A Phase 1 Study of FPA008, an Anti-Colony Stimulating Factor 1 Receptor (anti-CSF1R) Antibody in Healthy Volunteers and Subjects with Rheumatoid Arthritis (RA): Preliminary Results

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Study Design

Part 1: Single Ascending Dose (FPA008 given intravenously-IV)

- Dose escalation is based on the number of DLTs observed. DLTs defined as any sentinel subjects enrolled in Part 1.
- 8 healthy volunteers/dose cohort, randomized 6:2 to receive FPA008 vs placebo.

Part 2: Dual Ascending Dose (N=3) for 2 doses.

- On-target changes in CK, LDH, AST and ALT were dose-related, reversible and not associated with toxicity.

Treatment-Related Adverse Events Occurring in ≥10 Subjects Receiving Single or Dual Doses of FPA008

- No DLTs were observed.
- Pruritus, eyelid edema with or without facial edema, fatigue, and headache were reported in ≥20% of subjects who received FPA008.
- All events were Grade 1 or 2, and self-limiting.
- The adverse event profile is similar to what has been reported with other compounds targeting the CSF1R pathway.
- Eyelid edema along with facial edema started at 3 mg/kg, was mostly mild and self-limiting.
- At 10 mg/kg, all grade 3 events experienced moderate (Grade 2) eyelid edema or facial edema, some accompanied with swelling of the hands and feet, altered vision, and weight gain; the events lasted up to 3 months.
- There were no Grade 3 events reported regardless of drug.
- One SAE of Bartholin’s cyst was reported with 3 mg/kg dose cohort.

On-Target Changes in Serum CK, LDH, AST, and ALT Levels

- FPA008 has no clinical relevance with exposure increasing greater than dose proportionality, suggesting target- directed clearance.
- Total clearance ranged from 38.7 to 2.3 mL/day for the doses tested.
- 3 subjects in the 1 mg/kg single dose cohort had trace positive antibody titers which did not impact PK exposure (data not shown).

Pharmacokinetics of FPA008

- FPA008 had nonlinear clearance with exposure increasing greater than dose proportionality, suggesting target-directed clearance.
- Total clearance ranged from 38.7 to 2.3 mL/day for the doses tested.
- 3 subjects in the 1 mg/kg single dose cohort had trace positive antibody titers which did not impact PK exposure (data not shown).

Dose-Dependent Increase of Serum CSF1 and IL34 Levels

- Inhibition of CSF1R via FPA008 resulted in doses dependent increase of serum CSF1 and IL34 levels.

Dose-Dependent Reduction of Proinflammatory CD16+ Monocytes

- Whole blood samples were analyzed by flow cytometry for the absolute numbers of monocyte subsets based on the expression of CD14, HLA-DR, CD16, and CD15.

Dose-Dependent Reduction of Serum CTX and Trap5B Levels

- Dose-dependent decreases of bone turnover biomarkers were observed in serum samples analyzed after FPA008 treatment.

Conclusions

- FPA008 was well tolerated in healthy volunteers up to 3 mg/kg. The most common FPA008-related adverse event was eyelid edema along with facial edema, fatigue, and headache; all events were ≥Grade 1 and 2 self-limiting.
- On-target changes in CK, LDH, AST and ALT were dose-related, reversible and not associated with toxicity.
- FPA008 has saturable, nonlinear clearance and is able to support biweekly or less frequent dosing schedule.
- On-target changes in CK, LDH, AST and ALT serum enzymes are elevated due to on-target reductions in Kupffer cells (liver macrophage), expected with an agent targeting the CSF1R pathway (Rudl, 2011).
- According to dose-dependent elevations of ALT and LDH at N=12 and N=6 for two doses.
- Dose escalation is based on the number of DLTs observed. DLTs defined as any sentinel subjects enrolled in the first 29 days for Part 1 and 45 days for Part 2.
- In Part 2, 23 adverse events that met the following criteria for a DLT:
  - CK > 10 times upper limit of normal (ULN) or AST or ALT > 5 ULN (not all levels included for this cohort) and associated with total bilirubin >2 ULN.
  - RA subjects who have inadequate response to disease modifying anti- rheumatic drugs (DMARDs) and on stable dose of nonsteroids are eligible.
  - 3 sentinel dose cohort in open-label portion will receive FPA008 IV at the assigned dose level q 14 days for two doses.
  - Dose escalation is based on the number of DLTs observed within the first 21 days for dual open-label portion.
  - Upon completion of the open-label portion, 30 new subjects will be randomized to receive one or two different dose levels of FPA008 as placebo.

Part 1 and Part 2 Study Results – Demographics and Treatment Summary

- Race, white, n (%) 8 (100%) 6 (100%) 6 (100%) 6 (100%) 6 (100%) 4 (100%) 6 (100%) 6 (100%) 8 healthy volunteers/dose cohort, randomized 6:2 to receive FPA008 vs placebo.

Series Information

- Part 1 - Single Ascending Dose (FPA008 given intravenously-IV)
- Part 2 - Dual Ascending Dose (FPA008 given IV q 14 days)