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A randomized, placebo-controlled, single-blind, dose-escalation, first-time-in-human study to assess the safety and pharmacokinetics of single and repeat doses of srt3025 in normal healthy volunteers

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Abstract

SRT3025 is a selective activator of SIRT1. SIRT1 is a member of the Sirtuin family of nicotinamide adenine dinucleotide (NAD^+) dependent deacetylases with a number of cellular substrates including PGC-1α, NCoR, p300, NF□B, FOXO and p53. In animal models, SRT3025 improves glucose homeostasis and insulin sensitivity.

We initiated a first-in-human trial of SRT32025 to evaluate the safety and pharmacokinetics of SRT3025. In this dose escalating trial, 42 subjects received a single oral dose of 50 mg to 3000 mg/d and 18 subjects received 14 daily oral doses up of to 1000 mg/d.

The compound showed a dose proportional increase in exposure. Accumulation over Day 1 ranged across dose levels from 89-122% for $AUC_{(0-\tau)}$ and 57-90% for Cmax following 14 days of treatment. Adverse events were infrequent; diarrhea was the most common AE. However, a dose-dependent prolongation of QTc was observed. Non-clinical testing, including a dog cardiovascular study, did not predict a QTc signal, hence the QTc prolongation was not anticipated (mean QTcF prolongation at 3000 mg SD: 22 ms). The magnitude of the prolongation was greatest around Tmax and appeared therefore to be primarily a direct effect of the compound; the effect is thought to be related to the molecular scaffold rather than the drug class. QTc returned to pre-treatment levels following discontinuation of drug. No clinical signs of cardiac adverse effects were observed. Due to the impact on QTc, the compound will not be developed for T2DM, however, SIRT1 activation remains an interesting target for the management of T2DM.