



Nimbus Therapeutics Presents New Data on Oral Allosteric TYK2 Inhibitor at American Chemical Society Meeting

CAMBRIDGE, Mass. – August 24, 2022 – [Nimbus Therapeutics](#), a clinical-stage company that is working to design and develop breakthrough medicines through its powerful computational drug discovery engine, today presented research describing the chemical structure of NDI-034858, the company's investigational oral allosteric TYK2 (tyrosine kinase 2) inhibitor now in two Phase 2b clinical studies for moderate-to-severe plaque psoriasis and active psoriatic arthritis.

The data, presented in an oral session at the American Chemical Society Fall 2022 meeting, describe how Nimbus leveraged structural biology and computational chemistry insights to produce a novel TYK2 inhibitor with a potential best-in-class profile with respect to potency, selectivity and optimized pharmacokinetics/pharmacodynamics properties.

“Challenges in selectivity often arise when the easily druggable target sites are structurally similar to those of other proteins, as is the case with the TYK2 catalytic site. For this reason, we intentionally designed NDI-034858 to target the allosteric JH2 binding site, where key amino acid differences between TYK2 and JAKs 1, 2, and 3 can be exploited to dramatically favor binding to TYK2 over those other closely related kinases,” said Scott Edmondson, Ph.D., Senior Vice President and Head of Chemistry at Nimbus. “Preclinical and clinical data to date support this approach, showing that NDI-034858 can achieve high target inhibition at low clinical doses without evidence of the adverse safety effects observed with JAK inhibition.”

NDI-034858 was developed using structure-based drug design, an approach that applies computational chemistry and other analytical technologies to high-resolution protein-ligand co-crystal structures. Development focused on maximizing the small molecule's therapeutic benefit by achieving highly selective inhibition of the pseudokinase JH2 domain of TYK2. This allosteric interaction results in very high selectivity compared to the other homologous proteins in the Janus Kinase (JAK) family of non-receptor tyrosine kinases.

“Nimbus' TYK2 program is an excellent example of our leadership in structure-based drug design. By combining advanced computational methods together with our structural biology and medicinal chemistry expertise, we are able to identify and exploit unique binding pockets on our target proteins to achieve exquisite selectivity,” said Peter Tummino, Ph.D., Chief Scientific Officer at Nimbus. “This approach forms the basis of Nimbus' diversified portfolio of differentiated candidates in oncology, autoimmune diseases, and metabolic disorders, including our clinical-stage HPK1 program in immuno-oncology and promising preclinical work across numerous targets.”

In a Phase 1 clinical study, NDI-034858 demonstrated a good tolerability profile and evidence of clinical and pharmacodynamic activity across multiple measures of disease pathology in



psoriasis. Notably, it has been shown in cellular assays to be significantly more selective than Bristol Myers Squibb's TYK2 inhibitor deucravacitinib.

About Nimbus Therapeutics

Nimbus Therapeutics is a clinical-stage company working to design and develop breakthrough medicines through its powerful and comprehensive computational drug discovery engine. Nimbus' pipeline is comprised of multiple selective small molecule compounds targeting proteins that are known to be fundamental drivers of pathology in highly prevalent human diseases and have proven difficult for drug makers to tackle. Nimbus is headquartered in Cambridge, MA. To learn more about Nimbus, please visit www.nimbustx.com.

About the Nimbus TYK2 Program

TYK2 is an important signal-transducing kinase that mediates immune signaling and is important in both adaptive and innate immune cells. TYK2 inhibition is a potentially promising treatment approach for a wide range of autoimmune and inflammatory diseases due to the protein's central role in both the innate and adaptive immune responses. Nimbus is conducting a number of Phase 2 clinical studies to evaluate its novel allosteric TYK2 inhibitor, including an ongoing moderate-to-severe plaque psoriasis (NCT04999839) study and an ongoing psoriatic arthritis (NCT05153148) study. Additional trial details can be found by visiting ClinicalTrials.gov.

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