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

L Zhou[1], R Sikorski[1], S Rogers[1], S Costin[2], M Jaraczewska-Baumann[3], M Korkosz[4], É Péterfai[5], B Rojkovich[6], J Bartalos[7], E Masteller[1], H Xiang[1], B Wong[1], J Hambleton[1]

[1] Five Prime Therapeutics, Inc., South San Francisco, CA USA; [2]PRA Health Sciences, Berlin, Germany; [3]MedPolonia Sp. z o.o., Poznan, Poland; [4]The University Hospital in Krakow, Kraków, Poland; [5]Drug Research Center, Balatonfüred, Hungary; [6] Hospitaller Brothers of St. John of God, Budapest, Hungary; [7]PRA Hungary Ltd., Budapest, Hungary

FivePrime®

#2749

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 rheumatoid arthritis (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 assessed safety, pharmacokinetics (PK), and pharmacodynamic (PD) biomarkers of single and multiple doses of FPA008 in healthy volunteers, followed by Part 3 evaluation in RA patients.

Results of Parts 1 and 2 of this trial were previously reported (J Hambleton et al, 2014 ACR/ARHP meeting). No Dose Limiting Toxicity (DLT) was reported in healthy volunteers treated with FPA008 up to 10 mg/kg. The adverse event profile is similar to what has been reported with other compounds targeting the CSF1R pathway (e.g., RG7155, Cassier, 2014).

Here we are reporting preliminary results of Part 3 open label portion of the study as of October 16, 2015.

Part 3 Open Label Dose Escalation

FPA008 given intravenously every 14 days for 2 or 3 doses

Objectives
Primary: Safety and Tolerability
Secondary: PK and PD

- 1 mg/kg x 2 (N=3)
- 3 mg/kg x 2 (N=3)
- 3 mg/kg x 3 (N=3)
- 6 mg/kg x 2 (N=3)
- 6 mg/kg x 3 recruiting

- RA subjects who have inadequate response to disease modifying anti-rheumatic drugs (DMARDs) and are on stable dose of methotrexate are eligible.
- 3 subjects per dose cohort in the open-label portion received FPA008 IV at the assigned dose level every 14 days for two or three doses.
- Dose escalation is based on the safety profile observed within 6 weeks after the last assigned dose in the open-label portion.

Baseline Demographics and Disease Characteristics

FPA008 dose level (mg/kg)	1 mg/kg x 2 (n=3)	3 mg/kg x 2 (n=3)	3 mg/kg x 3 (n-3)	6 mg/kg x 2 (n=3)
Female, n (%)	2 (67%)	3 100%)	3 (100%)	3 (100%)
Race, white, n (%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)
Ages (years), median (min, max)	57 (53, 66)	61 (57, 63)	54 (39, 65)	27(27, 45)
Disease duration (years), median (min, max)	2.9 (1.0, 13.9)	5.9 (1.1, 17.4)	10.4 (5.5, 14.1)	3.8 (3.5, 12.5)
TJC 0-68, median (min, max)	15 (14, 31)	10 (8, 13)	26 (25, 38)	18 (9, 18)
SJC 0-66, median (min, max)	11 (10, 15)	21 (14, 23)	13 (12, 22)	12 (9, 14)
DAS 28-CRP, median (min, max)	4.4 (3.4, 7.1)	4.5 (4.2, 5.4)	4.8 (4.6, 5.5)	4.1 (4.1, 5.9)
HAQ-DI (0-3), median (min, max)	0.75 (0.5, 1)	1 (0.6, 2.5)	1.3 (1.1, 1.8)	1.5 (0.3, 1.9)
Concurrent RA medications at baseline				
Number of patients on methotrexate, n (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)
Dose (mg/week), median (min, max)	20 (20, 25)	15 (10, 20)	20 (20, 25)	15 (10, 25)
Number of patients on methylprednisolone	1 (33%)	2 (67%)	1 (33%)	1 (33%)
Dose for each patient	4 mg/day	4 mg/day, 2 mg/day	8 mg/day	7.5 mg/5 mg QoD

Treatment Related Adverse Events

Preferred Term	1 mg/kg x 2 (N=3) n (%)	3 mg/kg x 2 (N=3) n (%)	3 mg/kg x 3 (N=3) n (%)	6 mg/kg x 2 (N=3) n (%)
Number of patients with any events	-	2 (67%)	3 (100%)	3 (100%)
Eyelid/periorbital edema	-	2 (67%)	3 (100%)	2 (67%)
Headache	-	-	1(33%)	1(33%)
Abnormal sensation in eye	-	-	1 (33%)	-
Facial edema	-	-	1 (33%)	-
Rash	-	-	1 (33%)	-

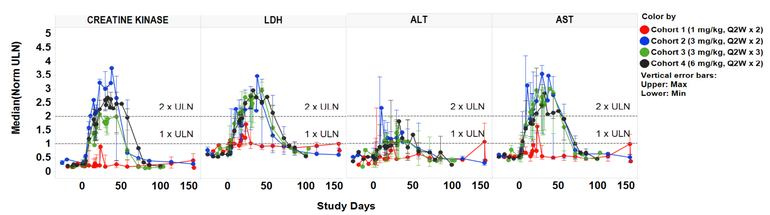
- All treatment-related events were expected and have been reported in other compounds targeting the CSF1R pathway (e.g., RG7155; Cassier, 2014).
- All adverse events regardless of the relationship were Grade 1 or 2, and reversible.
- No Grade ≥ 3 adverse events regardless of the relationship were reported. No SAEs were reported.
- Treatment with FPA008 up to 6 mg/kg x 2 doses was well tolerated.

Clinical Efficacy Measures

Cohorts	Time Points	ACR 20/50/70 response, n	EULAR Mod/good Response, n	Change in DAS28 from baseline, median (min, max)	ACR Hybrid Response, median (min, max)
1 mg/kg x 2 (N=3)	Week 4	0/1/0	2/0	1.04 (-0.38, 3.19)	11.0 (-5.14, 52.86)
	Week 12	0/1/0	2/0	1.08 (-0.28, 1.84)	6.29 (-6.00, 53.86)
3 mg/kg x2 (N=3)	Week 4	1/0/0	0/2	1.23 (0.37, 3.12)	19.99 (-1.43, 49.99)
	Week 12	0/0/0	3/0	0.77 (0.62, 0.96)	8.71 (8.57, 19.99)
3 mg/kg x 3 (N=3)	Week 4	0/1/0	1/0	0.23 (-0.55, 1.56)	-4.57 (-17.43, 50.00)
	Week 12	1/0/0	1/0	-0.64 (-1.11, 1.44)	-20.57 (-20.86, 49.99)
6 mg/kg x 2 (N=3)	Week 4	0/0/0	1/0	-0.03 (-0.53, 0.66)	-10.71 (-20.14, 15.86)
	Week 12	0/0/0	0/0	0.26 (-0.83, 0.50)	-0.14 (-52.71, 18.00)

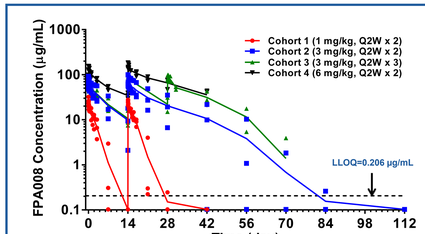
- ACR and EULAR responses were noted at Week 4 and some of the responses were sustained thru Week 12.

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



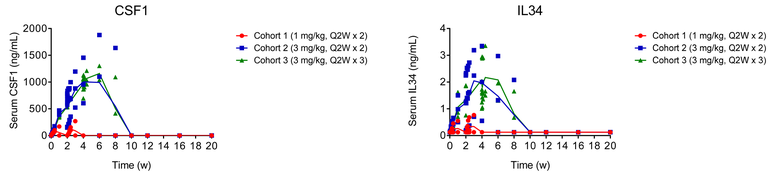
- CK, LDH, ALT, and AST serum enzymes are elevated due to on-target reductions in Kupffer cells (liver macrophages), which are expected with an agent targeting the CSF1R pathway (Radi, 2011).
- These elevations were reversible and were not associated with clinical signs/symptoms or abnormalities in total bilirubin, troponin, aldolase or clinical significant change in ECGs.
- The magnitude and duration of elevations were similar in 3 mg/kg and 6 mg/kg dose levels with notable inter-patient variabilities.

Pharmacokinetics of FPA008 In RA Patients



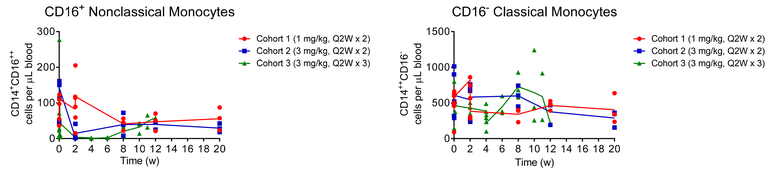
- FPA008 has nonlinear clearance from 1 to 6 mg/kg, suggesting target-mediated clearance.
  - Group mean total clearance post second dose ranged from 17.5 to 4.73 mL/day/kg for the doses tested.
  - High inter-subject variability.
  - Faster than in healthy volunteers.
- ADA was negative for all subjects.

Dose-Dependent Increase of Serum CSF1 and IL34 Levels



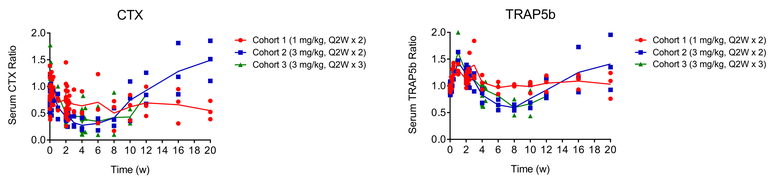
- Inhibition of CSF1R via FPA008 treatment resulted in dose-dependent increases of CSF1 and IL34 ligand concentrations in serum [Cohort 4 data (6mg/kgx2 doses) is not shown because it is not complete].
- Levels of both ligands rapidly returned to baseline after FPA008 cleared from serum.

Dose-Dependent Reduction of Proinflammatory CD16+ Monocytes



- Whole blood samples were analyzed by flow cytometry for the absolute numbers of monocyte subsets.
- FPA008 treatment resulted in the reduction of CD14+CD16++ non-classical monocytes.
- Maximal reduction of CD14+CD16++ non-classical monocytes was sustained through the 2 week dose period at doses ≥ 3 mg/kg.
- CD14++CD16- classical monocyte levels were not reduced by FPA008 treatment.
- Cohort 4 data (6 mg/kg x 2 doses) is not shown because it is not complete.

Dose-Dependent Reduction of Serum CTx and Trap5B Levels



- Dose-dependent decreases of bone turnover markers were observed in response to FPA008.
- Cohort 4 data (6 mg/kg x 2 doses) is not shown because it is not complete.

Conclusions

- This study provided useful information on safety, dosing and biomarker response in an RA patient population.
  - FPA008 was well tolerated in RA patients up to 6 mg/kg x 2 doses. The most common FPA008 treatment-related adverse event was eyelid/periorbital edema, which is a class effect for compounds targeting the CSF1R pathway. The events were Grade 1 or 2, and self-limiting.
  - Compared to healthy volunteers, FPA008 appears to be cleared faster in RA patients and significant inter-patient variabilities were noted.
  - Inhibition of CSF1R via FPA008 treatment resulted in dose-dependent increase in serum CSF1 and IL34 levels.
  - Dose-dependent changes of CD14+CD16++ non-classical monocytes and bone turnover markers demonstrate that FPA008 engages its target and inhibits CSF1R.
- There was no preliminary evidence of a dose response in RA patients with this limited dosing.
- The trial is ongoing, enrolling patients into FPA008 6 mg/kg x 3 doses to assess tolerability and PK of 3 doses.

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.

Hambleton J, Zhou L, Rogers S, Marle SV, et al. 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. 2014 ACR/ARHP annual meeting (abstract#1493)

©2015 Five Prime Therapeutics, Inc. All Rights Reserved