Safety, Pharmacokinetics and Target Engagement of novel RIPK1 inhibitor SAR443060 (DNL747) in Patients with Amyotrophic Lateral Sclerosis

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Introduction

Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) is a master regulator of inflammatory signaling and cell death. Increased RIPK1 activity is observed in human diseases characterized by excess cell death and inflammation, including in amyotrophic lateral sclerosis (ALS).[1] RIPK1 inhibition has been shown to protect against pathology and cell death in a range of preclinical cellular and animal models of neurodegenerative diseases.[2]

SAR443060 (DNL747) is a selective, orally bioavailable, CNS–penetrant, small-molecule, reversible inhibitor of RIPK1.

Objectives

The goal of this study was to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of 28 days of SAR443060 50 mg twice-daily (BID) dosing in 16 patients with ALS.

Methods

Multicenter, randomized, double-blind, placebo-controlled phase 1B study (NCT03757351), with a cross-over design consisting of two 28-day treatment periods, separated by 14 days of wash-out.

- Safety and tolerability: vital signs, ECG, standard laboratory safety assessments, physical and neurological examinations, and adverse events
- PK: drug concentrations in blood and cerebrospinal fluid (CSF)
- PD: target engagement via phosphorylation of RIPK1 at serine 166 (pRIPK1) in human peripheral blood mononuclear cells (PBMCs)

Results

RIPK1 inhibition was generally safe and well tolerated for 28 days in patients with ALS (n=15). There were no discontinuations due to study drug and no laboratory, vital sign, ECG or physical/neurological examination findings of clinical concern.

Patients with any, n (%)	Placebo (N=15)	SAR443060 (N=15)
TEAE	11 (73.3)	12 (80.0)
severe TEAE	0	0
treatment emergent SAE	0	0
TEAE leading to death	0	0
TEAE leading to treatment discontinuation	0	0
TEAE leading to study discontinuation	0	0
TEAE of special interest (AESI)	1 (6.7)	1 (6.7)

[1] Both AESIs were mild, and included seborrheic dermatitis in placebo and erythema in SAR443060

SAR443060 distributed into CSF after oral administration.

PK parameter	Single dose (SOT)†	Multiple dose (EOT)
C_{max} (µM)		
n	15	14
Mean (SD)	0.581 (0.405)	0.638 (0.267)
T_{max} (h)		
n	15	14
Median (Min; Max)	1.05 (0.47; 4.00)	1.25 (0.50; 4.52)
$AUC_{0\text{-}12}$ (µM · h)		
n	14	14
Mean (SD)	2.11 (1.89)	3.12 (1.20)
AUC R_{ac}		
n	N/A	14
Mean (SD)		1.48
CSF-to-unbound plasma ratio		
n	13	
Mean (SD)	1.00 (0.256)	

† The first patient received 200 mg twice daily for 21 days and is included in the descriptive statistics of the PK parameters after the 1st administration. As a result, SOT C_{max} and $AUC_{0\text{-}12}$ are likely overestimated, and AUC R_{ac} underestimated. The dose was lowered to 50mg twice daily due to adverse events in chronic preclinical tox studies.

SAR443060 demonstrated peripheral target engagement as measured by a reduction in pRIPK1 in PBMCs compared to baseline. Median (CI) percentage inhibition at steady state dosing (Day 29) was 92.34% (CI: 95.75, 68.11, n=14) at 2 hours post dose (around Tmax) and diminished overtime to 65.92% (CI: 79.3, 45.39, n=14) at 12 hours post-dose (trough) (**Figure 1**).

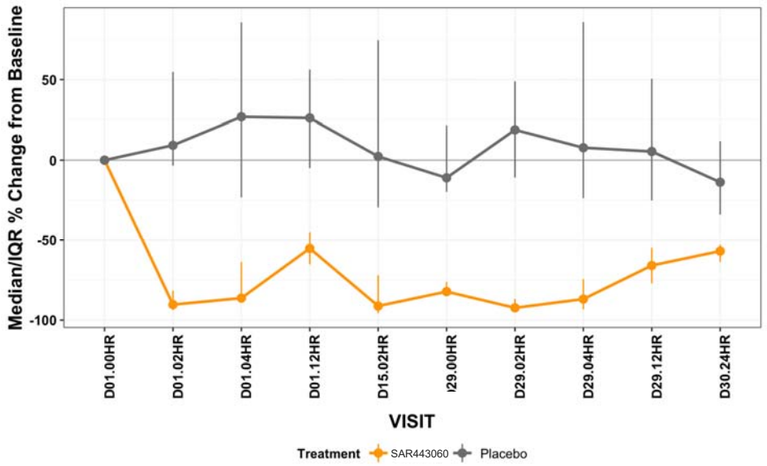

Figure 1: Median/IQR percentage pRIPK1 inhibition compared to baseline after SAR443060 and placebo administration in ALS patients

Conclusions

This study demonstrates short term safety, CNS penetration, and peripheral target engagement of SAR443060 in patients with ALS.

References:
1. Ito Y, et al. Science. 2016;353(6299):603-608. doi:10.1126/science.aaf6803
2. Mifflin L, et al. Nature Reviews Drug Discovery. Published online July 15, 2020. doi:10.1038/s41573-020-0071-y

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