Nested Therapeutics Announces FDA Clearance of Investigational New Drug (IND) Application for NST-628, a Novel Pan-RAF/MEK Molecular Glue

Company expects to initiate dosing in the Phase 1 study of NST-628 in patients with advanced solid tumors harboring genetic alterations in the MAPK pathway in first half of 2024

Cambridge, Mass., March 28, 2024 – Nested Therapeutics, a biotechnology company pioneering a next-generation precision medicine platform to address hard-to-treat cancers, today announced that the U.S. Food and Drug Administration (FDA) cleared the investigational new drug (IND) application for NST-628 for the treatment of patients with advanced solid tumors harboring genetic alterations in the RAS-MAPK pathway. NST-628 is a mechanistically novel, fully brain penetrant non-degrading pan-RAF/MEK molecular glue that targets RAF and MEK nodes in the RAS-MAPK pathway.

"The significant majority of KRAS-, NRAS-, and BRAF-mutant tumors are not addressable by currently approved therapies, creating a pressing need for new medicines that provide superior, durable efficacy and tolerability for people living with these hard-to-treat cancers," said Philip Komarnitsky, M.D., Ph.D., chief medical officer of Nested. "We believe that NST-628 has the potential to provide a differentiated clinical profile, including a superior therapeutic index and prevention of pathway reactivation, for patients with advanced solid tumors harboring RAS-MAPK pathway alterations. The IND clearance for NST-628 is an important step in the advancement of our first clinical-stage program, and with clinical trial sites already activated, we look forward to dosing the first patients in this trial in the first half of this year."

The Phase 1 open-label, single-arm, two-part study (NCT06326411) is intended to investigate the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of single agent NST-628 in adult patients with RAS-MAPK pathway mutated/dependent advanced solid tumors who have exhausted standard treatment options. The study includes two parts: dose escalation (Part A) followed by dose expansion (Part B). The primary objectives for Part A are delineating NST-628's safety profile and establishing the recommended dose for Part B. For more information, visit clinicaltrials.gov.

About NST-628

NST-628 is a fully brain-penetrant, mechanistically novel non-degrading molecular glue that targets multiple nodes in the RAS/MAPK pathway. NST-628 was developed based on Nested's proprietary structural insights of how signaling complexes form and function in cancer and addresses common pitfalls of other MAPK-targeted compounds, which remain unable to circumvent the risk of resistance via signaling pathway reactivation. Preclinical data evaluating all biomarkers relevant to RAS/MAPK-driven cell and patient-derived models collectively demonstrate superior anti-tumor activity, including in RAS and central nervous system-implanted tumor models, and tolerability of NST-628 compared to other MAPK-targeted compounds administered as either single agents or in combination. With a half-life and metabolic profile optimized to achieve a superior therapeutic index on a daily dosing schedule, as well as full intrinsic blood brain barrier penetrance, these data support NST-628's potential as a best-in-class treatment for RAS and RAF-driven cancers.

About Nested Therapeutics
Nested Therapeutics is a biotechnology company focused on discovering and developing novel, targeted, small molecule precision medicine therapies for patients with cancer by using mutation clusters to identify druggable pockets. With a platform that utilizes insights from genomics, computational chemistry, proteomics and AI, Nested is working to reach untapped mutations with the potential to improve outcomes for millions of patients. To learn more, visit www.nestedtx.com and follow Nested Therapeutics on Twitter (@Nestedtx) and LinkedIn.

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