PNQ-701

A highly selective JAK 1 inhibitor

PNQ-701: Summary

- A **potent and selective** JAK1 inhibitor, with a potential for being **best-in-class** due to superior selectivity within and/or outside JAK family targets as compared to competitor JAK inhibitors*
  - ✓ Potent (JAK1) in human whole blood assay (≈ Tofacitinib, > GLPG0634**)
  - ✓ Greater selectivity over JAK2 >>> GLPG0634 (211 vs 30 fold in human whole blood assay) – lower risk of anemia
  - ✓ Selective over JAK3 (~90 fold in kinase assay)- reduced risks from immunosuppression
  - ✓ Greater selectivity over a diverse panel of 100 kinases vs. GLPG0634- lower risk of general safety liabilities
  - ✓ **No ADME liabilities** (GSK compound has drug-drug interaction liability)
- **Robust efficacy** in a RA model (ED_{50}: 0.44 mg/kg, BID in rat AIA model)
- PCT filed in March 2012 and published in (WO2012127506) September 2012; US patent allowed.
- PK properties supportive of QD dosing in humans
- A safety profile that could provide a **wide therapeutic window**
  - ✓ Selectivity vs. 100 kinase and 123 Drug Matrix targets and hERG
  - ✓ Non-mutagenic in mini-Ames test
  - ✓ Well tolerated with dose-linear TK profile in 14-day safety study in rat (no safety concerns identified)

PNQ-701: Best in Class JAK 1 Inhibitor, based on a superior safety profile

PNQ-701 is potentially the **safest JAK 1 inhibitor** in development**,** based on superior selectivity over JAK2 and JAK3 .

PNQ-701 is likely to avoid the several side effects associated with other pan-JAK inhibitors including:

- Thrombocytopenia (low blood platelet count), anemia (low red blood cell count) and neutropenia;
- Non-melanoma skin cancer.
- Immunologic side effects
  - Herpes zoster (shingles) and case reports of opportunistic infections.
  - Risk of serious infections in particular tuberculosis and malignancy
  - Increase in the rate of varicella–zoster virus (VZV)
- Metabolic side effects including
  - Weight gain
  - Liver enzyme elevation
  - Hyper cholesterolemia

Potent JAK1 Inhibition with Superior Selectivity over JAK2

Compound	Biochemical Assay $ IC_{50} (nM)				Cell Based Assays in Human Whole Blood # IC_{50} (μM)		
	JAK1	JAK3	JAK2	Fold Selectivity JAK1 *vs* JAK3	JAK1	JAK2	Fold Selectivity JAK1 *vs* JAK2
Tofacitinib	4.8 ± 0.6	1.3 ± 0.2	3.4 ± 0.5	**2.5**	0.20 ±0.04	10.6 ± 2.4	**53**
GLPG0634*	10	810	28	**81**	~0.6	17.5	**30**
PNQ-701	9.4 ± 1.2	845 ± 94	22.1 ± 2.5	**90**	0.32 ± 0.07	67±3.9	**212**

$ Kinase assay format: Kinase-Glo® Luminescent Kinase Assay; # Effect on STAT-1 phosphorylation induced by IL-6 (JAK1/TYK2 pathway) or STAT-5 phosphorylation induced by GM-CSF (JAK2 pathway); for STAT-5 phosphorylation induced by IL-2 (JAK3/JAK1 pathway) ; *Data as reported by Galapogos

- PNQ-701 is a potent JAK1 inhibitor with improved selectivity over JAK2 and JAK3 than Tofacitinib and GLPG0634

Selectivity Over Other Kinases & Targets

- Kinase selectivity Screen -Diverse panel of 100 kinases.
  - No major liability
  - > 150 selectivity
  - >50% Inhibition for RET only at 1mM(69%).
  - GLPG0634 is only ~25-fold selective over FLT3, FLT4 and CSF1R*

- Drug Matrix Screen – Diverse panel of 123 targets
  - No major liability
  - >50% inhibition at 10 □M (PDE5 (human): 70%; CYP450, 2C19 (human): (68%) only

- Superior selectivity profile as compared to Tofacitinib and GLPG0634

Preclinical Efficacy Highlights

Rheumatoid Arthritis

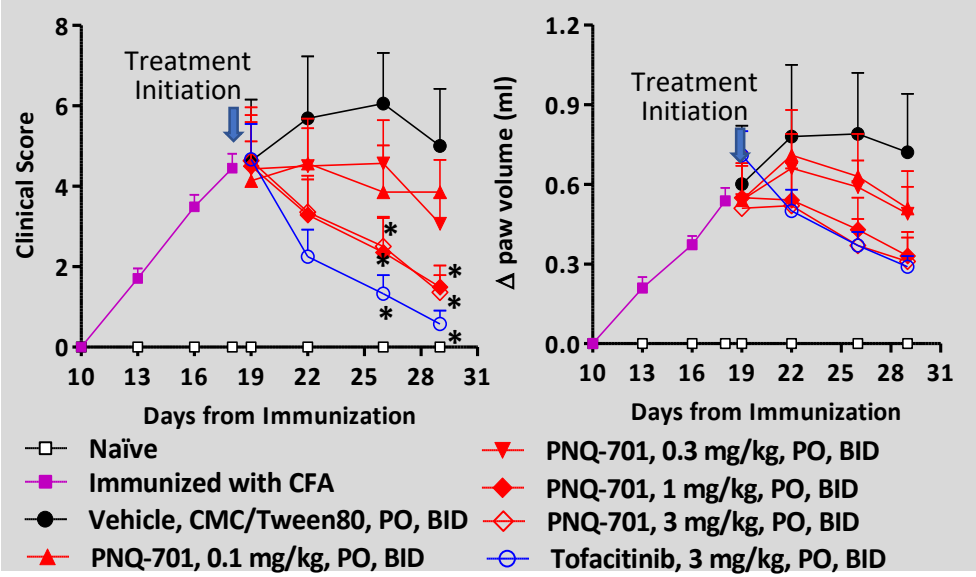
Adjuvant Induced Arthritis Model (Lewis Rat)
Collagen Induced Arthritis Model (DBA Mouse)

Psoriasis

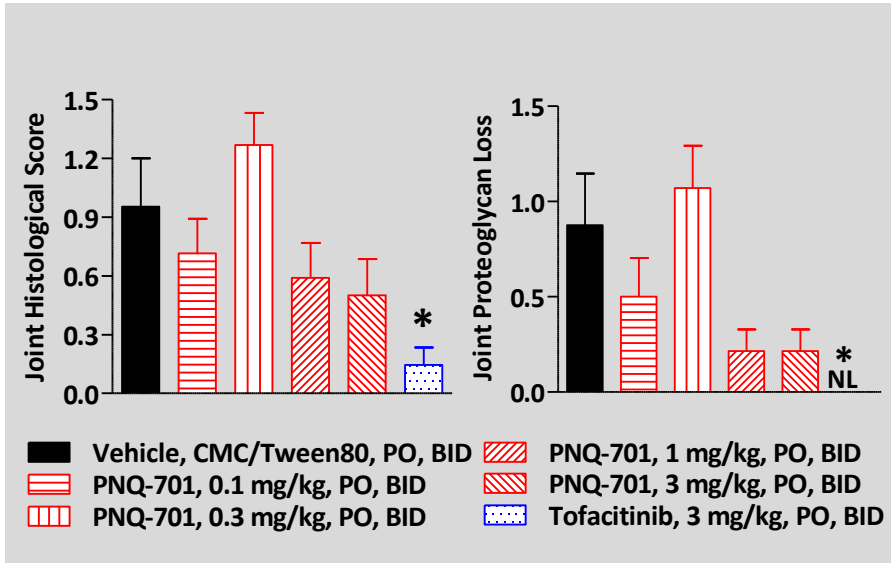
Imiquimod induced psoriasis (Mouse)

PNQ-701: A Best-in Class JAK 1 inhibitor: Efficacy in Adjuvant Induced Arthritic (AIA) Rats

Clinical Score and Paw Volume



Histopathology

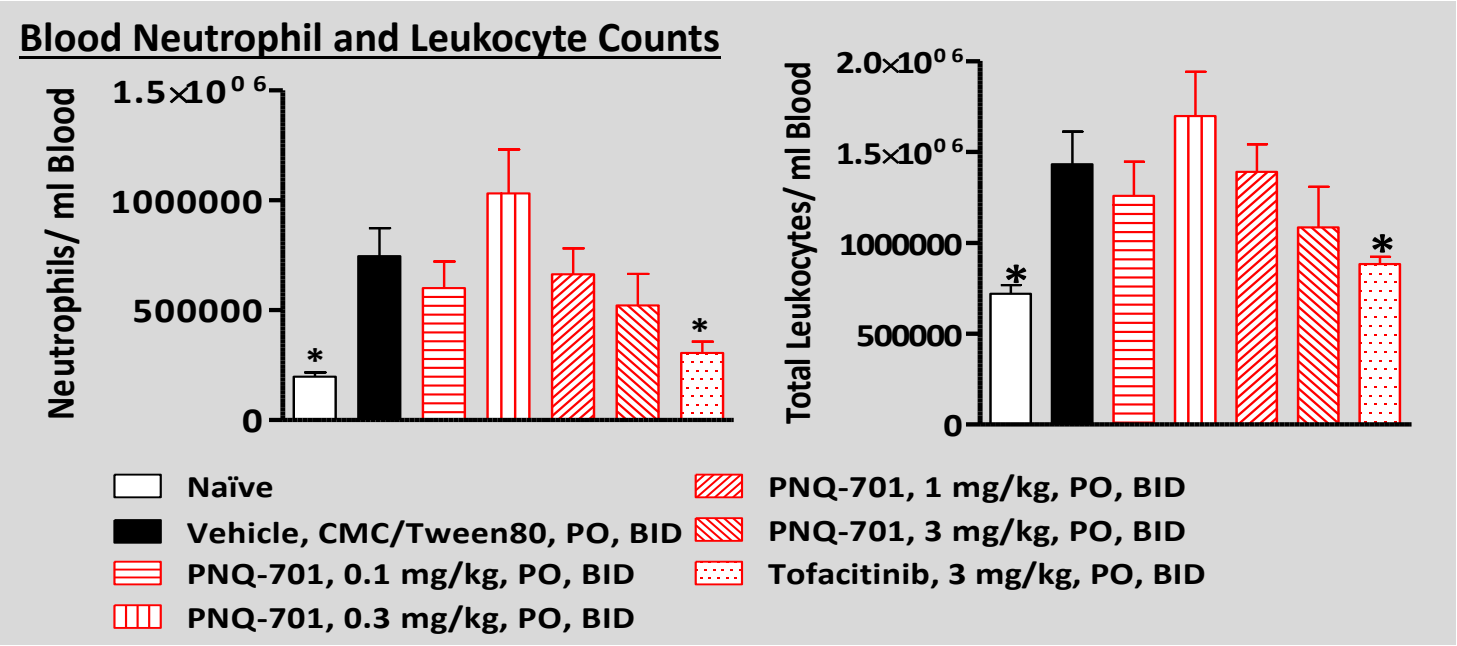


Adjuvant Induced Arthritic Model

- Significant reduction in clinical score (ED_{50}: 0.44 mg/kg, BID) and paw volume (ED_{50}: 1 mg/kg, BID)
- 37-47% reduction in joint inflammation and ~75% protection against joint proteoglycans loss at 1-3 mg/kg, BID (statistically not significant)
  - ✓ Tofacitinib showed significant reduction in joint inflammation and complete protection against joint proteoglycans loss

PNQ-701 : Significantly superior safety profile

- No significant decrease in blood neutrophil and leukocyte count at all doses of PNQ-701 compared to vehicle unlike Tofacitinib
  - ✓ No significant decrease in neutrophils likely to translate into lower risk of neutropenia
  - ✓ No significant decrease in leukocyte likely to translate into lower risks of infections and carcenogenesis



Data is represented as Mean±SEM (n=6-8). * P < 0.05, one-way ANOVA followed by Dunnett's test

- PNQ-701 also did not show any significant change in body weight, feed consumption and serum triglyceride levels compared to vehicle treated animals

PNQ-701: Summary of Efficacy & PD Studies

	Study	Doses	Outcomes
PK-PD	Adjuvant Induced Arthritis (Lewis Rat)	Day1 & Day12 PNQ-701 3mg/kg , BID doses and Tofacitinib 1mg/kg	PD effect correlated with plasma compound concentrations Effective JAK1 or JAK 1/3 inhibition for 12h ~ 50-70 suppression for 6h, < 50% at 18 h post 2nd dose JAK 1: IL6 Induced pSTAT1 JAK1/3:IL-2 induced pSTAT5
Efficacy	Adjuvant Induced Arthritis (Lewis Rat)	Therapeutic treatment PNQ-701 0.1, 0.3, 1 & 3 mg/kg , BID	Clinical Score: ED_{50} : 0.44mg/kg Paw volume : ED_{50} :1mg/kg 37-47% reduction in joint inflammation and ~75% protection against joint proteoglycans loss at 1-3 mg/kg, BID (statistically not significant) No significant change in serum triglycerides, feed consumption or body weight PNQ-701: No neutropenia at efficacious doses (>6/>3 fold of ED_{50}) Tofacitinib: Significant neutropenia at efficacious doses (~3/1 fold of ED_{50})
Efficacy	Collagen Induced Arthritis (DBA/1J Mouse)	Therapeutic treatment PNQ-701 3 - 100mg/kg, *bid* Tofacitinib 100mg/kg *bid*	Clinical Score: ED_{50} ~ 100mg/kg , BID PNQ-701 -50% decrease in clinical score at 100 mg/kg, BID dose ; Tofa -80 percent decrease Significant decrease in serum amyloid A (SAA) levels at 100mg/kg ,BID
Efficacy	Imiqumod Induced Psoriasis (Mouse)	PNQ-701 3,10 and 30 mg/kg , BID; Tofacitinib 30 and 100mg/kg	Significant decrease ear thickness day 14 (~30-40%) PNQ-701 (3, 10 & 30 mg/kg, PO,BID) showed significant improvement in Ear thickness vs. vehicle group on day 14. Comparable to Tofacitinib (30-40%) at doses tested

PNQ-701: Summary

PNQ-701 is a candidate molecule for further development

- Acceptable ADME profile
- No PXR Induction (up to 100 μM)
- Tofacitinib exhibits PXR induction with EC_{50} of 15 μM

- Non mutagenic in Mini Ames test
- Only mechanism related effects seen with all doses upto 60 mpk
- 14 day non-GLP Rodent studies completed with dose linear TK profile in 14 day rat study
- Process optimization and GLP tox studies to be undertaken to bring candidate to IND readiness

Thank You