A First-in-Human (FIH) Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Doses, and Alternative Formulations of R941552 (R552): A selective Receptor Interacting Protein 1 (RIP1) Kinase Inhibitor

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BACKGROUND

- RIPK1 (receptor-interacting serine/threonine kinase 1) mediates cell survival through NF-kB, or cell death through apoptosis or necroptosis downstream of TNF receptor activation.
- R552 is a potent and selective RIPK1 inhibitor that has been shown to block inflammatory cell death (necroptosis).
- R552 is being developed for the treatment of autoimmune and inflammatory disorders.
- Preclinical data suggested that solubility may limit exposure; alternative formulations were also assessed in this first-in-human (FIH) study.

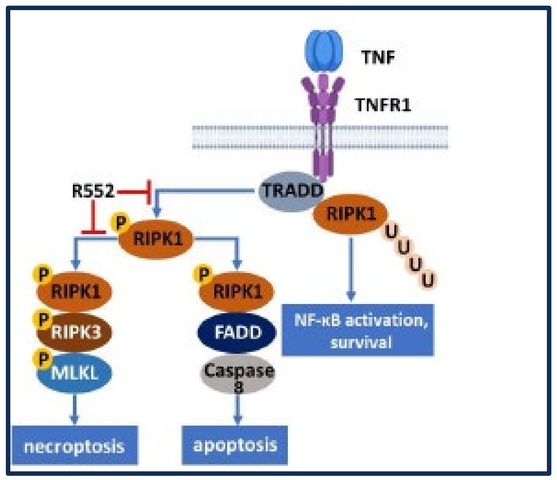

Figure 1. RIPK1 Inhibition by R552

- Definitions: TRADD – tumor necrosis factor receptor type 1-associated DEATH domain protein; FADD – Fas-associated protein with death domain; MLKL – Mixed Lineage Kinase Domain Like Pseudokinase; P – phosphorylated; U – polyubiquitinated

METHODS

- An FIH study was conducted to assess the safety, tolerability, and pharmacokinetics of R552, administered orally to healthy adult subjects.
- Part 1a – single dose administration
- Part 1b – *SDD ¥ALT1 and ALT2 suspension formulation assessment
- Part 2 – multiple dose 14-day administration
- Part 3 – bioavailability of the ALT1 tablet or ALT1 suspension formulation with or without high fat breakfast

Part	Investigational Medicinal Product	Dose Level (mg)	Dosing Frequency
1A (n=36, double blind, randomized, placebo-controlled)	Lipid solution or matching placebo	12	Once
		60	
		180	
	ALT1 suspension or matching placebo	300	
		750	
		1000	
1B (n=12, open label)	ALT1 suspension	180	
	ALT2 suspension	180	
2 (n=16, double blind, randomized, placebo-controlled)	ALT1 suspension or matching placebo	180	QD for 14 days
		500	
3 (n=9, open-label, randomized, cross-over)	ALT1 suspension	125	Once
	ALT1 Tablet	125	
		125	

Table 1. Dosing Regimen in Study

*SDD = spray dry dispersion;
¥ ALT = alternative

RESULTS - PHARMACOKINETICS

- Linear PK and dose-proportional exposure was observed over the dose range evaluated with Tmax of R552 at 1h to 4h, and T1/2 range from 13h to 15h.
- Steady state was attained at 4 to 6 days after multiple once-daily dose administrations.
- Inter-subject variability associated with exposure was low following single and multiple doses in all study parts, ranging from 6.0 % to 42.7 %.
- SDD ALT1 and ALT2 suspensions and SDD ALT1 tablet formulation showed similar median Tmax and comparable exposure to the lipid solution at the doses tested.
- Exposure of tablet formulation was similar with or without food, although median Tmax was delayed and the geomean Cmax was reduced by 34% with food intake.Figure 2. Pharmacokinetics of Parts 1A, 2, and 3

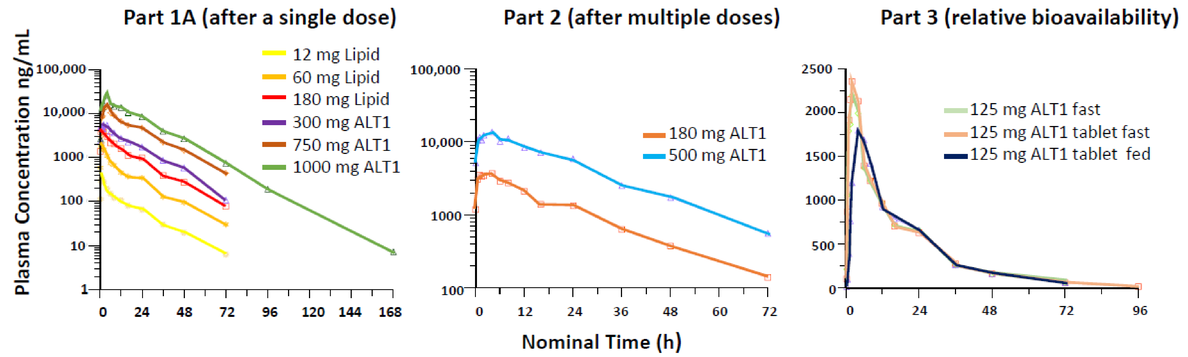

Figure 2. Pharmacokinetics of Parts 1A, 2, and 3

RESULTS - SAFETY

All adverse events (AEs) were mild, except one moderate AE of headache at a 1000 mg dose.

- The most common (>3 events) possibly drug-related AE was headache.
- No serious AEs or severe AEs were reported.

CONCLUSIONS

- R552 was generally safe and well tolerated at the doses tested.
- The pharmacokinetics of R552 was linear, and no clinically significant food effect was observed.
- A suitable tablet formulation for R552 was identified for future patient studies.

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