LFD-200, an Antibody Drug Conjugate that Selectively Delivers a Glucocorticoid Payload to Immune Cells, Has a Favorable Risk-Benefit Profile vs. Prednisone and Placebo in a First in Human Study

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INTRODUCTION

- LFD-200 is a novel antibody drug conjugate (ADC) composed of a monoclonal antibody (mAb) that is conjugated to 8 glucocorticoid (GC) payloads (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 relatively 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). 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 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 GxP 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 preliminary healthy participant data are presented here and include data from SAD cohorts 1-4 and MAD cohort 1

RESULTS

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).

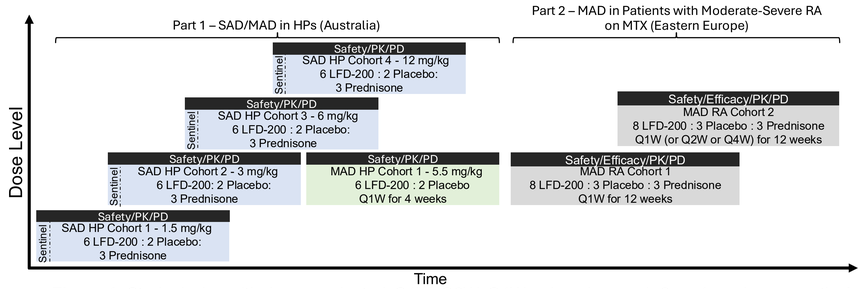


Figure 1: *Study design with doses evaluated.* Q1W, Q2W, Q4W = dosed every 1, 2, or 4 weeks, respectively

Baseline characteristics among the 44 and 8 HPs dosed in the SAD and MAD, respectively, were generally balanced across cohorts. The overall median (range) age was 25.5 (19-53) years and BMI was 23.2 (18.6-31.2) kg/m^2. Participants were 50% male, 58% white, and 35% Asian.

Safety: LFD-200 was 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 ≥4 HPs): injection site reactions (ISRs), headache, anemia
    - No TEAEs were dose responsive, except for ISRs, which occurred primarily at doses ≥5.5 mg/kg
- Laboratories/VS/ECG/PE: no concerning findings or trends

PK: LFD-200 plasma exposures were supportive of biweekly or monthly dosing

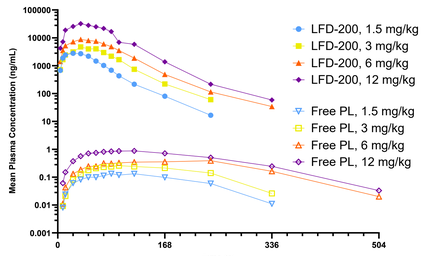


Figure 2: *Single dose LFD-200, GC payload (PL) PK profiles*

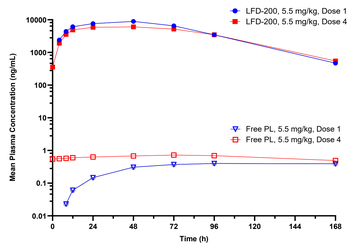


Figure 3: *Multiple dose PK profiles*

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 payload 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 did not affect cortisol, a sensitive marker for systemic GC toxicity

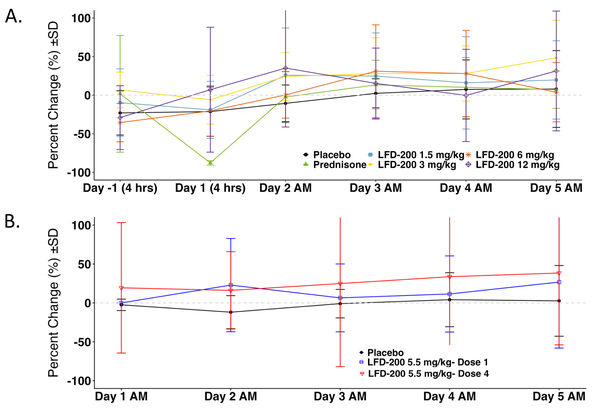
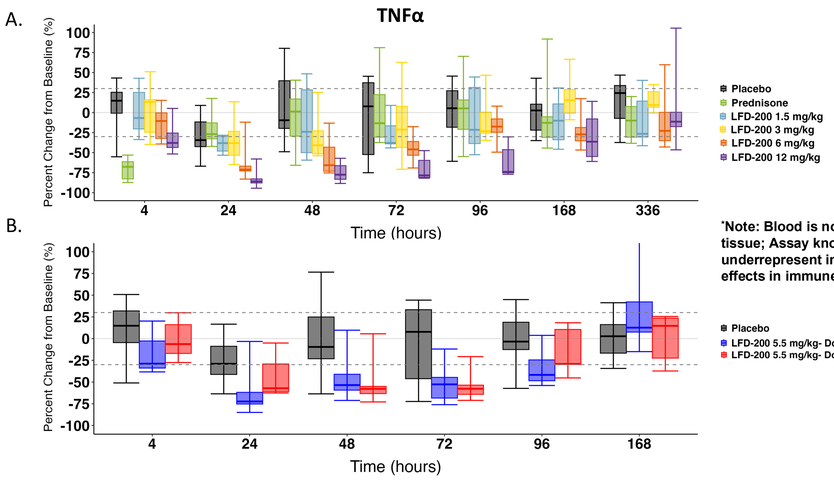


Figure 4

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*

PD: LFD-200 showed sustained and potent GC activity in whole 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); Prednisone, N=12; LFD-200, N=6 (1st dose), N=5 (4th dose).*

CONCLUSIONS

HP data from this Phase 1 study demonstrate the translation of our preclinical findings with LFD-200 into humans and further validate our VISTA-directed delivery to immune cells while avoiding harmful side effects. LFD-200 selectively targets its GC payload to immune cells delivering 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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