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

Day 29

Day 35

- Novel, investigational, allosteric, oral inhibitor of TYK2
- High specificity for TYK2 over JAK1, JAK2, JAK3 kinases
- Obligate signal transducer of receptors for interleukin (IL)-12, IL-23 and Type I interferon
- Heterodimer with JAK1 or JAK2: inhibition of either dimer impairs signal transduction
- Clinically validated target in psoriasis and psoriatic arthritis

NDI-034858 treatment showed high response to NDI-034858 treatment (Subject 101-104, 5mg)

NDI-034858 was given over 28 days to patients with moderate-to-severe plaque psoriasis

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

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. Skin biopsies were split at collection, with one half used for histologic assessment, including immunohistochemistry for known psoriatic 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 in lesional biopsies stained for keratin-16 levels.

Conclusions: The novel, investigational, allosteric, oral inhibitor of TYK2 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.

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

Safety Assessment Summary
- No deaths or SAEs observed
- Treatment-emergent adverse events occurred in 3 (37.5%), 4 (57.1%), 2 (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
- No significant reduction in Grade 3 neutropenia (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

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

NDI-034858 treatment for 28-days reduced the RNA expression levels of key cytokines and psoriasis signature genes 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 transcriptomes, PSTR) and comparing baseline vs. Day 28 lesional samples (NDI-034858 response) was assessed. Detailed methodology is available upon 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 transmembrane proteins 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 baseline vs. placebo in lesional skin biopsies (PSTR) (FC > 2, p < 0.005) shows high overlap with several published datasets after differentially-expressed genes in psoriatic lesional vs. non-lesional skin.

References:
- Gudjonsson et al., J Invest Derm, 2009
- Tian et al., J Invest Derm, 2012

PATS: Placebo
- Mean Decrease in PASI from baseline (% improvement)
- Mean % change in PASI score from baseline

Placebo (N = 5) 26% 0% (0/5) 0% (0/5) 0% (0/5)
10 mg (N = 7) 47% 0% (0/7) 0% (0/7) 0% (0/7)
30 mg (N = 5) 48% 20% (1/5) 20% (1/5) 20% (1/5)

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Ploteo, Ploteo YC (200), NODX (5), NODX (10), NODX (30)

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

Disclosures: J.J. McElwee and Dr. B. Srinivasa are full-time employees of Nimbus Therapeutics, LLC. Dr. J.G. Krueger received funding from Nimbus Laboratories Inc. during the conduct of the study. money for his institution from Abbvie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Demirci, Innovaxmed, Jansen, Lilly, Nimbis Laboratories, Novartis, Paratek, Pfizer, Proxeon, Regeneron, UCB, and Vifor: personal fees from AbbVie, Baxter, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Daienex, Demirci, Jansen, Radicon, Potella, Lilly, Merck, Novartis, Pfizer, Sarch, Sorion, Xenoprotein outside the submitted work.