Clinical evaluation of Lassa fever antiviral LHF-535 in a 14-day repeat dose study in healthy volunteers

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Abstract

#101

Objectives:
- Primary: To assess the safety and tolerability of 14 once-daily oral doses of LHF-535 in healthy participants
- Secondary: To evaluate the pharmacokinetics (PK) of 14 once-daily oral doses of LHF-535 in healthy participants

Study design:
- 14 daily oral doses of LHF-535
- Day-28 Check-in Day-1 Confinement to safety unit Day 1 Tol dose Fasting sample Day 15 discharge Day 17 follow-up Day 21 follow-up Day 42 follow-up

Cohort 3 dosing regimen: Rational for use of loading dose
- Achieve higher LHF-535 concentration on Day 1
- Prevent more robust antiviral activity with first dose
- Reach steady-state faster
- First dose = 2250 mg
- Double the daily maintenance dose (1125 mg/day)
- Safety supported by previous single ascending dose study

Pharmacokinetics:
- LHF-535 Pharmacokinetics: Day 1
- LHF-535 Pharmacokinetics: Day 14

Findings support evaluation in a patient population
- • Achieve higher LHF-535 concentration on Day 1
- • Prevent more robust antiviral activity with first dose
- • Reach steady-state faster
- • First dose = 2250 mg
- • Double the daily maintenance dose (1125 mg/day)
- • Safety supported by previous single ascending dose study

Conclusions
- • LHF-535 is well tolerated
- • No concerning adverse events
- • Pharmacokinetics are consistent with antiviral efficacy in animal models of Lassa fever
- • Findings support evaluation in a patient population

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Lassa fever is a viral hemorrhagic fever endemic in West Africa
- • No approved therapies
- • High case-fatality rate among hospitalized patients
- • Estimated 100,000-300,000 cases annually
- • Estimated 5000 deaths annually
- • Zoonotic disease

LHF-535 is potent small molecule antiviral
- • Inhibits viral entry
- • Validated in animal models of pathogenesis
- • Targets the viral envelope glycoprotein (GP)
- • Guinea pig (Lassa virus)
- • Cynomolgus macaque (Lassa virus)

LHF-535 was previously evaluated in KVHF-535-101
- • Single ascending dose in healthy volunteers
- • Six escalating cohorts
- • Weight-based dosing
- • 0.3 to 40 mg/kg
- • 23 to 3000 mg for a 75 kg participant
- • No concerning patterns of adverse events

LHF-535 Pharmacokinetics:
- Trough level (c24) following each dose
- AUC0-24h Cmax
- Cohort 1 3.3 2.0
- Cohort 2 4.9 3.2
- Cohort 3* 3.5 2.5

*Note that for cohort 3, the Day 1 dose (calculated using ratio of means)

Accumulation ratios between first and last (day 14) doses (calculated using ratio of means)

Concentration ratios for each cohort separately using Helmert contrasts
- Consistent with ~5 half-lives

Adverse Events (TEAEs)
- • Twenty-four participants
- • 11 (45%)
- • 10 females (42%)
- • Average age = 30.5 years
- • Range = 19 to 50 years
- • Range = 53 to 105 kg
- • 1 participant only received 10 doses due to family emergency
- • 1 participant withdrew early (9 days after final dose)
- • One participant withdrew for personal reasons unrelated to study drug
- • All treatment-related TEAE classified as mild (Grade 1)
- • No serious adverse events (SAEs)
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Study demographics
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- • 11 (45%)
- • 10 females (42%)
- • Average age = 30.5 years
- • Range = 19 to 50 years
- • Range = 53 to 105 kg
- • One participant withdrew early (9 days after final dose)
- • One participant only received 10 doses due to family emergency
- • One participant withdrew for personal reasons unrelated to study drug
- • All treatment-related TEAE classified as mild (Grade 1)
- • Two TEAEs classified as moderate (Grade 2), but deemed unrelated to study drug (one myalgia and one URTI), both in placebo group
- • No serious adverse events (SAEs)

Time to reach steady state = 9-12 days
- • Assessed for each cohort separately using Helmert contrasts
- • Consistent with ~5 half-lives
- • Median terminal elimination half-life = 49 h

Absorption ratios between first and last (day 14) doses (calculated using ratio of means)