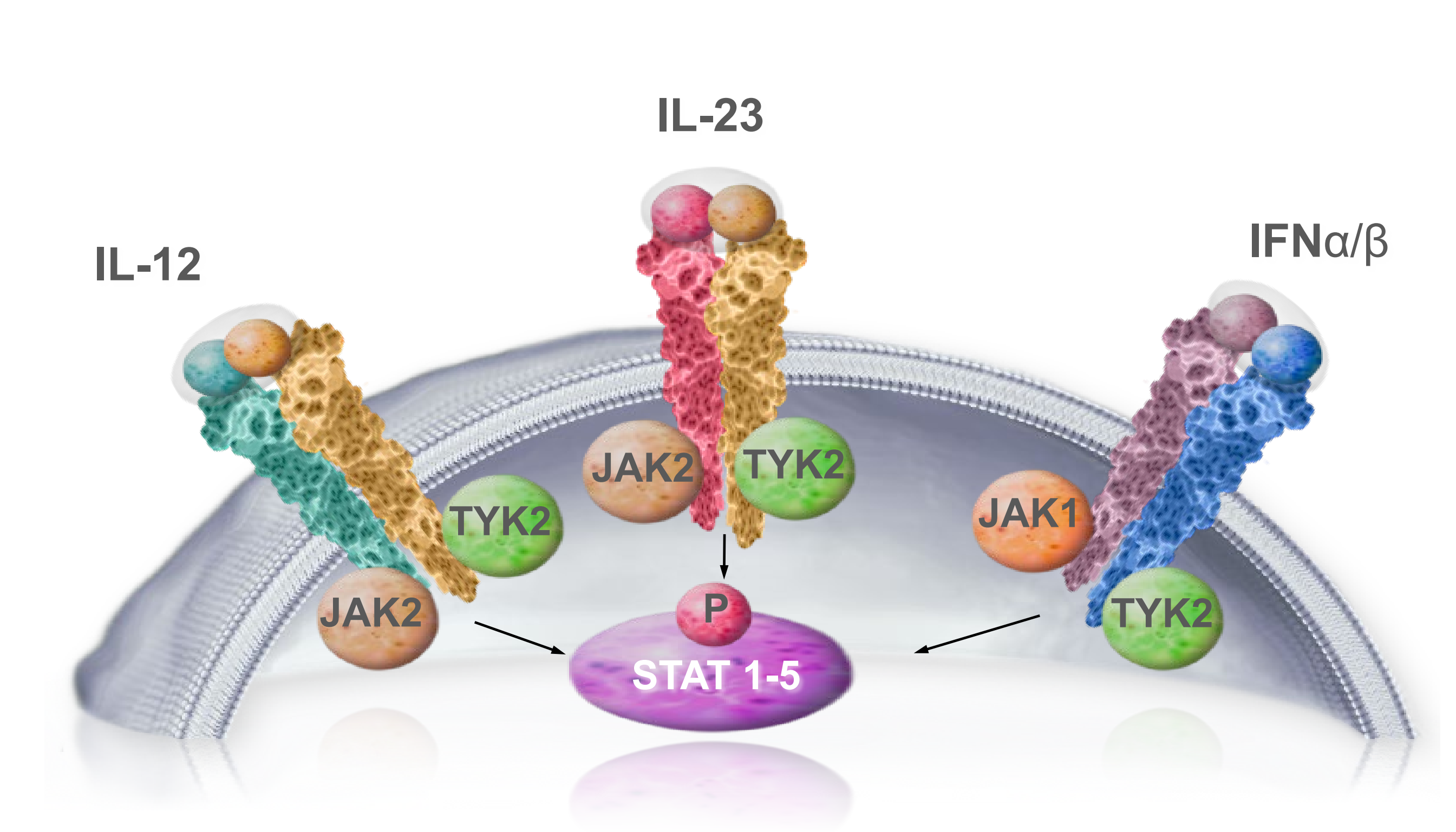


Analysis of histologic, molecular and clinical improvement in moderate-to-severe psoriasis: Results from a Phase 1b trial of the novel allosteric TYK2 inhibitor NDI-034858*

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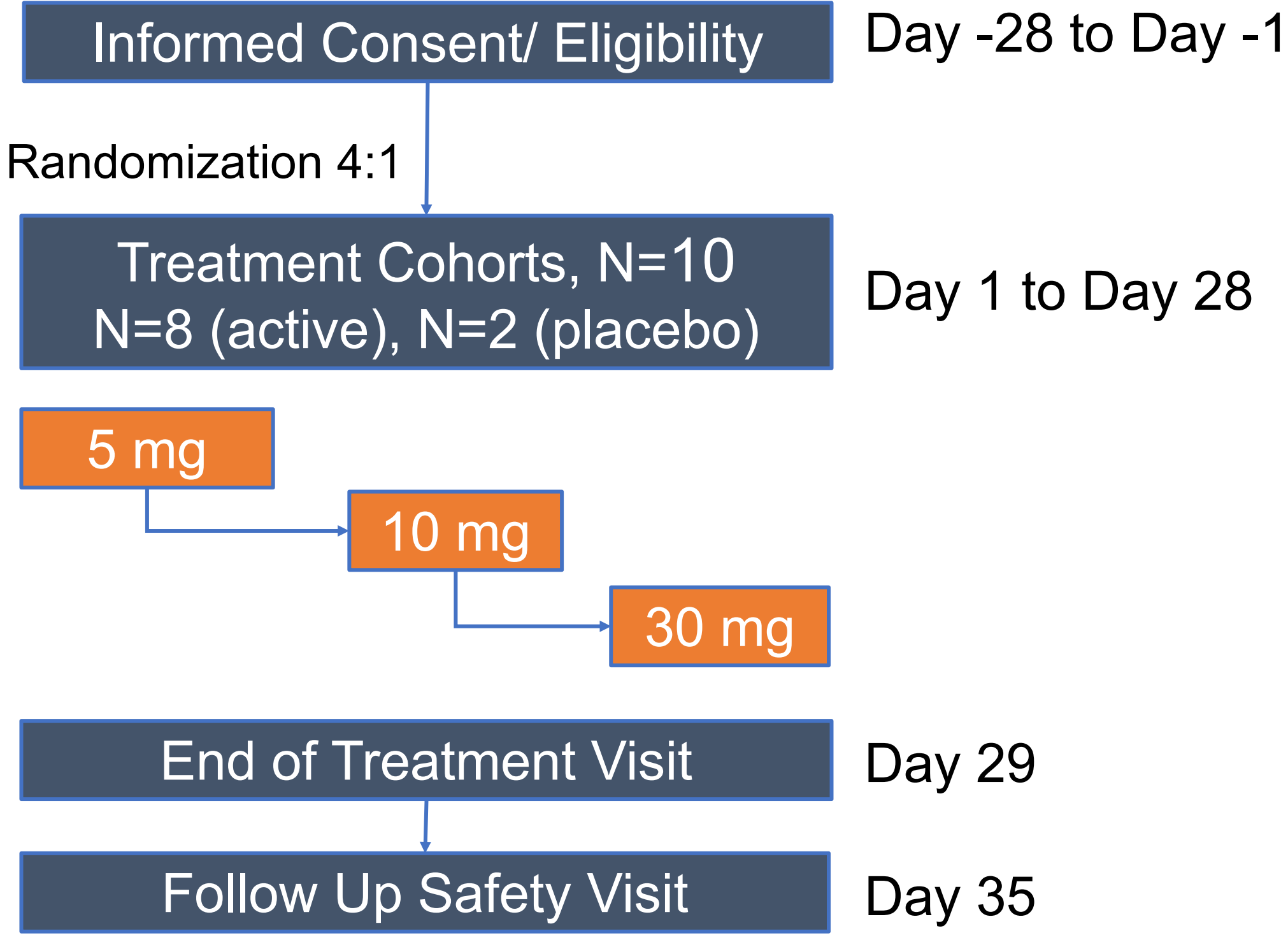
TYK2 (Tyrosine Kinase 2)

- Obligate signal transducer of receptors for interleukin (IL)-12, IL-23 and Type I interferon
- Heterodimer with JAK1 or JAK2; inhibition of either dimer moiety impedes signal transduction
- Clinically validated target in psoriasis and psoriatic arthritis

NDI-034858

- Novel, investigational, allosteric, oral inhibitor of TYK2
- High specificity for TYK2 over JAK1, JAK2, JAK3 kinases

Study design of Ph1b trial in patients with moderate-to-severe psoriasis



* (NDI-034858 was at the time of submission of the abstract known as NTX-973)

Safety and exploratory efficacy evaluation of NDI-034858 in Ph1b psoriasis trial

Primary objective: Assess safety and tolerability of multiple doses of NDI-034858 given over 28 days to participants with moderate-to-severe plaque psoriasis

Secondary objectives: Assess pharmacokinetics and pharmacodynamics of NDI-034858

Exploratory objectives:

- Assess the effect of NDI-034858 on histologic and mRNA transcriptional biomarkers in psoriatic skin plaques and inflammatory cytokines in peripheral circulation of participants with moderate-to-severe plaque psoriasis
- Describe clinical efficacy of NDI-034858 given over 28 days to participants with moderate-to-severe plaque psoriasis

Patient disposition

- 39 patients were screened; 26 patients were randomized
- Mean Psoriasis Area and Severity Index (PASI) score was 18.0 (range 12.2-50.0)
- 25 patients completed the study
 - 1 patient was discontinued from study on Day 1 due to a positive tuberculosis test

Safety Assessment Summary

- No deaths or SAEs observed
- Treatment-emergent adverse events occurred in 3 (37.5%), 4 (57.1%), 4 (66.7%), and 1 (20%) patients receiving 5, 10, and 30 mg, or placebo, respectively
 - All were Grade 1 (mild) or Grade 2 (moderate) except one Grade 3 (severe) event of neutropenia (30 mg) which led to study drug discontinuation
 - Significance of Grade 3 neutropenia unclear (rebound to normal within 3 days after drug discontinuation)
- Most common AEs (occurring in >1 patient) included diarrhea (Grade 1; 2 patients) and infections (Grade 1 or 2; 3 patients)
- No trends of adverse events with drug exposure

Exploratory Efficacy Assessment

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)

NDI-034858 showed a dose-dependent trend in exploratory clinical activity, measured by mean % decrease in PASI score at 4 weeks.

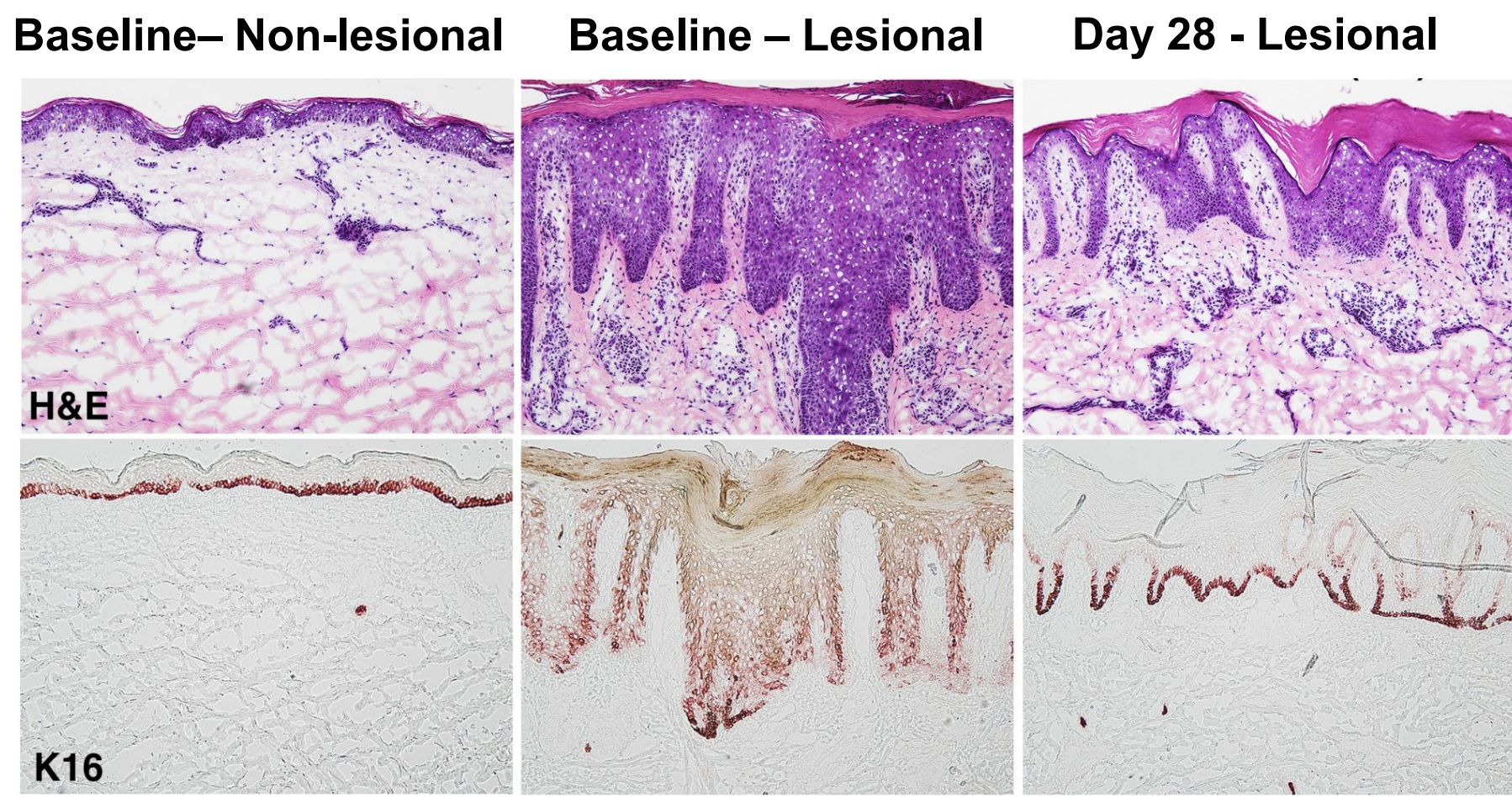
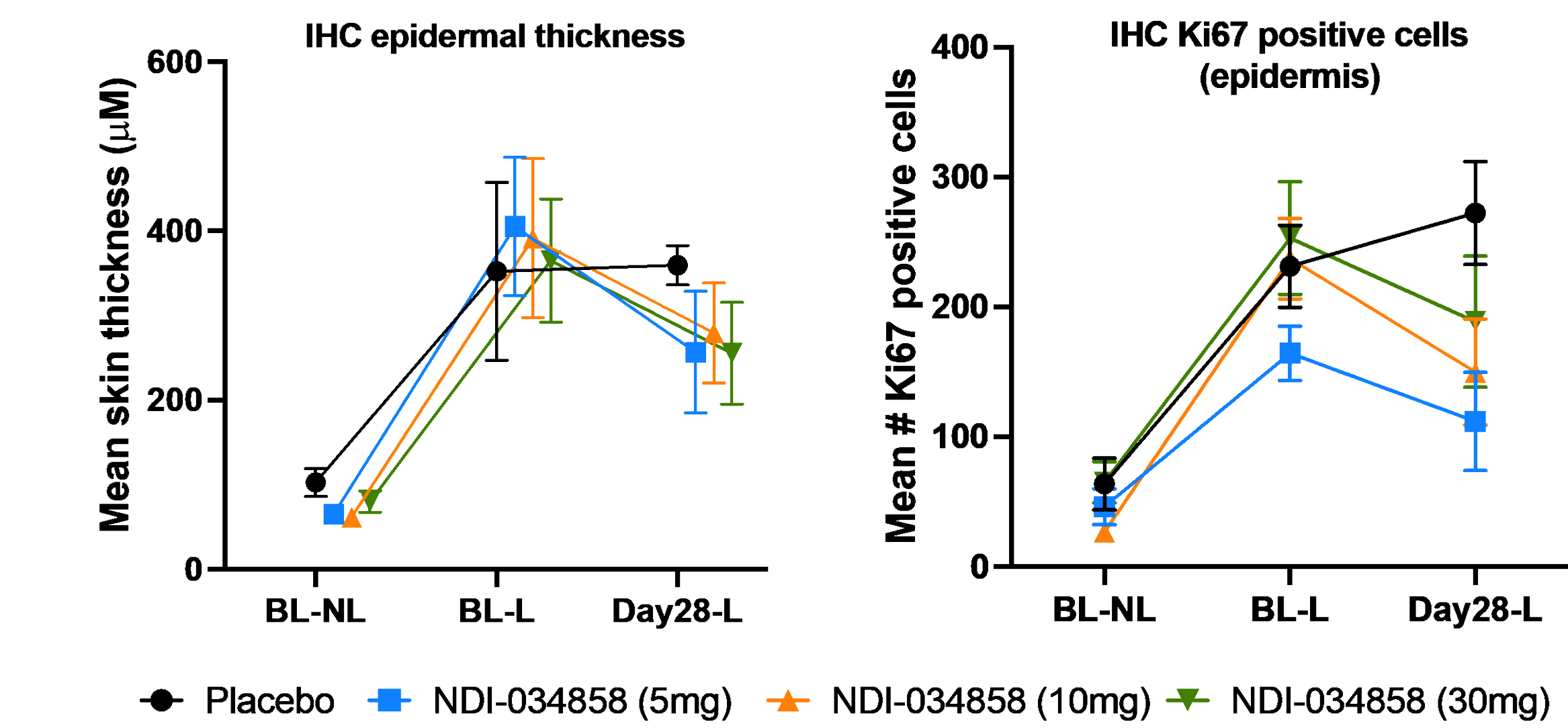
NDI-034858 treatment resulted in histological improvements in lesional skin

Methods: Two skin punch biopsies from lesional and non-lesional skin were isolated at baseline prior to the initiation of treatment, and a biopsy from the same lesional skin region was isolated on Day 28 of treatment to assess molecular markers of pharmacodynamic response to NDI-034858 treatment. Biopsies were split at collection, with one half used for histological assessment, including immunohistochemistry for known psoriasis and immune markers, and the other half was used to isolate RNA for gene expression studies.

Results: After 28 days of treatment with NDI-034858, decreases in the thickness of lesional skin epidermis and Ki67 expression (a marker of cell proliferation) were observed and a high proportion of subjects showed resolution of elevated keratin-16 expression compared to baseline.

Treatment group	N	Mean % change in epidermal thickness	% subjects with K16 resolution
Placebo	4	+70% (+/- 32%)	0% (0/4)
NDI-034858 (5 mg)	6	-41% (+/- 3%)	67% (4/6)
NDI-034858 (10 mg)	6	-20% (+/- 5%)	33% (2/6)
NDI-034858 (30 mg)	5	-32% (+/- 1%)	60% (3/5)

% change in epidermal thickness (+/- SEM) in lesional skin biopsies (Day 28 compared to baseline) for each subject was calculated. Lesional biopsies were stained for keratin-16 levels and assessed for improvement at Day 28 compared to baseline by an expert reader (Dr. J. G. Krueger), blinded to treatment allocation.



IHC of representative skin biopsy samples showing a good response to NDI-034858 treatment (Subject 101-104, 5mg) H&E: hematoxylin and eosin; K16: keratin-16 staining

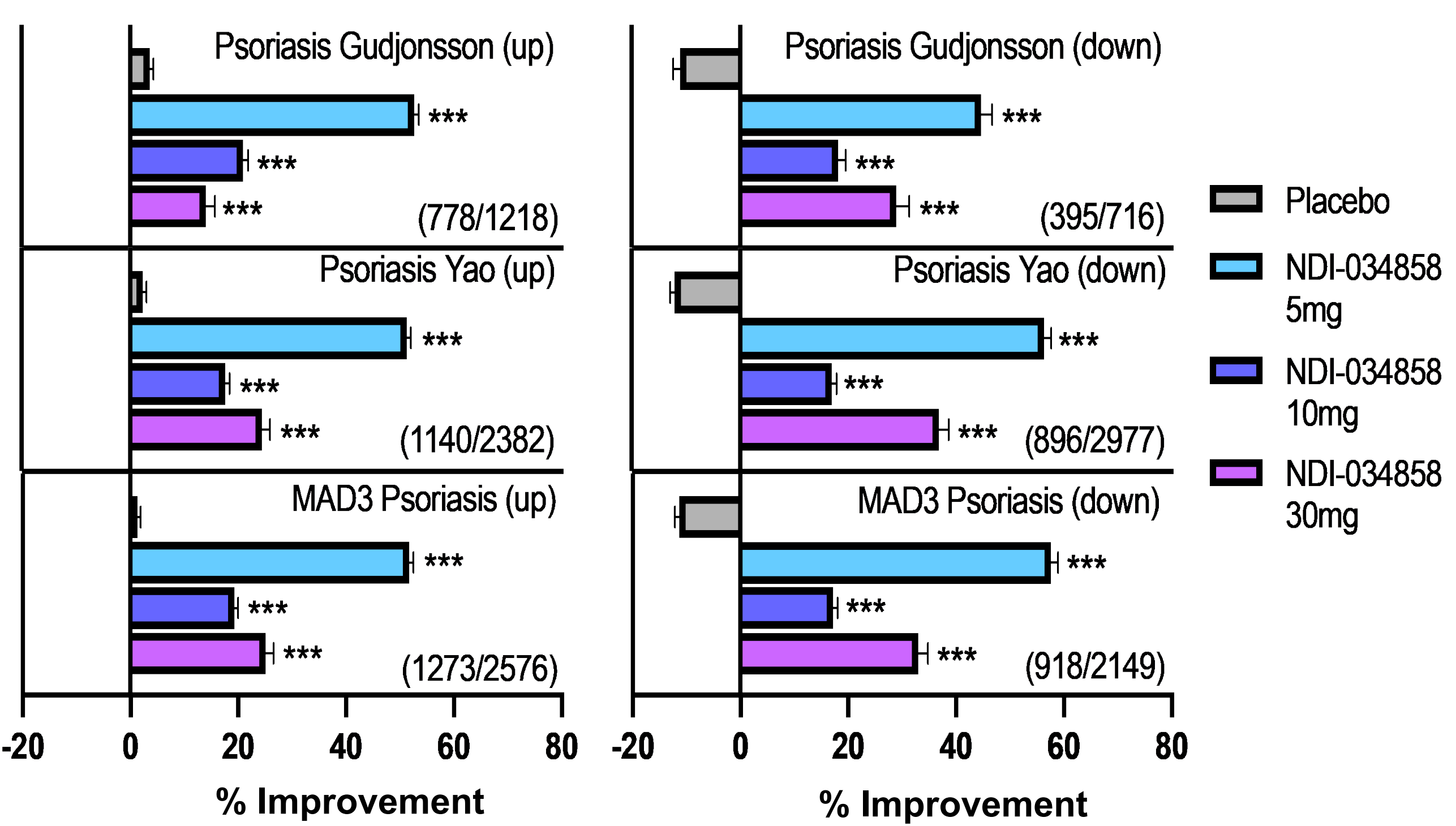
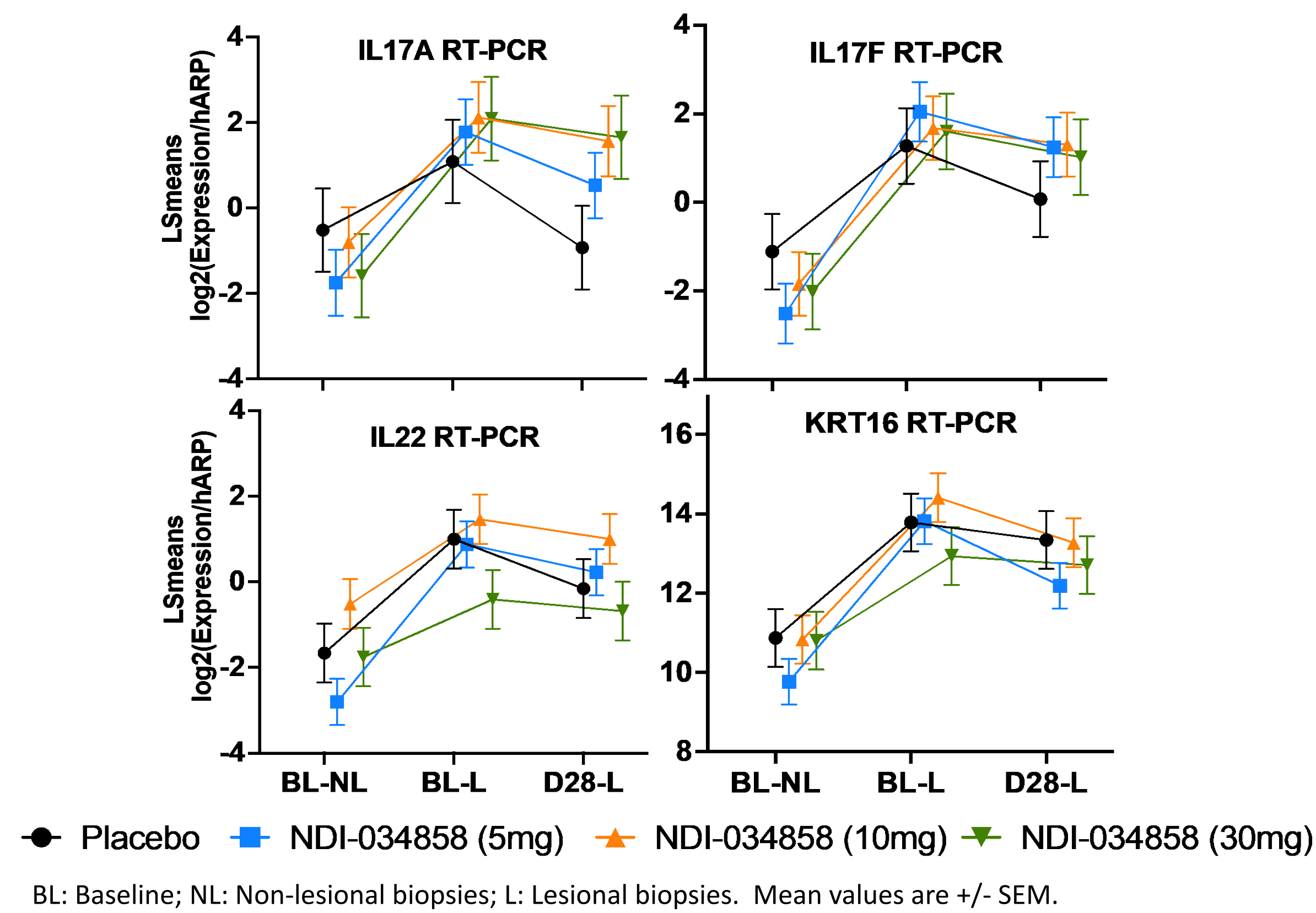
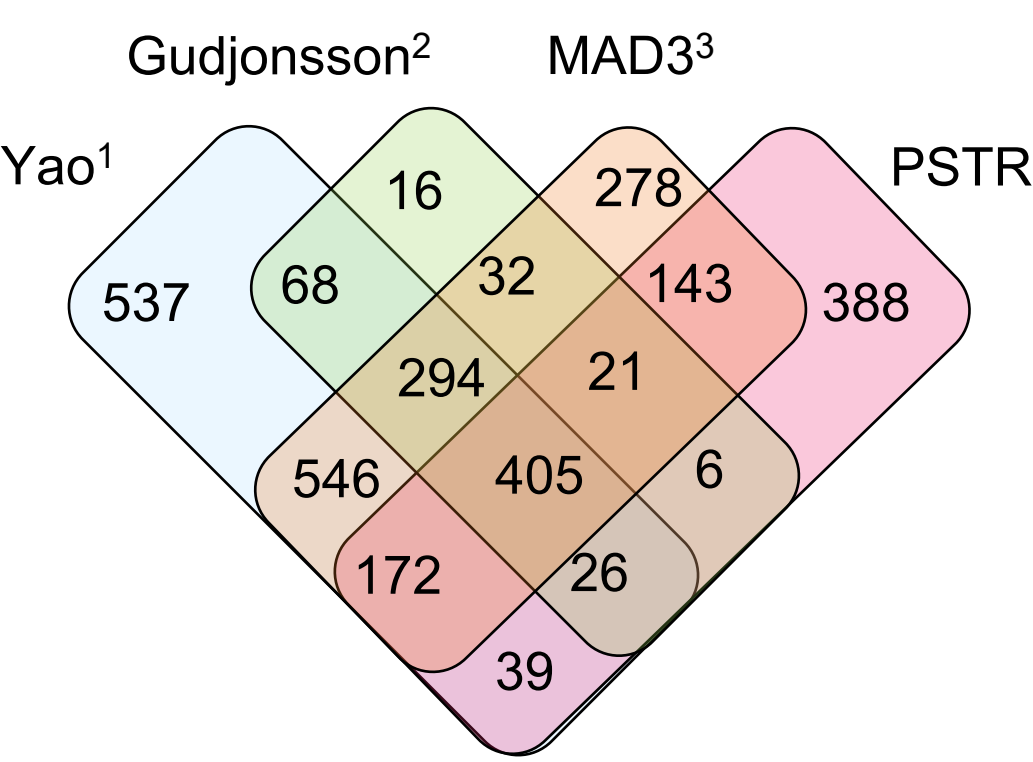
NDI-034858 treatment for 28-days reduced the RNA expression levels of key cytokines and psoriasis gene signatures in lesional skin

Methods: mRNA from skin biopsies was isolated and assessed for targeted (RT-PCR) or global (microarray) gene expression. For microarray analysis, differential gene expression comparing baseline lesional vs. non-lesional samples (psoriasis transcriptome, PSTR) and comparing baseline lesional vs. Day 28 lesional samples (NDI-034858 response) was assessed. Detailed methodology is available on request.

Results: Quantification of mRNA from skin biopsies showed suggestive decreases in the expression of several psoriasis-related genes by RT-PCR (such as KRT16, IL17A, IL17F, and IL22) and up to 50% improvement in the expression of skin transcriptomes previously associated with psoriasis in lesional skin through microarray analysis (p<0.001 compared to placebo treatment).

The set of genes that were significantly differentially-expressed in lesional vs. non-lesional baseline skin biopsies (PSTR) (FC ≥ 2, pval < 0.05) shows high overlap with several published datasets of differentially-expressed genes in psoriasis lesional vs. non-lesional skin.

References: ¹Yao et al., PLoS One, 2008; ²Gudjonsson et al., J Invest Derm, 2009; ³Tian et al., PLoS One, 2012



Genes that show up or down-regulation in published psoriasis skin datasets show significant improvement following 28-days of treatment with NDI-034858 at all doses. Numbers in parentheses are (probeset overlap of Nimbus PSTR and indicated dataset/Total # of probesets in dataset). Percent improvement is assessed as the mean % change (+/- SEM) in expression of the overlapping probesets toward baseline non-lesional expression (***) p < 0.001 comparing treatment vs. placebo).

- The novel, investigational, allosteric, oral TYK2 inhibitor NDI-034858 exhibited encouraging activity in this Phase 1b study in moderate-to-severe plaque psoriasis patients.
- Pharmacodynamic activity was consistent with decreases in PASI scores.
- These results support further development of NDI-034858 in psoriasis. A Phase 2 study in psoriasis is currently ongoing.

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