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LFD-200, an Antibody Drug Conjugate (ADC) that Selectively Delivers a Glucocorticoid Payload to Immune Cells, Provides Sustained Anti-inflammatory Effects Without Systemic Toxicity in Non-Human Primates

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Abstract #0494

INTRODUCTION

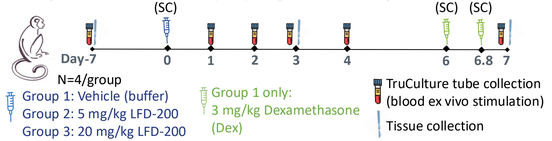
LFD-200 is a novel ADC that binds the cell surface protein V-domain immunoglobulin suppressor of T cell activation (VISTA), which is primarily expressed on immune cells. It carries a glucocorticoid (GC) receptor agonist payload via a protease-cleavable linker and has a drug-to-antibody ratio of 8. LFD-200 is designed for targeted GC delivery to immune cells to achieve an improved safety-efficacy profile vs. systemic GCs. It is intended to treat immune-mediated diseases, including rheumatoid arthritis (RA).

AIMS

- Characterize the distribution and anti-inflammatory activity of LFD-200 and its payload using *in vitro* and *ex vivo* assays
- Evaluate the systemic toxicity of LFD-200, including measurements of cortisol and bone biomarkers in non-human primates (NHPs)

METHODS

NHP pharmacokinetic (PK) & pharmacodynamic (PD) studies



Lipopolysaccharide (LPS)-stimulated cytokine release was measured in whole blood (TruCulture®) and bone marrow using ex vivo stimulation and quantified using Luminex. Tissues were analyzed by immunohistochemistry (IHC) with a payload-detecting antibody. A 2nd similar study included additional timepoints and sampling for cortisol. Bone biomarkers, cortisol, and systemic toxicity were also evaluated in a good laboratory practice (GLP) toxicology study where NHPs were dosed subcutaneously (SC) weekly with LFD-200 (25, 75, and 200 mg/kg) or unconjugated antibody (mAb) or payload (PL) alone (both equivalent to ~200 mg/kg LFD-200) for 13 weeks followed by a 4-week recovery period.

RESULTS

LFD-200 achieves ≥7-day GC payload exposure in immune cells

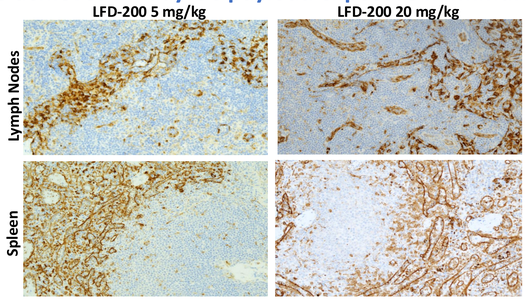


Figure 1. *GC payload (brown stain) was detectable in immune tissues 7 days after a single LFD-200 dose. No staining occurred with vehicle (not shown); 20x amplification.*

LFD-200 dose-dependently reduces inflammatory cytokines

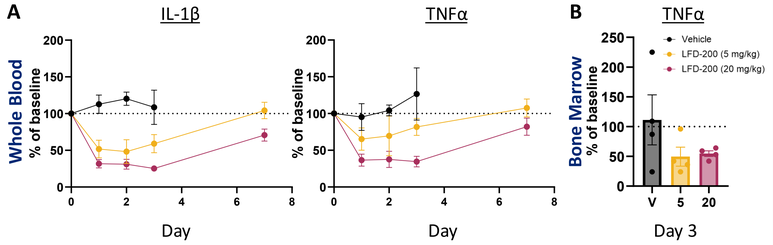


Figure 2. *LFD-200 dose-dependently reduced release of inflammatory cytokines in ex vivo stimulation of whole blood (A) & bone marrow (B) after a single dose. V = Vehicle, 5 = LFD-200 5 mg/kg, 20 = LFD-200 20 mg/kg; Mean ± SEM percent of baseline.*

LFD-200 does not suppress cortisol at clinically relevant doses

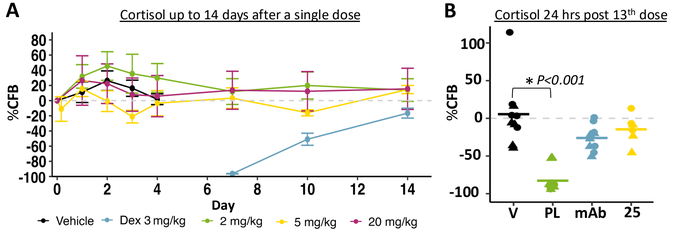


Figure 3. *A) No change was seen in cortisol after a single ≤20 mg/kg LFD-200 dose, unlike Dex control (mean ± SEM). B) No cortisol reduction was seen after receiving 13 clinically relevant doses of LFD-200 (25 mg/kg) or mAb. Cortisol was suppressed by payload alone and with supratherapeutic doses of LFD-200 (200 mg/kg; data not shown) following weekly dosing for 13 weeks. Mean ± SEM percent change from baseline (%CFB).*

LFD-200 does not suppress bone markers at clinically relevant doses

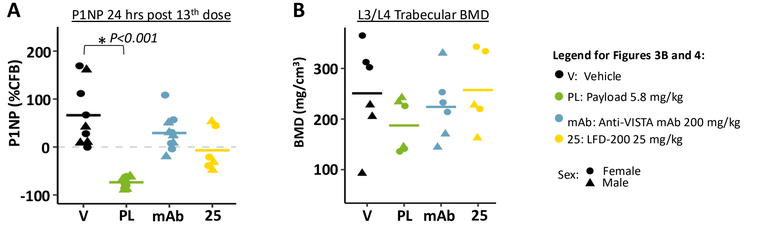


Figure 4. *After 13 weekly 25 mg/kg LFD-200 doses, no reduction in bone formation biomarker procollagen type 1 N-propeptide (P1NP; A) or bone mineral density (BMD; B) was seen. Reductions in these markers were only seen at supratherapeutic doses of LFD-200 or payload and subsequently recovered (not shown).*

No off-target toxicity seen after 13 weekly doses (≤75 mg/kg)

As expected, non-adverse, decreased lymphoid cellularity was seen in immune tissues; no off-target systemic toxicities were observed at doses up to 75 mg/kg.

CONCLUSIONS

- Administration of LFD-200 to NHPs resulted in sustained, dose responsive activity in relevant immune tissues and supports the potential for infrequent (e.g., every 1-4 weeks) SC dosing in the clinic.
- At clinically relevant doses (≤25 mg/kg), LFD-200 does not lead to systemic toxicity after 13 weekly injections in NHPs as measured by serum cortisol, bone biomarkers such as P1NP and BMD, and general toxicology assessments.
- Studies in NHPs demonstrate that LFD-200 delivers immune-targeted anti-inflammatory effects while bypassing toxicities associated with systemic GC exposure.
- A first-in-human study evaluating the safety, PK, and PD of single/multiple doses of LFD-200 in healthy participants and RA patients has been initiated (NCT07207954).

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