A Randomized Placebo-Controlled Study of INCB018424, a Selective Janus Kinase1& 2 (JAK1&2) Inhibitor in Rheumatoid Arthritis (RA)

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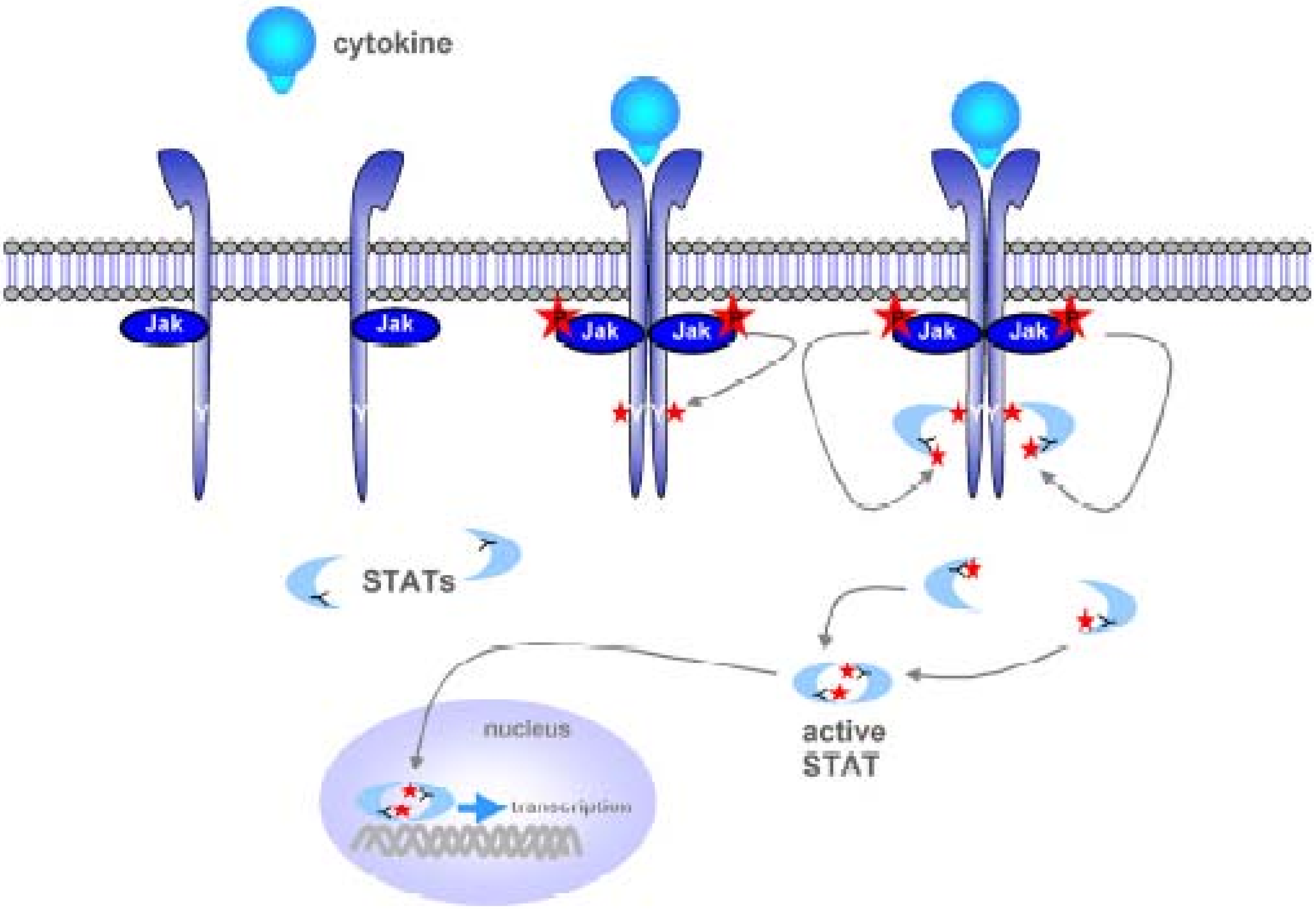
Disclosure: Dr. Moreland is also a paid consultant for Incyte

JAK-STAT Signaling

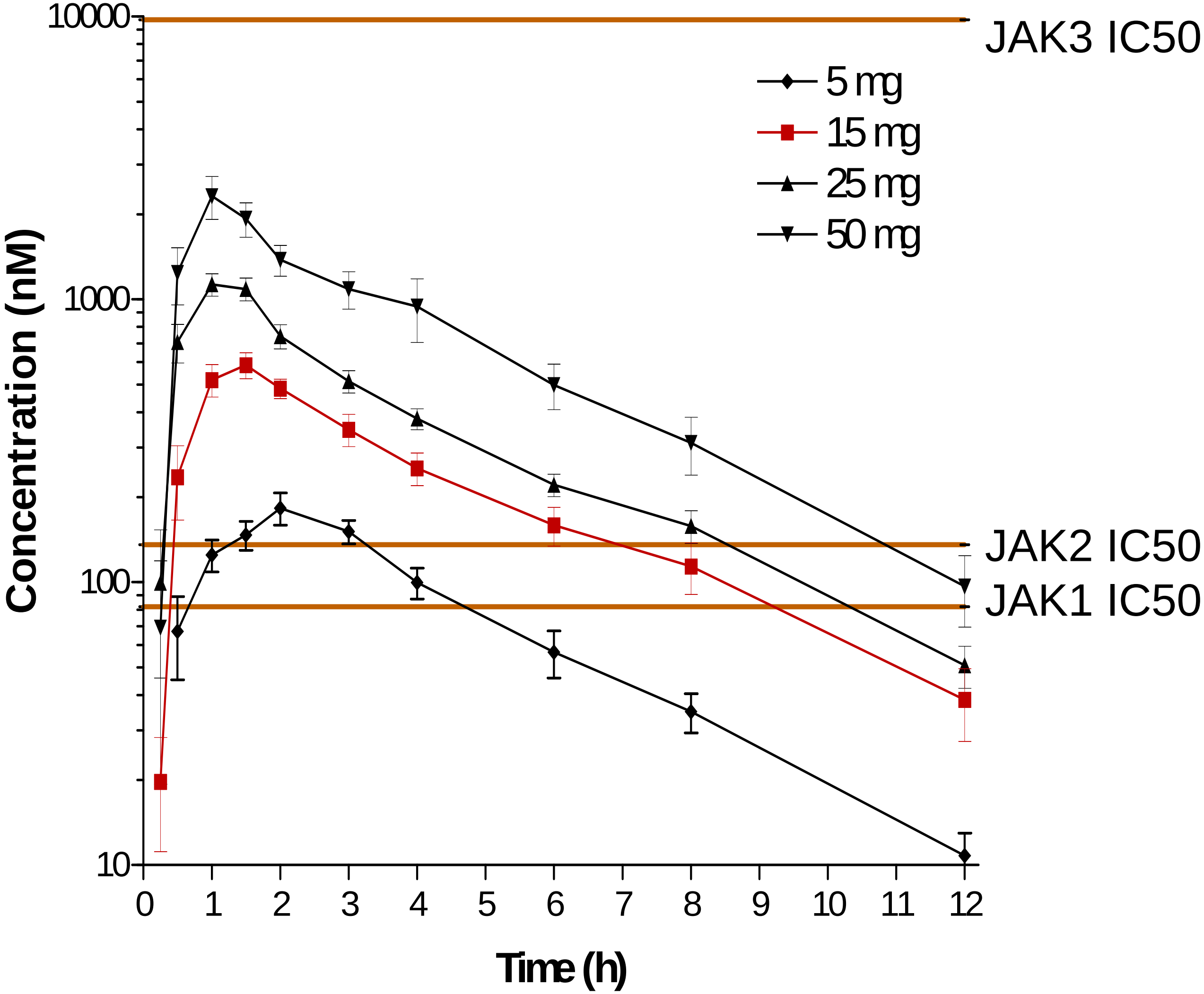


Biochem Pharmacol. 2006 Nov 30;72(11):1538-46. 2006 Apr 27.

JAK Inhibition in RA

- **JAKs mediate signal transduction for cytokines implicated in RA pathogenesis**
  - IL-6, IL-12, IL-15, IL-23, GM-CSF and IFNγ
- **Small molecule JAK inhibitors may therefore provide the efficacy of biologicals with oral administration**
- **INCB018424 is a potent, selective orally administered inhibitor of JAK enzymes**
  - Preferential activity against JAK1 and JAK2 with no inhibition of JAK3 at clinical doses
  - Initial clinical activity in RA will be described

Healthy Volunteer Data



- Human PK linear and predictable
- JAK1/2 IC50 exceeded for ~20% (5 mg BID), ~65% (15 mg BID), ~75% (25 mg BID), ~45% (50 mg QD) of each day
- JAK3 IC50 not reached at any dose

Annals Rheum Dis, 2008, v67SII:62

RA Phase 2a Study Design

- **Double-blind, placebo controlled study in active RA patients**
- **28 days of dosing**
- **Assessments at 1, 2 & 4 weeks**
- **Endpoints:**
  - Safety, ACR20/50/70, DAS28, % with DAS28 <3.2, change in individual ACR assessments, population PK, PD markers
- **Cohort 1: 15 mg BID vs placebo**
- **Cohort 2: 5 mg BID, 25 mg BID, 50 mg QD vs placebo**
- **Study sites in US and Poland**

RA Patient Population

- **Entry Criteria:**
  - Active RA
    - 6 or more tender, 4 or more swollen joints
    - ESR ≥ 28 mm/hr or CRP ≥ 15 mg/L
  - Stable Mtx/SFZ/anti-malarials
    - No biologicals or other DMARDs for 12 weeks
  - Prednisone ≤10 mg/d stable for 6 weeks

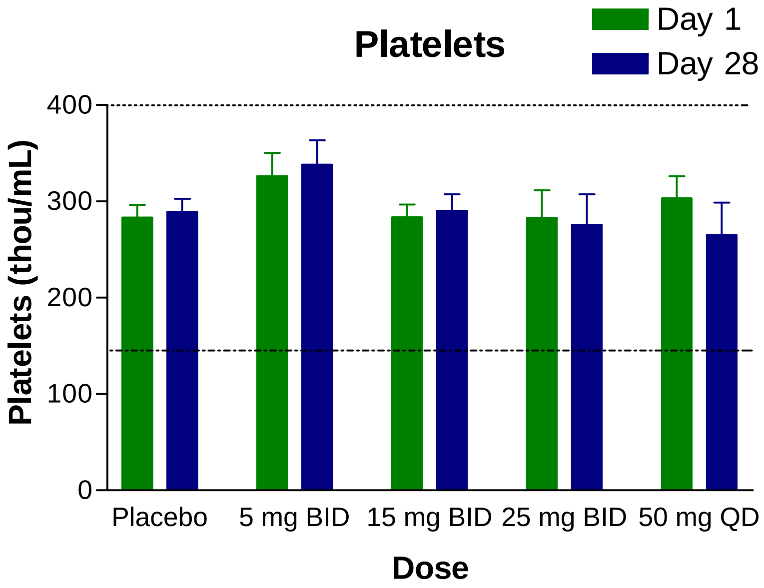
RA Patient Characteristics at Study Entry (Mean ± SEM)

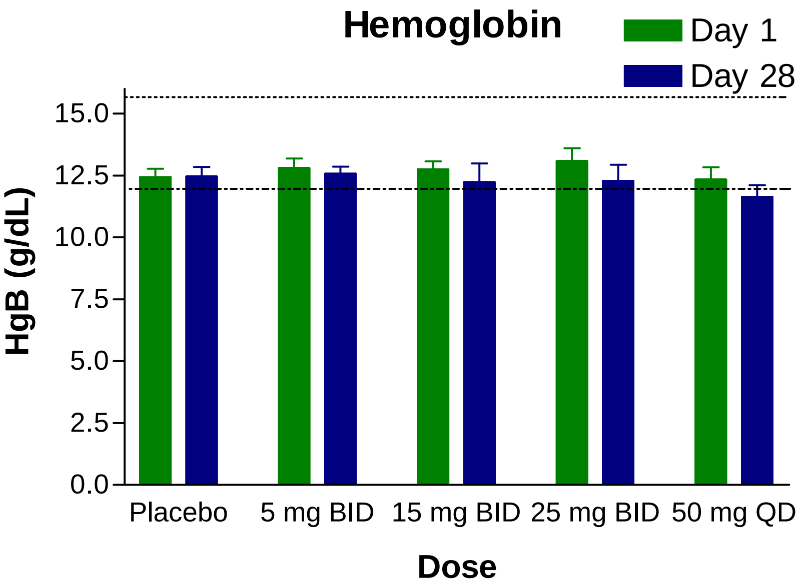
	Placebo (N=9)	5 mg BID (N=9)	15 mg BID (N=12)	25 mg BID (=10)	50 mg QD (N=10)
Tender Joint Count	14.4 ± 1.9	16.8 ± 2.5	11.8 ± 1.5	19.9 ± 2.3	19.6 ± 1.7
Swollen Joint Count	11.4 ± 1.6	16.1 ± 2.3	10.8 ± 1.2	14.4 ± 1.4	16.5 ± 2.0
DAS28	6.2 ± 0.27	6.76 ± 0.37	6.10 ± 0.19	7.07 ± 0.31	6.96 ± 0.27
DAS28 CRP	5.56 ± 0.27	6.22 ± 0.36	5.48 ± 0.24	6.30 ± 0.32	6.51 ± 0.27
% on DMARDS	78%	66%	75%	60%	80%

Safety Data

- **Safe and Well-Tolerated**
  - AEs seen in 21/41 (51%) active and 5/9 (56%) placebo subjects
  - AEs generally mild and self-limited with continued dosing and did not require intervention except:
    - One withdrawal due to abdominal pain, N&V (25 mg BID)
    - No other similar cases except vomiting in 2 placebo subjects,
  - One transient grade 3 neutropenia, improved with continued dosing (50 mg QD).
  - One grade 3 thrombocytopenia in a patient with a history of recurrent thrombocytopenia (ITP) (50 mg QD)
  - No serious infections

Hematology Parameters





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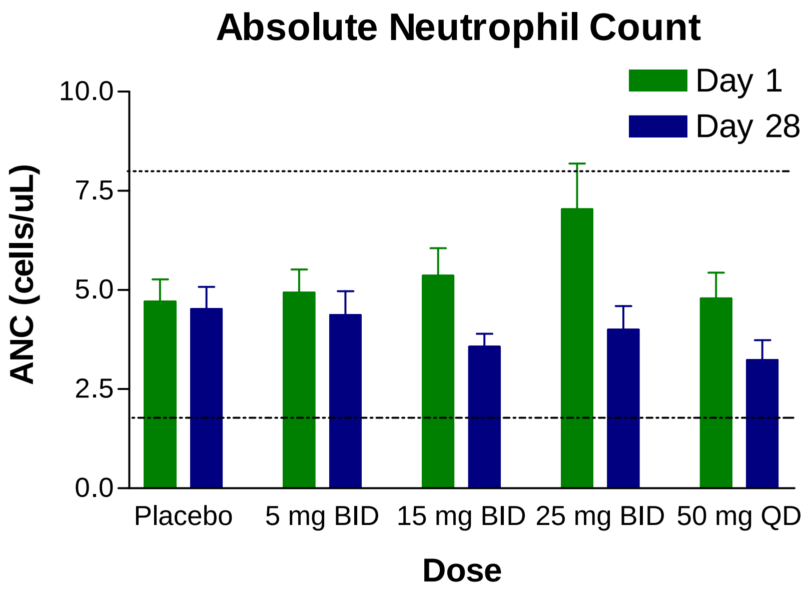
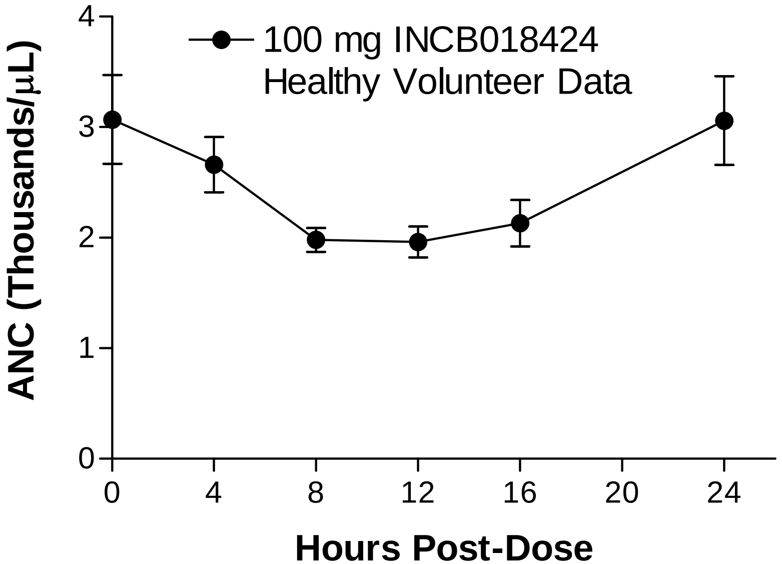
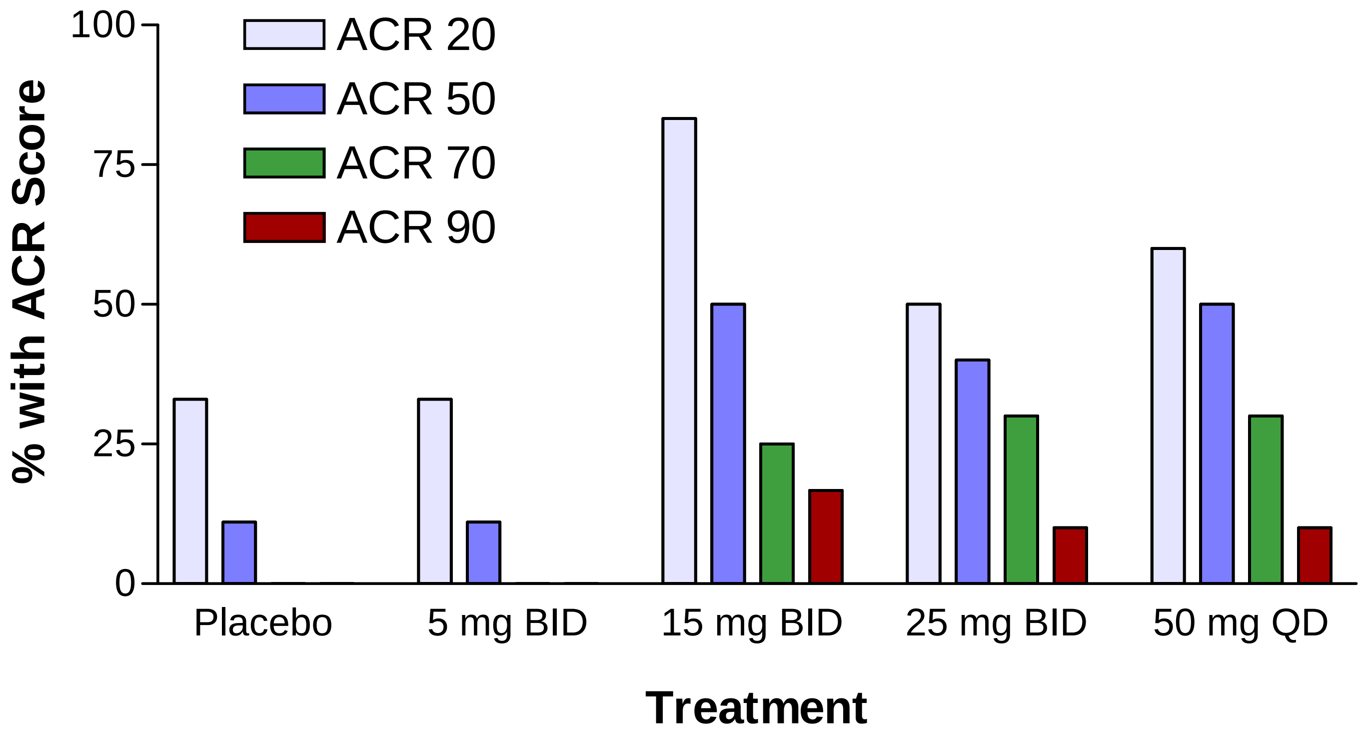




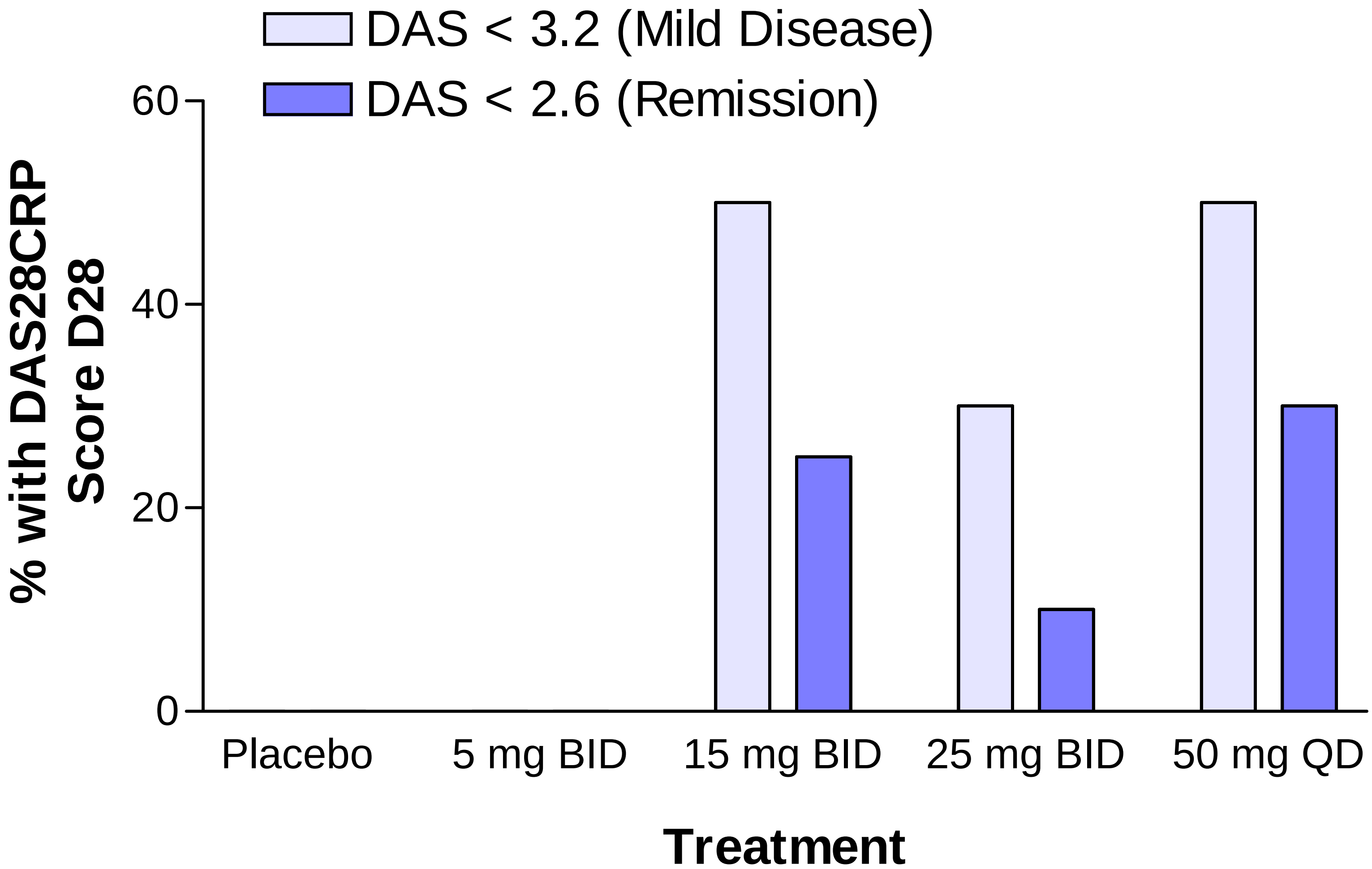
Efficacy Endpoints

- For efficacy endpoints, last observation carried forward (LOCF) was used for dropouts
- For subjects who dropped out due to AEs, they were counted as non-responders

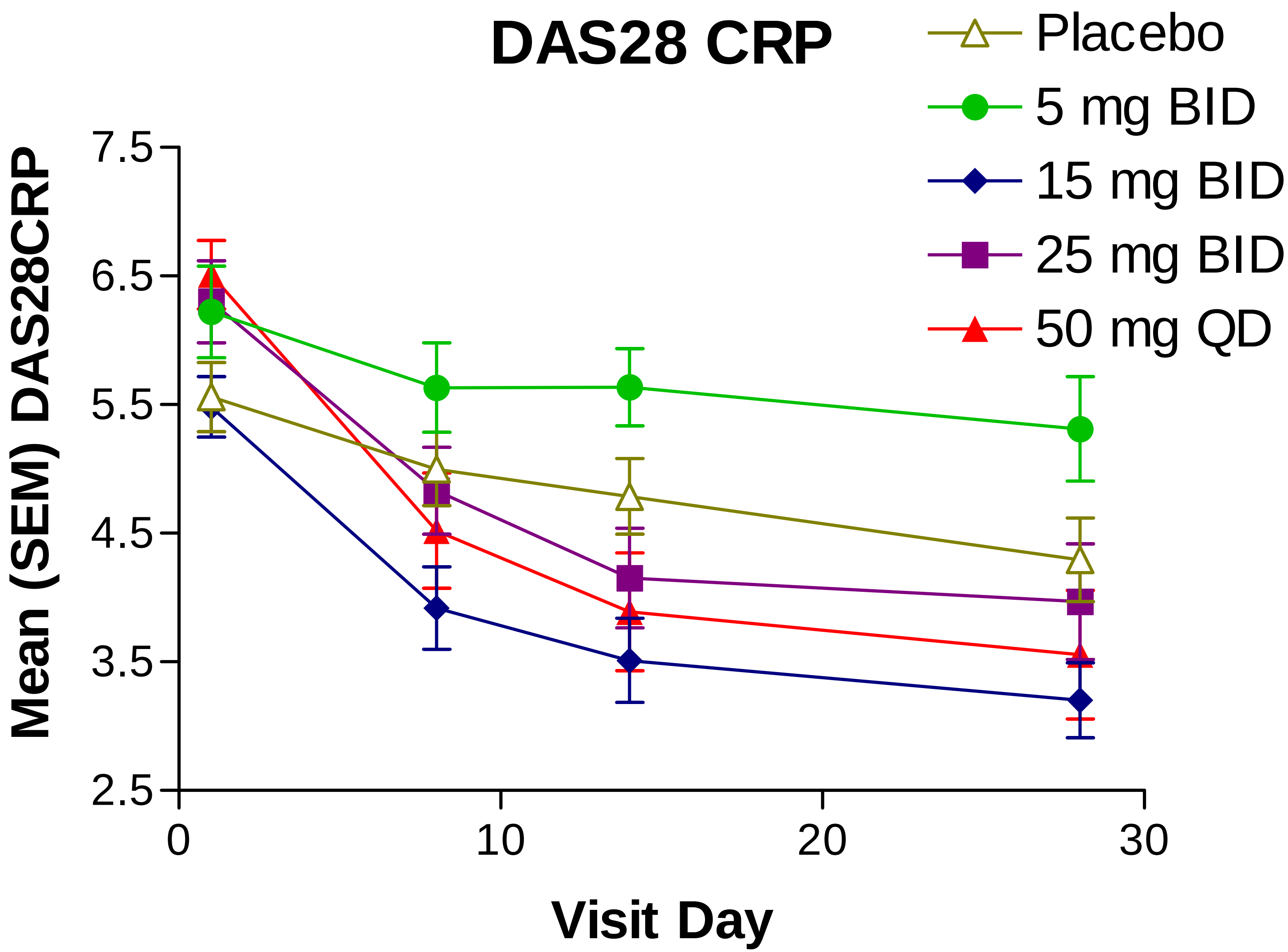
ACR Responses with INCB018424



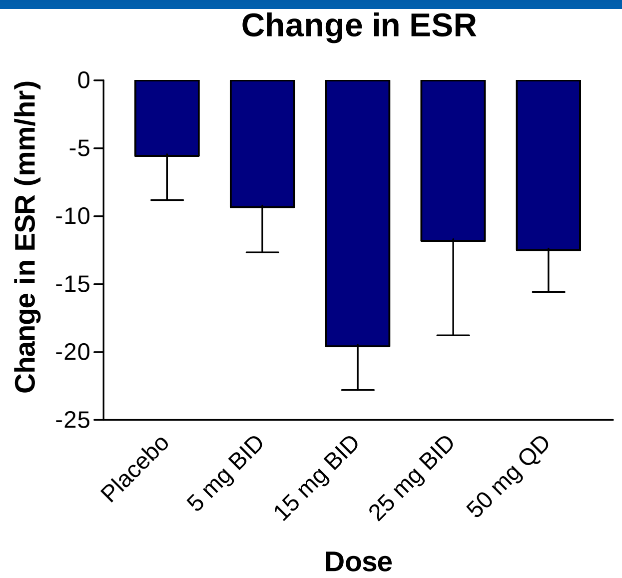
Change in DAS28CRP to Mild Disease and Remission

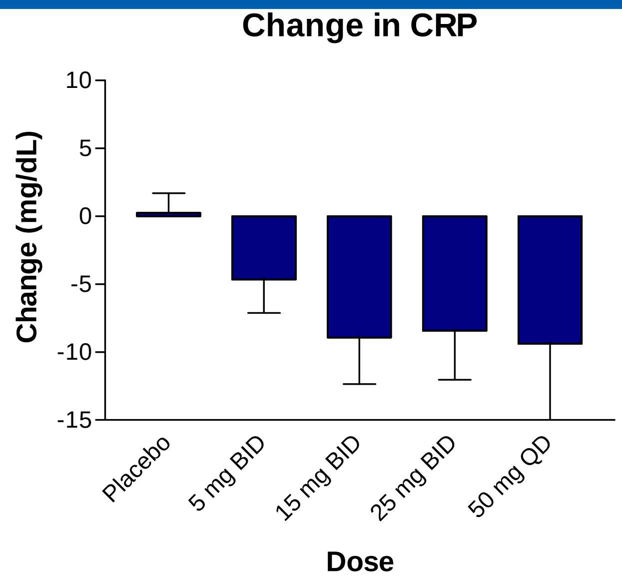


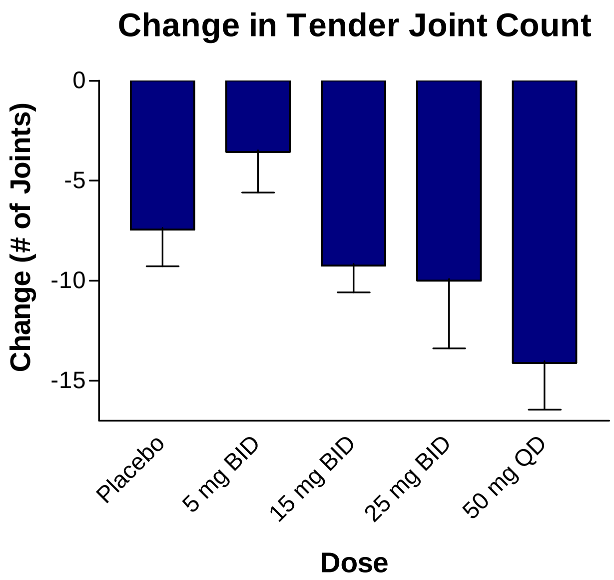
Change in DAS28CRP Over Time

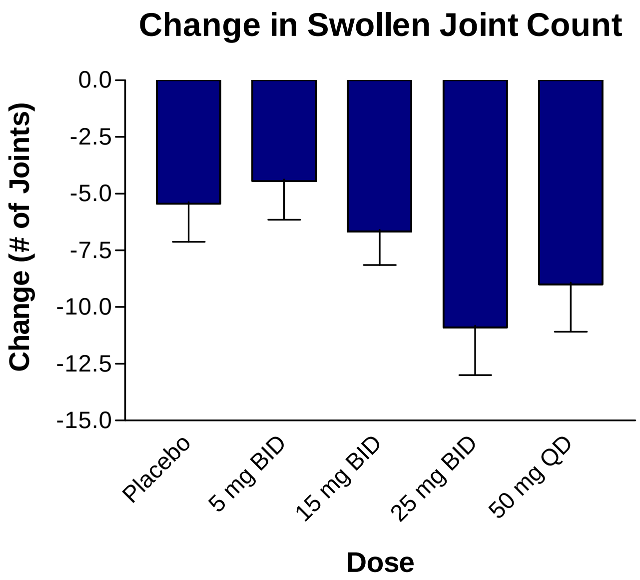


Change on Day 28 in Individual Assessments









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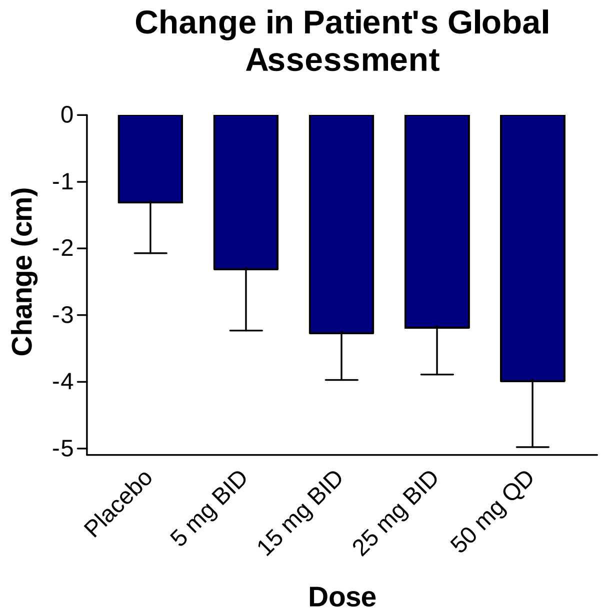
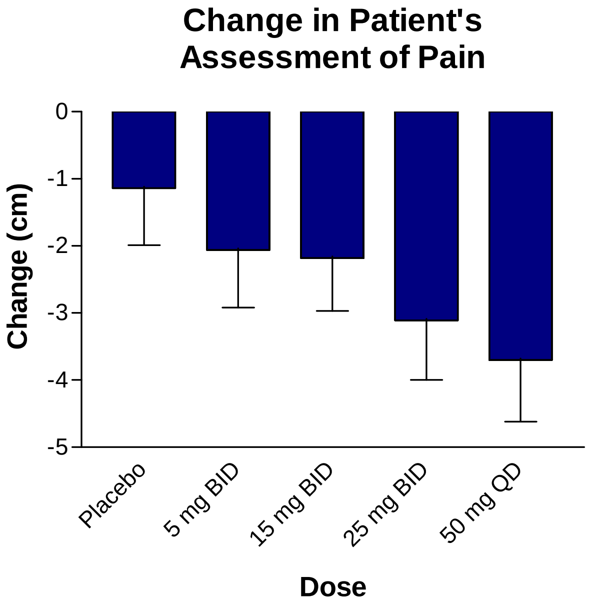
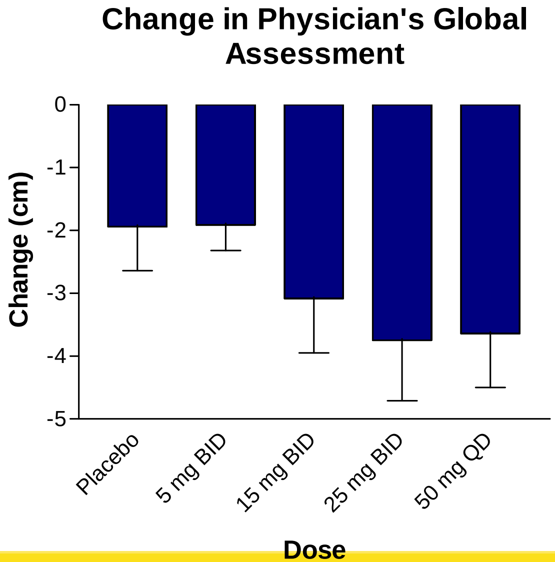
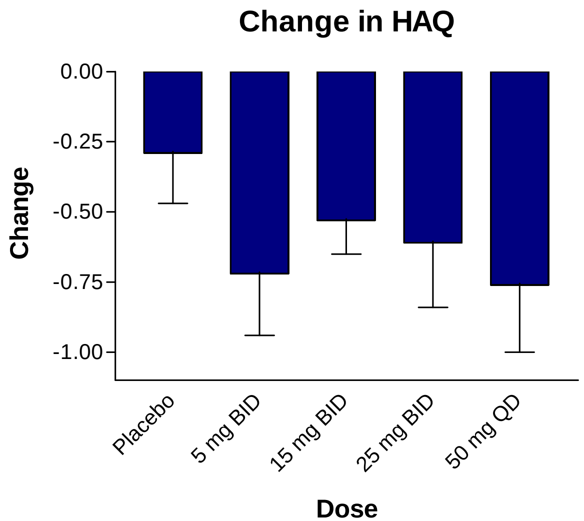






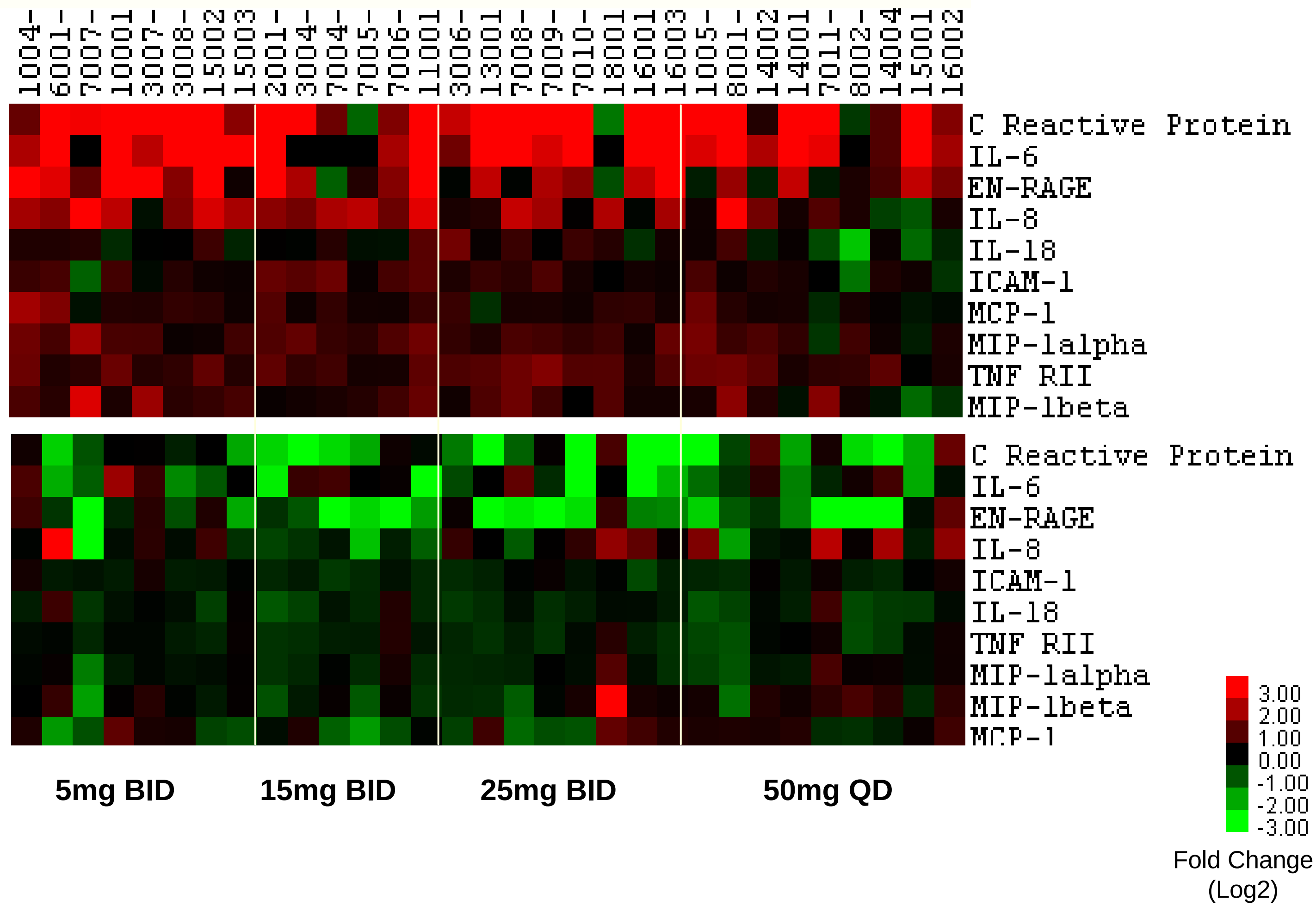


Inflammatory markers are elevated in RA and decreased by INCB018424 therapy

Subject:

Baseline values versus healthy volunteer values

Day 28 versus baseline values



Conclusions

- INCB018424 at doses of 5 - 25 mg BID and 50 mg QD for 28 days is safe and very well tolerated in RA patients
- ACR20/50/70 responses in up to 83%-50%-30% of patients treated for 1 month with 15 mg BID, 25 mg BID or 50 mg QD for 28 days
- Individual parameters of the ACR score all show similar trends of improvement
- Clinical activity is seen as early as 1 week of dosing
- Oral treatment with INCB018424 has the potential to be as or more effective than currently available RA therapy, including injectable biologicals
- Similar doses to be evaluated in Phase 2b to further differentiate doses during prolonged therapy in terms of safety and efficacy.