Randomized, placebo-controlled, double blind, multi-centre Phase IIb study to evaluate the efficacy and safety of HepaStem in patients with acute on chronic liver failure (ACLF).

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Ethical review	Approved WMO
Status	Pending
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON55256

Source
ToetsingOnline

Brief title
Dheliver

Condition

- Hepatic and hepatobiliary disorders

Synonym
Acute chronic liver failure

Research involving
Human

Sponsors and support

Primary sponsor: Promethera Therapeutics SA
Source(s) of monetary or material Support: Promethera Therapeutics SA

Intervention

Keyword: Celltherapy, Efficacy, Liverfailure, Safety

Outcome measures

Primary outcome

Primary endpoint:

Survival at Day 90: Whether the patients are still alive will be recorded up to

Day 90. Time and reason of death will be recorded.

Secondary outcome

The secondary efficacy endpoints include:

• Liver transplant-free survival (TFS) at Day 90.

• TFS at Day 90 while free of ACLF.

• TFS at Day 90 with MELD-Na score < 15.

• Duration of overall hospitalization and hospitalization in ICU and non-ICU

during the index

hospitalization up to Day 90.

The secondary safety endpoints include:

• Number, nature, severity, seriousness and relationship of AEs during the

whole study. This includes but is not limited to clinically changes in clinical

examinations, vital signs, laboratory tests, and imaging.

• Occurrence of systemic infection (sepsis/shock, bacteremia, invasive fungal

infection).

• Presence of anti-HLA Abs and donor-specific Abs (DSA) (thresholds > 1500 mean fluorescence intensity [MFI] and > 5000 MFI).

• Quantitative measurement of coagulation parameters: PT, INR, aPTT, fibrinogen, platelets, Ddimer.

• Any change in laboratory data at all visits, including data on serology, hematology,biochemistry. Abnormal laboratory results will only constitute an AE, and will be reported as such, if they are considered abnormal within the pathology of this study population.

• Physical examination and vital signs at all visits.

Study description

Background summary

Acute on Chronic Liver Failure (ACLF) encompasses an acute deterioration of liver function in patients with cirrhosis, which is usually associated with a precipitating event and results in the failure of one or more organs and high short-term mortality. Medical management of ACLF consists of early recognition, treatment of the precipitating event and supportive care. Most of ACLF management is focused on supportive care. At present, there is no specific treatment for ACLF that improves survival. Liver transplantation (LT) represents the only definitive therapeutic option for patients with ACLF.
Dysregulation of liver inflammation is a hallmark of chronic infection, autoimmunity and malignancy, which is mediated by multiple overlapping pathways in different liver diseases. While homeostatic inflammation and liver fibrosis are aspects of the healthy adult liver, a lack of resolution or chronic liver injury leads to progressive liver fibrosis and permanent liver damage. In these situations, pathological inflammation promotes the progression of liver fibrosis to cirrhosis and establishes a dysregulated balance between inflammation and immunosuppression within the liver (Robinson, Harmon, and O'Farrelly 2016).
In fibro-inflammatory chronic progressive liver diseases, it is expected that HepaStem will have immunomodulatory effects by direct cell-to-cell interactions with immune cells of the patient, and by paracrine effects through the various

cytokines, chemokines, matrix metalloproteinases, and growth factors they may secrete. By these combined effects, it is expected that HepaStem will play a favourable role in restoring the immunological disturbances observed in patients with fibro-inflammatory liver diseases such as ACLF and Non-alcoholic steatohepatitis (NASH), and ultimately will be able to restore liver homeostasis.

Study objective

The primary objective is:
to demonstrate the efficacy of 2 infusions (intravenous [i.v.]) of HepaStem at 1.0 million of cells/kg body weight (BW) (7 days apart) on the overall survival proportion at 90 days post first infusion.

The secondary objectives are :

• To assess the safety of 2 infusions (i.v.) of HepaStem at 1.0 million of cells/kg BW
(7 days apart) through 90 days post first infusion
• To assess the efficacy of 2 infusions (i.v.) of HepaStem at 1.0 million of cells/kg BW
(7 days apart):
o on the percentage of patients alive and free of liver transplantation (LT) at 90 days post first infusion
o on the percentage of patients alive, free of LT and free of ACLF at 90 days post
first infusion
o on the percentage of patients alive and free of LT with Model for End-Stage Liver
Disease (MELD)-Na score < 15 at 90 days post first infusion
o on the number of intensive care unit (ICU)-free days during the index hospitalization up to 90 days post first infusion
o on the number of hospital-free days during the index hospitalization up to 90 days post first infusion

Study design

This is an interventional, double blind, randomized (2:1), and placebo-controlled study of 2 infusions of a 1 dose regimen of HepaStem in patients recently diagnosed (<= 1 week) with ACLF grade 1 or 2 on top of standard of care (SoC), and for whom the diagnosis is not resolved on the day of infusion.

Intervention

During the study each patient will be administered 2 intra-venous infusions

which last 10-20 minutes each. The infusions contain HepaStem with 1.0 million cells/kg body weight (in de active arm) or placebo. Between the infusions there is a 7 days interval (+/-2 days).

Study burden and risks

The patients who will participate will be associated with the following burden and risks:
- a total of 9 visits in 3 months
- at each visit there will be a blood draw (with in total 405 ml). With permission 4x20 ml for genetic research and 2x 6 ml for biomarker research
- at all visits there will be a physical examination (including vital signs)
- at 4 visits the patient will be requested to complete questionnaires
- there will be one ECG taken.
- at 3 visits there will be Doppler measurements.

It must be taken into consideration that the patients will have 12 visits, but a significant part of these visits will take place while the patients are hospitalized. These hospitalizations can last up to 2 months.
Concerning adverse events we know that there are risks for:
Short-term:
• Thrombosis and bleeding). There will be close control of the blood clotting parameters throughout the study.
• Respiratory (no cases so far) - since Hepastem is going through the lungs before attending the liver, respiratory difficulties may occur.
• Hypersensitivity reaction or reaction to the infusion - this occurs when the body's immune system overreacts to something like medication. Hypersensitivity reactions may include: skin irritation, redness, itching, swelling, fluid discharge, crusting, skin rash, eruptions, coughing or shortness of breath, hoarse voice, headache, clogged or runny nose, sneezing, red (bloodshot) eyes, stomach pain, nausea, vomiting, diarrhea, fatigue, sore throat, dizziness. These reactions may be painful, uncomfortable or in some cases fatal (in the case of anaphylaxis). This is a very serious allergic reaction.
Medium or Long Term:
• The distribution of the cells in different organs may promote tumor development. Although such events have been rarely reported with immune response of cell therapy, as HepaStem is made of cells from another person which may eventually lead to cell rejection.
• HepaStem is an allogeneic (from another person) cell product. Immune response following HepaStem infusion cannot be excluded and if it develops could induce symptoms including, chills, nausea, ill feeling, fever or impact efficacy. This could lead to consequences in case of a future transplantation with a possible rejection. Anti-HLA antibodies and Donor Specific antibodies (DSA) will be measured in order to document the patient*s potential allogenic response and assess the potential risk of rejection for a future liver transplantation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must fulfill all of the following criteria in order to be eligible for trial enrollment:
1. Are adults aged between 18 and 70 years old.
2. Have an initial diagnosis of ACLF at the investigational site.
3. Have ACLF grade 1 or 2 according to the EASL-CLIF Consortium definition.
4. Have a total bilirubin >= 5 mg/dL.
5. Are able to read, understand and give written informed consent.
If the patient is unable to fully understand the study and based on the investigator*s judgment, the
ICF must be signed by a legal or authorized representative of the patient according to local
regulation. In case of hepatic encephalopathy (HE), the ICF must be signed by

the patient after
encephalopathy improvement, if possible.

Enrollment criteria
Patients must fulfill all of the following criteria in order to be enrolled in the trial at the end of the
Screening period:
1. Have completed all the procedures required at Screening.
2. Are still meeting all inclusion criteria and no exclusion criteria.

Infusion criteria
On the day of randomization and infusion, patients must fulfill all of the following criteria in order
to be infused with the IMP (HepaStem or the Placebo):
1. Have ACLF grade 1 or 2 (before first infusion).
2. Have been diagnosed with ACLF at the investigational site according to the EASL-CLIF
Consortium definition, no earlier than 8 days before randomization.
3. Have fibrinogen >= 80 mg/dL (as measured earlier on the same day before infusion).
4. Have platelets >= 50 x 10^3/mm^3 (as measured earlier on the same day before infusion).
5. Have no bleeding at a non-compressible site or no uncontrolled bleeding at a compressible site as deemed by the investigator.
6. Is expected to remain hospitalized for at least 24 hours post infusion.
7. Have not experienced an adverse event (AE) considered related to the IMP and associated
with an outcome defining an SAE (before the second infusion)
If the patient does not meet the infusion criteria prior to the first infusion, the patient will be
considered as a screening failure.
If the patient does not meet the infusion criteria prior to the second infusion, or the infusion
cannot be performed within the Day 8 Visit timeframe (±2 days), the infusion will not be
performed but the Day 8 Visit and further visits should be performed according to the protocol.
The missing infusion will not be replaced.

Exclusion criteria

Patients presenting with any of the following criteria will not be included in the study:
1. Have a MELD-Na score > 35.
2. Have underlying cirrhosis due to biliary disease.

3. Have underlying cirrhosis due to autoimmune hepatitis.
4. Have active bleeding at a non-compressible site or at a compressible site that, in the
opinion of the investigator, poses an unacceptable risk for the patient*s participation in the
study.
5. Have received treatment for bleeding complications during the current hospitalization
and has a persistent high risk for re-bleeding that, in the opinion of the investigator, poses an
unacceptable risk for the patient*s participation in the study.
6. Have a complete portal vein thrombosis.
7. Have coagulation disturbances defined as:
- fibrinogen < 80 mg/dL
- platelets < 50 x 10^3/mm^3
8. Are requiring chronic dialysis therapy.
9. Have had a cerebrovascular, myocardial, limb arterial thrombotic event, or history for
both thrombotic and hemorrhagic cerebrovascular events within 12 months prior to the Screening
and not considered stabilized by the investigator.
10. Have a previous history of myocardial infarction and/or cardiac failure, with an ejection
fraction rate (EFR) <= 40%.
11. Have an inability to maintain mean blood pressure (BP) > 60 mmHg despite use of
vasopressors.
12. Have severe pulmonary arterial hypertension defined as mean pulmonary arterial
pressure (MPAP) >= 45 mmHg (or right ventricular systolic pressure >= 50 mmHg) by echocardiography.
13. Have hepatopulmonary syndrome.
14. Are receiving mechanical ventilation due to respiratory failure.
15. Have known or suspected hypersensitivity or allergy to any of the components of theHepaStem diluent, dimethyl sulfoxide (DMSO), or bovine serum albumin.
16. Have a history of severe allergies to drugs and/or a history of severe anaphylactic
reactions.
17. Have undergone a major invasive procedure within 2 weeks of randomization. These are
open surgeries (the proper healing of the scar should be verified by the investigator).
- Liver biopsy (transjugular or percutaneous), paracentesis, and transjugular intrahepatic portosystemic shunt (TIPS) are not considered as major invasive procedures.
18. Had a previous organ transplantation and/or treatment with cell-based

therapy.
19. Are accepted as High Urgency status patient by the organ allocation system.
20. Have active primary or recurrent malignant disease (including hepatocellular carcinoma)
or have been in remission from clinically significant malignancy for < 5 years.
- Patients with cervical carcinoma in situ that has been resected with no evidence
of recurrence or metastatic disease for at least 3 years may participate in the study.
- Patients with basal cell or squamous epithelial skin cancers that have been completely resected with no evidence of recurrence for at least 3 years may participate in
the study.
21. Are receiving immunosuppressive drugs, except glucocorticoids.
- Patients receiving glucocorticoids administered for treatment of severe alcoholic
hepatitis may participate in the study.
22. Have a contraindication to or are unwilling to take glucocorticoids to prevent infusion-like
reaction.
23. Have persistently positive blood cultures despite 48 hours of antibiotic therapy that
indicates uncontrolled bacterial infection.
24. Have diagnosis of invasive aspergillosis.
25. Have known infection with human immunodeficiency virus (HIV).
26. Have a history of hepatitis D virus infection.
27. Are women of childbearing potential and decline to use highly effective contraception
methods during the study.
28. Are women who have been using hormonal oral contraception within 8 weeks of study
entry.
29. Are pregnant (i.e., positive blood or urine β-hCG test) or nursing/breastfeeding.
30. Have participated in any other interventional study within 4 weeks of study entry, or
participation and/or under follow-up in another interventional clinical trial.
31. Have any significant medical or social condition or disability that, in the investigator*s
opinion, may interfere with the patient*s optimal participation or compliance with the study
procedures.
32. Are committed to an institution by virtue of an order issued either by the judicial or the
administrative authorities.
33. Are employees of the Sponsor or investigator, or otherwise dependent on

them.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2021
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	08-01-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-04-2020

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-003051-11-NL
CCMO	NL71942.000.19