An Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Multiple Doses of ELA026 in Participants with Secondary Hemophagocytic Lymphohistiocytosis (sHLH).

Published: 08-04-2022
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Primary Objectives:• To determine the safety of ELA026 administered IV and SC to participants with sHLH.• To identify the RP3D and schedule for ELA026.Secondary Objectives:• To characterize the pharmacokinetic (PK) profile of ELA026 administered IV...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON55948

Source
ToetsingOnline

Brief title
An open-label study to evaluate safety and efficacy of ELA026.

Condition

- Immunodeficiency syndromes

Synonym
Secondary Hemophagocytic Lymphohistiocytosis (sHLH)

Research involving

Human

Sponsors and support

Primary sponsor: Electra Therapeutics Inc.
Source(s) of monetary or material Support: Electra Therapeutics Inc.

Intervention

Keyword: Secondary Hemophagocytic Lymphohistiocytosis (sHLH)

Outcome measures

Primary outcome

Primary Objective:

To determine the safety of ELA026 administered IV and SC to participants with

sHLH.

End point:

Incidence of adverse events (AEs) including dose-limiting toxicities (DLTs),

serious adverse events (SAEs), deaths, AEs leading to withdrawal from study.

Primary Objective:

To identify the RP3D (Recommended Phase 3 Dose) and schedule for ELA026.

End point:

Safety, efficacy, PD (overall assessment).

Secondary outcome

Secondary Objective:

To determine the efficacy of ELA026 administered IV and SC to participants

with HLH.

End points:

Best response by Week 4 defined as either complete response (CR) modified complete response (mCR) or partial response (PR) evaluated by objective clinical and laboratory parameters.

Secondary Objective:

To characterize the pharmacokinetic (PK) profile of ELA026 administered IV and SC to participants with sHLH.

End points:

Plasma concentrations and PK parameters of ELA026.

Secondary Objective:

To characterize the pharmacodynamic (PD) effect of ELA026 administered IV and SC to participants with sHLH.

End points:

Change from baseline in monocytes and CRP.

Secondary Objective:

To assess the immunogenicity of ELA026 administered IV and SC to participants with sHLH.

End points:

Incidence of anti-drug antibodies (ADAs) to ELA026.

Study description

Background summary

HLH is a rare and life-threatening inflammatory syndrome characterized by dysregulated immune function. HLH is classically divided into 2 types, primary HLH (pHLH) and secondary HLH (sHLH),

sHLH is a rare and life threatening inflammatory syndrome characterized by dysregulated immune function. The disease is associated with a massive systemic inflammatory response for which patients require immediate and aggressive treatment with intensive care

There are no approved therapies available for sHLH. But currently ELA026 is also under safety evaluation in healthy volunteers which is ongoing in Austria.

The proposed clinical study is a Phase 1b, open-label, multicenter study to investigate the safety, efficacy, PK, and PD of ELA026 following multiple dose levels administration in participants with treatment naïve or relapsed/refractory sHLH.

The proposed study will be conducted in up to 24 patients diagnosed with sHLH >=16 years. Based on the scientific rationale supporting the utility of ELA026 in sHLH, the significant unmet need and the potential benefit/risk profile, the Sponso is proposing to initiate development in sHLH.

Study objective

Primary Objectives:

• To determine the safety of ELA026 administered IV and SC to participants with sHLH.
• To identify the RP3D and schedule for ELA026.

Secondary Objectives:

• To characterize the pharmacokinetic (PK) profile of ELA026 administered IV and SC to participants with sHLH.
• To determine the efficacy of ELA026 administered IV and SC to participants with sHLH.
• To characterize the pharmacodynamic (PD) effect of ELA026 administered IV and SC to participants with sHLH.
• To assess the immunogenicity of ELA026 administered IV and SC to participants with sHLH.

Study design

This is a Phase 1b, open-label, multicenter study to investigate the safety,

efficacy, PK, and PD of ELA026 following multiple dose level administration in participants with treatment naïve or relapsed/refractory sHLH. As of DMC recommendation (issued 01Dec2023), participants with treatment-naïve or early refractory sHLH are eligible for this study. Early refractory is defined as a participant receiving approximately <1 week of any HLH-directed therapy with insufficient clinical or laboratory response judged by Investigator at screening.After signing an informed consent form, participants will be screened for study eligibility. Participants will receive dexamethasone as background therapy for sHLH and prophylaxis for bacterial, viral, and fungal/pneumocystis infections according to local institutional standards.
The study consists of a Screening period, a 12-week Treatment period (>=6 years of age), a Safety Follow-up period, an optional Extension phase for participants (>=12 years of age) exhibiting clinical benefit may be treated on a case-by-case basis beyond the 12-week treatment period with Sponsor approval, and a Long-term Survival Follow-up period with the overall goals of evaluating safety and selecting a dose and dosing regimen for Phase 3 testing.
An initial 3 participant cohort will be enrolled. Up to approximately 20 participants may be enrolled into Cohort 1 in order to obtain approximately 3-6 evaluable participants .The initial starting dose will be 0.1 mg/kg.The initial dose will be administered to the first 3 participants in the first cohort sequentially.

Successive participants in the first cohort will not be dosed until the preceding participant has received and tolerated at least one dose for a minimum of 24 hours. As of protocol Version 3.8, all newly enrolled participants in Cohort 1 will start at modified Dose Level 2 and receive a priming dose of 0.1 mg/kg on Day 1, and 0.3 mg/kg on Days 2 and 3. The Data Monitoring Committee (DMC) may define a new starting dose level based on emerging data.
Dosing of any additional participants added to Cohort 1 will proceed in parallel. Intra-participant dose escalation will be used in this first cohort to maximize benefit/risk in these participants and to facilitate subsequent cohorts being dosed with the appropriate starting dose.
Starting on Day 1 (Baseline), eligible Cohort 1 participants will receive ELA026 daily IV infusions. Prophylactic therapy must be initiated prior to administration of ELA026 and continued until completion of the first 2 doses of ELA026 for each dose level (refer to Section 6.7.1). After an individual participant has received 3 daily doses at a given dose level in Cohort 1 (or the 0.1 mg/kg priming dose followed by the 0.3 mg/kg dose on Days 2 and 3), the dose will be escalated until that participant: 1) demonstrates biomarker evidence of improvement, 2) develops a dose-limiting toxicity, or 3) receives the maximum allowable dose of 3 mg/kg. If dose-limiting toxicity occurs at the starting dose, the DMC may elect to add a cohort at a lower dose. IV administration will be over 6 hours on Day 1 and for the first dose of each new dose level, and then over 60 minutes for subsequent doses if the first dose is well tolerated.
In order to be enrolled into Cohort 1, eligible participants must be >= 12 years

of age. Cohort 1 participants who are tolerating drug and who have shown biomarker evidence of improvement will continue on the same IV dose level until they complete Week 4, at which point they can be transitioned to a SC dosing schedule as determined by the DMC in conjunction with the Sponsor. Total treatment duration will be up to 12 weeks. Biomarker evidence of improvement is defined as:

• Monocyte reduction AND
• Serum ferritin reduction >=20% compared to baseline or the most recent value prior to the next dose level dosing if baseline levels >=3000 ng/mL, OR if baseline levels <3000 ng/mL, any decrease in ferritin levels accompanied by an improvement in one or more of: fasting triglyceride levels, coagulation parameters, or sIL2 receptor levels compared to baseline.

A DMC will oversee the study and review the totality of the safety and efficacy experience for all participants. Enrollment into Cohort 1 will continue until approximately 3-6 evaluable participants have been enrolled or the DMC decides to initiate Cohort 2 enrollment, whichever occurs first. Enrollment may continue (no pause) unless a safety signal is under evaluation.
All Cohort 2 participants will be enrolled at a fixed dose regimen and route of administration (IV or SC) as determined by the DMC.
Based on the safety and efficacy experience from Cohort 2, the DMC may also add up to 2 additional cohorts (Cohorts 3 and 4) to explore new fixed-dose regimens and/or dose regimens for specific sHLH subtypes.

For Cohorts 2, 3, and 4, if a fixed-dose regimen is selected for further evaluation, the DMC may expand each cohort to up to approximately 20 participants to further investigate the preliminary efficacy of the dose regimen. As of protocol amendment 4.0, if the DMC decides to further evaluate additional participants with the fixed-dose regimen from Cohort 2, enrollment will only be open to participants >= 6 years of age who are treatment-naïve or early refractory sHLH.
All participants must complete a safety follow-up visit 4 weeks after the last dose of study drug. Long-term survival will be evaluated until study completion (i.e., date when the last data point required for statistical analysis or death occurs in the last participant evaluable in long-term survival follow-up, whichever occurs first). Participants (>=12 years of age) deriving ongoing clinical benefit may be treated on a case-by-case basis beyond the 12-week treatment period with Sponsor approval.

At any time during the study, if, in the opinion of the investigator, the participant*s condition is worsening, they may receive rescue treatment with added or alternative HLH therapy, after discussion with the Medical Monitor (when possible).

Intervention

Intervention Name: ELA026

Type: Biologic

Dose Formulation: Solution for IV infusion or SC injection.

Unit Dose Strength(s): Each vial contains 150 mg of ELA026 (50 mg/mL) solution for IV infusion/SC injection. The dosage of ELA026 will be diluted with 0.9% normal saline for a total volume of 30 mL for IV infusions. For SC administration, the dosage of ELA026 will be given as a bolus injection, with dilution at lower doses only as required. Multiple SC injections may be needed to deliver the required dosage of ELA026.

Route of Administration and Instructions:
1. Cohort 1 dose escalation phase: IV infusion over 6 hours on Day 1 of each dose level. IV infusion over 60 minutes for Days 2 and 3 of each dose level if first dose was well tolerated.
2. Cohort 1 Individual Fixed Dose Phase: IV infusion over 60 minutes or SC injection.
3. Cohorts 2, 3, and 4: SC injection or IV infusion over 6 hours for the first dose. IV infusion over 60 minutes for subsequent doses if first dose is well tolerated.

Dosage Level(s):
Dose Level 1: 0.1 mg/kg
Dose Level 2: 0.3 mg/kg
Dose Level 3: 1 mg/kg
Dose Level 4: 3 mg/kg

Sourcing: ELA026 will be provided to the site centrally by the Sponsor or designated representative.

Packaging and Labelling: ELA026 will be supplied as a liquid filled into a type 6R vial with a 3 mL fill volume. Label text will at a minimum include the protocol number, lot number, storage conditions, participant identifier and contact information.Labels comply with regulatory requirements for ELA026.

A. Non-clinical Interventions:
1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
i. Main Study Informed Consent: 1
ii. Review of Inclusion/Exclusion Criteria: 1
iii. Demographic data and medical history: 1
iv. Concomitant medications: 39
v. Adverse events: 40
vi. Prior medications: 1

2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
i. Main Study Informed Consent: 0
ii. Review of Inclusion/Exclusion Criteria: 0
iii. Demographic data and medical history: 0
iv. Concomitant medications: 0
v. Adverse events: 0
vi. Prior medcations: 0

3. Average time taken per intervention/procedure (minutes, hours or days)
i. Main Study Informed Consent: 60 mins
ii. Review of Inclusion/Exclusion Criteria: 60 mins
iii. Demographic data and medical history: 30 mins
iv. Concomitant medications: 60 mins
v. Adverse events: 60 mins
vi. Prior medcations: 30 mins

4. Details of who will conduct the intervention/procedure, and where it will take place.
i. Main Study Informed Consent: The Investigator or his/her representative will explain the nature of the study to the participant or his/her LAR and answer all questions regarding the study.
ii. Review of Inclusion/Exclusion Criteria: The study doctor will review the inclusion and exclusion criteria with the participant to make sure that the participant still qualify for the study. The participant will be assessed to determine their eligibility for the study based upon the inclusion and exclusion criteria at site.
iii. Demographic data and medical history: By the study doctor or their delegate.
iv. Concomitant medications: Concomitant medications necessary for the health and well being of the participant and that do not interfere with study assessments are permitted during the study at the Investigators discretion. This includes the use of appropriate medications for the treatment of AEs and/or concurrent illnesses under the direction of the Principal Investigator. All medications must be recorded in the source and on the appropriate electronic case report forms (eCRFs).
v. Adverse events: The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention. AEs will be classified according to the NCI CTCAE, version 5.
vi. Prior medcations: Prior medication will be discussed and recorded during the time of screening.

B. Clinical Interventions:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
i. PK blood sampling: 46
ii. PD blood sampling: 7
iii. Blood sampling for research cytokine analysis: 7
iv. Blood sampling for ADA: 2
v. Cardiac telemetry monitoring: 15
vi. Soluble CD25 analysis: 5
vii. Blood sample exploratory analysis: 5

2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
i. PK blood sampling: 0
ii. PD blood sampling: 0
iii. Blood sampling for research cytokine analysis: 0
iv. Blood sampling for ADA: 0
v. Cardiac telemetry monitoring: 0
vi. Soluble CD25 analysis: 0
vii. Blood sample exploratory analysis: 0

3. Average time taken per intervention/procedure (minutes, hours or days)
i. PK blood sampling: 10 mins
ii. PD blood sampling: 10 mins
iii. Blood sampling for research cytokine analysis: 10 mins
iv. Blood sampling for ADA: 10 mins
v. Cardiac telemetry monitoring: 120 mins
vi. Soluble CD25 analysis: 10 mins
vii. Blood sample exploratory analysis: 10 mins

4. Details of who will conduct the intervention/procedure, and where it will take place.
i. PK blood sampling: The study doctor or suitably trained delegate at site.
ii. PD blood sampling: The study doctor or suitably trained delegate at site.
iii. Blood sampling for research cytokine analysis: The study doctor or suitably trained delegate at site.
iv. Blood sampling for ADA: The study doctor or suitably trained delegate at site.
v. Cardiac telemetry monitoring: The study doctor or suitably trained delegate at site.
vi. Soluble CD25 analysis: The study doctor or suitably trained delegate at site.
vii. Blood sample exploratory analysis: The study doctor or suitably trained delegate at site.

Study burden and risks

The potential downsides and risks of participating in the study are that patients will have a series of routine exams that can be inconvenient or slightly painful. Examination procedures related to disease treatment are performed in the hospital by a qualified nurse, doctor, or appropriately trained health professional.

Strategies will be implemented during the course of the trial to minimize study participant*s risk* those include close monitoring of patients' health status through prolonged hospitalization of study participants for the treatment of sHLH at centers with access to emergency assistance equipment.

All patients will be fully informed of all study tests and what is required of them to take part in the study. Each patient will be asked to complete the consent form in order to participate in the study. Patients will be asked to provide written Informed Consent to screening assessments and also written informed consent to undergo study specific activities.

Currently ELA026 is also under evaluation in Healthy Volunteers which is ongoing in Austria so safety data will be collected.

Throughout the study the health of the subject will be regularly monitored and appropriate medical intervention will be available if required. The only information on side effects comes from studies in animals.

The study drug could cause lower white blood cell that may lead to infections. Sometimes participants can have allergic reaction. The potential risks based on non-clinical studies have been described in the Investigator's brochure (section 6.9).

Risk associated with the study procedures:
Blood samples: May cause discomfort, pain and minor infection but it can be easily treated.
Cardiac monitoring: ECG electrodes may cause local allergic reaction.
Abdominal ultrasound: There is no risk.

Measures to minimize the study participant's risk include:
- Lower dose levels, slower infusion and sequential dosing in the first cohort.
- Premedication with steroids, anti-histamines.
- Close monitoring through laboratory parameters, as well as cardiac telemetry, pulse oximetry and blood pressure measurements prior, during and post drug administration.
- Available interventional support.

Due to COVID, the Sponsor will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to study participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

Overall Benefit: Risk Conclusion:
Taking into account the measures taken to minimize risk to participants taking part in this study, the potential risks associated with ELA026 are justified by the anticipated benefits that may be afforded to participants with sHLH.

Contacts

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Age
1. >=12 years at the time of sHLH diagnosis (Cohort 1)
2. >=6 years at the time of sHLH diagnosis (Cohorts 2-4)

Type of Participant and Disease Characteristics (Cohort 1-2)
1. Treatment naïve (participants >=12 years of age only), OR
2. Relapsed or refractory sHLH defined as:
a. Participant has failed to respond to 2 weeks of treatment with tociluzumab, anakinra, or other HLH therapy with a less than 50% decrease in serum ferritin, OR
b. Participant has received 4 doses of etoposide with a less than 50% decrease in serum ferritin 72 hours after last dose, OR
c. On a case-by-case basis as determined by the Medical Monitor

Type of Participant and Disease Characteristics (Cohort 2 as of amendment 4, Cohort 3-4)
1. Treatment naïve, OR
2. Early refractory sHLH defined as:
a. The participant receiving approximately <1 week of any HLH-directed therapy with insufficient clinical or laboratory response judged by investigator at screening, OR
b. On a case-by-case basis as determined by the Medical Monitor

3. Participants must meet one of the following:
a. Participant has an sHLH confirmed diagnosis (inclusive of MAS) based on fulfilling at least 5 of the 8 modified HLH-2004 criteria below. These criteria may have been assessed prior to the screening period. Participants not fulfilling at least 5 of the 8 modified HLH-2004 criteria may be considered on a case-by-case basis if the diagnosis of sHLH is clinically established especially if one of the criterion is a specialized test result that is performed by a reference laboratory and is not yet available.

Clinical Criteria
1. Fever
2. Splenomegaly
Laboratory Criteria
1. Cytopenia (affecting >=2 of 3 lineages in the peripheral blood): Hemoglobin (<90 g/L), Platelet (<100 x 10*9/L), Neutrophil (<1.0 x 10*9/L)
2. Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides >=265 mg/dL or >=3.0 mmol/L, fibrinogen <=1.5 g/L
Histopathologic Criteria
1. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver
2. Low or absent NK-cell activity (according to laboratory reference)
3. Ferritin >=500 microgram/L (or ng/mL)
4. Elevated sCD25 (e.g., soluble CD25, also known as soluble IL-2 receptor)
OR
b. Participants may be diagnosed with malignancy-associated HLH (mHLH) by meeting the optimized HLH inflammatory (OHI) Index of

sCD25 >3900 U/mL (or 23,400 in pg/mL) and ferritin >1000 ng /mL (Zoref-Lorenz et al, 2022).

Sex and Contraception
1. Male or female
Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
2. Female participants must be either of non-reproductive potential (ie., premenarchal or post menopausal by history with no menses for >=1 year; or have a history of hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or, if of childbearing potential, must have a negative pregnancy test in serum prior to trial entry and must be willing to practice at least one of the following highly effective methods of birth control (<1% failure rate per year) at least from 28 days prior to study drug initiation to 30 days after the last dose of study drug:
a. True abstinence, when this is in line with the preferred and usual lifestyle of the participant, from sexual intercourse with a member of the opposite sex;
b. Sexual intercourse with vasectomized male;
c. Hormonal female contraceptive (oral, parenteral, intravaginal, implantable, or transdermal) for at least 3 consecutive months prior to study intervention administration (when not clinically contraindicated as in breast, ovarian and endometrial cancers);
d. Use of an intrauterine contraceptive device.
3. Male participants must be willing to use a condom during penilevaginal intercourse with female partners of child-bearing potential, throughout the study and up to 60 days after the last dose.

Informed Consent
1. Participant or legally authorized representative(s) (LAR) capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Minor participants must be capable of giving written assent as appropriate per the applicable age (per local regulatory requirements)

Exclusion criteria

Medical Conditions
1. Known or previous treatment for primary HLH.
2. Any other significant concurrent, uncontrolled medical condition that in the opinion of the Investigator contraindicates participation in this study.
3. Unknown trigger for sHLH
4. Active, relapsed/refractory malignancy for which no suitable

therapies are available to treat the malignancy triggering the HLH
Prior/Concurrent Therapy
1. Allogeneic hemopoietic stem cell transplant (HSCT) within 100 days of the first dose of ELA026.
2. Ongoing administration of any therapies used primarily to treat HLH excluding dexamethasone.
3. Live or attenuated vaccine received within 6 weeks or bacille Calmette-Guerin (BCG) vaccine within 12 weeks prior to Screening.
Other
1. History of hypersensitivity or allergy to dexamethasone.
2. History of hypersensitivity or allergy to any components of ELA026.
3. Currently breastfeeding.
4. Unwilling or unable to comply with trial.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ELA026
Generic name:	ELA026

Ethics review

Approved WMO

Date:	08-04-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2024
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	EUCTR2021-001387-20-NL
CCMO	NL79393.000.22

Study results

Summary results
Trial never started