Poster 089

ADX-324 is novel siRNA drug that provides deep and long-lasting suppression of prekallikrein levels for HAE

H. Henry Li, MD, PhD[1]; Lauge Farnaes, MD, PhD[2]; A. Robert MacLeod, PhD[2]; Masako Murai, MD, PhD[2]; Rui Zhu, PhD[2]; Zhen Li, PhD[2]; Marc Riedl, MD[3]
1. Institute for Asthma and Allergy, Chevy Chase, MD; 2. ADARx Pharmaceuticals, San Diego, CA; 3. University of California San Diego, San Deigo, CA

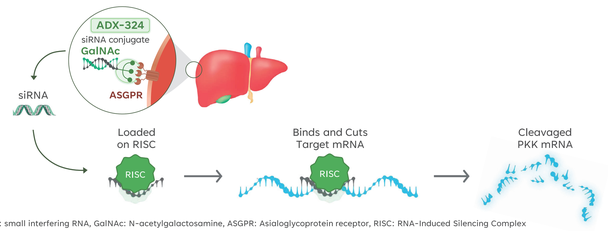
Introduction

Hereditary angioedema (HAE) is a rare genetic disorder caused by dysregulation of the plasma kallikrein pathway, leading to recurrent, unpredictable attacks of swelling that can be painful, disabling, and life-threatening.

ADX-324 is an investigational siRNA therapy designed to inhibit prekallikrein (PKK) generation at the mRNA level and reduce the production of plasma PKK, thereby averting bradykinin generation and potentially preventing HAE attacks.

Compared to currently approved prophylactic treatments, ADX-324 is expected to decrease PKK to a greater degree, offering the potential for greater and more durable control of kallikrein activity, which is expected to result in a higher proportion of patients remaining attack-free with a less frequent dosing regimen.

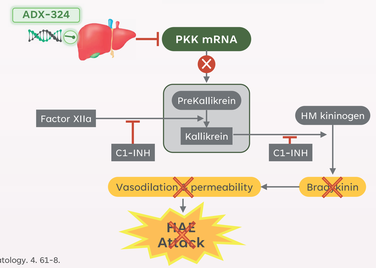
ADX-324 Mechanism of Action



siRNA: small interfering RNA, GalNAc: N-acetylgalactosamine, ASGPR: Asialoglycoprotein receptor, RISC: RNA-Induced Silencing Complex

ADX-324 and HAE Attack Prevention

- PKK is a clinically validated target in HAE.
- Several approved long-term prophylaxis (LTP) drugs are available.
- However, unmet medical needs remain due to the low attack free rate and high treatment burden associated with frequent dosing.



Adapted from: Farkas & Varga. (2011). Clinical, cosmetic and investigational dermatology. 4. 61-8.

Rationale

Improving patients' attack free rate, minimizing treatment burden and enhancing patients' quality of life are essential goals in hereditary angioedema (HAE) management.

ADX-324 has the potential to transform the current HAE LTP treatment paradigm by delivering rapid, deep, and durable target knockdown through an siRNA-based approach.

A Phase 3 study evaluating ADX-324 as a long-term prophylactic therapy for HAE with subcutaneous (SC) administration of 300 mg every six months (Q6M) has been initiated.

Methods

Phase 1, placebo-controlled, single-dose escalation study of ADX-324	• conducted in healthy participants • 38 dosed, 11 placebo (total 49) • one cohort received two 140 mg doses 3 months apart
Ongoing open-label Phase 2 study in HAE patients	• involves SC ADX-324 dosing Q6M • 3 HAE patients • plasma PKK-KK protein levels and safety were assessed through Day 445, the longest follow-up

Results

In Phase 1, a single SC injection of ADX-324 at 300 mg (±25 mg) achieved a mean PKK-KK reduction from baseline of over 90% at nadir, with >80% reduction maintained through Day 169. In Phase 2, one HAE patient received 122.5 mg and two patients received 245 mg.

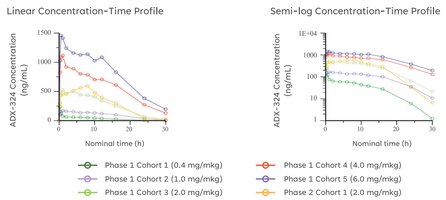
Their PKK-KK reductions patterns were similar to those observed in healthy participants dosed with ADX-324 within the approximate dose range, supporting the Phase 3 target >80% PKK-KK reduction throughout 6 months in HAE patients at the 300 mg dose. Notably, Phase 2 patients experienced no attacks when PKK-KK levels were reduced by ≥80%, further supporting the potential of 300 mg Q6M to produce high attack-free rates.

Pharmacokinetics (PK) and Pharmacodynamics (PD) Data

ADX-324 demonstrates dose-dependent PK and PD in both healthy volunteers (HV) and HAE patients

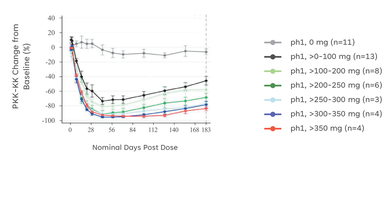
Dose-dependent ADX-324 exposure was observed, with plasma mean t½ ranging from 3.73 to 7.16 hours

Mean plasma concentration-time profiles in HV and HAE



Rapid, deep and durable PKK-KK suppression were observed in a dose-dependent manner

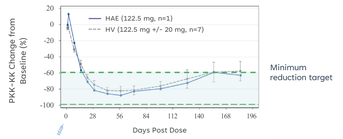
Mean % change from baseline in PD in HV



PKK-KK response in HAE patients in Phase 2 is similar to those in HVs

% PKK-KK reduction from baseline in HV and HAE patients were similar at similar doses.

Mean % PKK-KK reduction from baseline in HV and HAE patients receiving similar dose

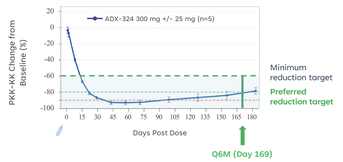


Draft data as of April 2025

In HV, the 300 mg dose, not a lower one, achieved a 93% mean PKK-KK reduction at nadir and an 80% mean reduction at 6 month

For HAE patients, 300 mg Q6M subcutaneous (SC) injection projected to maintain 80% (preferred) mean reduction target at 6-month.

Phase 3 design with the goal of achieving best-in-class profile with a semi-annual SC injection.



Draft data as of Dec 4, 2024

Positive feedback from FDA to move forward with Phase 3 STOP-HAE study.

Safety

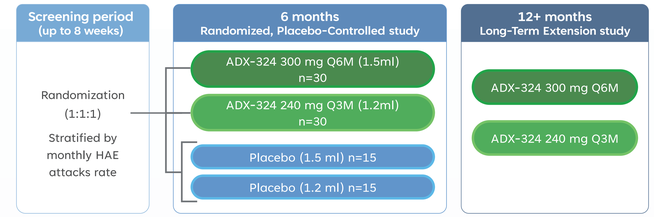
A well-tolerated profile with no long-term risks identified.

No Serious Adverse Events (SAE's) were reported in 38 healthy volunteer phase 1 participants and 3 phase 2 HAE patients.

There was no discontinuations of therapy due to drugs effects. Repeat dosing at 6-month intervals in phase 2 HAE patients was not associated with any safety signal.

STOP-HAE Phase 3 Study Design

The Phase 3 **STOP-HAE** clinical trial of ADX-324 is a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy of ADX-324 in preventing HAE attacks in adults with Type I and Type II HAE.



Approximately 90 patients will be enrolled and randomized to receive ADX-324 300 mg every 6 months, ADX-324 240 mg every 3 months, or placebo during the study. The first patient was dosed in Q4 2025. Patients completing the trial will be eligible to enroll in a long-term open-label extension study.

The trial will also assess safety, pharmacokinetics (PK), pharmacodynamics (PD), and patient reported health-related quality of life (HRQoL).

Patient population

- HAE type I or Type II
- ≥18 years old
- ≥1 HAE attack in the first 4 weeks of Screening or ≥2 HAE attacks in 8 weeks of Screening
- Access to acute medication(s) for attacks
- LTP washout must be completed before Screening, if applicable

Primary endpoint

Monthly HAE attacks rate in 300mg Q6M vs PBO

Key Secondary endpoints

- Monthly HAE attacks required acute therapy in ADX-324 vs PBO
- Monthly moderate to severe HAE attacks in ADX-324 vs PBO
- % Attack free in 6M in ADX-324

Visits

Screening, Day 1 (Dose 1), W3, W5, W9, W13 (Dose 2), W17, W21, W25 (EoS)

Exploratory endpoints

- Safety and tolerability
- PK/PD
- AE-CT/AE-QoL

AECT: Angioedema Control Test, AE-QoL: Angioedema Quality of Life

Conclusions

- ADX-324 is a novel siRNA drug that suppresses prekallikrein (PKK) levels
- ADX-324 provides deep suppression, potentially lasting 6 months
- Ph1 study showed no drug-related serious adverse events
- Global phase 3 clinical trial underway in 20+ countries

Acknowledgements

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