In vivo CRISPR/Cas9 editing of KLKB1 in patients with Hereditary Angioedema: A First-in-Human Study

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Clinical Trial Registration # NCT05120830
Hereditary Angioedema (HAE) is a genetic disease associated with significant morbidity.

WHAT IS HAE?
• Rare, autosomal dominant genetic disease
• Associated with frequent, severe and unpredictable attacks of painful swelling due to dysregulated bradykinin production

~1 in 50,000
HAE patients worldwide

SYMPTOMS OF HAE
• Painful swelling attacks in extremities, face, stomach and GI tract
• Swelling of throat may cause difficulty swallowing or breathing, and in severe cases, can be fatal

Every 7-14 days
Average frequency of attacks for untreated patients

Significant treatment burden exists
Chronic dosing is required with current treatments

Targeting *KLKB1* gene expression for long-term prophylaxis of HAE attacks

Knocking out *KLKB1* gene is intended to prevent production of kallikrein.

Decreasing kallikrein rebalances the pathway by reducing bradykinin production.

Reducing bradykinin prevents HAE attacks.

Kallikrein is a clinically validated therapeutic target for preventing HAE attacks.


This presentation includes data for an investigational product not yet approved by regulatory authorities.
NTLA-2002 is a novel, investigational CRISPR/Cas9-based in vivo gene editing therapy

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NTLA-2002 global Phase 1/2 study design:
Two-part, multi-center study of NTLA-2002 in adults with HAE Types I and II

Today's interim data cover the Phase 1 part of the study (Data cut-off: 28 September 2022)

**PHASE 1**
Open-label, single-ascending dose

**Intervention:**
Single dose administered via an intravenous (IV) infusion

**PRE-TREATMENT REGIMEN**
**Day -1:** Oral dexamethasone 8 mg (or equivalent)
**Day 1:** IV dexamethasone 10 mg (or equivalent), IV or oral H1 and H2 blocker, C1-INH

**PHASE 1 OBJECTIVES**
Evaluate safety & tolerability

**OTHER OBJECTIVES**
PK, PD, clinical efficacy (attacks)

**Dose Levels:**
- 75 mg (n=3)
- 50 mg (n=4)
- 25 mg (n=3)

**PHASE 2**
Expansion study to confirm recommended dose

**Primary Objectives**
Clinical efficacy (attacks through week 16)

**Other Objectives**
PD, safety & tolerability, PK, QoL

**Randomized**
- Dose 1 (n=10)
- Dose 2 (n=10)
- Placebo Arm (n=5)

50 mg cohort allowed up to 6 patients per protocol

C1-INH, C1 Esterase Inhibitor; H1, Histamine Receptor 1; H2, Histamine Receptor 2
PD, Pharmacodynamics; PK, Pharmacokinetics; QoL, Quality of Life
Key eligibility criteria (Phase 1)

**INCLUSION**

✓ Documented diagnosis of Type I or Type II HAE

✓ At least 3 investigator-confirmed HAE attacks within 90 days prior to screening

✓ Access to acute therapies to treat HAE attacks

✓ Concurrent therapy with standard-of-care, long-term prophylaxis allowed

**EXCLUSION**

✗ Concomitant use of ecallantide or lanadelumab

✗ Known hypersensitivity or prior infusion-related reaction to LNP components

✗ History of cirrhosis, Hepatitis B, Hepatitis C or HIV
# Patient demographics & characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>25 mg n = 3</th>
<th>50 mg n = 4</th>
<th>75 mg n = 3</th>
<th>All patients N = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age, years</strong> (Min, Max)</td>
<td>30 (26, 52)</td>
<td>65 (52, 73)</td>
<td>45 (27, 49)</td>
<td>51 (26, 73)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (100%)</td>
<td>1 (25%)</td>
<td>2 (67%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>–</td>
<td>3 (75%)</td>
<td>1 (33%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td><strong>Median Weight, kg</strong> (Min, Max)</td>
<td>83 (78, 135)</td>
<td>86 (74, 107)</td>
<td>72 (64, 84)</td>
<td>83 (64, 135)</td>
</tr>
<tr>
<td><strong>HAE Type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>2 (67%)</td>
<td>1 (25%)</td>
<td>2 (67%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Type II</td>
<td>1 (33%)</td>
<td>2 (50%)</td>
<td>1 (33%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>–</td>
<td>1 (25%)</td>
<td>–</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>

*Patient diagnosed based on C1-INH functional assay alone

Data Cut Off: 28 September 2022

HAE, Hereditary Angioedema

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### Patient reported HAE attack history

<table>
<thead>
<tr>
<th>Parameter</th>
<th>25 mg n = 3</th>
<th>50 mg n = 4</th>
<th>75 mg n = 3</th>
<th>All patients N = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Use of Long-Term Prophylaxis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (67%)</td>
<td>4 (100%)</td>
<td>3 (100%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>No</td>
<td>1 (33%)</td>
<td>–</td>
<td>–</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Concomitant Long-Term Prophylaxis*, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (67%)</td>
<td>3 (75%)</td>
<td>1 (33%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>No</td>
<td>1 (33%)</td>
<td>1 (25%)</td>
<td>2 (67%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Historical Monthly Attack Rate, Mean (SD)</td>
<td>6.0 (6.92)</td>
<td>1.2 (0.47)</td>
<td>7.7 (8.00)</td>
<td>4.6 (5.83)</td>
</tr>
<tr>
<td>Typical Attack Severity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (33%)</td>
<td>2 (50%)</td>
<td>1 (33%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (33%)</td>
<td>2 (50%)</td>
<td>1 (33%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (33%)</td>
<td>0</td>
<td>1 (33%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>

*Ongoing at time of study drug infusion

This presentation includes data for an investigational product not yet approved by regulatory authorities.
NTLA-2002 was generally well-tolerated across all dose levels evaluated

- Across all dose levels, the most frequent AEs were infusion-related reactions and fatigue
  - All TEAEs were mild or moderate in severity (Grade 1 or 2 only)
  - All infusion-related reactions were considered mild (n = 5) or moderate (n = 2), resolving without clinical sequelae
  - All patients received a full dose of NTLA-2002

- No clinically significant laboratory findings observed
  - No increases in activated partial thromboplastin time

- No treatment emergent SAEs or ≥ Grade 3 TEAEs were observed
Majority of adverse events were mild in severity

<table>
<thead>
<tr>
<th>Adverse events occurring in ≥ 2 patients</th>
<th>25 mg n = 3</th>
<th>50 mg n = 4</th>
<th>75 mg n = 3</th>
<th>All patients N = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr. 1</td>
<td>Gr. 2</td>
<td>Gr. 1</td>
<td>Gr. 2</td>
</tr>
<tr>
<td>Any TEAE (max grade)</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>COVID-19</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Headache</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

All other AEs (abdominal discomfort, abdominal pain, abdominal pain upper, arthralgia, asthenia, chest injury, depressed mood, diarrhea, disease prodromal stage, flank pain, insomnia, myalgia, rhinitis, sinusitis, soft tissue injury, somnolence, vomiting) were reported in one patient.

Patients counted once per row with highest grade reported.

Gr., Grade; TEAE, treatment-emergent adverse event
NTLA-2002 resulted in rapid and deep plasma kallikrein reduction at all dose levels

Mean (SD) % Plasma Kallikrein Reduction by Dose Level

-81%

-64%

-92%

Baseline

4 8 15 22 28

Days

8 16 24 32

Weeks

Dashed line represents targeted minimum reduction

SD, Standard Deviation

This presentation includes data for an investigational product not yet approved by regulatory authorities.
Clinically meaningful reductions in investigator-confirmed monthly attack rate observed through pre-specified 16-week follow-up period

<table>
<thead>
<tr>
<th>Administration of NTLA-2002</th>
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<tbody>
<tr>
<td>SCREENING</td>
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<tr>
<td></td>
</tr>
<tr>
<td>25 mg n = 3</td>
</tr>
<tr>
<td>Patient 1</td>
</tr>
<tr>
<td>Patient 2</td>
</tr>
<tr>
<td>Patient 3</td>
</tr>
<tr>
<td>75 mg n = 3</td>
</tr>
<tr>
<td>Patient 1</td>
</tr>
<tr>
<td>Patient 2</td>
</tr>
<tr>
<td>Patient 3</td>
</tr>
</tbody>
</table>

Analysis including 90-Day patient reported historical and screening period resulted in mean (SD) percent change of -94% (10%) and 90% (13%) in monthly attack rate for Week 1 to 16 in the 25 mg and 75 mg cohorts, respectively.

SD, Standard Deviation

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All patients have an ongoing attack-free interval with range of 2.3 to 10.6 months.

### SCREENING PERIOD

- **Historic monthly attack rate prior to screening**
  - Pt. 1: 1.9
  - Pt. 2: 14.0
  - Pt. 3: 2.2

### PRIMARY OBSERVATION PERIOD

- **Administration of NTLA-2002**
- **Week 16**

### POST-PRIMARY OBSERVATION PERIOD

- **No concomitant prophylaxis**
  - Pt. 1: 10.6 months
  - Pt. 2: 5.5 months
  - Pt. 3: 8.3 months

#### ATTACK SEVERITY:
- **Mild**
- **Moderate**
- **Severe**

#### PROPHYLAXIS WITHDRAWAL:
- **Danazol withdrawn at day 151**
- **Berotralstat withdrawn at day 112**

#### Days
- -56 -42 -28 -14 0 14 28 42 56 70 84 98 112 126 140 154 168 182 196 210 224 238 252 266 280 294

#### Weeks 1-16

#### Months 4-10

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Data Cut Off: 28 September 2022
A single dose of NTLA-2002 led to robust, dose-dependent and durable reductions in total plasma kallikrein levels

- Mean plasma kallikrein reductions between 65% and 92% were observed at nadir, with responses persisting for the duration of follow-up
- All patients in 25 mg and 75 mg cohorts have an ongoing attack-free interval of 2.3 to 10.6 months
  - First three patients treated have now been attack-free for 5.5 – 10.6 months
- Mean reductions in attacks from baseline of 89% at both 25 mg and 75 mg dose level (weeks 5-16)
- Patients who discontinued prophylactic therapy after NTLA-2002 infusion remained attack-free
- NTLA-2002 was generally well-tolerated; all AEs were of mild or moderate severity
- No further dose escalation is planned, Phase 2 expected to commence in first half of 2023

These data support the promise of CRISPR-based in vivo genome editing in humans
Acknowledgements

Study participants and their families and caregivers

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  – Pharmacy: Ben Oldfield, Yining Han, Sandy Chang

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