Pharmacokinetics, Pharmacodynamics, and Safety of FLX475, an Orally-Available, Potent, and Selective Small-Molecule Antagonist of CCR4, in Healthy Volunteers

Sjoerd van Marle, MD[1], Ewoud-Jan van Hoogdalem, PhD, RPh[1], Daniel Johnson[2], Abood Okal, PhD[2], Paul D. Kassner, PhD[2], David J. Wustrow, PhD[2], Steven A. Smith[7], and William Ho, MD, PhD[2]

[1]PRA Health Sciences, Groningen, Netherlands; [2]FLX Bio, Inc., South San Francisco, CA

SITC 2018
Abstract P484

Abstract

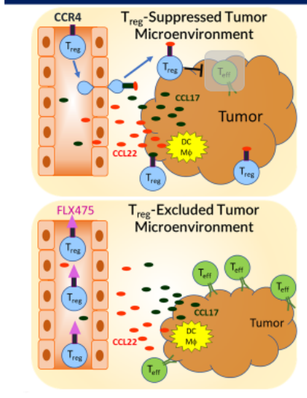
Regulatory T cells (T_{reg}) are essential for immune tolerance to self antigens, but can also dampen anti-tumor immune responses in the tumor microenvironment (TME). The predominant chemokine receptor on human T_{reg} is CCR4, the receptor for the chemokines CCL17 and CCL22, which are produced by tumor cells, tumor-associated macrophages and dendritic cells, as well as by effector T cells (T_{eff}) in the setting of an inflammatory anti-tumor response.[1] Preclinical studies with orally-available CCR4 antagonists have demonstrated potent inhibition of T_{reg} migration into tumors, an increase in the intratumoral T_{eff}/T_{reg} ratio, and anti-tumor efficacy as a single agent and in combination with checkpoint inhibitors.[2]

A first-in-human, randomized, double-blind, placebo-controlled trial was conducted to examine the safety, pharmacokinetics (PK), and pharmacodynamics (PD) in healthy volunteers (HVs) of single and repeat dosing of FLX475, an orally-available, potent, and selective small-molecule antagonist of CCR4. Seven cohorts of 8 subjects each (6 drug, 2 placebo) were administered single doses ranging from 5 mg to 1000 mg. Six cohorts were administered daily doses of FLX475 for 14 days ranging from 25 mg to 150 mg, including two cohorts evaluating a loading dose administered on Day 1. FLX475 was well-tolerated, with no significant laboratory abnormalities or dose-limiting clinical adverse events. Dose-dependent increases in exposure were observed with low peak-to-trough ratios and a half-life of approximately 72 hours. Daily dosing without a loading dose demonstrated approximately 4-5x accumulation of FLX475 over 14 days. A receptor occupancy (RO) PD assay using study subject peripheral blood T_{reg} demonstrated a tight PK/PD relationship, suggesting that doses of approximately 75 mg PO QD and above are sufficient to maintain target drug exposure above the IC_{90} for human in vitro T_{reg} migration.

In this first-in-human HV study, the oral CCR4 antagonist FLX475 was demonstrated to be well tolerated with outstanding PK properties. A robust PD assay measuring receptor occupancy on circulating T_{reg} demonstrated the ability to safely achieve exposure levels predicted to maximally inhibit T_{reg} recruitment into tumors via CCR4 signaling.[3] These data have enabled the optimized design of an ongoing Phase 1/2 study of FLX475 both as monotherapy and in combination with checkpoint inhibitor in cancer patients.

Background

FLX475: Designed to Enhance the Anti-Tumor Immune Response



- Immune cells follow chemokines to migrate into target tissues
- CCR4 is a chemokine receptor expressed on T_{reg}
- In response to inflammation, tumor cells and other cells in the TME highly express the chemokines CCL17 and CCL22 (ligands for CCR4), inducing the migration of T_{reg} into tumors
- T_{reg} can suppress the anti-tumor activity of effector T cells
- FLX475 is a potent, orally-available, small molecule antagonist of CCR4 that specifically blocks the recruitment of T_{reg} into tumors
  - Shifting the T_{eff}/T_{reg} balance in favor of tumor elimination

Methods

Study Schema

SAD Cohorts	MAD Cohorts
5 mg	25 mg x 14d
25 mg	50 mg x 14d
75 mg	75 mg x 14d
200 mg *200 mg Food Effect	100 mg x 14d
400 mg	300 mg Day 1, 100 mg x D2-14
750 mg	300 mg Day 1, 150 mg x D2-14
1000 mg	

- Double-Blind, Placebo Controlled
- 8 healthy volunteers per cohort (2 placebo, 6 FLX475 capsules)
  - *Bioavailability of tablet formulation and effect of high-fat meal also tested in 200 mg SAD cohort subjects
- Monitored inpatient through 72 hours post (last) dose and approximately 2 week additional follow up
- Cardiac telemetry for 24-hour period of Day 1 (and Day 14 for MAD) dose
  - Triplicate ECGs at other timepoints

Subject Demographics

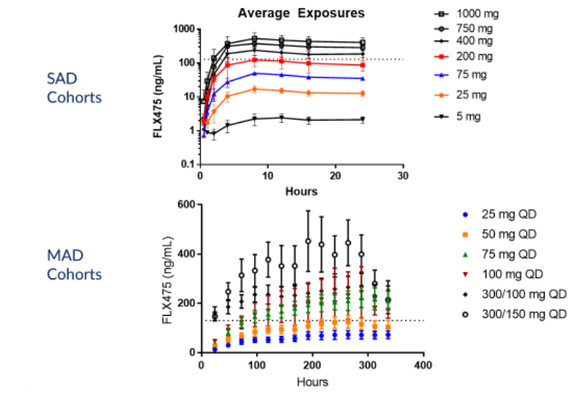
SAD Cohort	M/F	Age (mean)	Weight in kg (mean)	Height in cm (mean)	BMI kg/m2 (mean)
Placebo (#14)	4/10	19-54 (35)	55.5-92.4 (74.4)	161-179 (170.1)	20.5-29.5 (25.6)
5 mg (#6)	1/5	18-53 (28)	53.5-80.9 (68.1)	160-179 (169)	20.4-29.4 (23.8)
25 mg (#6)	1/5	18-27 (21)	59.6-68.5 (65.8)	171-184 (176.7)	20.8-23.4 (21.1)
75 mg (#6)	0/6	21-36 (25)	57.7-71.6 (65.6)	160-173 (166.2)	21.2-26.3 (23.7)
200 mg (#6)	3/3	27-55 (46.8)	51.9-99 (80.8)	153-195 (177)	22.2-29.7 (25.5)
400 mg (#6)	1/5	20-49 (27.3)	56.3-73.7 (66.2)	160-172 (164.2)	21.9-29.7 (24.5)
750 mg (#6)	4/2	19-54 (27.7)	65-86.8 (75.7)	167-197 (180.8)	20.4-25.7 (23.2)
1000 mg (#6)	1/5	19-55 (36.2)	54.7-90.5 (68.2)	157-177 (165.8)	19.4-29.7 (24.6)
Total	15/41	18-55 32.5	51.9-99.0 (71.1)	153-197 (171.1)	19.4-29.7 (24.3)

MAD Cohort	M/F	Age (mean)	Weight in kg (mean)	Height in cm (mean)	BMI kg/m2 (mean)
Placebo (#12)	5/7	18-41 (26.3)	57.3-74.2 (65.3)	157-191 (172)	19.0-27.4 (22.2)
25 mg (#6)	1/5	20-43 (26.2)	54.3-99.1 (66.6)	161-187 (170)	20.8-28.3 (22.8)
50 mg (#6)	2/4	19-48 (28)	56.6-81.8 (69.6)	167-187 (174.5)	20.8-25.3 (22.8)
75 mg (#6)	2/4	19-53 (30.3)	55-80.2 (65.8)	158-181 (166.8)	19.5-27.8 (23.7)
100 mg (#6)	2/4	21-30 (26.5)	70.3-89.9 (76.1)	170-188 (177)	20.2-29.7 (24.4)
300/100 mg (#6)	1/5	18-38 (26.2)	51.2-90.9 (71.6)	161-189 (172.7)	19.5-29.3 (24.0)
300/150 mg (#6)	1/5	18-40 (27.3)	55.9-83.8 (66.5)	160-187 (171.3)	19.7-27.1 (22.6)
Total	14/34	18-53 (27.1)	51.2-99.1 (68.4)	157-191 (172.0)	19.0-29.3 (23.1)

Results

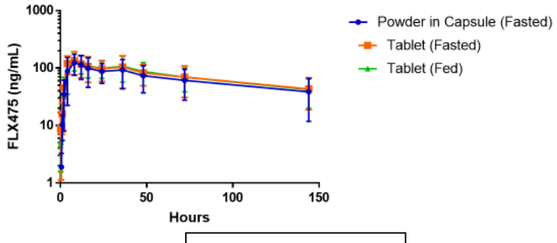
Pharmacokinetics

Mean Exposures by SAD/MAD Cohort



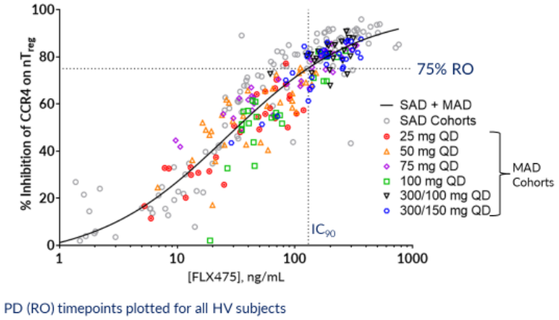
- Long terminal $T_{1/2}$ (~72 hours)
- ~4-fold accumulation over 14 days of dosing

Capsule and Tablet Formulations Have Similar Bioavailability and No Effect of High-Fat Meal



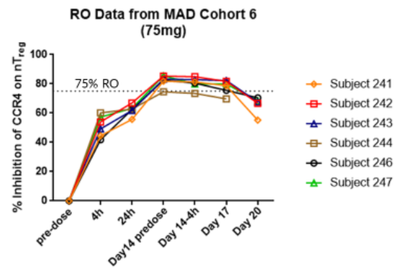
Pharmacodynamics

Excellent PK-PD Relationship of FLX475 Observed with T_{reg} Receptor Occupancy (RO) Assay

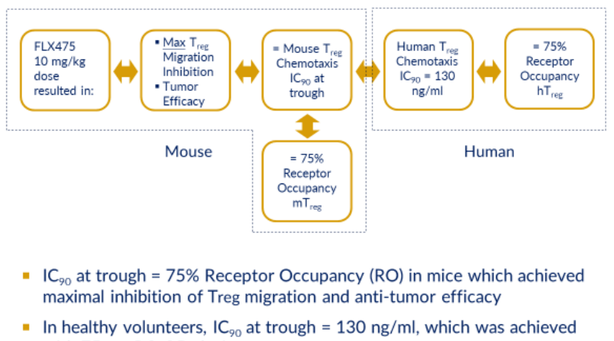


- All PD (RO) timepoints plotted for all HV subjects
- RO = reduced signal of binding/internalization of fluorescently-labeled CCL22 using flow-based assay when FLX475 is bound to CCR4 on circulating T_{reg}
- 75% receptor occupancy correlates with IC_{90} in a chemotaxis assay in 100% human serum

75 mg PO QD Dosing Achieves Target Receptor Occupancy (RO) at Steady State in All Subjects



Foundation for Target PK and PD in Humans: Efficacy is Linked to Exposure



- IC_{90} at trough = 75% Receptor Occupancy (RO) in mice which achieved maximal inhibition of Treg migration and anti-tumor efficacy
- In healthy volunteers, IC_{90} at trough = 130 ng/ml, which was achieved with 75 mg PO QD dosing

Safety

Grades 1 & 2 SAD Adverse Events in >5% of HVs

AE	Placebo (#14)	5 mg	25 mg	75 mg	200 mg	400 mg	750 mg	1000 mg
Headache	14% (21%)/0	33%/17%	0/0	0/0	17%/33% (17%)	17%/17%	50%/0	67%/17%
Abdominal pain	0/0	0/0	0/0	0/0	17%/0	33%/0	0/0	67%/0%
Cannula Pain/ Hematoma	7%/0	17%/0	0/0	17%/0	50%/0	33%/0	33%/0	17%/0
Flu-like Sx/URI/ rhinitis/sore throat	21%/0	0/0	0/17%	0/0	17%/33%	0/0	0/0	33%/0
Soft/loose stool	7%/0	17%/0	33%/0	0/0	0/0	0/0	0/0	33%/0
Electrode Irritation	14%/0	17%/0	17%/0	0/0	17%/0	0/0	17%/0	0/0
Fatigue/asthenia	0/0	0/0	0/0	0/0	0/0	0/0	0/0	50%/0
Muscle pain/stiffness	7%/7%	0/0	17%/0	17%/0	17%/0	0/0	0/0	0/0
Nausea	7%/0	0/0	17%/0	0/0	17% (17%)/0	0/0	0/0	0/0
Rash/erythema, dry skin	0/0	0/0	0/0	0/0	17%/0	17%/0	0/0	0/0
Dizziness/ Syncope	7%/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Anorexia	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

Not or Unlikely Related
Possibly Related

Grades 1 & 2 MAD Adverse Events in >5% of HVs

AE	Placebo (#12)	25 mg	50 mg	75 mg	100 mg	300/100 mg	300/150 mg
Headache	25% (8%)/0	33%/17%	50%/17%	67%/0	33%/0	0/0	83%/0
Fatigue/Asthenia	25%/0	0/0	17%/0	33%/0	67%/0	50%/0	50%/0
Abdominal Discomfort/Pain	8% (8%)/0	17%/0	0/0	17% (17%)/0	17%/0	50%/0	33%/0
Soft/Loose Stool	8%/0	0/0	17%/0	17% (17%)/0	67%/0	17%/0	0/0
Muscle Pain/ Stiffness	0/0	0/0	17%/0	50%/0	0/0	0/0	67%/0
Cannula Irritation/ Hematoma	33%/0	0/0	17%/0	17%/0	33%/0	17%/0	17%/0
Electrode Irritation	17%/0	0/0	17%/0	17%/0	17%/0	33%/0	0/0
Anorexia	8% (8%)/0	0/0	0/0	0/0	17%/0	17%/0	0/0
Nausea	8% (8%)/0	17%/0	0/0	0/0	33%/0	0/0	17%/0
Flu-like Sx/URI/ Rhinitis	8%/0	0/0	0/0	0/0	0/0	0/0	0/0
Rash/Erythema/ Dry Skin	0/0	17%/0	50%/0	0/0	17%/0	17%/0	17%/0
Dizziness/Syncope	25%/0	17%/0	33%/0	0/0	17%/0	0/0	50%/0

Not or Unlikely Related
Possibly Related

Safety Findings

- Clinical Adverse Events (AEs)
  - Only Grade 1 and Grade 2 clinical AEs reported (see Tables)
  - No immune-related AEs observed
  - Nearly all designated as not or unlikely related
    - Few noted as possibly related
    - None noted as likely or definitely related
  - No clinical AEs resulted in dose reductions or missed doses
- Safety Labs and Monitoring
  - No significant laboratory changes noted
  - No changes in peripheral immune cell populations
  - At least 1 subject with Grade 1 QTc prolongation observed in nearly every cohort (including placebo)
    - No QTc prolongation beyond Grade 1 were observed in MAD subjects through the 300/100 mg dose level
    - At the highest MAD cohort dose (300/150 mg), 3 subjects had transient Grade 2 QTc prolongation, correlated with exposures nearly 5x above that needed to achieve IC_{90}
    - 2 subjects in 300/150 mg cohort met stopping criteria (>60 ms prolongation from baseline) leading to early discontinuation of study treatment (Day 9 and 13), one with Grade 2

Conclusions

- FLX475 is a highly potent and specific orally-available CCR4 antagonist
- Plasma FLX475 levels increased in a dose-proportional manner, with low peak-to-trough ratios, and a mean $T_{1/2}$ of ~72 hours in healthy volunteers
- Tablet formulation showed similar bioavailability to capsule formulation used in the HV study, with no apparent food effect
- A strong PK/PD correlation was observed between plasma drug levels and CCR4 receptor occupancy, with human T_{reg} chemotaxis IC_{90} FLX475 plasma levels resulting in 75% CCR4 receptor occupancy on peripheral HV T_{reg}
- 75 mg PO QD achieved drug levels predicted to maximally inhibit in vivo human T_{reg} migration
- Consistent with the mechanism of action of FLX475 which specifically blocks the recruitment of tumor T_{reg} without cellular depletion or nonspecific immune activation, no autoimmunity or immune-related AEs were observed
- No significant clinical AEs or laboratory changes were noted
- No significant QTcF prolongation was observed at exposures ≤3-5X the target drug exposure predicted to maximally inhibit human T_{reg} migration
- These findings have enabled an accelerated Phase 1/2 study in cancer patients testing FLX475 both as monotherapy and in combination with pembrolizumab (NCT03674567)

References

[1]Talay O et al. Potent and selective C-C chemokine receptor (CCR4) antagonists potentiate anti-tumor immune responses by inhibiting regulatory T cells (Treg). AACR 2017.
[2]Talay O et al. Potent and selective C-C chemokine receptor 4 (CCR4) antagonists inhibit regulatory T cell recruitment, increase effector T cell numbers, and potentiate anti-tumor responses in mice. Journal for ImmunoTherapy of Cancer 2017, 5(Suppl 2):P467.
[3]Okal A, Ho W, Wong B, Kassner P, and Cutler G. Patient selection strategies and pharmacodynamic assays for CCR4 antagonists. Journal for ImmunoTherapy of Cancer 2017, 5(Suppl 2):P44