NodThera Ltd

("NodThera" or the "Company")

NodThera Publishes Preclinical Data Demonstrating Reversal of Obesity and Inflammation with Clinical-stage Brain-penetrant NLRP3 Inflammasome Inhibitors

- **Data published in *Journal of Pharmacology and Experimental Therapeutics***
- **NodThera's brain-penetrant NLRP3 inhibitors matched weight loss driven by GLP-1 receptor agonist semaglutide (Wegovy®) or calorie restriction, while also providing enhanced improvements in disease-relevant biomarkers of cardiovascular inflammation and lipid metabolism**
- **Findings indicate NLRP3 activation in the brain is implicated in driving obesity which can be reversed with brain-penetrant NLRP3 inhibitors**
- **Additionally, combinations of an NLRP3 inhibitor and a GLP-1 receptor agonist were shown to be additive on weight loss in as-yet unpublished data**
- **NodThera's lead candidate NT-0796 is currently in Phase Ib/IIa development in cardiometabolic disease and Parkinson's disease**

BOSTON, MA, February 19, 2024 – NodThera, a leading clinical-stage biotech developing brain-penetrant NLRP3 inhibitors to treat chronic inflammatory diseases, today announces the publication of preclinical data demonstrating its clinical-stage investigational compounds reversed diet-induced obesity (DIO) and inflammation in an animal model of disease.

The data are published in the *Journal of Pharmacology and Experimental Therapeutics* in a paper titled 'Reversal of high fat diet-induced obesity, systemic inflammation and astrogliosis by the NLRP3 inflammasome inhibitors NT-0249 and NT-0796'[1].

The NLRP3 inflammasome is a highly validated anti-inflammatory drug target, and these findings demonstrate that NLRP3 plays a key role in controlling obesity and obesity-associated inflammation through the modulation of hypothalamic gliosis. Both NT-0796 and NT-0249, two structurally distinct NLRP3 inhibitors in clinical development by NodThera, have generated a wealth of preclinical and clinical data demonstrating brain-penetration and broad anti-inflammatory effects, with NT-0796 being the first NLRP3 inhibitor to show reduced neuroinflammation in the clinic.

In this latest publication, NodThera's researchers show for the first time the ability of NT-0796 and NT-0249 to reverse DIO in a murine model, providing comparisons against the effects of the GLP-1 receptor agonist (GLP-1RA) semaglutide (Wegovy®) and calorie restriction. While all three therapeutic approaches led to statistically significant reductions in body fat in DIO mice, only the NLRP3 inhibitors reduced disease-relevant cardiovascular inflammatory biomarkers such as fibrinogen, sVCAM-1, suPAR, and PCSK9, suggesting their potential to further reduce cardiovascular risk in obese populations. NodThera has additionally explored alternative treatment scenarios where NLRP3 inhibitors can be combined with a GLP1-RA or used as a follow-on therapy for patients who do not tolerate GLP-1RA drugs. Yet-to-be-published preclinical findings have demonstrated an additive weight loss effect when combining the brain-penetrant NLRP3 inhibitors with low dose GLP-1RAs, and

stable weight maintenance following cessation of GLP-1RA therapy by dosing of a brain-penetrant NLPR3 inhibitor, thereby preventing body mass regain.

Obesity is a global health concern that predisposes individuals to chronic disease such as diabetes and cardiovascular disease at least in part by promoting systemic inflammation.

Alan Watt, Chief Executive Officer of NodThera, said: "These remarkable findings – the first in the field of NLRP3 inflammasome research – suggest that in obese mice consuming a high-fat diet, brain-penetrant NLRP3 inhibition and the resulting anti-inflammatory effect confers not only reversal of obesity but metabolic benefits that extend well beyond this. While GLP-1 receptor agonists have undoubtedly delivered significant achievements in the management of obesity, their adverse event profile is well established, presenting difficulties for some patients. Our brain-penetrant NLRP3 inhibitors deliver robust weight loss and broad cardiometabolic benefits by targeting a novel molecular mechanism with the convenience of oral dosing and an exceptional safety profile. Our ongoing Phase IIa study in obese individuals at cardiovascular risk will further validate these pre-clinical findings."

References:

1. *Reversal of High Fat Diet-Induced Obesity, Systemic Inflammation, and Astrogliosis by the NLRP3 Inflammasome Inhibitors NT-0249 and NT-0796*. Peter Thornton, Valérie Reader, Zsofia Digby, Pamela Smolak, Nicola Lindsay, David Harrison, Nick Clarke and Alan P. Watt. Journal of Pharmacology and Experimental Therapeutics March 2024, 388 (3) 813-826; DOI: https://doi.org/10.1124/jpet.123.002013

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About NodThera

NodThera is a leading clinical-stage biotech developing brain-penetrant NLRP3 inflammasome inhibitors to treat chronic inflammatory diseases. Led by an experienced management team, NodThera is combining a deep understanding of NLRP3 inhibition, pharmaceutical neuroscience expertise and precision molecular chemistry. Its two lead clinical candidates are oral, small molecule NLRP3 inflammasome inhibitors, which have demonstrated differentiated, potentially best-in-class clinical profiles with significant anti-inflammatory effects and the ability to penetrate different areas of the brain, offering distinct opportunities to treat multiple indications. The Company is backed by top-tier investors including 5AM Ventures, Blue Owl Capital, Epidarex Capital, F-Prime Capital, Novo Holdings, Sanofi Ventures and Sofinnova Partners. NodThera is headquartered in Boston, MA, with additional operations in Cambridge, UK and Seattle, WA. Learn more at www.nodthera.com or follow the Company on LinkedIn.