Poster #293

A First-in-Human Phase 1 Randomized, Single-Ascending Dose Study of Lonigutamab, an Anti-IGF-1R Monoclonal Antibody, in Healthy Volunteers

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INTRODUCTION

- Thyroid eye disease (TED) is a vision-threatening autoimmune condition characterized by orbital inflammation due to activated fibroblasts[1]
  - Clinical manifestations include periorbital edema, lid retraction, proptosis, diplopia, corneal breakdown, and, in rare cases, optic nerve compression
- Therapeutic monoclonal antibodies (mAbs) targeting insulin-like growth factor-1 receptor (IGF-1R), such as teprotumumab,[2] have been shown to be effective in TED treatment
- IGF-1R internalization resulting from anti-IGF-1R and the resulting signaling blockade ameliorate immune responses in TED[3]
- **Lonigutamab** is a novel humanized mAb against IGF-1R with high affinity and specificity, enabling highly efficient receptor internalization
  - Lonigutamab was discovered by screening for IGF-1R internalization
  - Lonigutamab binds IGF-1R with picomolar affinity (k_D = 30 pM) to a distinct binding epitope
  - Lonigutamab induces >85% IGF-1R receptor internalization
  - Lonigutamab-induced receptor internalization occurs within minutes at picomolar concentrations and reaches maximal concentration within 1 hour, as observed from in vitro pharmacology studies[4]
- Despite treatment advances, there is opportunity for greater depth and durability of response in TED, and current therapies can be optimized by reducing treatment-limiting side effects
  - Hearing impairment is reported in a substantial proportion of subjects treated with currently available therapy[5]
- Pharmacokinetic (PK) properties of lonigutamab are hypothesized to support subcutaneous (SC) administration, offering an additional advantage over currently available intravenous (IV) therapy

Lonigutamab may offer distinct treatment advantages relating to efficacy, safety, and convenience, due to its uniquely differentiated characteristics. A phase 1 study was conducted to support clinical development.

KEY FINDINGS

- Single-dose lonigutamab up to 3.0 mg/kg IV and up to 250 mg SC was safe and well tolerated in healthy volunteers
- SC dose levels maintained receptor saturation for >4 weeks after a single dose, administered in ≤2 mL dose volume
- The observed PK/PD is evidence of IGF-1R receptor internalization, which is associated with therapeutic benefit in TED
- Lonigutamab concentrations were maintained above a threshold of maximal receptor internalization, supporting continued pharmacological effect and predicted therapeutic benefit
  - This threshold appears to occur around 3 µg/mL
  - The potency shift between teprotumumab, an FDA-approved treatment for TED, and lonigutamab is ~75× (as referenced: lonigutamab[4] and teprotumumab[7]) determined via both binding and functional assays
  - Maintaining teprotumumab minimum concentrations above 200 µg/mL was found to support improved efficacy[3]
  - The equivalent lonigutamab concentration predicted to maintain efficacy is therefore 3 µg/mL, further supporting this concentration as a target for IGF-1R internalization and efficacious dosing

Subcutaneously administrated lonigutamab offers the potential for efficacious TED treatment, with the potential opportunity to optimize efficacy, safety, and patient convenience. It is currently being studied in a phase 1b study in subjects with TED.

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DISCLOSURES

GFK, TM, ND, ST: consultants of ACELYRIN, Inc.
AG: employee of ACELYRIN, Inc.

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OBJECTIVE

- To evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of single ascending doses (SAD) of IV and SC lonigutamab in healthy participants

METHODS

- Eight cohorts of healthy volunteers participated in this phase 1, single-center, randomized, double-blind, placebo-controlled, sequential SAD study of 4 IV and 4 SC cohorts with escalating doses
  - Participants were randomized to lonigutamab (n=6/cohort) or matching placebo (n=2/cohort)
  - IV cohort: 0.1, 0.3, 1.0, or 3.0 mg/kg over 60 minutes via infusion
  - SC cohort: 20, 40, 125, or 250 mg fixed-dose injections in ≤2 mL volume
- Participants defined as healthy per study protocol, ages 18 to 55 years old, and with a BMI of >18.0 and <32.0 kg/m^2 at screening
- Routine laboratory, audiology, PK, and PD assessments were performed at specified timepoints in each cohort
- Safety and tolerability were evaluated through the assessment of adverse events (AEs) and were monitored over 99 days
- PK was tested with a validated immunoassay, and receptor occupancy (RO) was tested using a qualified flow cytometry assay

RESULTS

Participant Disposition

- 63 participants were enrolled in the study: lonigutamab, n=47; placebo, n=16
  - 4 participants discontinued because they were lost to follow-up or other reasons (1 participant, military deployment), which were deemed to not impact the primary analyses

Baseline Characteristics

- Demographics and baseline characteristics are in **Table 1**
- There were no meaningful differences across treatment groups

Table 1. Baseline Characteristics

		Safety Population (n=63)
Age	(years)	35.7 (19-55)
Sex	Male	48 (76.2)
	Female	15 (23.8)
Race	American Indian or Alaska Native	1 (1.6)
	Black/African American	34 (54)
	White	23 (36.5)
	Unknown	3 (4.8)
	Multiple	2 (3.2)
Weight	(kg)	78.2 (52.9-100.1)
BMI	(kg/m^2)	25.67 (20.0-29.6)

n (%) or mean (range). BMI, body mass index.

SAFETY/TOLERABILITY Single Doses of Lonigutamab Were Well Tolerated With No Dose-Related Safety Findings

- All AEs were mild or moderate in severity; no serious adverse events (SAEs) occurred
- A preliminary summary of treatment-emergent adverse events (TEAEs) is presented in **Table 2**

Table 2. Overall Summary of TEAEs

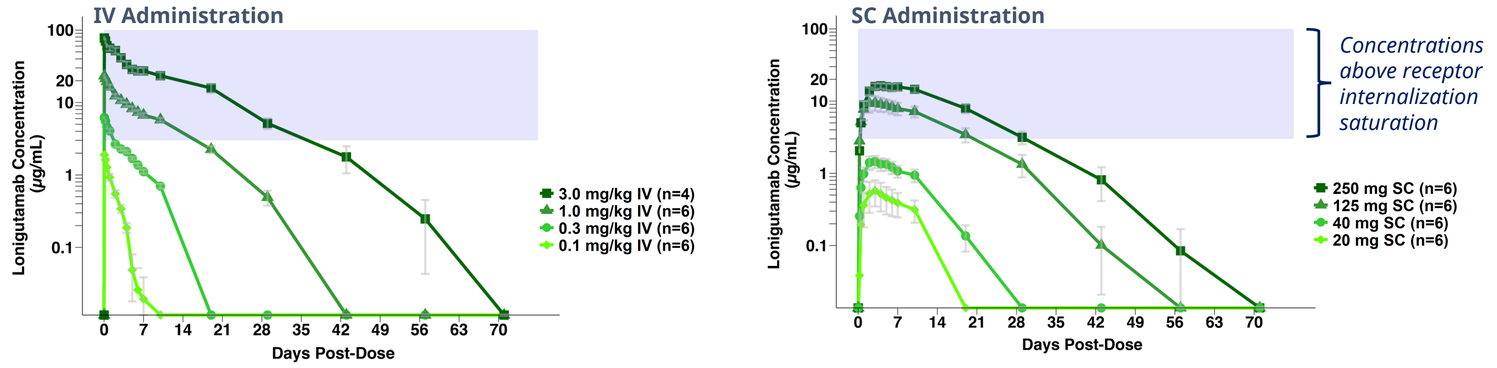
	IV Lonigutamab					SC Lonigutamab					Overall Safety Population (n=63)
	0.1 mg/kg (n=6)	0.3 mg/kg (n=6)	1.0 mg/kg (n=6)	3.0 mg/kg (n=5)[a]	Placebo (n=8)	20 mg (n=6)	40 mg (n=6)	125 mg (n=6)	250 mg (n=6)	Placebo (n=8)	
Number of TEAEs	5	9	2	10	2	11	11	7	1	1	59
Number of related TEAEs	1	0	0	0	0	6	2	0	1	0	10
Number of serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Number of TEAEs leading to study discontinuation	0	0	0	0	0	0	0	0	0	0	0
Participants with at least 1 TEAE, n (%)	3 (50)	4 (66.7)	2 (33.3)	3 (60)	1 (12.5)	3 (50)	3 (50)	4 (66.7)	1 (16.7)	1 (12.5)	25 (39.7)
Participants with a related TEAE	1 (16.7)[b]	0	0	0	0	1 (16.7)[b,c]	1 (16.7)[b]	0	1 (16.7)[b]	0	4 (6.3)
Participants with a serious TEAE	0	0	0	0	0	0	0	0	0	0	0
Participants with a TEAE leading to study discontinuation	0	0	0	0	0	0	0	0	0	0	0

Adverse events of special interest (AESI) based on the modality and mechanism of action included: allergic reactions type I/anaphylaxis, hyperglycemia, infusion-related reactions, diarrhea/inflammatory bowel disease exacerbation, hearing impairment, and muscle spasms. [a]Six participants were screened for cohort 3.0 mg/kg; the sixth participant failed screening criteria, and only 5 patients were enrolled. [b]One participant: infusion-related reaction, 3 participants: injection site reactions "possibly" or "probably" related to lonigutamab. All reactions were mild and self-limited, resolving within a few hours without medical intervention. [c]One participant: gastrointestinal disorders (abdominal pain, abdominal distention, and frequent bowel movements) "possibly" or "probably" related to lonigutamab (participant reported more than 1 TEAE) in the 20 mg SC cohort. IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event.

PHARMACOKINETICS Lonigutamab Concentrations Are Maintained Above Threshold of Receptor Internalization

- Mean serum concentrations of lonigutamab increased in a greater than dose-proportional manner over the dose ranges tested, as expected for a mAb undergoing target-mediated drug disposition (TMDD; **Figure 1**)
  - TMDD occurs when a therapeutic mAb binds to its target (here, IGF-1R), and the resulting complex is degraded.[6] At low concentrations, drug levels decline rapidly as drug efficiently binds its target and is degraded; at high concentrations, target binding is saturated, and drug levels decline more slowly, representing drug that is available to bind to a newly generated target
  - In conjunction with the known lonigutamab pharmacology, TMDD is evidence of receptor internalization
- The TMDD threshold, above which receptor internalization is saturated, appears to occur around 3 µg/mL
- SC lonigutamab overcomes TMDD to maintain pharmacologically relevant concentrations

Figure 1. Mean ± SE Serum Lonigutamab Concentration-Time Profiles Following IV and SC Administration

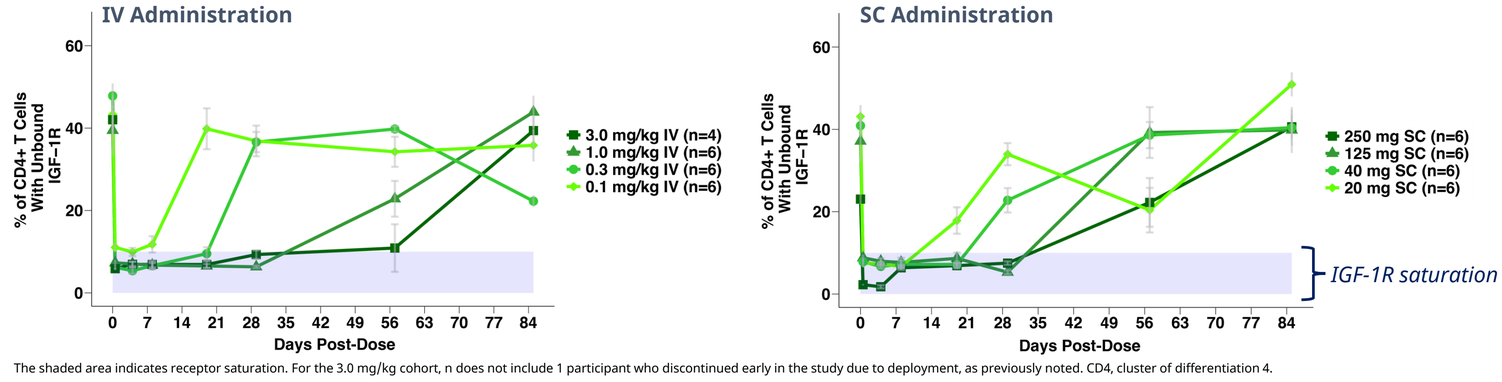


Samples below the limit of quantification (0.1 µg/mL) are plotted as 0 µg/mL. For the 3.0 mg/kg cohort, n does not include 1 participant who discontinued early in the study due to deployment, as previously noted.

PHARMACODYNAMICS Receptor Saturation Is Maintained for >4 Weeks Following SC Dosing

- Maximal IGF-1R occupancy was observed by the first timepoint (12 hours) in all cohorts (**Figure 2**)
- Duration of receptor saturation increased with increasing dose
- 1.0 and 3.0 mg/kg IV and 125 and 250 mg SC dose levels maintained maximal RO for at least 4 weeks post-dose

Figure 2. Mean ± SE Lonigutamab Receptor Occupancy-Time Profiles Following IV and SC Administration



The shaded area indicates receptor saturation. For the 3.0 mg/kg cohort, n does not include 1 participant who discontinued early in the study due to deployment, as previously noted. CD4, cluster of differentiation 4.

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