Phase 1/2 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of NTLA-2002 in Adults with Hereditary Angioedema (HAE)

Published: 30-07-2021
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This study has been transitioned to CTIS with ID 2024-512317-40-00 check the CTIS register for the current data. Phase I Primary Objective• To evaluate the safety of NTLA-2002 and identify dose(s) for use in Phase 2Secondary Objectives• To evaluate...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON54405

Source
ToetsingOnline

Brief title
NTLA-2002 in Adults with Hereditary Angioedema (HAE)

Condition

- Congenital and hereditary disorders NEC

Synonym
HAE, Hereditary Angioedema

Research involving
Human

Sponsors and support

Primary sponsor: Intellia Therapeutics, Inc.
Source(s) of monetary or material Support: Commercial Study

Intervention

Keyword: HAE, Hereditary Angioedema, Intellia, NTLA-2002

Outcome measures

Primary outcome

Phase 1

• Safety and tolerability as determined by adverse events (AEs)

• Dose-limiting toxicities (DLTs)

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Phase 2

• Number of HAE attacks per month (by HAE Attack Assessment and Reporting Procedure and Reporting Procedure - see Section 10.3), Weeks 1 to 16

Secondary outcome

Phase 1 Secondary

• Change from baseline in total plasma prekallikrein/kallikrein protein level.

• Plasma and urine concentrations for DMG-PEG2k, LP000001, clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) messenger ribonucleic acid (mRNA), and single guide RNA (sgRNA).

Phase 1 Exploratory

• Number of HAE attacks per month (by HAE Attack Assessment and Reporting Procedure - see Section 10.3) and number of HAE attacks requiring acute therapy per month (Weeks 1 to 16, Weeks 5 to 16)

• Incidence and titer of anti-drug antibodies (ADA) to NTLA-2002 and anti-Cas9 protein antibodies.

• Change from baseline in plasma kallikrein activity

Phase 2 Secondary

• Safety and tolerability as determined by adverse events (AEs).

• Number of HAE attacks per month (by HAE Attack Assessment and Reporting Procedure - see Section 10.3) (Weeks 5 to 16) and number of HAE attacks requiring acute therapy per month (Weeks 1 to 16, Weeks 5 to 16)

• Number of moderate or severe HAE attacks per month (Weeks 5 to 16)

• Change from baseline in total plasma prekallikrein/kallikrein protein level.

• Plasma and urine concentrations for DMG-PEG2k, LP000001, Cas9 mRNA, and sgRNA

Phase 2 Exploratory

• Incidence and titer of ADA to NTLA-2002 and anti-Cas9 protein antibodies

• Change from baseline in utilization of on-demand HAE medications for attacks (Weeks 1 to 16, Weeks 5 to 16)

• Change from baseline in healthcare utilization for HAE attacks (Weeks 1 to 16, Weeks 5 to 16)

• Change from baseline in quality of life (QoL) parameters as measured by MOXIE Angioedema QoL instrument, EQ-5D-5L, and WPAI-GH.

• Change from baseline in plasma kallikrein activity

Study description

Background summary

Hereditary Angioedema (HAE) is a rare, autosomal dominant genetic disorder characterized by severe recurring and unpredictable inflammatory attacks in various organs and tissues of the body which can be painful, debilitating, and life-threatening. When a person has HAE, it means that they were born with a mutation on the Serping 1 gene, causing a haploinsufficiency of C1INH protein activity. This mutation causes the production of abnormal PKK which, in turn, causes an abnormal increase in a protein called *bradykinin* which is responsible for the symptoms of HAE. NTLA-2002 has been developed to potentially treat HAE, by disabling the KLKB1 gene within the liver. NTLA 2002 consists of a CRISPR/Cas9 gene editing system, which can disable the KLKB1 gene in DNA. Because the KLKB1 protein is produced in the liver, NTLA-2002 is packaged within *lipid nanoparticles* (LNP) which are able to deliver NTLA-2002 directly into the liver and avoid other organs and tissues.
If enough copies of the abnormal KLKB1 gene are removed from the liver, then it will stop the production of PKK, which will stop the excessive build-up of bradykinin. As a result of this decreased bradykinin, HAE disease symptoms may also be reduced.
NTLA-2002 is an investigational drug being studied as a potential new treatment for HAE and this study will investigate the effects of NTLA-2002 in patients with HAE. The purposes of this study are to:
• Evaluate how safe and well-tolerated different doses of NTLA-2002 is, in patients with HAE.
• Evaluate how much and how quickly NTLA-2002 is absorbed into the blood, and then broken down or eliminated from the body.
• Evaluate the effect of NTLA-2002 on HAE attacks.
• Assess the body*s immune response to NTLA-2002
• Evaluate change in utilization of on-demand HAE medication and in healthcare for HAE attacks

Study objective

This study has been transitioned to CTIS with ID 2024-512317-40-00 check the CTIS register for the current data.

Phase I
Primary Objective
• To evaluate the safety of NTLA-2002 and identify dose(s) for use in Phase 2
Secondary Objectives
• To evaluate the pharmacodynamics (PD) of NTLA-2002
• To evaluate the pharmacokinetics (PK) of NTLA-2002
Exploratory Objectives
• To evaluate the effect of NTLA-2002 on Hereditary Angioedema (HAE) attacks

• To evaluate the immune response toNTLA-2002
• To evaluate alternate measures of the PD of NTLA-2002
Phase 2
Primary Objective
• To evaluate the effect of NTLA-2002 on HAE attacks
Secondary Objectives
• To evaluate the safety of the selected dose(s) NTLA-2002
• To evaluate alternate measures of the effect of NTLA-2002 on HAE attacks
• To evaluate the PD of NTLA-2002
• To evaluate the PK of NTLA-2002
Exploratory Objectives
• To evaluate the immune response to NTLA-2002
• To evaluate disease related outcomes
• To evaluate patient reported outcomes
• To evaluate alternate measures of the PD of NTLA-2002

Study design

The study design consists of 2 parts: Phase 1 and Phase 2. The Phase 1 portion of this study is an open-label, single ascending dose design of up to 30 Type I and II Hereditary Angioedema (HAE) subjects to characterize safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD). Analysis and review of the Phase 1 data will be used to identify up to 2 safe, active, and potentially efficacious doses that will be further evaluated in a randomized, double-blind, placebo-controlled expansion study (Phase 2) in up to 25 Type I and Type II HAE subjects to more fully assess the relationship among NTLA-2002 dose, the primary intended PD effect of reduction in total prekallikrein/kallikrein protein, safety, and therapeutic activity. Together, the 2 parts of this study will be used to identify and confirm the optimal biological dose (OBD) for future studies. The OBD is a dose that demonstrates safety, tolerability, and achieves maximum clinically meaningful reduction in HAE attacks. The screening period will be up to 42 days for subjects in Phase 1 and up to 56 days in Phase 2. Subjects will be observed continuously for at least 6 hours after therapy. For both Phase 1 and Phase 2, the primary observation period will be 16 weeks, followed by a long-term observation period lasting 88 weeks (104 weeks total observation after treatment). Some study visits may be conducted away from the study site (see Schedule of Activities [Section 1.3]). Options for these visits include, for example, a phone call, assessments by medical personnel at a subject*s home, or assessment by the subject*s local physician.
Phase 2 will enroll up to 25 subjects in up to 3 arms, including up to 2 arms receiving different doses of NTLA-2002 and 1 arm receiving saline placebo. NTLA-2002 doses selected for Phase 2 will be doses determined in Phase 1 to be safe and well-tolerated, with at least 60% reduction in mean prekallikrein/kallikrein protein measurements from baseline to nadir, and evidence of reduction in HAE attacks. Should 2 dose levels be proposed, the low dose level would be the minimum dose likely to achieve 60% reduction in

kallikrein protein by Week 4 in the typical (mean) subject. The high recommended dose level would be the minimum dose likely to achieve 60% reduction in kallikrein protein by Week 4 in 90% of the subjects. Acute medications to treat angioedema attacks may be used during the entire course of the study. After the 16-week primary observation period, a subject may also initiate other therapy to treat their HAE at the discretion of the Investigator. Once the OBD is identified in Phase 2, subjects who received a lower dose than the OBD in Phase 1 or 2 may be offered a single follow-on dose at the OBD. Subjects who received placebo will be offered a single dose at the OBD, after all subjects complete the Week 16 assessments (or have discontinued the study prior to Week 16 assessments) and the study has been unblinded. Subjects choosing these options will be required to re-start the Schedule of Activities from Dosing onwards. Detailed information for such subjects defining post follow-on dose endpoints, eligibility, and subsequent assessments will be informed by study data and provided in a substantial amendment prior to any subjects receiving a follow-on dose. of a minimum of 3 DLT evaluable subjects and maximum of 6 DLT evaluable subjects. The study also allows for up to 2 optional dose reduction cohorts, each consisting of a minimum of 3 DLT evaluable subjects and maximum of 6 DLT evaluable subjects. In total, up to 30 DLT evaluable subjects may be enrolled in Phase 1. NTLA-2002 will be dosed as shown in the table Cohort Dosing Overview (below and Table 6), with possible modifications of escalation/reduction as described.

Intervention

Non Clinical:
Informed Consent
Recivew of Inclusion/Exclusion Criteria
Demographic data and medical history
Concomitant medications use
HAE attack history
AE-QoL
Adverse events

Clinical:
Physical examination
Vital Signs
Focused PE
HBV and HCV serologies
safety laboratory tests
C1-INH
Drug Administration: an infusion of 250ml over 4 hours.
PK/PD/Biomarker/Immunogenicity Assessments

Study burden and risks

The risks involved in this study have been carefully assessed in animal studies, and in the Phase 1 portion of this study in adults with HAE. NTLA-2002 has been given to adults with HAE at doses of 25mg, 50mg, and 75mg.

Based on the studies using NTLA-2002 and safety information from other types of human drugs that contain lipid nanoparticles, the following risks have been identified:

• Infusion Related Reactions Reactions related to the IV infusion of the study drug have been seen in patients receiving NTLA-2002. These could include signs and symptoms such as fever, chills, low or high blood pressure, flushing, abdominal pain, headache, nausea, back pain sweating, slow or fast heart rate, rash, and/or shortness of breath occurring during the infusion or soon after the infusion. This type of reaction can overlap with symptoms of an allergic reaction, which may also include hives and wheezing. People with HAE may have an increased risk of an HAE attack occurring at the time of any medical procedure, including the IV infusion of study drug. Your doctor will discuss the best way for you to prepare for an HAE attack at the time of infusion and may recommend you receive C1 inhibitor prior to study drug infusion.
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Other potential risks of NTLA-2002 include:

• Increased Liver Enzymes (which may be a sign of inflammation or damage to the cells in the liver).
• Increased Risk of Thrombosis (formation of a blood clot).
• Decreased Ability to Form Blood Clots and Stop Bleeding.
• Unintended permanent changes in your DNA. The study drug (NTLA-2002) is designed to make specific, permanent changes at a particular location in your genetic material (KLKB1 gene). It has become apparent from previous laboratory research with the study drug, in human cells and using higher doses than given in this study, that administration of this medicine may also cause permanent genetic changes at other locations in your DNA. We do not know whether there is also a risk of changes occurring at other locations in your DNA in this study. In any case, we cannot rule out the risk of this. We think it is important that you know this because changes in your DNA may have serious consequences, such as the increasing the risk of developing cancer for example. All participants in trials of NTLA-2002 and related compounds will be asked to participate in follow-up studies for 15 years after they receive the study medication.

Allergic reactions are always possible with a drug that you have not taken before. Serious allergic reactions can be life-threatening. Symptoms of an allergic reaction may include:

o Rash or itching
o Sneezing or runny nose
o Swelling of face, tongue, or throat
o Abdominal pain or diarrhoea

o Difficulty breathing (wheezing)
o Irregular or racing heart rate
o Light-headedness or fainting
o Seizures

The medicinal product we are investigating can also have side effects that we do not know about at the moment.

Contacts

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Scientific
Intellia Therapeutics, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.
Participants are eligible to be included in the study only if all of the

following criteria apply:
1. Subjects >= 18 years of age at the time of signing the informed consent.
2. Documented diagnosis of HAE (Type I or II) confirmed by laboratory assessment of functional C1-INH level and C1-INH concentration:
a. For HAE Type I: Both functional C1-INH level AND C1-INH concentration should be <50% of normal limits (or per local standard)
b. For HAE Type II: Functional C1-INH level should be <50% of normal limits (or per local standard). C1-INH concentration may be normal or above normal.
C1-INH testing during screening, at either the central or an accredited local laboratory, or previously documented results from an accredited local laboratory may be used to confirm eligibility. If frequent use of C1-INH for the prevention or treatment of HAE attacks would confound interpretation of C1 INH testing, genetic testing for known variants in the SERPING1 gene in a local laboratory may be used to confirm eligibility upon consultation with the Sponsor.
3. Investigator-confirmed attacks (per Appendix 3 in Section 10.3):
a. Phase 1 only: Subjects must have an Investigator-confirmed and documented historical HAE attack number of at least 3 during the previous 3 months (90 days) from the start of screening.
b. Phase 2 only: Subjects must have an Investigator-confirmed and documented historical HAE attack number of at least 3 during the previous 3 months (90 days) to enter the Screening/Run-In period and an Investigator-confirmed and documented HAE attacks number of at least 2 during the up to 8-week (up to 56-day) Screening/Run-In period (or at least 3 to be eligible for early enrollment and randomization).
c. Netherlands only: For both Phase 1 and Phase 2, subjects must have had inadequate control of HAE attacks, as determined by the Investigator, while receiving at least one prior prophylactic regimen, or have required discontinuation from, or otherwise be ineligible for, available prophylactic agents.
4. Phase 2 only: Subjects must agree to refrain from the use of prophylactic therapies from within 5 half-lives prior to the start of the Screening/Run-In period through the end of the 16-week primary
observation period, and the Investigator must confirm that this is medically appropriate and does not place the subject at undue safety risk. See Section 10.2 for a list of prophylaxis agents, half-lives, and recommended wash-out period.
5. Subjects must have access to, and the ability to use, >= 1 acute medication(s) to treat angioedema attacks.
6. Subjects must meet the following laboratory criteria during Screening:
a. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin (see exception for Gilbert's Syndrome below) <= upper limit of normal (ULN) range at Screening.
b. For subjects with a history of Gilbert's Syndrome, total bilirubin <= 2 × ULN on screening evaluation.
c. Serum creatinine is <= ULN, or, for subjects in whom serum creatinine is above the ULN, they can be included if the estimated glomerular filtration rate

(eGFR) is > 60 mL/min/1.73 m2 as measured by the Modification of Diet in Renal Disease equation at Screening.
d. Platelet count >= 100,000 cells/mm3 at Screening.
e. Within reference range or Principal Investigator (PI)-determined clinically non-significant activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen and d-dimer levels at Screening.
7. Male subjects with partners of childbearing potential must agree to using a condom as of the date of informed consent and for 4 months after study drug administration.
8. Male subjects must agree not to donate sperm for 4 months after study drug administration. The time frame may be extended beyond the 4 months if sperm donation is contraindicated based on country-specific guidelines.
9. Female subjects of childbearing potential must agree to use a protocol-specified highly effective method of contraception (see Section 10.5) from completion of the informed consent process through 12 months after the last study drug administration. This is not required of female subjects who are either: a. Postmenopausal (defined as no menses for 12 months without an alternative medical cause) prior to Screening. In addition, at least 2 high follicle stimulating hormone (FSH) measurements in the postmenopausal range may be used to confirm a postmenopausal state in women with less than 12 months of amenorrhea and not using hormonal contraception or hormonal replacement therapy; OR
b. Surgically sterile (i.e., hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) at least 1 month prior to Screening.
10. Subjects must agree not to participate in another interventional study for the duration of this trial.
11. Subjects must be capable of providing signed informed consent.
12. France only: Adults subjects under guardianship are not considered able to provide informed consent.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:
1. Use of ecallantide from 1 week prior to the start of Screening through the 16-week primary observation period.
2. Use of C1 esterase inhibitor (C1-INH) for HAE within 5 half-lives of the agent before initiation of the Phase 2 Screening/Run-In period, i.e., 24-hour washout is required before starting the Screening/Run-In period after the use of rabbit purified C1-INH (ruconest), and 4-day washout is required before starting the Screening/Run-In period after the use of human plasma purified C1-INH (berinert). Note: during the Screening/Run-In period, C1-INH may be used to treat an acute HAE attack.
3. Concurrent diagnosis of any other type of recurrent angioedema, including acquired or idiopathic angioedema.

4. Subjects who have known hypersensitivity to any lipid nanoparticles (LNP) component (or its excipients) or who have previously received LNP and experienced any treatment-related clinically significant laboratory abnormalities or AEs listed below:
a. ALT or AST > 3 × ULN if baseline was normal or > 3 × baseline if baseline was above normal.
b. INR, aPTT or d-dimer > 1.5 × ULN if baseline was normal or > 1.5 × baseline if baseline was above normal.
c. Any LNP treatment-related AEs classified as CTCAE Grade 3 or higher.
d. Infusion-related reaction (IRR) to an LNP-containing product (or excipients) requiring treatment or discontinuation of infusion; NOTE: slowing of the infusion rate to mitigate an IRR is not considered exclusionary.
e. Any LNP treatment-related AEs which in the opinion of the Investigator should be exclusionary.
5. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption within 90 days prior to study drug administration.
6. Unable or unwilling to take the required pre-treatment medication regimen.
7. Female subjects of childbearing potential are excluded from the study if they:
a. are breastfeeding or plan to breastfeed during treatment and for an additional 12 months after the last study drug administration.
b. have a positive pregnancy test at screening and/or Day 1.
8. Antithrombotic therapy other than aspirin (e.g., warfarin, dabigatran, apixaban) within 14 days prior to study drug administration.
9. History of thrombophilia, or positive genetic test for Factor V Leiden and/or prothrombin 20210.
10. History of cirrhosis.
11. Known or suspected systemic viral, parasitic, or fungal infection including coronavirus disease (COVID-19) or received antibiotics for bacterial infection within 14 days prior to Screening.
12. History of Hepatitis B or C infection or positive Hepatitis B surface antigen (HbsAg) or Hepatitis C virus antibody (HCVAb) test at Screening.
13. History of positive human immunodeficiency virus (HIV) status.
14. Prior liver, heart, or other solid organ transplant or bone marrow transplant or anticipated transplant within 1 year of Screening. Note: prior history of or planned corneal transplant is not exclusionary.
15. Subject has a history of alcohol or drug abuse within 3 years prior to Screening.
16. Any condition, laboratory abnormality, psycho-social stressor, pattern of behavior, or other reason that, in the Investigator's opinion, could adversely affect the safety of the subject, impair the assessment of study results, or preclude compliance with the study.
17. Unwilling to comply with study procedures including follow-up as specified by the protocol or unwilling to cooperate fully with the Investigator.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-04-2022
Enrollment:	4
Type:	Actual

Ethics review

Approved WMO Date:	30-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-03-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	26-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-02-2024
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)

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
EU-CTR	CTIS2024-512317-40-00
EudraCT	EUCTR2021-001693-33-NL
ClinicalTrials.gov	NCT05120830
CCMO	NL78549.000.21