POCBP), or
8.2. A POCBP who agrees to follow the contraceptive guidance during the treatment period and for ≥ 16 weeks after the last dose of study drug.

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
75 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Liver Biopsy
1. Contraindication or ineligibility for percutaneous liver biopsy Laboratory and Imaging Findings
2. Vitamin D ≤ 12 ng/mL. Individuals with values > 12 ng/mL but < 20ng/mL should agree to receive vitamin D supplementation according to the standard of care or local guidelines to ensure rapid repletion.
3. ALT or AST ≥ 5 × upper limit of normal (ULN)
4. Total bilirubin ≥ 1.3 mg/dL. Individuals with documented Gilbert's syndrome may be enrolled if they experienced an isolated increase in total bilirubin of ≥ 1.3 mg/dL and direct bilirubin is ≤ 20% of total bilirubin; otherwise, the individual will be excluded.
5. Serum albumin ≤ 3.5 g/dL
6. International normalized ratio (INR) ≥ 1.3 not due to therapeutic anticoagulation. Individuals receiving chronic anticoagulant treatment with higher INR values may be enrolled at the discretion of the Investigator and Study Medical Monitor CONFIDENTIAL 301160 Protocol Amendment 1 Final 14 Jan 2026 55
7. Alkaline phosphatase (ALP) ≥ 2 × ULN
8. Hemoglobin (Hb) ≤ 11.0 g/dL for males and ≤ 10.0 g/dL for females
9. Neutrophils ≤ 1500/mm3 (Black participants: ≤ 1200/mm3); individuals with documented benign ethnic neutropenia may be enrolled at the discretion of the Study Medical Monitor.
10. Platelet (PLT) count < 140,000/mm3; individuals with a PLT count between 110,000/mm3 and 140,000/mm3 may be enrolled after discussion with the Study Medical Monitor.
11. Serum creatinine ≥ 1.5 mg/dL or creatinine clearance ≤ 60 mL/min/1.73 m2 by Chronic Kidney Disease Epidemiology Collaboration equation (2021).
12. Alpha-fetoprotein ≥ 20 ng/mL
13. Thyroid-stimulating hormone outside the normal reference range unless free thyroxine value is within the normal range
14. Triglycerides ≥ 500 mg/dL
15. HbA1c ≥ 9.0%
16. Model for End-Stage Liver Disease (MELD) score ≥ 12 unless the score is elevated in the absence of liver dysfunction (eg, Gilbert's syndrome)
17. Phosphatidylethanol (PEth) ≥ 80 ng/mL at Screening Medical History Findings
18. Evidence of infection with any of the following:
18.1. Human immunodeficiency virus
18.2. Hepatitis B virus (detectable HBsAg at Screening)
18.3. Hepatitis C virus (HCV) Note: Individuals with a positive HCV antibody test should have HCV ribonucleic acid (RNA) levels determined using polymerase chain reaction (PCR); those with positive (ie, detectable) HCV RNA are excluded. Individuals with a positive HCV antibody test and a negative screening PCR test must also be negative for ≥ 6 months before Screening.
19. Chronic liver disease from any other cause, including, but not limited to, alcoholic liver disease; evidence of portal hypertension; viral hepatitis or any history or evidence of cirrhosis on screening liver biopsy; or decompensated liver disease such as clinical ascites, bleeding gastroesophageal varices, hepatorenal syndrome, or hepatic encephalopathy prior to Screening or Day 1.
20. Current or chronic history of biliary disease (including symptomatic or complicated cholelithiasis) or a history of acute cholecystitis, biliary surgery, or intervention within the previous 6 months.
21. History or evidence of pancreatic disease, including pancreatitis. Note: Participants with a history of acute gallstone pancreatitis >6 months before Screening may be eligible if the event

has resolved without complications, cholecystectomy has been performed, and the common bile duct is clear
22. History of type 1 diabetes or positive glutamic acid decarboxylase autoantibodies (latent autoimmune diabetes in adults), or major T2DM complications, including, but not limited to, severe gastroparesis and autonomic neuropathy
23. History of significant bone disease, such as osteoporosis, consistent with a history of bone density ≥ 2.5 standard deviations (SD) below the young-adult mean, osteomalacia, or history of bone fracture or bone surgery (ie, hardware placement, joint replacement, bone grafting, or amputation) within 12 weeks prior to Screening
24. History of adrenal gland disease (eg, Cushing syndrome, Addison's disease) or using treatment that affects the hypothalamic-pituitary-adrenal axis (eg, chronic oral glucocorticoids)
Other Medical Findings
25. Current or history of clinically significant cardiac abnormality or dysfunction, such as congestive heart failure; pulmonary hypertension; complex congenital heart disease; significant arrhythmia; active cardiac ischemia; or a clinically significant cardiovascular event in the 6 months prior to Screening such as acute coronary syndrome, transient ischemic attack, poorly controlled hypertension, or cerebrovascular accident

Date of first enrolment
30/10/2025

Date of final enrolment
03/06/2028

Locations

Countries of recruitment
United Kingdom

Argentina

Australia

Austria

Belgium

Brazil

Bulgaria

Canada

Chile

China

France

Germany

Greece

Hong Kong

India

Israel

Italy

Japan

Korea, South

Mexico

Netherlands

New Zealand

Poland

Saudi Arabia

Singapore

Spain

Taiwan

United States of America

Study participating centre
-
-
-
England
-

Sponsor information

Organisation
GlaxoSmithKline (United Kingdom)

ROR
https://ror.org/01xsqw823

Funder(s)

Funder type

Funder Name
GlaxoSmithKline

Alternative Name(s)
GlaxoSmithKline plc., GSK plc., GlaxoSmithKline plc, GSK

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date