Characterization of pharmacokinetics, pharmacodynamics, tolerability and clinical activity in Phase I studies of the novel allosteric tyrosine kinase 2 (TYK2) inhibitor NDI-034858

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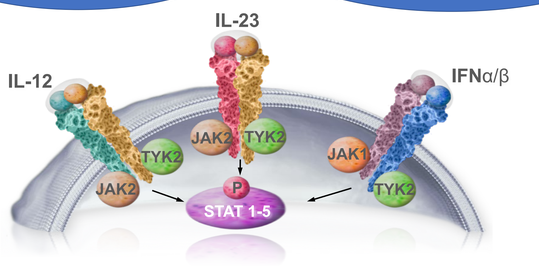
INTRODUCTION

TYK2 (Tyrosine Kinase 2) – A clinically validated target in psoriasis and psoriatic arthritis

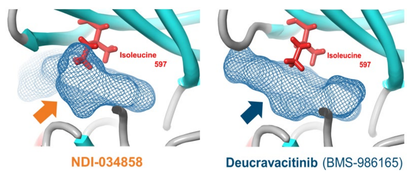
Obligate signal transducer of receptors for interleukins IL-12 and IL-23 as well as Type I interferon

Heterodimerizes with JAK1 or JAK2; inhibition of either dimer moiety impedes signal transduction



NDI-034858 – A highly specific allosteric inhibitor of TYK2

- Novel, investigational, oral, allosteric inhibitor of TYK2.
- High specificity for TYK2 over JAK1, JAK2, JAK3 kinases.
- Single amino acid difference at allosteric binding pocket may account for greater TYK2 selectivity of NDI-034858 over deucravacitinib.
  - Figure below illustrates a model of binding of NDI-034858 and deucravacitinib (represented by netting) to the JAK1–JH2 domain. Modeling indicates a steric clash between NDI-034858 and the isoleucine in position 597, which prevents binding to JAK1, whereas the modeling does not show steric clash for deucravacitinib binding, consistent with measured K_D <1nM.



NDI-034858 | Deucravacitinib (BMS-986165)

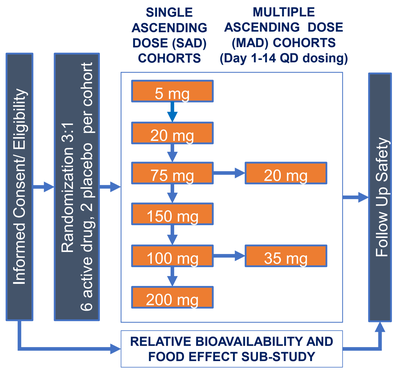
	NDI-034858	Deucravacitinib
TYK-2 –JH2 binding K_D	0.0034 nM	0.0045 nM
JAK1 –JH2 binding K_D	5000 nM	0.49 nM
Biochemical Selectivity (Fold)	1.5 x 10^6	109
Fold Selectivity (vs. deucravacitinib)	1.3 x 10^4	

Source: Nimbus proprietary structure based computational modeling; side-by-side evaluation of biochemical potency of NDI-034858 and deucravacitinib (synthesized by Nimbus for nonclinical research purposes only).

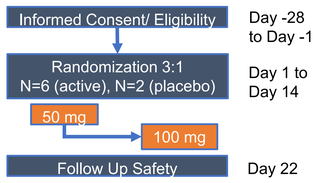
PHASE I PLACEBO-CONTROLLED TRIALS - SCHEMA

Healthy Volunteers (HV)

Study 101

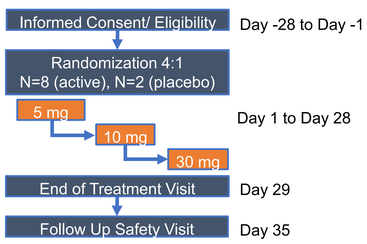


Study 104 (Multiple Dose)



Patients with moderate-to-severe psoriasis (PsO)

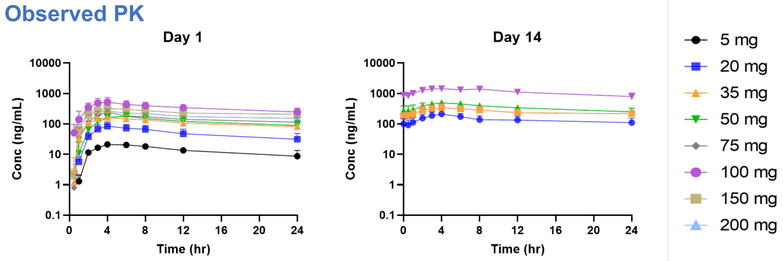
Study 102



Abbreviations: AE: Adverse Event; ANC: Absolute Neutrophil Count; AUC: Area under the concentration curve; C_L: Clearance; C_{max}: Maximal concentration; D1: Day 1; HV: Healthy Volunteer; IC50: Drug concentration for 50% inhibition; IC90: Drug concentration for 90% inhibition; JAK: Janus Kinase; JH2: JAK Homology 2; Kd: dissociation constant; LLN: Lower Limit of Normal; MD: Multiple Dose; PASI: Psoriasis Area and Severity Index; PI: Principal Investigator; RAC: Accumulation ratio; sPGA: static Physician Global Assessment; TEAE: Treatment-Emergent Adverse Event; $t_{1/2}$: Half-life; T_{max}: Time at C_{max}; V_z: volume of distribution

PHARMACOKINETICS of NDI-034858 in HV

Observed PK

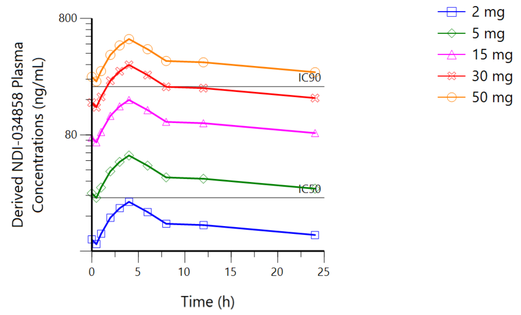


Dose (mg)	Day	N	C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-24} (hr*ng/mL)	$t_{1/2}$ (hr)	CL (L/hr)	Vz (L)	RAC_{Cmax}	RAC_{AUC}
5	1	6	21.6	5.0	306.1	20.3	8.5	248.6	NA	NA
20	1	5	78.7	4.0	1077.5	16.5			NA	NA
20	14	5	206.7	4.0	3160.3	21.5	6.3	196.2	2.6	2.9
35	1	6	150.6	4.0	2451.5	24.4			NA	NA
35	14	6	324.9	4.0	5838.5	22.8	6.0	197.2	2.2	2.5
50	1	6	184.0	6.0	2639.9	25.4			NA	NA
50	14	6	494.5	4.0	8055.8	24.1	6.2	216.0	2.7	3.1
75	1	6	237.4	4.0	3289.8	30.7	9.0	397.5	NA	NA
100	1	6	508.5	4.0	7895.3	20.9			NA	NA
100	14	6	1456.1	4.0	26209.7	21.3	3.8	117.4	2.9	3.2
150	1	6	316.9	4.0	5252.0	22.6	12.3	400.7	NA	NA
200	1	6	250.0	4.0	4128.7	22.3	22.2	713.8	NA	NA

[a]Median, All other parameters: Geometric Mean; NA = Not Applicable
CL=CL/F for SD cohorts, CL=CL/Fss for MD cohorts; Vz=Vz/F for SD cohorts, CL=CL/Fss for MD cohorts

- Absorption of NDI-034858 demonstrated mean peak plasma concentrations observed at a median T_{max} of 4-6 hours post-dose on Day 1(single dose) as well as Day 14 (steady state).
- The C_{max} and AUC_{0-24} increased in an approximately dose-proportional manner from 5 mg up to 75 mg and in a less than dose proportional manner at doses above 75 mg.
- The half-life was consistent across dose levels tested and ranged from 16.5 to 30.7 hours.
- Upon multiple dose administration, the accumulation ratio for C_{max} and AUC was 2.2-to-2.9 and 2.5-to-3.2, respectively.

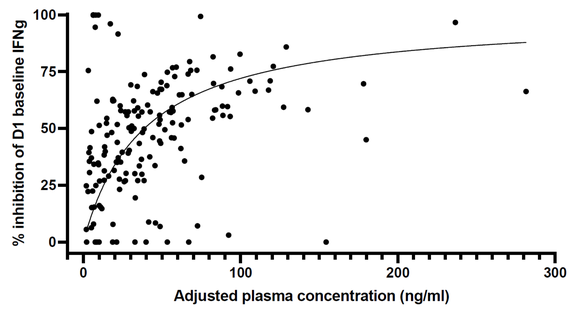
Predicted steady state plasma concentrations of NDI-034858 relative to inhibitory concentration in the human whole blood assay



Methods: Concentrations of NDI-034858 were measured by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay and were used for the PK analyses. Exposure predictions were made at 2, 5 ,15, 30, and 50 mg daily doses based on steady-state exposures obtained from the 20 mg cohort in Study 101. IC_{50} and IC_{90} values were derived from a TYK2-dependent human whole-blood interferon-alpha induced C-X-C motif chemokine (CXCL10) in-vitro assay.

- At 5 mg and 50 mg daily, NDI-034858 is expected to cover the TYK2 IC50 and IC90, respectively, for 24 hours.

PHARMACODYNAMIC ACTIVITY in HV



Methods: Pharmacodynamic activity was assessed using an ex-vivo immune-assay measuring the amount of interferon gamma (IFNγ) produced by whole blood samples, stimulated with cytokines IL-12 and IL-18, at baseline (pre-dose) and following treatment. Measured levels of NDI-034858 in plasma were adjusted based on dilution of blood in the assay. Using the PK and PD data, nonlinear regression was used to characterize the concentration-response relationship.

- Blockade of TYK2 signaling by NDI-034858 led to inhibition of ex-vivo IFNγ production in HV within 4 hours (not shown).
- Increasing exposures to NDI-034858 led to greater reduction in IFNγ production, supporting a robust effect of this compound on biological pathways relevant to the pathogenesis of several autoimmune diseases.

TOLERABILITY – HV and PsO STUDIES

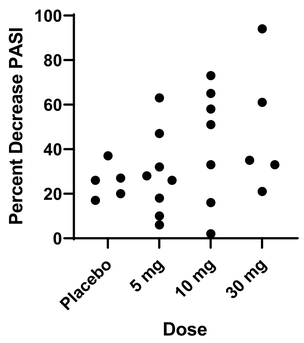
	SAD HV (101)		MAD HV (101)		MD HV (104)		PsO 1b (102)	
	Active n=35	Placebo n=12	Active n=12	Placebo n=4	Active n=12	Placebo n=4	Active n=21	Placebo n=5
Any TEAE	14 (40%)	3 (25%)	12 (100%)	2 (50%)	6 (50%)	2 (50%)	11 (52%)	1 (20%)
Preferred Terms with n>1								
Acneiform dermatitis	7 (20%)	0 (0%)	8 (67%)	0 (0%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)
Papular rash	0 (0%)	0 (0%)	3 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Aphthous ulcer	1 (3%)	0 (0%)	3 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache	3 (9%)	0 (0%)	1 (8%)	0 (0%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)	0 (0%)
Any infection	2[1] (6%)	0 (0%)	4[2] (33%)	0 (0%)	0 (0%)	0 (0%)	3[3] (14%)	0 (0%)

[1] Includes oral herpes and pharyngitis
[2] Includes oral herpes, paronychia, upper respiratory infection, and viral infection
[3] Includes otitis externa, fungal infection, urinary tract infection

- There were no SAEs or deaths.
- Dermatologic events (acneiform dermatitis, papular rash) and aphthous ulcer were common in HVs but did not occur in psoriasis patients.
  - All events were mild and most improved without intervention.
- Infections in HVs or psoriasis patients were mild except one moderate infection (otitis externa), and none led to discontinuation of study drug.
- Grade 3 lab abnormalities among subjects treated with drug included:
  - Non-fasting triglyceride elevation (2 patients, 5 mg and 10 mg, study 102)
  - CPK elevation (1 HV, 20 mg MD, study 101)
    - Not associated with increased serum creatinine or abnormal urinalysis.
      - 1 HV each in Studies 101 and 104 on placebo also had Grade 3 CPK elevation.
      - Grade 3-4 CPK elevations have been reported upon TYK2 inhibition in psoriasis patients (Papp et al., 2018*).
  - Neutropenia (1 patient, 30 mg, study 102 as previously reported#)
    - Reported as "possibly related" due to quick rebound to baseline (3 days following study drug discontinuation).
    - 1/5 (20%) of psoriasis patients dosed with placebo vs. 3/21 (14%) treated with active drug experienced neutropenia Grade 2 or greater. None of these patients experienced infection.
    - Grade 3 neutropenia has been reported previously with inhibition of TYK2 in phase 3 studies of deucravacitinib.**

EXPLORATORY EFFICACY IN PSORIASIS

Dose	Mean Decrease in PASI (from baseline)	PASI 50 %, (n)	PASI 75 %, (n)	PASI 90 %, (n)
5 mg (N = 8)	30%	13% (1/8)	0% (0/8)	0% (0/8)
10 mg (N = 7)	47%	57% (4/7)	0% (0/7)	0% (0/7)
30 mg (N = 5)	48%	40% (2/5)	20% (1/5)	20% (1/5)
Placebo (N = 5)	26%	0% (0/5)	0% (0/5)	0% (0/5)



- Treatment with NDI-034858 showed a dose-dependent trend in reduction of disease severity as assessed by % reduction in PASI score.
- PASI 50 was achieved in 13%, 57% and 40% of patients in the 5, 10, and 30 mg groups, respectively, compared to 0% in the placebo group,
- PASI 75 was achieved in one subject (1/5; 20%) in the 30 mg group; the same subject also achieved PASI 90.
- Treatment with NDI-034858 also improved the sPGA score compared to placebo (data not shown), with one subject in the 30-mg cohort achieving an sPGA of 1 (minimal disease) at Day 28.

CONCLUSIONS

- The novel, investigational, allosteric, oral TYK2 inhibitor NDI-34858 exhibited pharmacodynamic and clinical activity in phase I studies.
- Early safety profile was as expected for TYK2 inhibition.
- Pharmacokinetic profile supports once daily dosing. At 50 mg daily, NDI-034858 is expected to cover IC90 for 24 hours.
- These results support further development of NDI-034858 in autoimmune disease.
- Phase 2 studies in psoriasis and psoriatic arthritis are currently ongoing.

References:
*Papp K et al., N Engl J Med 2018; 379:1313-1321
McElwee J et al, AAD 2022
**Thaçi et al, EADV 2021

Disclosures: All the authors are / were employees or consultants of Nimbus Therapeutics, LLC

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