Abstract #493

Pharmacodynamics and Pharmacokinetics of Donidalorsen in Patients with Hereditary Angioedema

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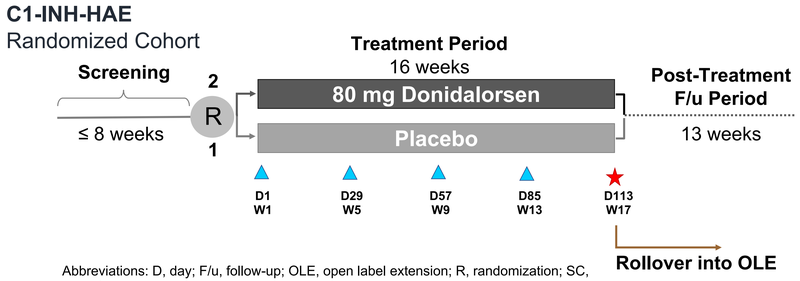
Rationale

Donidalorsen is a ligand-conjugated antisense oligonucleotide designed for targeted delivery to the liver to decrease production of hepatic prekallikrein (PKK). The pharmacodynamics, pharmacokinetics and efficacy of Donidalorsen were evaluated in a Phase 2 study in patients with hereditary angioedema (HAE)

Methods

In a double-blind, placebo-controlled phase 2 study, patients with HAE due to C1-inhibitor deficiency were randomized 2:1 to either 80 mg Donidalorsen (n=14) or placebo (n=6) administered subcutaneously every 4 weeks for 12 weeks. Plasma PKK, plasma proenzyme activation (PPA) and cleaved high molecular weight kininogen (cHK) were measured at selected time points. Donidalorsen plasma concentrations were determined using sparse sampling

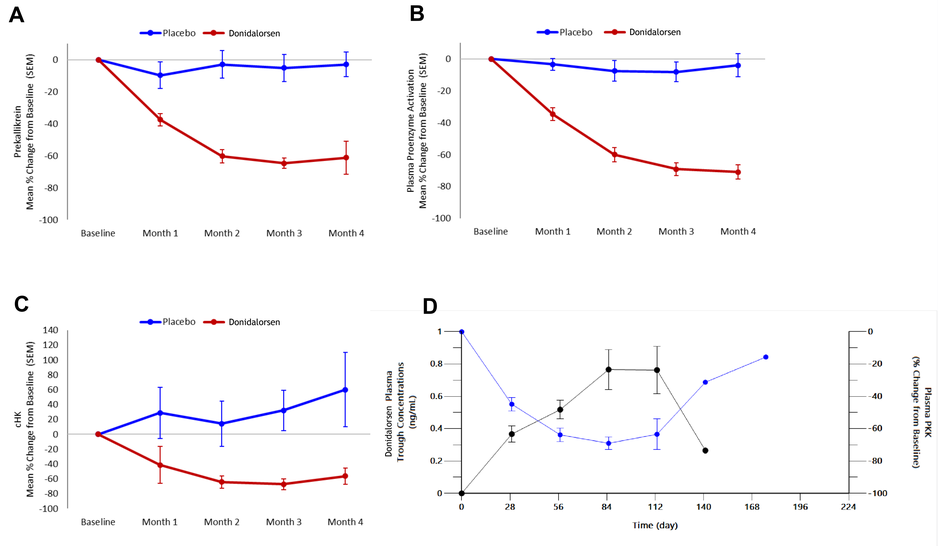


Abbreviations: D, day; F/u, follow-up; OLE, open label extension; R, randomization; SC, subcutaneous; W, week.

Trial Design. Patients with C1-INH-HAE were randomized to receive subcutaneous (SC) injections of Donidalorsen 80 mg or placebo in a 2:1 ratio (Donidalorsen:placebo). Solid blue triangles correspond to dose days. The primary endpoint readout is indicated by the red star

Results

Donidalorsen treatment resulted in a robust reduction of plasma PKK, PPA and cHK concentration. There was a significant reduction two weeks after the first dose. The nadir for PKK and PPA was reached by Day 85 with a mean reduction of 65% in PKK and 69% in PPA, respectively. There was a significant reduction (mean 67%) in cHK to within the normal range for all active treated subjects. From Day 85 on there were no HAE attacks reported. Donidalorsen was rapidly absorbed into the systemic circulation with a median T_{max} of 1 hour. No accumulation was seen in C_{max} after multiple doses of Donidalorsen, however, the plasma trough concentrations increased over time which correlated with the time course of PKK reduction



Pharmacodynamic measures by mean percentage change from baseline in **A**) Prekallikrein, **B**) Plasma Proenzyme Activation, and **C**) cHK. Data shown are the monthly observations during the treatment period for the randomized placebo-controlled C1-INH-HAE and the open-label nC1-INH-HAE cohorts, **D)** Correlation between Donidalorsen plasma trough concentrations and reduction of plasma PKK over time

Conclusion

Donidalorsen is an investigational drug that significantly reduced plasma PKK, PPA and cHK levels. The reduction in plasma PKK correlated with clinical improvement in HAE attacks

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