



**NTLA-2002:
CRISPR/Cas9-Mediated Gene
Knockout of *KLKB1* for
Hereditary Angioedema**

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Jessica Seitzer | February 27, 2021

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NTLA-2002: CRISPR/Cas9-mediated gene knockout of *KLKB1* to treat hereditary angioedema

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Rationale: Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of debilitating and potentially fatal swelling in various parts of the body including face, hand and airways. Prophylactic treatment options for HAE patients have dramatically improved in recent years, significantly reducing the frequency of attacks and overall disease burden but all require chronic, potentially life-long administration. The emergence of genome editing technologies as a new therapeutic modality offers the promise of curing many genetic diseases. To this end, Intellia Therapeutics is developing NTLA-2002, an investigational CRISPR/Cas9-based therapy targeting *KLKB1* for the treatment of HAE.

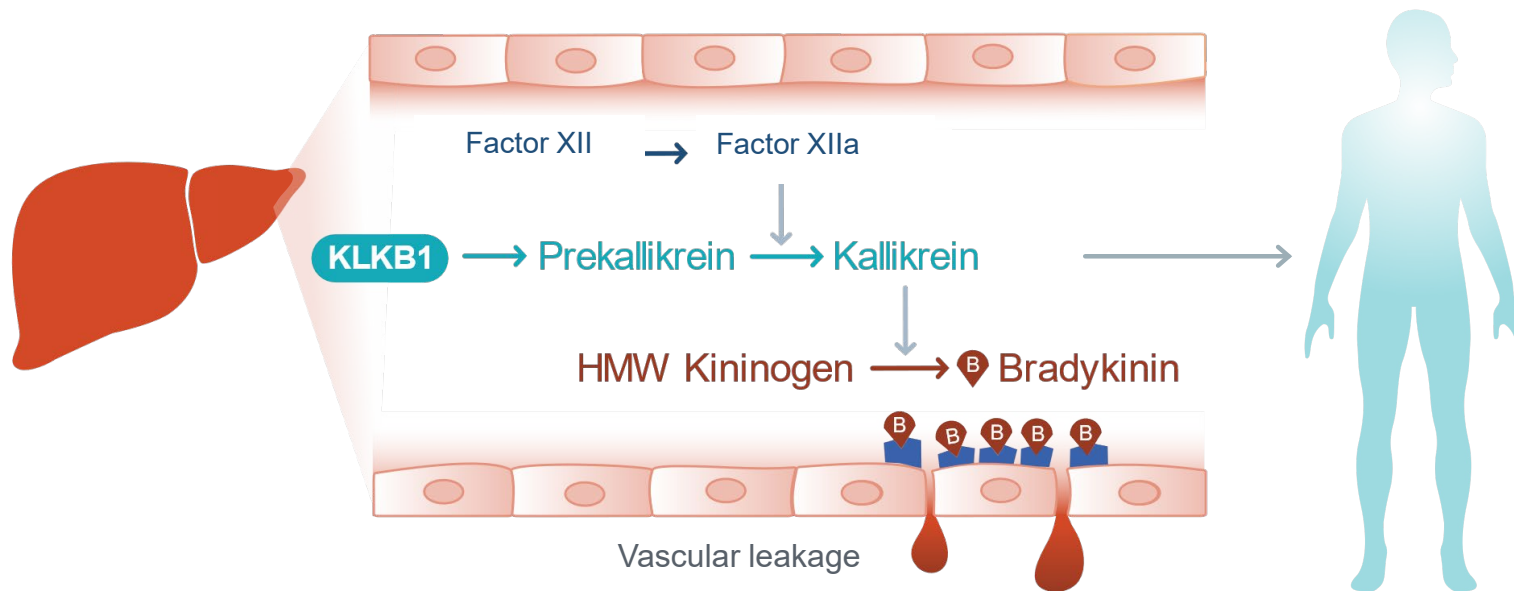
Methods: Guide RNA targeting human- and cynomolgus monkey-specific *KLKB1* were identified and formulated using Intellia's modular CRISPR/Cas9 lipid nanoparticle (LNP) platform technology. These formulations were evaluated in a humanized *KLKB1* mouse model (hu*KLKB1*) and the cynomolgus monkey. *KLKB1* gene editing, plasma kallikrein concentration and activity, and vascular leakage were evaluated.

Results: In the hu*KLKB1* mouse, a single administration of NTLA-2002 resulted in robust *KLKB1* gene editing (~70%), subsequent reductions in total plasma kallikrein (>90%) and abrogation of captopril-induced vascular leakage. In the monkey, a single administration of cyno-specific LNP formulation resulted in robust gene editing (~70%) and reductions in both total kallikrein protein and activity (>95%). Further, these reductions have been maintained for at least 15 months in an ongoing monkey study.

Conclusions: A single administration of NTLA-2002 resulted in robust, durable reduction of kallikrein protein and activity, supporting further development as a potential one-time treatment option for patients with HAE.

Dysregulated Kallikrein-Bradykinin Cascade Mediates Hereditary Angioedema Attacks

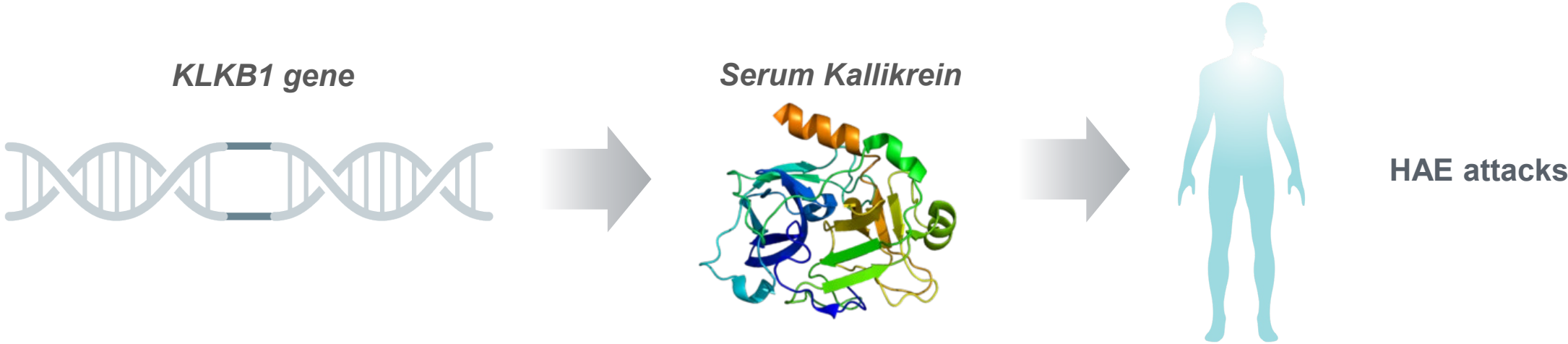
PEOPLE WITH HEREDITARY ANGIOEDEMA (HAE)



C1-INH deficiency results in unregulated release and buildup of bradykinin, activating endothelial cells and leading to angioedema in potentially any part of the body

- Attacks can occur every **7-14** days on average for untreated patients¹
- **1 in 50,000** HAE patients worldwide¹
- **Chronic dosing** is required with current treatments

Intellia's HAE Strategy: Achieve Profound, Stable Prophylaxis by Permanently Disabling the Kallikrein Gene Using CRISPR/Cas9 Gene Editing

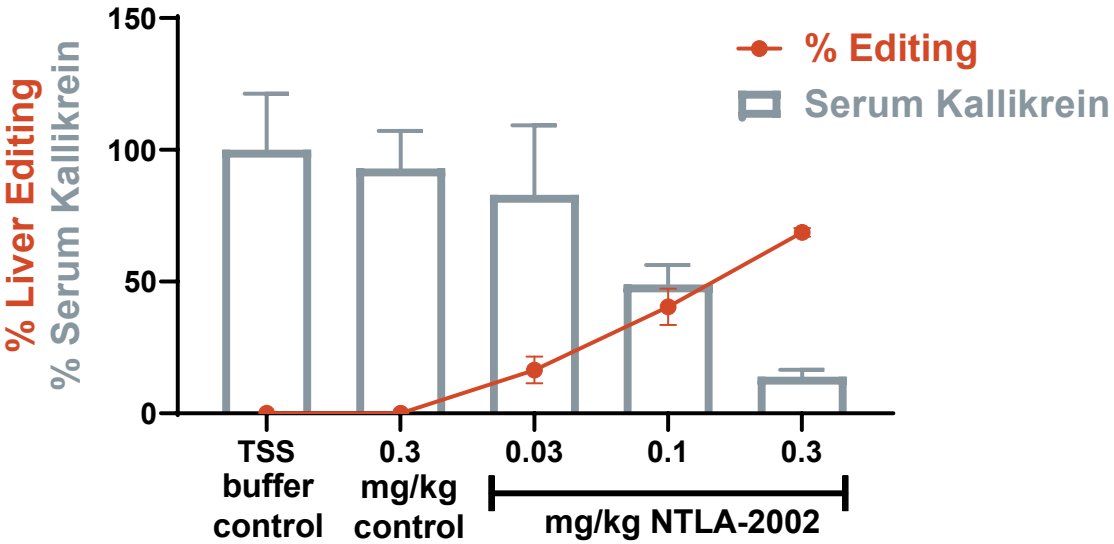


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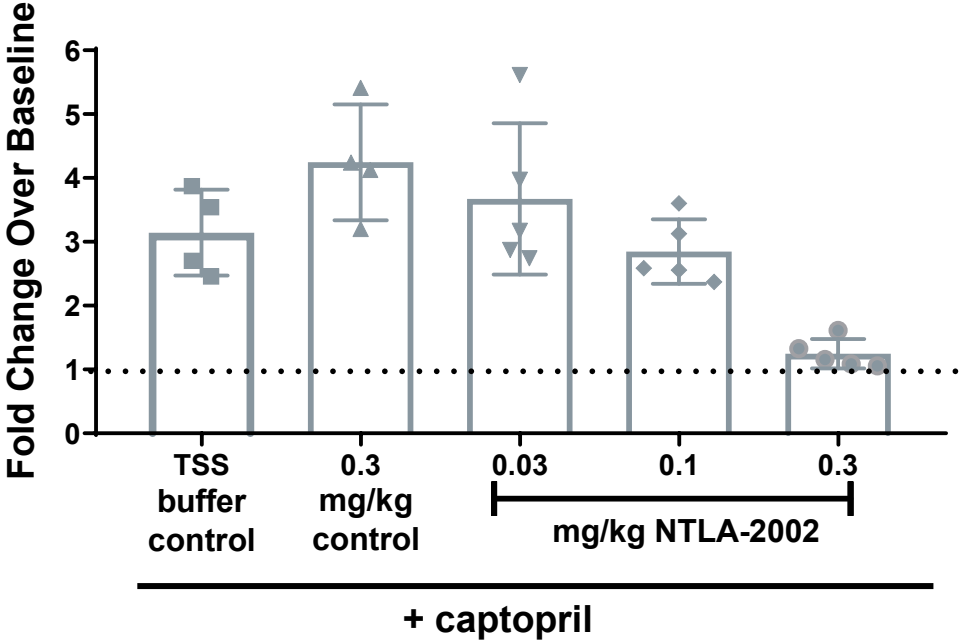


NTLA-2002 Prevents Vascular Leakage in huKLKB1 Captopril-Induced Permeability Mouse Model

huKLKB1 Mouse Liver Editing and Serum Kallikrein

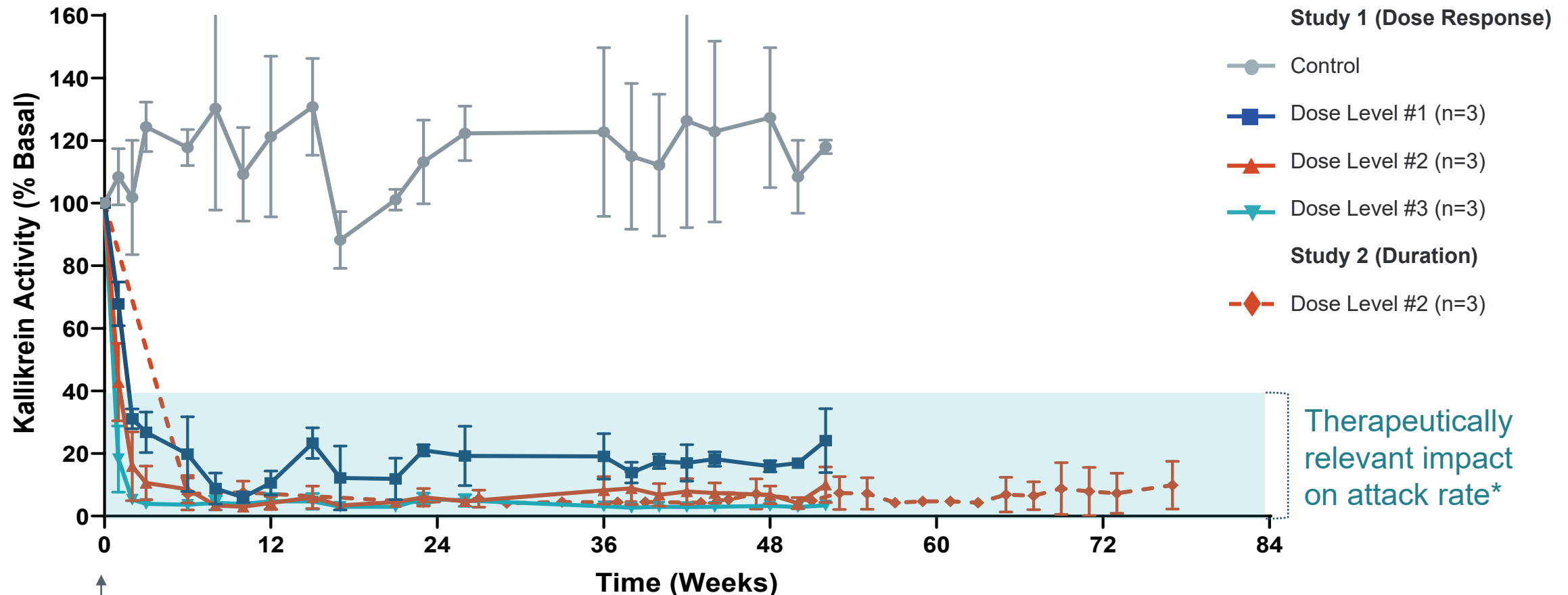


huKLKB1 Mouse Vascular Permeability¹



¹Vascular permeability was induced thirteen days post-dose using an intraperitoneal injection of the angiotensin converting enzyme (ACE) inhibitor captopril measured by Evans Blue Dye extravasation into the colon.

Achieved Sustained Therapeutically Relevant Kallikrein Activity Reduction After a Single Dose in NHPs



Single Dose

Kallikrein protein reduction tracks similarly to kallikrein activity reduction (data not shown).

Key Takeaways

- NTLA-2002 employs CRISPR/Cas9 technology to **knockout the *KLKB1* gene in the liver as a single course treatment for HAE.**
- Editing of *KLKB1* gene in HuKLKB1 mouse model shows **dose-dependent reduction of kallikrein protein and reduction in captopril-induced vascular leakage** holding promise for preventing attacks.
- Editing of *KLKB1* gene results in **therapeutically relevant reduction of kallikrein activity** in NHPs.
- **Kallikrein activity reduction sustained for at least 77 weeks** in NHPs; suggests possibility of “one-and-done” treatment.
- **NTLA-2002 is advancing toward the clinic:** Expect to submit an IND or IND-equivalent in 2H 2021

Intellia

THERAPEUTICS