LFD-200, an Antibody Drug Conjugate That Selectively Delivers a Glucocorticoid to Immune Cells, has Anti-Inflammatory Activity and was Well Tolerated Without Systemic Side Effects in an Ongoing Phase 1 Study

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INTRODUCTION

- LFD-200 is a novel antibody drug conjugate (ADC) comprised of a monoclonal antibody (mAb) that is conjugated to 8 glucocorticoid (GC) payloads (PL; modified budesonide) via protease-cleavable linkers. The mAb component of LFD-200 is designed to selectively bind to the immune cell surface protein V-domain immunoglobulin suppressor of T cell activation (VISTA). This results in targeted delivery of the GC payload to immune tissues while avoiding systemic GC toxicity (e.g., cortisol suppression) due to limited and short exposure in blood.
- In studies in non-human primates (McClure et al., ACR 2025), subcutaneous (SC) dosing with LFD-200 resulted in sustained (≥7 day) GC payload exposures in lymph nodes and spleen. Additionally, ex vivo stimulation of whole blood cells and bone marrow was suppressed as measured by a dose-dependent reduction in pro-inflammatory cytokine levels. No evidence of cortisol suppression was observed in these studies.

AIMS

Evaluate in a first in human (FIH) study (NCT07207954) the preliminary risk-benefit profile of LFD-200 vs. placebo and prednisone in healthy participants (HPs) and patients with moderate to severe rheumatoid arthritis (RA).

METHODS

- Study LFD200A11 (**Figure 1)** is a single and multiple ascending dose (SAD/MAD), randomized, double-blind, placebo- and active-controlled FIH study designed to evaluate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of LFD-200. This is a 2-part study evaluating cohorts of HPs in Part 1 [N=11/cohort (SAD) or N=8/cohort (MAD)] and, in Part 2, cohorts of patients with moderate to severe RA (N=14/cohort). Only the starting dose in SAD cohort 1 was pre-specified (1.5 mg/kg) – all subsequent doses in the study were selected by a Safety Review Committee based on emerging study data. Participants in each SAD HP cohort were randomized to receive a single dose of either oral prednisone (10 mg, open label; N=3), SC LFD-200 (N=6) or SC placebo (N=2). Participants in each MAD HP cohort were randomized to receive 4 weekly (Q1W) SC doses of LFD-200 (N=6) or placebo (N=2). Randomization in each cohort in Part 2 is 8 LFD-200: 3 placebo: 3 prednisone with a dosing duration of 12 weeks.
- Study assessments include:
  - Safety: adverse events (AEs), laboratories, vital signs (VS), electrocardiograms (ECGs), and physical examinations (PE)
  - PK: maximum concentration (C_{max}), area under the curve (AUC), time of maximum concentration (T_{max}) and last measurable concentration (T_{last})
  - PD: biomarkers, including cortisol and cytokines
  - Efficacy (Part 2): multiple endpoints (e.g., DAS28-CRP, ACR 20/50/70)
- Analytical methods for assessments include:
  - Cortisol measured using a qualified liquid chromatography/mass spectrometry (LC/MS) assay
  - Quantification of cytokines after ex vivo lipopolysaccharide (LPS)-stimulation of whole blood (TruCulture®)
  - PK analysis using validated LC-MS/MS for conjugated antibody (LFD-200) and free payload
- Available data in Part 1, which has now completed study conduct, are presented. HPs receiving prednisone and placebo were pooled across cohorts.

RESULTS

Study design, doses evaluated

In Part 1, single SC doses of 1.5, 3, 6, and 12 mg/kg were evaluated in the SAD study and four weekly 5.5 mg/kg SC doses were evaluated in the MAD (**Figure 1**). This dose range delivers an estimated modified budesonide dose range of 3-24 mg in a 70 kg human, which is approximately equivalent to 21-170 mgs of prednisone (adjusted for potency) per dose of LFD-200.

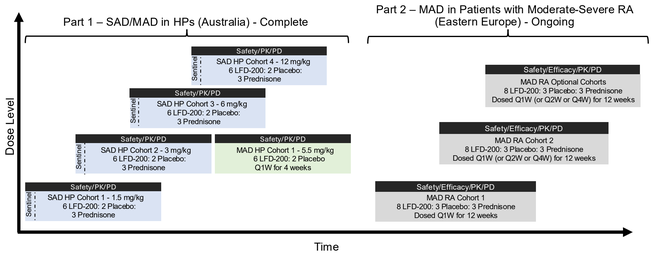


Figure 1: *Study design with doses evaluated. Q1W, Q2W, Q4W = dosed every 1, 2, or 4 weeks, respectively*

Baseline Characteristics: Typical for HPs and generally balanced across arms

Baseline Characteristic	SAD Dose Level (mg/kg) (N)						MAD Dose Level (mg/kg) (N)	
	1.5 (N=6)	3 (N=6)	6 (N=6)	12 (N=6)	Placebo (N=8)	Prednisone (N=12)	5.5 (N=6)	Placebo (N=2)
Age (yrs; median (range))	24 (19-33)	26 (19-48)	29 (19-36)	32 (19-51)	31 (19-53)	26 (22-49)	24.5 (21-44)	25 (24-26)
BMI (kg/m^2, median (range))	22.0 (19.4-29.5)	23.6 (19.4-28.7)	26.6 (23.4-27.6)	24.4 (18.6-27.9)	23.4 (20.5-31.2)	22.3 (20.2-30.6)	25.0 (22.8-26.9)	21.2 (21.0-21.4)
Gender (% Male)	50%	50%	33.3%	66.7%	50%	50%	66.7%	0%
Race (%)								
- White	83.3%	16.7%	66.7%	66.7%	25%	75%	66.7%	50%
- Asian	16.7%	83.3%	33.3%	16.7%	50%	25%	33.3%	0%

Table 1: *Baseline characteristics of all dosed healthy participants by treatment group*

Safety: Single, multiple doses of LFD-200 were well tolerated

- Serious AEs: none
- Treatment emergent AEs (TEAEs)
  - Leading to drug discontinuation: N=1 (unrelated COVID-19 infection)
  - Grade ≥3: none
  - Grade ≤2:
    - Most commonly reported (in ≥3 (SAD) or ≥2 (MAD) HPs): injection site reactions (ISRs; SAD & MAD), anemia (SAD)
    - No TEAEs were dose responsive, except for ISRs and dysmenorrhea, which occurred at LFD-200 doses ≥5.5 mg/kg
    - No concerning findings or trends
- Laboratories/VS/ECG/PE: no concerning findings or trends
- No signs of GC toxicity (e.g., no hypertension, hyperglycemia, mood swings, insomnia, fatigue) among LFD-200 treated HPs

PK: LFD-200 plasma exposures support biweekly or monthly dosing

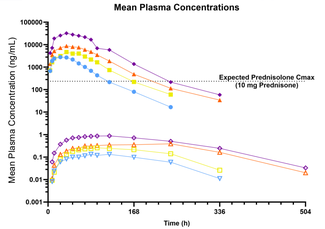


Figure 2: *Single dose LFD-200, free PL PK profiles*

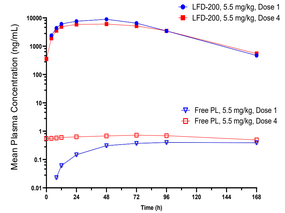
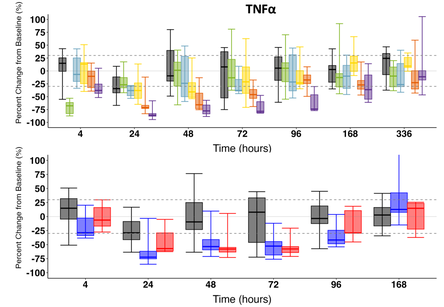


Figure 3: *Multiple dose PK profiles*

Single Dose PK (**Figure 2**)
- LFD-200
  - Serum half-life ($t_{1/2}$) ~30 hours, which is consistent with active uptake into VISTA+ target cells
  - ADC is dose proportional between 1.5-6 mg/kg and greater than proportional between 6-12 mg/kg
- Free PL exposure
  - Dose proportional over entire dose range
  - Persists beyond ADC detection, which suggests tissue compartment exposure ≥2 weeks
  - >400-fold below estimated C_{max} for 10 mg prednisone

Multiple Dose PK Through 4 Doses (**Figure 3**)
- No accumulation or loss of ADC exposure observed
- Steady state exposures are reached for all analytes by the 2nd weekly dose

PD: LFD-200 showed sustained and potent anti-inflammatory activity in blood*



***Note: Blood is not the target tissue; assay known to underrepresent in vivo effects in immune tissue**

Figure 5: *TNFα levels after ex vivo LPS-stimulation of whole blood samples in the SAD (A) and MAD (B). LFD-200 demonstrated a dose responsive effect that was comparable to the effect seen after a single 10 mg dose of prednisone and was sustained. A similar effect was seen for IL-6 and IL-1β (data not shown). Box spans 25th – 75th percentile with line indicating median. Whiskers = 5th and 95th percentiles. Placebo, N=8 for SAD and N=10 for MAD (SAD+MAD HPs); Prednisone (SAD), N=12; LFD-200, N=6 (SAD; MAD 1st dose), N=5 (MAD 4th dose)*

PD: LFD-200 did not affect cortisol, a sensitive marker for systemic GC toxicity

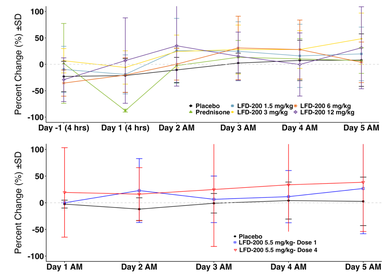


Figure 4:

A) *SAD: No cortisol suppression after single ≤12 mg/kg LFD-200 doses (in setting of sustained free PL exposures); expected suppression seen in first 24 hours after single 10 mg dose of prednisone. N=12 for prednisone group, N=8 for placebo group, N=6 for all LFD-200 groups. Mean ± SD*

B) *MAD: No cortisol suppression after 4 weekly doses (in setting of sustained free PL exposures). N=10 for placebo (all SAD + MAD cohorts), N=6 (1st dose), N=5 (4th dose) for LFD-200 groups. Mean ± SD*

CONCLUSIONS

HP data from this Phase 1 FIH study validate that VISTA-mediated delivery of a high dose GC payload to immune cells avoids harmful side effects typically seen when high doses of a GC are administered systemically. LFD-200 delivered anti-inflammatory activity in a dose-responsive manner with no impact on serum cortisol, a sensitive marker for systemic GC toxicity. Single and multiple doses of LFD-200 were well tolerated and PK profiles were consistent with rapid uptake into VISTA+ immune cells, supporting infrequent dosing (e.g., Q2W-Q4W). Dosing in Part 2 of this study in patients with moderate to severe RA is ongoing.

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