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

J Hambleton[1], L Zhou[1], S Rogers[1], S van Marle[2], T van Iersel[2], J Zanghi[1], E Masteller[1], H Xiang[1], K Baker[1], B Wong[1]
[1]Five Prime Therapeutics, Inc., South San Francisco, CA USA; [2]PRA Health Sciences, Groningen, Netherlands

#1493

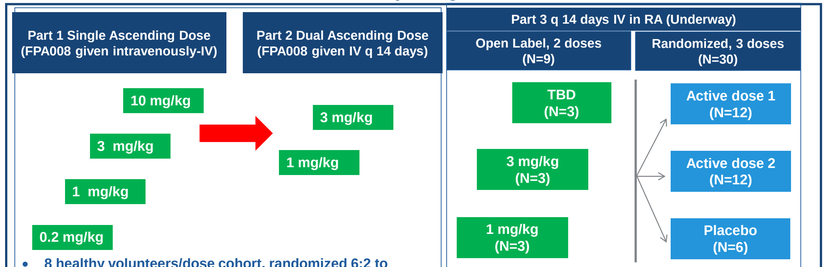
Background

Activation of CSF1R via the ligands IL34 and CSF1 results in activation, differentiation, and survival of monocytes, macrophages, and osteoclasts. Synovial macrophages, through their ability to release inflammatory cytokines, chemokines, and other factors, play a central role in the pathology of RA. Importantly, macrophage numbers and cytokine products are associated with disease activity and disease progression in RA. Mice deficient in CSF1 are resistant to the induction of collagen-induced arthritis (CIA), and therapeutic administration of an anti-CSF1R monoclonal antibody reduces CIA-induced synovitis and bone destruction in wild-type mice. Therefore, strategies specifically designed to target the activation or survival of macrophages in synovial tissue may be of therapeutic benefit.

FPA008 is a humanized IgG4 anti-CSF1R monoclonal antibody that blocks both CSF1 and IL34 ligand binding, and has shown activity in preclinical models of RA.

This first-in-human trial consists of three parts: Parts 1 and 2 assess safety, pharmacokinetics (PK), and pharmacodynamic (PD) biomarkers of single and multiple doses of FPA008 in healthy volunteers, followed by Part 3 evaluation in RA subjects. Here, we are reporting results from Parts 1 and 2 of the study.

Study Design



- 8 healthy volunteers/dose cohort, randomized 6:2 to receive FPA008 vs placebo.
- Sentinel subjects enrolled in Part 1.
- Dose escalation based on the number of dose limiting toxicities (DLTs) observed within the first 29 days for Part 1 and 43 days for Part 2.
- DLTs defined as any Grade ≥3 adverse events that are considered related to FPA008 treatment with the exception of asymptomatic elevations of CK, AST, or ALT due to expected on-target reduction of Kupffer cells (liver macrophage). These laboratory values need to meet the following criteria for a DLT:
  - CK >10x upper limit of normal (ULN)
  - AST or ALT >8x ULN or
  - AST or ALT >3x ULN and associated with total bilirubin >2x ULN

- RA subjects who have inadequate response to disease modifying anti-rheumatic drugs (DMARDs) and on stable dose of methotrexate are eligible.
- 3 subjects/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 43 days in the 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 or placebo.

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

Baseline Information	Part 1 - Single Ascending Dose					Part 2 –Dual Ascending Dose		
FPA008 dose level (mg/kg)	Placebo (n=8)	0.2 mg/kg (n=6)	1 mg/kg (n=6)	3 mg/kg (n=6)	10 mg/kg (n=6)	Placebo (n=4)	1 mg/kg (n=6)	3 mg/kg (n=6)
Female, n (%)	5 (63%)	5 (83%)	4 (67%)	2 (33%)	6 (100%)	3 (75%)	1 (17%)	4 (67%)
Race, white, n (%)	8 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	6 (100%)	6 (100%)
Median ages (years) (min, max)	32 (21, 55)	23 (21, 53)	23 (21, 55)	24 (22, 40)	28 (22, 53)	26 (22, 48)	36 (21, 55)	23 (21, 43)
Median weight (kg) (min, max)	76.8 (57.2, 85.0)	68.2 (62.8, 86.7)	70.7 (65.0, 99.7)	78.8 (68.8, 105.6)	72.8 (48.8, 92.3)	69.3 (61.1, 73.9)	77.3 (58.5, 87.7)	74.8 (58.4, 98.5)
Median BMI (kg/m^2) (min, max)	24.5 (20.3, 28.4)	23.6 (23.3, 28.6)	25.0 (22.0, 28.5)	25.0 (22.0, 29.9)	25.1 (18.1, 31.4)	21.4 (20.9, 25.3)	23.2 (20.6, 27.4)	24.1 (19.1, 26.8)
# of subjects who completed dosing as planned, n (%)	8 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	5[a] (83.3%)	2[b] (33.3%)

a. One subject did not receive the second dose due to a positive screening HBcAb, but completed scheduled follow-up assessments.

b. Four subjects received one dose only: two withdrew consent for second dose; two were withdrawn due to concurrent health conditions (need for hip surgery, acute anxiety attack). All four subjects completed their scheduled follow-up visits.

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

Part 1 - Single Ascending Dose

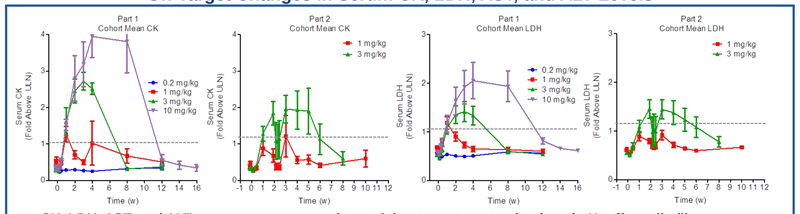
	Placebo (n=8)	0.2 mg/kg (n=6)	1 mg/kg (n=6)	3 mg/kg (n=6)	10 mg/kg (n=6)	All Active (n=24)
Pruritus	1 (13%)	–	4 (67%)	3 (50%)	4 (67%)	11 (46%)
Eyelid Edema	–	–	–	4 (67%)	5 (83%)	9 (38%)
Headache	1 (13%)	3 (50%)	1 (17%)	1 (17%)	3 (50%)	8 (33%)
Fatigue	2 (25%)	1 (17%)	1 (17%)	2 (33%)	2 (33%)	6 (25%)
Local Swelling	–	–	–	–	5 (83%)	5 (21%)
Facial Swelling	–	–	–	–	5 (83%)	5 (21%)
Pruritus Generalized	–	–	–	2(33%)	1 (17%)	3 (13%)
Vision Blurred	–	–	–	–	3 (50%)	3 (13%)

Part 2- Dual Ascending Doses q 14 days

	Placebo (n=4)	1 mg/kg (n=6)	3 mg/kg (n=6)	All Active (n=12)
Pruritus Generalized	–	1 (17%)	4 (67%)	5 (42%)
Eyelid Edema	–	–	4 (67%)	4 (33%)
Acne	–	–	3 (50%)	3 (25%)
Fatigue	–	–	3 (50%)	3 (25%)
Facial Swelling	–	–	3 (50%)	3 (25%)
Pruritus	1 (25%)	1 (17%)	1 (17%)	2(17%)

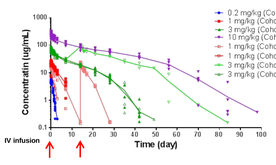
- No DLTs were observed.
- Pruritus, eyelid edema with or without facial swelling, fatigue, and headache were reported in >20% of subjects who received FPA008.
- All events were Grade 1 or 2, and self-limiting.
  - The adverse event profile is similar to what has been reported with other compounds targeting the CSF1R pathway (e.g., RG7155; Cassier, 2014).
  - Eyelid edema along with facial swelling started at 3 mg/kg, was mostly mild and self-limiting.
  - At 10 mg/kg, all 6 active subjects experienced moderate (Grade 2) eyelid edema or facial swelling, some accompanied with swelling of the hands and feet, blurred vision, and weight gain; the events lasted up to 3 months.
- There were no Grade ≥3 events reported regardless of drug relationship.
- One SAE of Bartholin's cyst was reported from one subject in 10 mg/kg dose cohort. The event was considered unlikely related.

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



- 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 (Radi, 2011).
- Asymptomatic dose-dependent elevations of serum CK and LDH were noted at doses ≥1 mg/kg. AST elevation of up to 2.4x ULN occurred at doses ≥3 mg/kg (not shown); and mild ALT elevation of up to 1.2x ULN occurred at 10 mg/kg in one subject (not shown).
- These elevations were reversible and were not associated with clinical signs/symptoms or abnormalities in total bilirubin, CK isoenzymes, or troponin.

Pharmacokinetics of FPA008

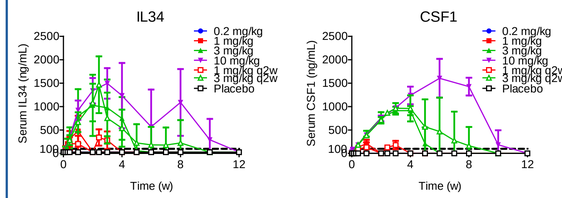


Estimated PK Parameters (Group Mean ± SD)									
Dose Cohort	Dose mg/kg	n	C_{max} (µg/mL)	C_{max} /Dose (µg/mL)/(mg/kg)	AUC_{last} (day* µg/mL)	AUC_{last}/Dose (day* µg/mL)/(mg/kg)	CL (mL/day/kg)	V_{ss} (mL/kg)	
1	0.2	6	5.25 ± 0.253	26.2 ± 1.27	4.91 ± 0.639	24.6 ± 3.20	38.7 ± 5.32	32.5 ± 1.91	
2	1	6	24.5 ± 2.61	24.5 ± 2.61	85.9 ± 16.2	85.9 ± 16.2	11.5 ± 2.36	40.5 ± 4.21	
3	3	6	78.6 ± 7.75	26.2 ± 2.58	696 ± 31.6	232 ± 10.5	4.31 ± 0.200	45.9 ± 4.65	
4	10	6	278 ± 51.0	27.8 ± 5.10	3978 ± 494	398 ± 49.3	2.55 ± 0.293	53.0 ± 8.04	
5	1, 1*	5	20.7 ± 2.26	20.7 ± 2.26	70.2 ±7.38	7.02 ± 0.735	13.5 ± 0.614	NC	
5	1	1	7.75	7.75	11.4	11.4	NC	NC	
6	3, 3*	2	89.9	30.0	1310	435	4.00	NC	
6	3	4	70.8 ± 14.8	23.6 ± 4.94	632 ± 67.5	211 ± 22.5	NC	NC	

Estimated PK parameters (mean ± SD) using noncompartmental analysis by WinNonlin.
*PK parameters were estimated post second dose. NC=not calculated; C_{max}=maximum serum concentration; AUC_{last}=area under the serum concentration-time curve from time to last measureable time point; CL=serum total clearance; V_{ss}=volume of distribution at steady state.

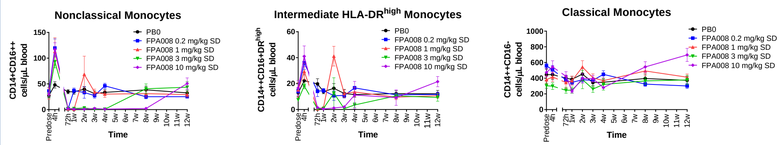
- FPA008 has nonlinear clearance with exposure increasing greater than dose proportionality, suggesting target-mediated clearance.
- Total clearance ranged from 38.7 to 2.55 mL/day/kg for the doses tested.
- 3 subjects in the 1 mg/kg single dose cohort had trace positive antibody titers which did not impact PK exposure (data not shown).

Dose-Dependent Increase of Serum CSF1 and IL34 Levels



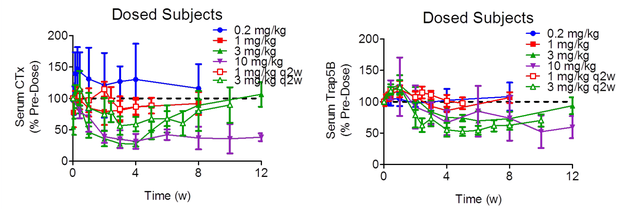
- Inhibition of CSF1R via FPA008 treatment resulted in dose-dependent increase of CSF1 and IL34 ligand concentration in serum.
- Both ligands rapidly restore to baseline after FPA008 clears from serum.

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 CD45, HLA-DR, CD14, and CD16.
- FPA008 treatment resulted in the rapid and sustained reduction of CD14$^+$CD16^{++} nonclassical and CD14^{++}CD16$^+$HLA-DR^{high} intermediate monocytes.
- Intermediate HLA-DR^{high} monocytes were less sensitive to FPA008 treatment and recovered before nonclassical monocytes.
- FPA008 did not affect the levels of CD14^{++}CD16$^-$ classical monocytes.

Dose-Dependent Reduction of Serum CTx and Trap5B Levels



- Dose-dependent decreases of bone turnover markers were observed in response to FPA008 treatment.

Conclusions

- FPA008 was well tolerated in healthy volunteers up to 3 mg/kg. The most common FPA008 treatment-related adverse events were pruritus, eyelid edema along with facial swelling, fatigue, and headache; all events were Grade 1 or 2 and self-limited.
- 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.
- Inhibition of CSF1R via FPA008 treatment resulted in dose-dependent increase in serum CSF1 and IL34 levels.
- Dose-dependent changes of PD markers suggest that FPA008 engages its target and inhibits CSF1R, and these changes may track with clinical benefit in RA patients:
  - Reduction of CD14$^+$CD16^{++} nonclassical and CD14^{++}CD16$^+$HLA-DR^{high} intermediate monocytes.
  - Decrease of bone turnover biomarkers CTx and Trap5B.
- Enrollment for the open-label portion in patients with RA has begun.

References

Cassier PA, Gomez-Roca CA, Italiano A, Cannarile M, Ries C, Brillouet A, et al. Phase 1 study of RG7155, a novel anti-CSF1R antibody, in patients with locally advanced pigmented villonodular synovitis (PVNS). J Clin Oncol, 2014;32:5s (suppl; abstract 10504).

Radi Z, Koza-Taylor P, Bell R, Obert L, Runnels H, Beebe J, et al. Increased serum enzyme levels associated with Kupffer cell reduction with no signs of hepatic or skeletal muscle injury. Am J Pathol, 2011;179:240-247.