NorthSea Therapeutics Announces Publication of Positive Results from Phase 2b ICONA Clinical Trial of Icosabutate in Biopsy-Confirmed F1-F3 MASH in *Journal of Hepatology*

Improvements in fibrosis observed using 3 pre-specified methods of histological analysis: conventional,
AIM-MASH (PathAI) and qFibrosis (Histoindex)

Mechanistically, icosabutate improved fibrosis independent of reductions in liver fat or body weight, emphasizing its unique mechanism and promise for combination with GLP-1RAs to optimize both clinical benefits and success in longer term outcome studies

Positive results support advancement of icosabutate into further clinical development in MASH patients as an anti-fibrotic, particularly in patients with more advanced disease and/or with underlying diabetes

Amsterdam, The Netherlands, 6 March 2025 – NorthSea Therapeutics B.V. ('NST', or the 'Company'), a private, late-stage clinical biotechnology company developing novel strategies to treat metabolic, cholestatic, and fibrotic diseases, today announced that results from the Phase 2b ICONA clinical trial of icosabutate in biopsy-confirmed F1-F3 metabolic dysfunction-associated steatohepatitis (MASH) were published in the *Journal of Hepatology.*

The publication, "A phase IIb randomised-controlled trial of the FFAR1/FFAR4 agonist icosabutate in MASH" reported that treatment with icosabutate demonstrated highly encouraging results in the most clinically meaningful endpoint, fibrosis improvement, as assessed by both artificial intelligence (AI)-assisted digital pathology tools *(*DP/AI) tools and conventional histological assessment.

"The data presented in this publication, both conventional and AI-assisted histology, suggest improvements in fibrosis in patients treated with icosabutate" said Arun Sanyal, M.D., Director of the Stravitz-Sanyal Institute for Liver Disease and Metabolic Health and the last author of the *Journal of Hepatology* paper. "The unique mechanism of action, unrelated to a decrease in liver fat, will provide patients with metabolic dysfunction-associated steatotic liver disease, or MASLD, with more options for therapy in the future."

The results are consistent with icosabutate's anti-fibrotic effects in pre-clinical models and anti-proliferative effects in isolated stellate cells[1,2]. Key findings include:

AI-assisted digital pathology

- 49.2% (p=0.02 vs placebo) of 600 mg treated patients achieving a ≥1-stage improvement in fibrosis versus 25.7% of placebo treated patients as assessed by qFibrosis (Histoindex).
- 32.7% (p=0.004 vs placebo) of F3-F4 patients treated with 600 mg icosabutate achieved ≥1-stage improvement in fibrosis without worsening of MASH versus 9.6% of placebo treated patients as assessed by AIM-MASH (PathAI).

Conventional histological analysis

- 30.8% (p=0.036 vs placebo) and 28.3% (p=0.065 vs placebo) of F2-F3 patients treated with icosabutate 300 and 600 mg respectively achieving a ≥1-stage improvement in fibrosis versus 13% of placebo treated patients.
- 28.6% (p=0.003 vs placebo) and 21.2% (p=0.013 vs placebo) of Type 2 diabetic patients treated with icosabutate 300 and 600 mg respectively achieving a ≥1-stage improvement in fibrosis versus 0% of placebo treated patients.

The clinical relevance of the AIM-MASH findings is highlighted by recently published data demonstrating that continual scores in AIM-MASH determined F3-F4 MASH patients strongly predicted progression free survival[3].

A 3-panel read method was used for the conventional histological analysis. To provide a more relevant cross-study comparison, we also performed an exploratory analysis of fibrosis improvement using the same pathologist used in the current study and in multiple single reader F2-F3 phase 2 MASH studies. A ≥1-stage improvement in fibrosis was seen in 17.5%, 29.2% and 40.9% of patients (F2-F3) in the placebo, 300 mg and 600 mg arms respectively.

The publication also highlights the broad therapeutic effect of 600 mg icosabutate on multiple biomarkers of liver health, systemic inflammation and glycemic control, including but not limited to:

- Significant reductions in fasting plasma glucose, insulin and HOMA-IR in conjunction with a ~1% placebo adjusted decrease in HbA1c in type 2 diabetic patients with poor glycemic control at baseline.
- Significant improvements in ALT, AST, GGT, ALP and bilirubin.
- Significant improvements in ELF score (a marker of fibrosis), PRO-C3 (~20% reduction from baseline) and hsCRP (median reduction of 40% from baseline).

Icosabutate was generally safe and well tolerated, with mild to moderate treatment emergent adverse events (TEAEs) and no reports of drug induced liver injury. As expected, icosabutate did not significantly decrease either liver fat or body weight. This aspect of icosabutate's therapeutic profile may make it ideally suited for combination therapy in tandem with incretin-based therapies that successfully target body weight and liver fat. Pre-clinical studies have demonstrated the synergistic effects of GLP-1RA and icosabutate on hepatic fibrosis reduction.

Rob de Ree, Chief Executive Officer of NorthSea Therapeutics, said, “We’re very pleased with the overall ICONA dataset. The MASH landscape has changed dramatically since we started the ICONA study. Firstly, the importance of improving fibrosis as the most clinically relevant and therapeutically challenging endpoint has become even more firmly entrenched. Secondly, the potential utility of artificial intelligence driven scoring as both a validated and alternative approach to conventional manual pathology has progressed rapidly. We believe there’s an important place for a safe, well-tolerated, oral anti-fibrotic with add-on benefits on glycemic control, inflammation and atherogenic lipids in the MASH therapeutic landscape, and we look forward to further developing icosabutate in more advanced MASH patients as a monotherapy or as a combination therapy.”

About Phase 2b ICONA Clinical Trial

The Phase 2b ICONA clinical trial was a 52-week randomized, double-blind, placebo-controlled trial that evaluated the safety and histological impact of icosabutate at 300 and 600 mg compared to placebo in 168 biopsy-confirmed MASH patients with moderate-to-severe fibrosis (stage F1, F2 or F3) with NAS ≥4. Patients were randomized to receive 300 mg or 600 mg icosabutate or placebo, taken orally once daily. An end-of-trial biopsy was assessed by 3 pathologists for histological endpoints using a consensus read approach. Liver biopsies were also analyzed using two independent AI-based digital pathology tools (pre-specified).

About NorthSea Therapeutics

NorthSea Therapeutics B.V. is a private, late-stage clinical biotechnology company developing novel strategies to treat metabolic, cholestatic, and fibrotic diseases. Its proprietary structurally engineered fatty acids (SEFAs) are designed to target key disease pathways, offering potential first-in-class treatments. With multiple clinical programs in progress, the company leverages a strong scientific foundation to drive innovation and advance new therapeutic approaches for diseases with serious unmet medical needs. NorthSea's $80M Series C financing was co-led by Ysios Capital and Forbion Growth and supported by venBio, Novo Seeds, Sofinnova, BGV and New Science Ventures. Headquartered in the Netherlands, NorthSea also has a presence in Norway and the U.S. To learn more, visit https://northseatherapeutics.com/en/

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[1]Stokman G, van den Hoek AM, Denker Thorbekk D, et al. Dual targeting of hepatic fibrosis and atherogenesis by icosabutate, an engineered eicosapentaenoic acid derivative. Liver Int. 2020;40(11):2860-76.
[2]Fraser DA, Wang X, Lund J, et al. A structurally engineered fatty acid, icosabutate, suppresses liver inflammation and fibrosis in NASH. J Hepatol. 2022;76(4):800-11.

[3]Iyer JS, Juyal D, Le Q, et al. AI-based automation of enrollment criteria and endpoint assessment in clinical trials in liver diseases. Nat Med. 2024;30(10):2914-23.