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Phase II, double-blind, randomized, placebo-controlled, multicentre study to evaluate the safety, efficacy, and pharmacokinetics of TAK-242 and Granulocyte Colony-Stimulating Factor (G-CSF) (G-TAK) in subjects with severe alcoholic hepatitis (sAH) and acute-on-chronic liver failure (ACLF)

Submission date
05/04/2022

Recruitment status
Recruiting

Registration date
05/12/2022

Overall study status
Ongoing

Last Edited
22/05/2025

Condition category
Digestive System

[X] 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 clinical research study is a medical study that helps answer important questions about how safe the investigational medications are and whether and how well they work. The investigational medication, TAK-242, is aimed at stopping an “over-reaction” of the immune system (the body’s defence system) whilst G-CSF encourages the liver cells to grow. In patients with severe alcoholic hepatitis (sAH) and acute-on-chronic liver failure (ACLF), this over-reaction may cause the liver and other organs in the body to suddenly stop working (organ failure). It is hoped that by blocking this over-reaction and encouraging patients' liver cells to grow their condition may improve. The aim of this study is to learn more about whether the investigational medications, (TAK-242 and G-CSF) work and how safe they are compared with a placebo in people with severe alcohol-related liver disease.

Who can participate?
Patients aged between 18 and 75 years with severe alcoholic hepatitis and acute-on-chronic liver failure

What does the study involve?
The patients who will be enrolled in the study will receive the investigational medication and/or placebo in combination plus the standard of care. The length of participation in the study will depend on the patient's condition. If their condition worsens they may have to leave the study. The maximum duration of study participation is 90 days (about 3 months). There are up to three study visits, including a stay at the study centre for at least 13 days during the screening and

treatment periods. Eligible patients who participate in the study will undergo a number of different procedures and assessments including a physical examination, ECG, EEG, blood and urine tests, completion of questionnaires and a liver biopsy.

What are the possible benefits and risks of participating?
It is possible that the symptoms of their condition will not improve during the study or may even worsen. Treatment with these investigational medications may also involve risks to their future health that are currently not known. Participants may experience some discomfort when blood samples are taken, such as pain at the site where the blood has been drawn, bruising, occasional light-headedness and, rarely, fainting. The ECG may irritate participants' skin and cause itching and redness. The study team might need to shave any chest hair so that the pads can stick to their skin. Removal of the sticky pads might cause their skin to sting for a few seconds. To receive the study medications, a qualified member of the study team will insert an intravenous cannula. Participants may be given a local anaesthetic to numb the skin where the thin tube is inserted into the vein. There is also a risk of infection. Participants may experience discomfort and bruising at the site of the injection. For the liver biopsy, a needle will be used (into the participants' abdomen or through a thin tube in their neck) to take a small piece of their liver tissue. They may experience pain and/or bleeding at the needle/tube insertion site after the liver biopsy. If this happens, the study doctor may prescribe medication for the pain. Although rare, there is a chance of infection or damage to another nearby organ. Only some study centres will be taking liver biopsies.

Where is the study run from?
Yaqrit Ltd (UK)

When is the study starting and how long is it expected to run for?
March 2022 to October 2027

Who is funding the study?
Horizon 2020

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
2022-000128-39

IRAS number
1005490

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
G-TAK-ES-01, IRAS 1005490

Study information

Scientific Title
Phase II, double-blind, randomized, placebo-controlled, multicentre study to evaluate the safety, efficacy, and pharmacokinetics of TAK-242 and Granulocyte Colony-Stimulating Factor (G-CSF) (G-TAK) in subjects with severe alcoholic hepatitis (sAH) and acute-on-chronic liver failure (ACLF)

Acronym
A-TANGO Phase II Study

Study objectives
The purpose of this Phase II clinical trial is to investigate:
1. The safety of TAK-242 in combination with G-CSF (G-TAK) in patients with severe alcoholic hepatitis (sAH) and acute-on-chronic liver failure (ACLF)
2. The effect of TAK-242 in combination with G-CSF (G-TAK) on the disease severity of ACLF

To better understand the impact of TAK-242 alone or the combination G-CSF and TAK-242 (G-TAK) administration on efficacy, safety, pharmacokinetics, organ function and the development of complications during the course of ACLF.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/05/2022, East Midlands - Nottingham 2 Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8169, +44 (0)2071048035, +44 (0)20 71048016; nottingham2.rec@hra.nhs.uk), ref: 22/EM/0087

Study design
Randomized placebo-controlled double-blind parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
https://a-tango.eu/

Health condition(s) or problem(s) studied
Severe alcoholic hepatitis (sAH) and acute-on-chronic liver failure (ACLF)

Interventions
Multicentre, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of TAK-242 alone or in combination with G-CSF in three dosing cohorts.

78 patients to be randomized (1:1:1) in an online tool to one of the following three arms:
1. Standard of care (SOC) plus placebo for TAK-242 plus placebo for G-CSF
2. Standard of care (SOC) plus continuous IV infusion of TAK-242 for 10 days (Day 1-10) plus placebo for G-CSF.
3. Standard of Care (SOC) plus continuous IV infusion of TAK-242 for 10 days (Day 1-10) plus daily subcutaneous G-CSF injections for 5 days (Day 1-5) and on Day 8 (six injections in total).

TAK-242 (or matching placebo) will be administered as a continuous IV infusion starting with a loading dose of 0.9 mg/kg administered over 30 minutes, followed by a continuous, constant rate infusion of 1.8 mg/kg/day for 10 days.
G-CSF (or matching placebo) will be given subcutaneously once daily at a dose of 5 µg/kg.

Follow-up visits will occur on Day 14 (±4 days), Day 28 (±5 days), and Day 84 (±7 days).
For each patient, the total duration of subject participation in the study including screening will be 84 ± 7 days.
The Data and Safety Monitoring Board (DSMB) will review safety and pharmacokinetic (PK) data analysis after randomization of in total of 18 patients (n = 6 in each treatment arm) with complete PK analysis until Day 4 (±1 days) (D4). The DSMB will assess the relevance of drug-related adverse events and drug-drug interactions in this particular subgroup of ACLF patients.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
TAK-242, Granulocyte Colony-Stimulating Factor (G-CSF)

Primary outcome measure
The safety of TAK-242 in combination with G-CSF and alone in subjects with sAH and ACLF compared to placebo from baseline to Day 14, assessed using:
1. The percentage of subjects who experience at least one treatment-emergent AE (TEAE) or SAE
2. The percentage of subjects who discontinue the study drug due to an AE (including methemoglobinemia)
3. The percentage of subjects who experience at least one treatment-emergent clinical laboratory test result or abnormal ECG that meets the Sponsor’s markedly abnormal criteria

Secondary outcome measures
These secondary endpoints have been chosen in order to better understand the impact of TAK-242 alone or the combination G-CSF and TAK-242 (G-TAK) administration on efficacy, safety, pharmacokinetics, organ function and the development of complications during the course of ACLF.
1. Organ failure measured using CLIF-C OF score in subjects treated with G-TAK compared with placebo from baseline to Day 14
2. Organ failure measured using CLIF-C OF score in patients treated with TAK-242 alone compared with G-TAK as well as CLIF C ACLF-CRP score between all arms from baseline to Day 14
3. Pharmacokinetics of TAK-242 alone or the combination G-TAK in patients with ACLF, measured using plasma Cmax and Cav of TAK-242 and G-CSF and metabolites on Day 1, Day 2, Day 7 and Early Termination
4. Key biomarkers for inflammation, cell death, liver function, regeneration and senescence

measured using total bilirubin (TB), Cytokeratin-18 (M30), cleaved Cytokeratin-18 (M65), transforming growth factor beta 1 (TGFb1), interleukin 22 (IL-22) and interleukin 22 binding protein (IL-22BP), high sensitivity CRP (hs-CRP), hepatic growth factor (HGF), SDF-1, soluble urokinase-type plasminogen activator receptor (suPAR), DNA methylation, and circulating RNAs (genes MYLK3, SLC22A13, TPRG1-AS1, AC020633.1, TPRG1-AS1, NUDT4P1 (40) from baseline to Day 14
5. Transplant-free and overall survival measured using patient medical records on Day 28 and Day 84
6. Organ function (hepatic, renal, brain, coagulation, respiratory, cardiovascular) measured using CLIF-C OF, CLIF-C ad, CLIF-C ACLF-CRP scores and Systemic Inflammatory Response Score (SIRS) from Day 1 to Day 10
7. Inflammatory markers and ACLF-related panel including, but not limited to, IL-6, TNF-α, IL-10, M30/M65, sCD163, sCD206 measured using inflammation and plasma/serum biomarkers lab test from baseline to Day 4, 7 and 14
8. Quality of life measured using EQ5D5L from baseline to Day 14

Health economics:
9. Number of days in intensive care/intensive therapy unit measured using patient medical records from baseline to the end of the study
10. Total costs of hospital treatment measured using discharge summary information with a time horizon of 90 days. The cost analysis is limited to hospital care

Overall study start date
31/03/2022

Completion date
31/10/2027

Eligibility

Key inclusion criteria
1. Male and female subjects ≥18 years of age and ≤75 years of age
2. With a diagnosis of severe alcoholic hepatitis defined by a Lille score of >0.45 in those treated with steroids and/or contraindication to steroids
3. Eligible subjects will have Grade 1- 3 ACLF with a maximum of three organ failures using the CLIF-C OF score AND the CLIF-C ACLF-CRP score of >35 and <60

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex

Both

Target number of participants
78

Key exclusion criteria
1. Refusal to give informed consent
2. Mechanical ventilation due to respiratory failure and/or need for renal replacement therapy and or requiring inotropes for circulatory support with a noradrenaline requirement of >0.5 ug /kg/min to maintain mean arterial pressure >70 mmHg
3. Subject has received any investigational drug within 30 days of randomization
4. Subject has any of the following conditions:
4.1. History of liver transplantation
4.2. Postoperative decompensation after partial hepatectomy
4.3. Liver failure without evidence of underlying chronic liver disease
5. Any untreated infections (<48h antibiotic therapy) including gram-positive infections, active tuberculosis or coinfection with HIV
6. Chronic or pre-existing kidney failure, survival prognosis of <6 months due to severe co-morbid conditions that might confound study results or compromise subject safety
7. Methemoglobinemia, clinically-significant disseminated intravascular coagulation, uncontrolled bleeding, sickle cell anaemia
8. Uncontrolled seizures, Creutzfeldt-Jakob disease, glucose-6-phosphate dehydrogenase deficiency
9. Active malignancy, premalignant haematological disorders (e.g. myelodysplastic syndrome, chronic myeloid leukaemia) or multiorgan failure (≥4 organ failures)
10. Pregnancy or nursing women

Date of first enrolment
30/06/2025

Date of final enrolment
30/12/2026

Locations

Countries of recruitment
England

France

Germany

Portugal

Spain

United Kingdom

Study participating centre

Uni Klinikum Leipzig
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Study participating centre
Charité - Universitätsmedizin Berlin_CKV
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Universitätsklinikum RWTH Aachen
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Sponsor type
Industry

Funder(s)

Funder type
Government

Funder Name
Horizon 2020

Alternative Name(s)
EU Framework Programme for Research and Innovation, Horizon 2020 - Research and Innovation Framework Programme, European Union Framework Programme for Research and Innovation

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Other publication
6. Submission to regulatory authorities

The anonymised data will be shared with Assistance Publique Hospital De Paris (APHP), IMAC (International Market Access Consulting Gmbh (IMAC) and Hepyx Limited (HPX) for the generation of a business plan.

Intention to publish date
31/12/2028

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No