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

Sean M. Amberg[1], Portia A. Vliet-Gregg[1], Alison E. Heald[2], Eric J. Tarcha[1], Jeff Posakony[1], Clinical Network Services (CNS) Pty Ltd[3], and Nucleus Network[4]

[1]Kineta, Inc., Seattle, WA, USA; [2]University of Washington, Seattle, WA, USA; [3]Hamilton QLD, Australia; and [4]Melbourne VIC, Australia

Abstract #101

Lassa fever is a viral hemorrhagic fever endemic in West Africa
- No approved therapeutics
- 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
- Targets the viral envelope glycoprotein (GP)
- Validated in animal models of pathogenesis
  - Mouse (Tacaribe virus)
  - Guinea pig (Lassa virus)
  - Cynomolgus macaque (Lassa virus)

KVHF-535-102

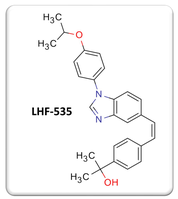
A double-blind, placebo-controlled, dose-escalation study of the safety, tolerability, and pharmacokinetics of multiple oral doses of LHF-535 (LHF-535-SDD) in healthy participants

Principal Investigator: Benjamin Snyder, MB BS (Hons), FRACP

Objectives:

Primary: • To assess the safety and tolerability of 14 once-daily oral doses of LHF-535 in healthy participants

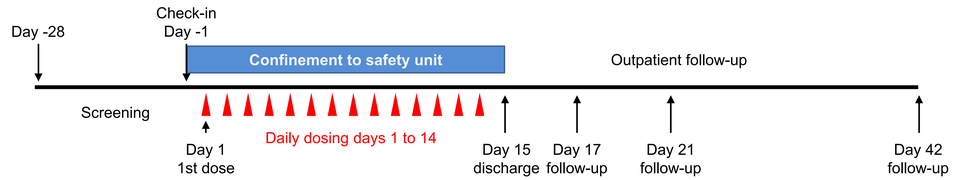
Secondary: • To evaluate the pharmacokinetics (PK) of 14 once-daily oral doses of LHF-535 in healthy participants



- Formulated as a spray-dried dispersion (SDD) with inert polymer HPMCAS (hydroxypropylmethylcellulose acetate succinate) at a weight ratio of 30 LHF-535 to 70 HPMCAS
- Oral administration of LHF-535-SDD in flavored compounding vehicle (Ora-Blend) at 100 mg/mL SDD (30 mg/mL LHF-535)
- Fixed dosing
- 3 cohorts with escalating dose
- For each cohort, 6 subjects received LHF-535, 2 subjects received placebo (randomized)

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

Study design: 14 daily oral doses of LHF-535



Each cohort (n = 8) randomized { **LHF-535 (n = 6)** **Placebo (n = 2)**

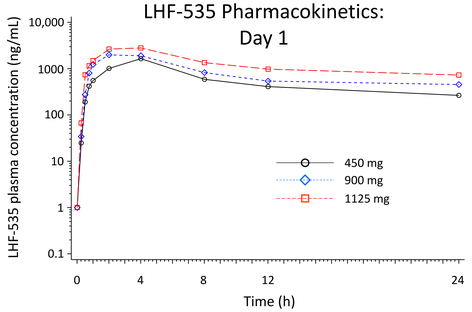
First subject screened: 17 September 2019
Last subject completed: 17 January 2020
ClinicalTrials.gov NCT03993704

Cohort	Dose (mg/day)	Loading dose
1	450	N / A
2	900	N / A
3	1125	Day 1 = 2250 mg

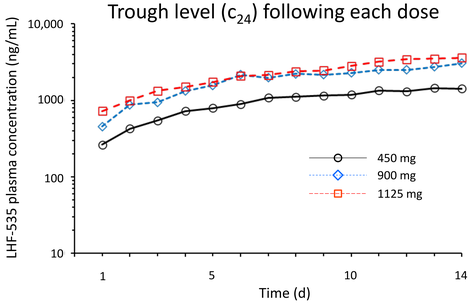
Cohort 3 dosing regimen: Rationale for use of loading dose
- Achieve higher LHF-535 concentration on Day 1
  - Provide more robust antiviral activity with first dose
- Reach steady-state faster
- First dose = 2250 mg
  - Double the daily maintenance dose (1125 mg/day)
  - Safety supported by previous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

Study demographics
- Twenty-four participants
  - 14 males (58%)
  - 10 females (42%)
- Average age = 30.5 years
  - Range = 19 to 50 years
- Average weight = 76 kg
  - Range = 53 to 105 kg
- Disposition of participants
  - One participant withdrew early
    - Withdrew for personal reasons unrelated to study drug
    - Received all doses (days 1-14)
    - Withdrew on day 23 (9 days after final dose)
  - All other participants completed study
    - One participant only received 10 doses due to family emergency

LHF-535 Pharmacokinetics: Day 1



LHF-535 Pharmacokinetics: Trough level (c_{24}) following each dose



Treatment-Related Treatment-Emergent Adverse Events (TEAEs)
- Overall treatment-related TEAE frequency
  - 17% of LHF-535 subjects
  - 50% of placebo subjects
- Most common treatment-related TEAE was headache
  - 1 participant in the placebo group (17%)
  - 1 participant in the LHF-535 groups (6%)
  - Headache in the LHF-535 groups was at the lowest dose (450 mg)
- 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

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

	$AUC_{0\text{-}24h}$	C_{max}
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 was 2X the maintenance dose

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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