UPDATED SAFETY AND EFFICACY OF NTLA-2002, A CRISPR/CAS9-BASED GENE EDITING THERAPY TARGETING *KLKB1*, IN A PHASE 1 STUDY OF PATIENTS WITH HEREDITARY ANGIOEDEMA

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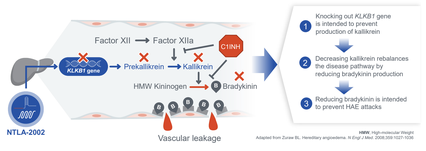
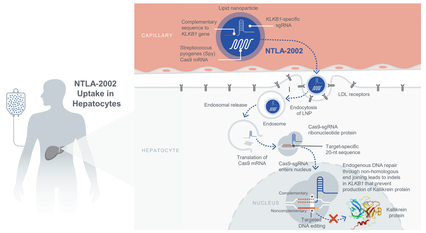
BACKGROUND

FIGURE 1: TARGETING *KLKB1* GENE EXPRESSION FOR LONG-TERM PROPHYLAXIS OF HEREDITARY ANGIOEDEMA (HAE) ATTACKS



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

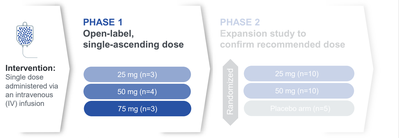
FIGURE 2: NTLA-2002 MECHANISM OF ACTION



- NTLA-2002 is a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy for the treatment of HAE

METHODS

FIGURE 3: NTLA-2002 PHASE 1/2 STUDY DESIGN: TWO-PART, MULTICENTER STUDY IN ADULTS WITH HAE TYPES I AND II



- After a single dose of NTLA-2002, the primary observation period was 16 weeks, followed by a long-term observation period lasting 88 weeks for a total of 104 weeks of observation
- The data cutoff date was 17 February 2023

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

- x Concomitant use of ecallantide or lanadelumab
- x Known hypersensitivity or prior infusion-related reaction to LNP components
- x History of cirrhosis, Hepatitis B, Hepatitis C or HIV

RESULTS

TABLE 1: PATIENT DEMOGRAPHICS & CHARACTERISTICS

Parameter	25 mg n = 3	50 mg n = 4	75 mg n = 3	All patients N = 10
Age, years Median (range)	30 (26-52)	65 (52-73)	45 (27-49)	51 (26-73)
Sex, n (%) Male Female	3 (100) –	1 (25) 3 (75)	2 (67) 1 (33)	6 (60) 4 (40)
Weight, kg Median (range)	83 (78-135)	86 (74-107)	72 (64-84)	83 (64-135)
HAE Type, n (%) Type I Type II	2 (67) 1 (33)	2 (50) 2 (50)	2 (67) 1 (33)	6 (60) 4 (40)
Prior Use of Long-Term Prophylaxis, n (%) Yes No	2 (67) 1 (33)	4 (100) –	3 (100) –	9 (90) 1 (10)
Concomitant Long-Term Prophylaxis*, n (%) Yes No	2 (67) 1 (33)	3 (75) 1 (25)	1 (33) 2 (67)	6 (60) 4 (40)
Historical Monthly Attack Rate, Mean (SD)	6.0 (6.92)	1.2 (0.47)	7.7 (8.00)	4.6 (5.83)
Typical Attack Severity, n (%) Mild Moderate Severe	1 (33) 1 (33) 1 (33)	2 (50) 2 (50) 0	1 (33) 1 (33) 1 (33)	4 (40) 4 (40) 2 (20)

*Ongoing at time of study drug administration.
SD, Standard Deviation.

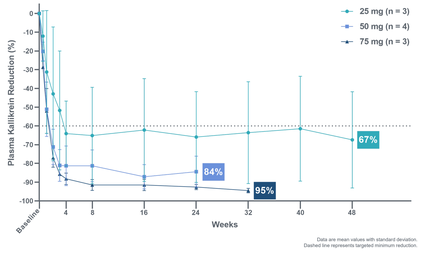
TABLE 2: TREATMENT-EMERGENT ADVERSE EVENTS (TEAEs)

Adverse events occurring in ≥ 2 patients	25 mg n = 3		50 mg n = 4		75 mg n = 3		All patients N = 10	
	Gr. 1	Gr. 2	Gr. 1	Gr. 2	Gr. 1	Gr. 2	Gr. 1	Gr. 2
Any TEAE (max grade)	2	1	2	1	1	2	5	4
Infusion-related reaction	2	–	1	1	2	1	5	2
Fatigue	1	–	2	1	2	–	5	1
COVID-19	3	–	1	–	1	–	5	–
Upper respiratory tract infection	1	–	1	–	2	–	4	–
Oropharyngeal pain	2	–	–	–	1	–	3	–
Abdominal pain	1	–	–	–	1	–	2	–
Headache	–	–	–	–	2	–	2	–
Viral upper respiratory tract infection	–	–	–	–	2	–	2	–

Patients counted once per row with highest grade reported.
Gr., Grade (NCI-CTCAE version 5.0); **TEAE**, Treatment-emergent Adverse Event

- NTLA-2002 was generally well-tolerated across all dose levels evaluated
- No clinically significant laboratory findings were observed
- No treatment-emergent serious AEs or ≥ Grade 3 TEAEs were observed
- Median duration of follow-up for all patients was 9 months (range, 5.6-14.1 months)

FIGURE 4: MEAN REDUCTION IN PLASMA KALLIKREIN BY DOSE LEVEL



Data are mean values with standard deviation.
Dashed line represents targeted minimum reduction.

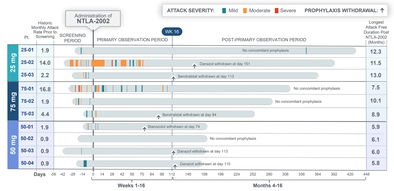
- NTLA-2002 resulted in dose-dependent and durable reductions in plasma kallikrein protein

TABLE 3: REDUCTION FROM BASELINE IN INVESTIGATOR-CONFIRMED MONTHLY ATTACK RATE

	25 mg n = 3	50 mg n = 4	75 mg n = 3	All patients N = 10
Week 1-16	-91% (16%)	-97 (5%)	-80% (30%)	-89 (19%)
Week 5-16	-89% (19%)	-100% (0%)	-87% (23%)	-92% (16%)
Week 1-24	-94% (11%)	-98% (3%)	-86% (20%)	-93% (13%)
On-study period	-95% (4%)	-98% (3%)	-93% (11%)	**-95% (6%)**

Data are mean % change from baseline (standard deviation).
Baseline is defined as up to 42 days screening period prior to the administration of NTLA-2002.
On-study period is defined as the time from the dosing of NTLA-2002 through the last HAE attack assessment as of the data cutoff date.

FIGURE 5: HAE ATTACKS DURING SCREENING, PRIMARY OBSERVATION, AND ONGOING POST-PRIMARY OBSERVATION PERIOD



- Robust and durable attack reductions observed in all patients after a single dose of NTLA-2002
  - Across all patients, NTLA-2002 led to a 95% mean reduction in monthly HAE attack rate through latest follow-up assessment; 89% mean reduction in the 16-week primary observation period
  - Longest attack-free interval is 13.0 months and ongoing through the latest follow-up assessment
- All 6 patients who were taking concomitant long-term prophylaxis (LTP) at study start were able to withdraw their prophylaxis with no subsequent attacks
- Patient 25-01 experienced a mild swelling of the hand precipitated by a sports injury on Day 343
  - Investigator confirmed this as a mild HAE attack, but no medical intervention or acute therapy was needed with swelling resolving within 2 days
  - Patient 25-01 was the only patient who did not achieve the targeted 60% minimum kallikrein reduction post NTLA-2002 administration; reduction at week 48 was 40%

CONCLUSIONS

- NTLA-2002 was generally well-tolerated at all doses; all AEs were either Grade 1 or 2
- NTLA-2002 resulted in dose-dependent and durable reductions in plasma kallikrein protein
- Robust and durable attack reductions observed in all patients after a single dose of NTLA-2002
  - Across all patients, NTLA-2002 led to a 95% mean reduction in monthly HAE attack rate through the latest follow-up assessment; 89% mean reduction in the 16-week primary observation period
  - Longest ongoing attack-free interval is 13.0 months and ongoing through latest follow-up assessment
  - All patients were well controlled, with 9 out of 10 patients remaining completely attack free, following the 16-week observation period
- Patients who discontinued concomitant long-term prophylaxis after administration of NTLA-2002 remained well-controlled, with no subsequent HAE attacks
- The Phase 2 portion of the study is underway with enrollment expected to be complete in the second half of 2023

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Conflict of Interest Disclosures:

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