# *The New England Journal of Medicine publishes the* results of the NATIVE Phase IIb clinical trial with lanifibranor in NASH

- In the Phase IIb NATIVE, lanifibranor met both the primary and key secondary endpoints, including NASH resolution with no worsening of fibrosis and improvement of liver fibrosis with no worsening of NASH
- NATIVE was the first clinical trial demonstrating an effect on the composite histology endpoint of NASH resolution and improvement of fibrosis
- NATiV3[1], a pivotal phase III trial of lanifibranor in NASH is currently ongoing with first clinical trial sites initiated and patients screened in the United States and if topline results, expected H2 2024, are positive, intent is to seek U.S. accelerated approval and EU conditional approval

**Daix (France), Long Island City (New York, United States), October 20, 2021** – Inventiva (Euronext Paris and Nasdaq: IVA), a clinical-stage biopharmaceutical company focused on the development of oral small molecule therapies for the treatment of non-alcoholic steatohepatitis (NASH), mucopolysaccharidoses (MPS) and other diseases with significant unmet medical needs, today announced the publication of the results from its NATIVE (NAsh Trial to Validate IVA337 Efficacy) Phase IIb clinical trial evaluating lanifibranor for the treatment of NASH in the prestigious, peer-reviewed medical journal *The New England Journal of Medicine (NEJM).*

In the 24-week clinical trial, lanifibranor, an orally-available small molecule and the only pan-PPAR agonist currently in clinical development for the treatment of NASH, at 1200mg/day met the primary endpoint with a statistically significant reduction of the Steatosis Activity Fibrosis score (SAF), which combines assessments of hepatocellular inflammation and ballooning, with no worsening of fibrosis in the Intention To Treat (ITT[2]) and the Per Protocol populations (PP[3]).

Lanifibranor also met key secondary endpoints, including NASH resolution with no worsening of fibrosis[4] and improvement of liver fibrosis with no worsening of NASH[5] in both ITT and PP populations, as well as the composite endpoint of NASH resolution and improvement of liver fibrosis. With these latter results, lanifibranor is the first orally available drug candidate to achieve statistically significant results on the two U.S. Food and Drug Administration (FDA) and European Medicine Agency (EMA) primary endpoints relevant for seeking U.S. accelerated approval and EU conditional approval during Phase III clinical development.

The results of NATIVE were reported in June 2020 in accordance with the study protocol and Statistical Analysis Plan design using a single imputation method of missing data, a conservative method that consider missing end-

[1] For more details, please refer to: clinicaltrial.gov/NCT04849728
[2] ITT: includes all patients randomized in the trial.
[3] PP: includes all patients with paired biopsies and without deviation impacting efficacy assessment.
[4] *NASH resolution* and *no worsening of fibrosis* defined as CRN Lobular inflammation score equal to 0 or 1 and CRN Hepatocyte ballooning score equal to 0 and no worsening of the CRN-Fibrosis score.
[5] *Improvement of liver fibrosis with no worsening of NASH* defined as improvement of CRN-Fibrosis score ≥ 1 stage and no increase of CRN-Steatosis score and no increase of CRN-Inflammation score and no increase of CRN-Ballooning score.

of-study biopsy data as non-responders. The data presented in The New England Journal of Medicine showed additional analyses presented in accordance with the journal requirements using a multiple imputation method of missing end-of-study biopsy data.

The different statistical methods lead to similar results as shown in the table below, confirming the robustness of NATIVE results.

| | | **Primary and main secondary endpoints**<br>**Intention to Treat Population (ITT)** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Single Imputation Method** | | | **Multiple Imputation Method** | | |
| | | **Placebo (N = 81)** | **Lanifibranor** | | **Placebo (N = 81)** | **Lanifibranor** | |
| | | | **800mg (N = 83)** | **1200mg (N = 83)** | | **800mg (N = 83)** | **1200mg (N = 83)** |
| **Primary endpoint** | Decrease of ≥2 points of SAF activity score(1) | 27% | 41% | 49% | 33% | 48% | 55% |
| | Risk Ratio [95%CI](5) | | 1.52 [0.98-2.12] *P=0.061* | 1.82 [1.24-2.40] *P=0.004* | | 1.45 [1.00-2.10] *P=0.073* | 1.69 [1.22-2.34] *P=0.007* |
| **Secondary endpoints** | Resolution of NASH and no worsening of fibrosis (2) | 19% | 33% | 45% | 22% | 39% | 49% |
| | Risk Ratio [95%CI] (5)(6) | | 1.75 [1.02-2.68] *P=0.043* | 2.41 [1.53-3.35] *P<0.001* | | 1.70 [1.07-2.71] *P=0.039* | 2.20 [1.49-3.26] *P<0.001* |
| | Improvement of fibrosis by at least one stage and no worsening of NASH (3) | 24% | 28% | 42% | 29% | 34% | 48% |
| | Risk Ratio [95%CI] (5)(6) | | 1.18 [0.68-1.86] *P=0.530* | 1.80 [1.16-2.51] *P=0.011* | | 1.15 [0.72-1.85] *P=0.561* | 1.68 [1.15-2.46] *P=0.017* |
| | Resolution of NASH and improvement of fibrosis (4) | 7% | 21% | 31% | 9% | 25% | 35% |
| | Risk Ratio [95%CI] (5)(6) | | 2.71 [1.16-5.40] *P=0.017* | 4.25 [2.02-7.37] *P<0.001* | | 2.57 [1.2-5.51] *P=0.018* | 3.95 [2.03-7.66] *P<0.001* |

(1). Response is defined as a decrease from baseline to week 24 of at least 2 points of the SAF Activity score (SAF-A) with no worsening of the CRN Fibrosis score (CRN-F). No worsening means that score remains stable or decreases.
(2). Resolution of NASH with no worsening of fibrosis at week 24: CRN-I = 0 or 1 (CRN-Inflammation), CRN-B = 0 (CRN-Ballooning) and no worsening of CRN-F from baseline.
(3). Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH at week 24: Improvement of CRN-F ≥ 1 stage and no increase of CRN-S, CRN-I or CRN-B.
(4). Resolution of NASH and improvement of fibrosis at week 24: CRN-I = 0 or 1, CRN-B = 0 and an improvement of CRN-F ≥ 1 stage.
(5). Risk ratio was calculated using the Cochran–Mantel–Haenszel method stratified by diabetic status at baseline, and can be interpreted as the ratio of % responders in lanifibranor to % responders in placebo.
(6). As per recommendations of the New England Journal of Medicine, p values were not included on secondary endpoints and will not appear in the publication.

Throughout the Company's NATIVE Phase IIb clinical trial, lanifibranor also showed an overall favorable tolerability profile, consistent with observations from previous clinical studies. The drop-out rates for adverse events were 3.6% in 1200mg, 4.8% in 800mg, and 3.7% in placebo, with the vast majority being mild or moderate in intensity. The rate of severe treatment-emergent adverse events (TEAE) was similar in the three arms (<4%) and two serious TEAEs were assessed as drug-related (mild heart failure; urticaria), both occurring in the placebo group.

The Native phase IIb results contributed in obtaining FDA Breakthrough Therapy designation in NASH in 2020 and allowed Inventiva to start a pivotal phase III trial which is currently ongoing following the activation of first clinical

sites and start of patient screening in the United States in September 2021.. Topline results of this study are expected H2 2024 and, if positive, should allow us to seek U.S. accelerated approval and EU conditional approval.

**Pierre Broqua, Chief Scientist Officer and cofounder of Inventiva, commented:** *"We are delighted to see the results of our NATIVE Phase IIb clinical trial in NASH published in the renowned and influential The New England Journal of Medicine, which reflects the clinical significance and scientific rigor of our lanifibranor development program. Backed by these strong Phase IIb results and following the recent initiation of the Phase III clinical trial, we are convinced that lanifibranor, with its unique characteristics as a pan-PPAR agonist, is ideally positioned in the NASH field and we now look forward to advancing with its pivotal development phase."*

**Prof. Sven Francque, M.D., Ph.D., Antwerp University Hospital and co-principal investigator of the Phase IIb NATIVE clinical trial, said**: "*The publication of the results of the Phase IIb NATIVE in The New England Journal of Medicine is an important scientific accomplishment and represents a milestone for the patients who have committed to this trial and those waiting for a treatment. The Inventiva team and all the investigators, including myself, are deeply grateful for all the patients who have participated to NATIVE and the ones who will be participating in NATiV3. This publication is a major contribution to the field of NASH."*

**Prof. Manal Abdelmalek, M.D., M.P.H., Duke University and co-principal investigator of the Phase IIb NATIVE clinical trial, added:** *"It is important when considering treatment strategy to have a therapeutic available that will target not only NASH but also fibrosis, the primary predictor of mortality in patients with NASH. NATIVE was the first phase IIb to meet the composite histology endpoint of NASH resolution and fibrosis improvement, achieving both* FDA and EMA regulatory endpoints*. While a modest increase in body weight was observed during the trial, patients receiving lanifibranor were metabolically healthy and had better lipids and glycemic profiles which are key for cardiovascular risk reduction in patients at increased risk of cardiovascular disease . The Phase IIb data certainly give us great optimism and enthusiasm for NATiV3, the phase III clinical trial."*

**Jean-Louis Junien, Chairman of Inventiva's Scientific Advisory Board, commented**: *"This article translates the expertise and deep understanding of the Inventiva team of the mechanism of actions of nuclear receptors, and more specifically of PPARs, which associated with their strong experience in biology, chemistry and pharmacology has allowed Inventiva to develop lanifibranor."*

## Publication details

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|---|---|
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## About lanifibranor

Lanifibranor, Inventiva's lead product candidate, is an orally-available small molecule that acts to induce anti-fibrotic, anti-inflammatory and beneficial vascular and metabolic changes in the body by activating all three peroxisome proliferator-activated receptor (PPAR) isoforms, which are well-characterized nuclear receptor proteins that regulate gene expression. Lanifibranor is a PPAR agonist that is designed to target all three PPAR isoforms in a moderately potent manner, with a well-balanced activation of PPARα and PPARδ, and a partial activation of PPARγ. While there are other PPAR agonists that target only one or two PPAR isoforms for activation, lanifibranor is the only pan-PPAR agonist in clinical development. Inventiva believes that lanifibranor's moderate and balanced pan-PPAR binding profile contributes to the favorable tolerability profile that has been observed in clinical trials and pre-clinical studies to date. The FDA has granted Breakthrough Therapy and Fast Track designation to lanifibranor for the treatment of NASH.

## About NASH

Nonalcoholic steatohepatitis (NASH) is a serious liver disease characterized by excessive fat accumulation in the liver, chronic inflammation and tissue injury (hepatitis), resulting in progressive fibrosis that can lead to cirrhosis, and subsequently portal hypertension, liver insufficiency and potential liver cancer. The prevalence of NASH is rapidly increasing globally in parallel with the growing epidemics of obesity and type 2 diabetes; correspondingly, the proportion and number of liver transplants attributable to NASH has expand continuously in past years. To date, there are still no drug therapies approved for the treatment of NASH.

## About the NATIVE Phase IIb trial

The NATIVE (NAsh Trial to Validate IVA337 Efficacy) clinical trial was a 24-week randomized, double-blind, placebo-controlled Phase IIb clinical trial evaluating lanifibranor for the treatment of patients with NASH. The main purpose of the trial was to assess the efficacy of lanifibranor in improving liver inflammation and ballooning, the two histological markers included in the definition of the regulatory endpoint of NASH resolution. To be considered for inclusion, patients were required to have: a diagnosis of NASH confirmed by liver biopsy; a cumulative score of inflammation and ballooning (as measured using the SAF scoring system) of three or four out of four, indicating the presence of moderate to severe inflammation and ballooning; a steatosis score greater than or equal to one, indicating the presence of moderate to severe steatosis; and a fibrosis score less than four, indicating the absence of cirrhosis. The primary endpoint of the trial was a reduction in the combined inflammation and ballooning score of two points compared to baseline, with no worsening fibrosis, as measured by the SAF score. Secondary endpoints included NASH resolution, improvements in each of the steatosis, inflammation, ballooning and fibrosis scores from baseline as measured using the SAF score, improvements in various other fibrosis measures, improvements in several metabolic markers, improvements in steatosis, inflammation and ballooning as measured using the NAS score (NAFLD activity score), and safety.

The trial randomized 247 patients with NASH in 71 sites in Australia, Canada, Europe, Mauritius and the United States.

## About Inventiva

Inventiva is a clinical-stage biopharmaceutical company focused on the development of oral small molecule therapies for the treatment of NASH, MPS and other diseases with significant unmet medical need.

Leveraging its expertise and experience in the domain of compounds targeting nuclear receptors, transcription factors and epigenetic modulation, Inventiva is currently advancing two clinical candidates, as well as a deep pipeline of earlier stage programs.

Lanifibranor, its lead product candidate, is being developed for the treatment of patients with NASH, a common and progressive chronic liver disease for which there are currently no approved therapies. Inventiva recently announced positive topline data from its Phase IIb clinical trial evaluating lanifibranor for the treatment of patients

with NASH and obtained Breakthrough Therapy and Fast Track designation for lanifibranor in the treatment of NASH.

Inventiva is also developing odiparcil, a second clinical stage asset, for the treatment of patients with subtypes of MPS, a group of rare genetic disorders. Inventiva announced positive topline data from its Phase IIa clinical trial evaluating odiparcil for the treatment of adult MPS VI patients at the end of 2019 and received FDA Fast Track designation in MPS VI for odiparcil in October 2020.

In parallel, Inventiva is in the process of selecting an oncology development candidate for its Hippo signalling pathway program. Furthermore, the Company has established a strategic collaboration with AbbVie in the area of autoimmune diseases. AbbVie has started the clinical development of ABBV-157, a drug candidate for the treatment of moderate to severe psoriasis resulting from its collaboration with Inventiva. This collaboration enables Inventiva to receive milestone payments upon the achievement of pre-clinical, clinical, regulatory and commercial milestones, in addition to royalties on any approved products resulting from the collaboration.

The Company has a scientific team of approximately 70 people with deep expertise in the fields of biology, medicinal and computational chemistry, pharmacokinetics and pharmacology, as well as in clinical development. It also owns an extensive library of approximately 240,000 pharmacologically relevant molecules, approximately 60% of which are proprietary, as well as a wholly-owned research and development facility.

Inventiva is a public company listed on compartment C of the regulated market of Euronext Paris (ticker: IVA - ISIN: FR0013233012) and on the Nasdaq Global Market in the United States (ticker: IVA). www.inventivapharma.com

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*generated any revenue from product sales, Inventiva will require additional capital to finance its operations, Inventiva's future success is dependent on the successful clinical development, regulatory approval and subsequent commercialization of current and any future product candidates, preclinical studies or earlier clinical trials are not necessarily predictive of future results and the results of Inventiva's clinical trials may not support Inventiva's product candidate claims, Inventiva may encounter substantial delays in its clinical trials or Inventiva may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities, enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be made more difficult or rendered impossible by multiple factors outside Inventiva's control, Inventiva's product candidates may cause adverse drug reactions or have other properties that could delay or prevent their regulatory approval, or limit their commercial potential, Inventiva faces substantial competition and Inventiva's business, and preclinical studies and clinical development programs and timelines, its financial condition and results of operations could be materially and adversely affected by the current COVID-19 pandemic. Given these risks and uncertainties, no representations are made as to the accuracy or fairness of such forward-looking statements, forecasts and estimates. Furthermore, forward-looking statements, forecasts and estimates only speak as of the date of this press release. Readers are cautioned not to place undue reliance on any of these forward-looking statements.*

*Please refer to the Universal Registration Document for the year ended December 31, 2020 filed with the Autorité des Marchés Financiers on March 15, 2021, the Annual Report on Form 20-F for the year ended December 31, 2020 filed with the Securities and Exchange Commission on March 15, 202, Amendment No. 1 to our Annual Report on Form 20-F for the year ended December 31, 2020 filed with the Securities and Exchange Commission on March 24, 2021, as well as the full-year financial report for the year ended December 31, 2020 for additional information in relation to such factors, risks and uncertainties.*

*Except as required by law, Inventiva has no intention and is under no obligation to update or review the forward-looking statements referred to above. Consequently, Inventiva accepts no liability for any consequences arising from the use of any of the above statements.*