PNQ-401

A selective JAK 1/3 inhibitor

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PNQ-401: Summary

- A potent JAK3 & JAK1 (**a JAK3/1>>>>JAK2)** inhibitor with 56X selectivity over JAK2 in human whole blood assay

- Efficacy in Preclinical PoC studies
  - Superior potency and efficacy vs. Tofacitinib in 2 RA models
  - Superior Selectivity towards JAK3/1 vs, JAK2
  - Robust efficacy in RA models with QD dosing suggesting QD potential in humans (vs. BID with Tofacitinib)
- Suitable for small oral once a day dosing
  - PD effect on biomarker-: up to 18hr (vs. 4hr of Tofacitinib)
- Clean preclinical safety profile
  - 28 D study in rats completed
  - No safety issues or off target activity observed
  - Acceptable selectivity in multiple screens
  - Non-mutagenic in mini-Ames test
- Long patent life till 2032
  - PCT filed in Mar 2012 and published in (WO2012127506) September 2012; US patent allowed.
- CMC
  - Process optimization for scale up synthesis completed

Potent JAK1/3 Inhibition with Selectivity over JAK2

	Biochemical assays[$]: IC_{50} (nM)			Cell-based assays in human whole blood*: IC_{50} (μM)				
	JAK3	JAK1	JAK2	JAK3-JAK1**	JAK1	JAK2	JAK1/3 *vs* JAK2	JAK1 *vs* JAK2
							Fold Selectivity	
Tofacitinib	1.3 ± 0.2	4.8 ± 0.6	3.4 ± 0.5	0.13 ± 0.01	0.27 ± 0.04	8.7 ± 2	**67**	**32**
PNQ-401	2.3 ± 0.3	3.1 ± 0.2	3.5 ± 0.4	0.13 ± 0.03	0.08 ± 03	7.3 ± 1.3	**56**	**86**

[$] Kinase assay format: Kinase-Glo® luminescent assay with purified kinase domains
- Effect on STAT-5 phosphorylation induced by IL-2 (JAK3-JAK1 pathway) or GM-CSF (JAK2 pathway) or STAT-1 phosphorylation induced by IL-6 (JAK1/TYK2 pathway)

**Distinguishing JAK3 and JAK1 signaling not practical in this assay as both are associated with IL-2 receptor

- PNQ -401 is a potent JAK1/3 inhibitor with selectivity over JAK2 in human whole blood assay
- Potency & selectivity better than Tofacitinib in whole blood assay

Selectivity Over Other Kinases & Targets

- Kinase selectivity Screen -Diverse panel of 150 kinases
  - No major liability
    - **> 130 –fold selectivity against 144 kinases**
    - >33-44 fold selectivity against other 6 kinases

      (Aurora A&B, AMPK-related kinases NUAK1, NUAK2, QIK & MARK1)
- Drug Matrix Screen – Diverse panel of 123 targets
  - No major liability

- PNQ -401 is a Selective JAK1/3 Kinase Inhibitor
- Excellent selectivity over other diverse kinases and other targets

Preclinical Efficacy Highlights

Rheumatoid Arthritis

Adjuvant Induced Arthritis Model (Lewis Rat)
Collagen Induced Arthritis Model (DBA Mouse)

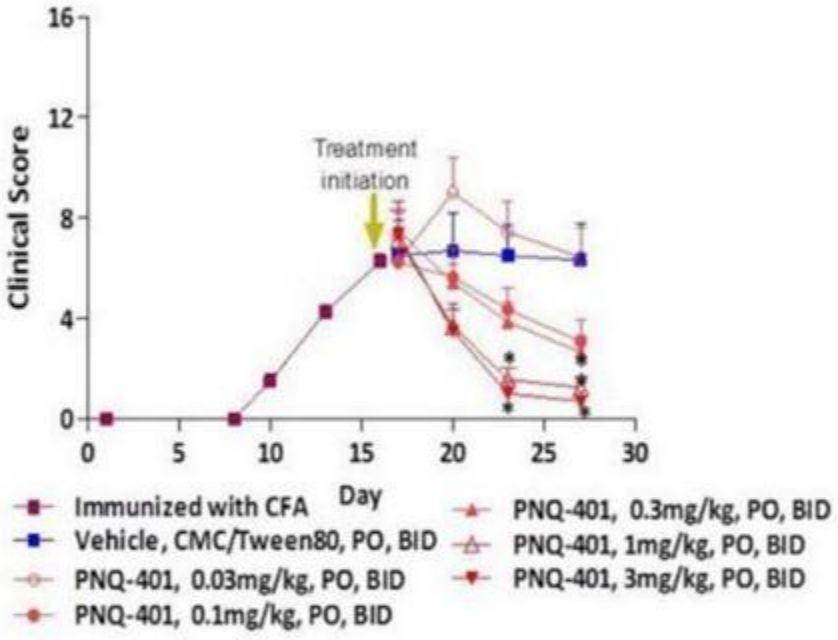
Psoriasis

Imiquimod induced psoriasis (Mouse)

Robust Efficacy – Rat Adjuvant Induced Arthritis (AIA) Model

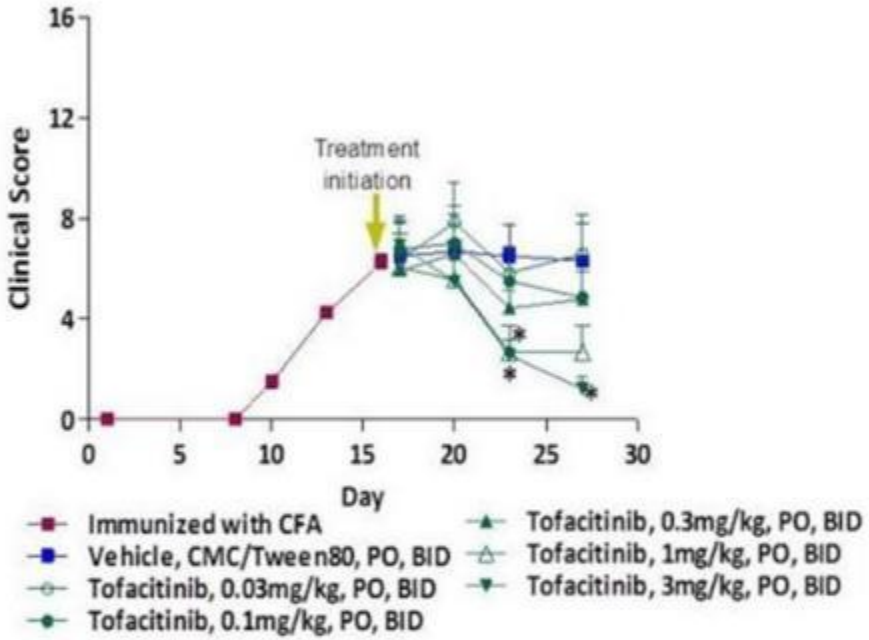
PNQ -401

Clinical Score – ED_{50} 0.1 mg/kg, bid



Tofacitinib

Clinical Score – ED_{50} 0.8 mg/kg, bid

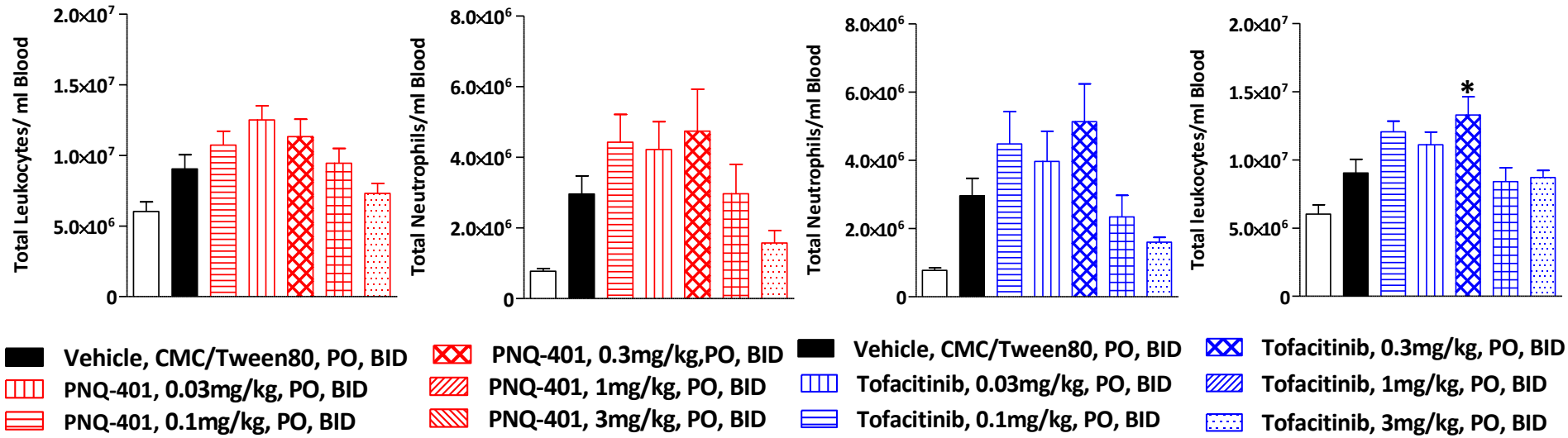


- Excellent efficacy in Rat AIA model on therapeutic treatment
- Potency superior to Tofacitinib

PNQ-401 Shows Improved Safety Markers in the AIA Rats

- PNQ-401 at 3 mg/kg showed trend towards normalization of total leukocyte count in the blood.
- PNQ-401 at 3 mg/kg decreased neutrophil count in blood by ~45% (ED_{50} > 3 mg/kg)

Blood Neutrophil and Leukocyte Counts



Data is represented as Mean±SEM (n=5-8) *p<0.05 vs Vehicle; ANOVA followed by Dunnett's test

PNQ-401: Summary of Efficacy & PD Studies

	Study	Doses	Outcomes
Efficacy + PK/PD on Day 13	Adjuvant Induced Arthritis (Lewis Rat)	PNQ-401 0.1, 0.3, 1 & 3 mg/kg , BID	Clinical Score: ED_{50} : 0.1mg/kg Paw volume : ED_{50} : 0.5mg/kg Dose dependent reduction in joint inflammation and inhibition of loss of joint proteoglycans; PD effect correlated with plasma compound concentrations
Efficacy	Collagen Induced Arthritis (DBA1/J Mouse Model)	Therapeutic treatment PNQ-401 BID 3,10,30 and 100mg/kg Tofacitinib 100mg/kg	Clinical Score: ED_{50} ~ 27mg/kg , BID Shows better efficacy/potency than Tofacitinib ED_{50} ~ >100mg/kg Significant reduction in clinical score after 10 days of Treatment; (ED50> 100 mg/kg for Tofacitinib). No change in anti-collagen II IgG , serum triglycerides, No adverse events/deaths after 2 week of treatment
Efficacy	Imiqumod Induced Psoriasis (Mouse)	PNQ-401 3,10 and 30 mg/kg , BID; Tofacitinib 30 and 100mg/kg	Significant decrease ear thickness day 14 (~30-40%) PNQ-401 showed significant improvement in Ear thickness vs. vehicle group on day 14. Comparable to Tofacitinib (24-40%) at doses tested

PNQ-401 *In vivo* Pharmacology: Summary

- **Robust PD effect in mice**
  - JAK3/1-mediated effect; Selectivity vs. JAK2
- **Robust efficacy in standard RA models**
  - Rat AIA model:
    - ~ 8 fold more potent vs. Tofacitinib (in BID dosing regimen)
      - PNQ-401 ED_{50} = 0.1 mg/kg BID and 0.44 mg/kg, QD
      - Tofacitinib ED_{50} = 0.8 mg/kg BID
  - Mouse CIA model:
    - Relatively more potent than Tofacitinib
      - PNQ-401 ED_{50} ~27 mg/kg BID and ~30-100 mg/kg, QD
      - Tofacitinib ED_{50} ~30-100 mg/kg BID and ~100 mg/kg, QD
- **No overt adverse event findings in these studies**

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PNQ-401: Safety

- Acceptable selectivity vs. 150 kinase and 123 DrugMatrix targets (see slide on off-target activity)
- hERG inhibition (patch clamp assay) IC_{50} = 22 µM
- Non-mutagenic in mini-Ames test
- 28-day GLP tox study in rats completed; well tolerated with dose-proportional TK profile

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PNQ-401 Summary

- Acceptable ADME profile
- All IND directed safety studies except all dog studies completed
- CMC : Process optimization for scale up in progress
- PNQ-401 is a candidate molecule 6 months from IND filing

Thank You