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Onvuzosiran Provides Deep and Sustained Reduction of Plasma Kallikrein Levels for the Treatment of HAE

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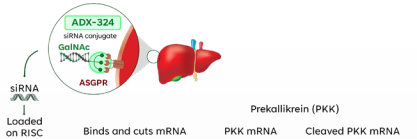
Background

Hereditary angioedema (HAE):
- is a devastating genetic disorder
- results in uncontrolled kallikrein activation
- leads to unpredictable attacks of swellings
- can be painful, debilitating, and life threatening

Onvuzosiran (ADX-324) is a small interfering RNA (siRNA) therapy consisting of short oligonucleotides that:
- inhibits prekallikrein (PKK) production at the mRNA level
- results in sustained reduction of circulating PKK protein levels
- is given subcutaneously every 6 months



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

Onvuzosiran Mechanism of Action and HAE Attack Prevention

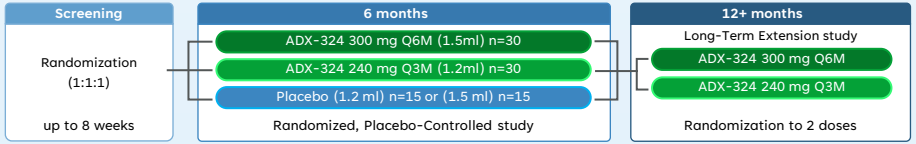
Adapted from: Farkas & Varga. (2011). Clinical, cosmetic and investigational dermatology. 4. 61-8.

Onvuzosiran has the potential to transform current HAE LTP treatment by delivering deep and sustained target knockdown through an siRNA-based approach

Methods

Phase 1	Randomized, placebo-controlled, single–ascending-dose trial of subcutaneous (SC) onvuzosiran (0.4 mg/kg to 6 mg/kg) conducted in healthy adults across 5 doses with an additional group of repeat-dosing every 3 months
Phase 2	Open-label Phase 2 study of 245 mg or 122 mg every 6 months in HAE patients is completing follow-up
Phase 3	• **ACTIVELY ENROLLING – at least 60 sites in 22 countries** • **A 90 Patient randomized, double-blind, placebo-controlled study** • **Evaluating semi-annual and quarterly SC dosing. First patient dosed in Q4 2025.**

STOP-HAE Phase 3 Study Design – Actively Recruiting



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 provided for all study participants
- LTP washout must be completed before Screening, if applicable

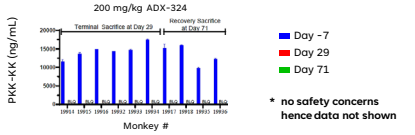
Primary Endpoint
- Monthly HAE attack rate in 300 mg Q6M vs PBO

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

Results

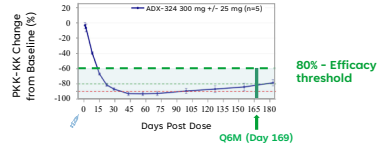
NHP study shows deep suppression of prekallikrein with no safety concerns at supratherapeutic doses*

Individual Serum PKK in the 200 mg/kg dose group

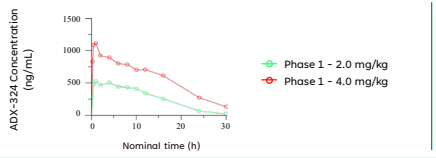


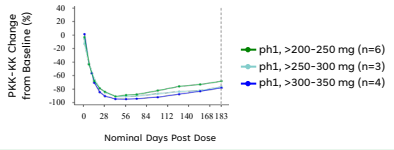
* no safety concerns hence data not shown

Phase 1 data shows 80% suppression over 6 months with a single SC dose



Very Short Circulatory Time Produces Long Durability





In Phase 1, a single SC injection of onvuzosiran at 300 mg (±25 mg) achieved:
- mean PKK-KK reduction from baseline of over 90% at nadir
- >80% reduction maintained through Day 169

Safety
- In 49 healthy volunteer phase 1 participants and 3 phase 2 HAE patients, no Serious Adverse Events (SAEs) were reported in patients treated with onvuzosiran
- There was no discontinuations of therapy due to drugs effects

Conclusions

- **Onvuzosiran is a novel siRNA drug that provides deep and sustained reduction of plasma kallikrein levels**
- **Onvuzosiran is given in a small volume subcutaneous injection**
- **Onvuzosiran provides deep and sustained suppression, potentially lasting 6 months**
- **Ph 1/2 study showed no drug-related serious adverse events**
- **Global phase 3 clinical trial underway in 20+ countries**

Acknowledgements

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