

Preclinical Characterization of INCB028050, a JAK1/JAK2 Selective Clinical Candidate

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ABSTRACT

Purpose: Multiple kinase inhibitors have been advanced into clinical trials for the treatment of rheumatoid arthritis (RA) and represent a new class of oral DMARD therapies with immense potential. Direct and indirect inhibition of the Janus family of non-receptor tyrosine kinases (JAKs), with small molecule inhibitors like INCB018424 or neutralizing antibodies such as the anti-6.6 receptor antibody tocilizumab, have demonstrated rapid and dramatic improvement in clinical measures of disease – consistent with their respective preclinical experiments. Therefore, it is of interest to develop additional JAK inhibitors with unique profiles to maximize therapeutic opportunities.

Methods: Using both in vitro and in vivo assays to establish structure-activity relationships, compounds were synthesized to yield molecules with distinctive disposition profiles and excellent potency and selectivity. Candidate compounds were advanced into efficacy and safety studies to select molecules suitable for clinical development. In addition, plasma samples from these studies were subjected to proteomic analysis to identify and characterize potential pharmacodynamic (PD) markers of activity.

Results: INCB028050 was identified as a structurally unique orally bioavailable JAK1/JAK2 inhibitor with nanomolar potency against JAK1 (1.1 nM) and JAK2 (0.3 nM). INCB028050 demonstrated considerable selectivity over JAK3 in addition to a panel of > 25 additional kinases. INCB028050 potently inhibited signaling of multiple pro-inflammatory cytokines including IL-6 and IL-23 at concentrations less than 50 nM. In in vitro assays, INCB028050 did not inhibit cyclochrome P450 (e.g. 2D6 and 3A4). INCB028050 demonstrated excellent PK properties in rodents with a high free fraction (~50%) and exceptional potency in a whole blood stage of inflammatory cytokine signaling. Moreover, oral bioavailability (50%) and compound half-life (approximately 6 hours) in rodents were favorable. Significant efficacy, as assessed by improvements in clinical score and radiological signs of disease, was achieved in the therapeutic phase of the aggressive rat adjuvant induced arthritis model with total daily doses of 2 mg/kg. INCB028050 was also effective in multiple murine models of arthritis with no signs of adverse hematological effects, consistent with a significant therapeutic window. Proteomic analysis identified several candidate PD markers with clinical potential.

Conclusion: INCB028050 is a selective JAK1/JAK2 inhibitor with attractive potency and PK characteristics. It is efficacious in multiple rodent models of RA at doses lacking suppressive effects on a panel of hematological parameters. Clinical evaluation of INCB028050 in RA is planned.

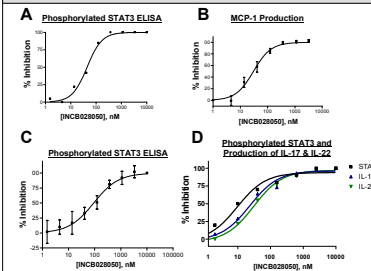
1. Identification of potent and selective inhibitors of JAK kinases

Compound	Kinase Potency* (nM)			
	JAK1	JAK2	JAK3	Tyk2
INCB028050	2.5	4.3	560	53
INCB018424	2.7	4.5	322	19

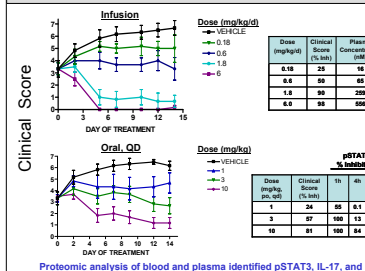
INCB028050 was evaluated against a broad panel of 28 non-JAK kinases and demonstrated no significant inhibition at a concentration > 100x its potency against JAK1/2

INCB028050 was screened against a panel of receptors, channels, and transporters at a concentration 1000x higher than its JAK1/2 IC50 and demonstrated no significant activity

2. INCB028050 inhibits the signaling (A, C, and D) and function (B and D) of inflammatory cytokines in human PBMCs, T-cells, and whole blood



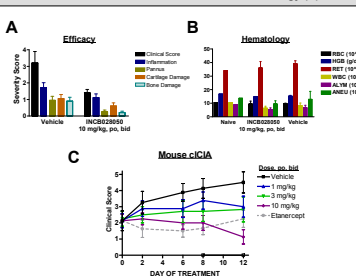
3. Dose-dependent inhibition of the clinical signs of disease in the rat adjuvant induced arthritis model – therapeutic mode



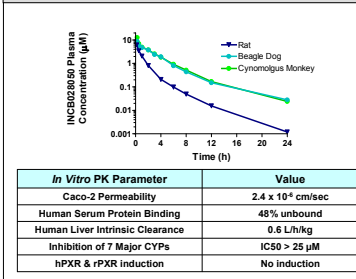
4. Dramatic radiological improvement by INCB028050 in the aggressive rat adjuvant induced arthritis model – therapeutic mode



5. INCB028050 improves measures of disease in the mouse passive transfer (A) and CIA (C) models of arthritis without adverse effects on hematology (B)



6. Non-clinical pharmacokinetics of INCB028050



CONCLUSIONS

- INCB028050 is a potent and selective inhibitor of JAK1 & JAK2
- The signaling, secretory, and mitogenic effects of multiple inflammatory cytokines are antagonized by INCB028050
- INCB028050 minimizes clinical and radiological signs of disease in the rAIA model of arthritis
- Efficacy in murine models of arthritis is achieved without adverse effects on hematological parameters
- INCB028050 has favorable preclinical PK properties consistent with the QD dosing in patients
- Clinical evaluation of INCB028050 is ongoing

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