Inventiva announces the publication in *Nature Communications* of additional results from NATIVE Phase IIb clinical trial demonstrating improvement of markers of cardiometabolic health in patients with MASH/NASH treated with lanifibranor

- Improvements were observed for insulin resistance (insulin levels, HOMA-IR), lipid metabolism (triglycerides, HDL-cholesterol, apolipoproteins), control of glycemia (HbA1c, fasting glucose (FG) levels), systemic inflammation (hs-CRP, ferritin), hepatic steatosis and diastolic blood pressure.

- Among the patients who had prediabetes at study entry and were treated with lanifibranor, the majority had fasting glucose levels within the normal range at the end of treatment. No patient treated with lanifibranor with normal glucose levels at study entry progressed to prediabetes during treatment, unlike in the placebo arm.

- Adiponectin levels were increased by lanifibranor while they remained low and unchanged under placebo. Adiponectin increase was correlated with improvement of cardiometabolic health.

- A greater proportion of patients with MASH/NASH and high cardiovascular risk treated with either dose of lanifibranor saw their cardiovascular risk improved to intermediate or low risk compared to patients in the placebo arm.

- Improvements in cardiometabolic health markers were similar regardless of the patients' diabetes and obesity status and regardless of weight change during treatment with lanifibranor.

Daix (France), Long Island City (New York, United States), May 13, 2024 – Inventiva (Euronext Paris and Nasdaq: IVA), a clinical-stage biopharmaceutical company focused on the development of oral small molecule therapies for the treatment of metabolic dysfunction-associated steatohepatitis ("MASH"), also known as non-alcoholic steatohepatitis ("NASH"), and other diseases with significant unmet medical needs, today announced the publication in the peer-reviewed scientific journal *Nature Communications* of additional results from its NATIVE Phase IIb clinical trial demonstrating the improvement of markers of cardiometabolic health in patients with MASH/NASH treated with lanifibranor.

In the NATIVE Phase IIb clinical trial which demonstrated improvement on liver histology following a 24-week period with lanifibranor 800mg and 1200mg daily, including NASH resolution and fibrosis improvement, a broad panel of markers of cardiometabolic health were also measured. Following lanifibranor treatment, the trial demonstrated significant improvement in patients with MASH/NASH with and without Type 2 Diabetes and with or without obesity of markers of insulin resistance (fasting insulin level, HOMA-IR), glycemic control (fasting glucose, HbA1c), lipid metabolism (triglycerides, HDL-C, APO-B, APO-B/APO-A1), adiponectin, systemic inflammation (hs-CRP, ferritin), diastolic blood pressure and hepatic steatosis (histological grading and ultrasound-based (Fibroscan CAP™)) (see table below).

Importantly, lanifibranor treatment also led to lower fasting glucose to normal levels in 71% of patients with MASH/NASH and prediabetes treated with the 1200mg dose and 67% of patients treated with the 800mg dose versus 11% of patients on placebo. In addition, no patients treated with either dose of lanifibranor with MASH/NASH and normoglycemia at baseline progressed to prediabetes at week 24, versus 26% of patients in the placebo arm.

Furthermore, 38% and 44% of patients with MASH/NASH and high cardiovascular risk (based on markers of lipids and inflammation) treated with 1200mg and 800mg of lanifibranor, respectively, improved to intermediate or low cardiovascular risk at week 24, and 44% and 35% of patients at intermediate risk improved to low risk when treated with 1200mg and 800mg of lanifibranor, respectively. However, in the placebo arm, only 26% of patients at high cardiovascular risk improved to intermediate risk and 13% improved from intermediate to low cardiovascular risk.

The weight gain observed in a portion of the patient population treated with lanifibranor was shown to be associated with improvement of all markers of cardiometabolic health, similarly to patients treated with lanifibranor who maintained a stable weight throughout the study. This finding is in contrast to the weight gain observed in patients on placebo, which was associated with a worsening of cardiometabolic markers. These results highlight the critical difference between the weight gain that can be observed with lanifibranor which can be defined as metabolically healthy and is associated with an improvement in insulin resistance, and the weight gain observed in patients under placebo which is metabolically unhealthy and is influenced by lifestyle.

In addition, the increase in adiponectin levels following treatment with 1200mg and 800mg of lanifibranor occurred in 95% and 86% of patients, respectively, versus only in 10% of patients in the placebo arm. The increase in adiponectin level at week 24 was correlated with improvement of markers of insulin resistance, glycemic control, lipid metabolism and steatosis, as well as hs-CRP, aminotransferases and improvement in liver histological endpoints for disease activity and fibrosis.

Michael Cooreman, M.D., Chief Medical Officer at Inventiva, commented: *"Patients with MASH/NASH generally present with poor metabolic health resulting to a large extent from insulin resistance, affecting their glucose and lipid metabolism, causing systemic inflammation and significantly increasing their risk for cardiovascular events. It is key for these patients to target the hepatic manifestations of the disease and also improve their cardiometabolic health. We believe these results from the NATIVE trial demonstrates the potential of lanifibranor to address the broad disease biology of MASH/NASH from insulin resistance to fibrosis. We use this opportunity to express our appreciation and thanks to all patients, investigators and their staff for having made this relevant clinical study possible."*

Prof. Manal Abdelmalek, M.D., M.P.H., Mayo Clinic and co-principal investigator of the NATIVE Phase IIb clinical trial, added: *"This cardiometabolic dataset from the NATIVE Phase IIb clinical trial exemplifies the need for a comprehensive and multidisciplinary management of patients with MASH/NASH and increases our confidence in the potential for lanifibranor as a treatment option for patients with MASH/NASH, who typically have a cardiometabolic profile associated with cardiovascular disease."*

Prof. Sven Francque, M.D., Ph.D., Antwerp University Hospital and co-principal investigator of the Phase IIb NATIVE clinical trial, said: *"This analysis of results from the NATIVE trial on the cardiometabolic health markers adds to the body of evidence for lanifibranor's potential. Furthermore, these new data shed more light on the importance of managing the full-spectrum of MASH/NASH disease."*

***Prof. Arun Sanyal, Director of the Stratvitz-Sanyal Institute for Liver Disease and Metabolic Health and Interim Chair of the Division of Gastroenterology, Hepatology and Nutrition, Virginia commonwealth University, commented**: "This publication highlights the need to treat MASH/NASH more holistically, taking into account the competing threats to life from mainly cardiometabolic and hepatic risks. It is exciting to note that lanifibranor, which is now in advanced Phase III clinical development for the treatment of NASH also significantly improved the cardiometabolic risk profile and insulin sensitivity as central component of the disease process. These compelling data further support the promise of lanifibranor for this patient population."*

Summary of lanifibranor treatment versus placebo on cardiometabolic health markers at Week 24 (n=247 patients)

	Adjusted mean difference versus placebo at EOT (SE)	
	Lani 800mg	**Lani 1200mg**
Insulin Resistance		
Fasting insulin levels (pmol/L)	-83 (16) ***	-79 (17) ***
HOMA-IR[+]	-4.0 (0.9) ***	-4.1 (0.9) ***
Glycemic control		
Fasting glucose (mmol/L)	-1.02 (0.16) ***	-0.84 (0.16) ***
HbA1c (%)	-0.45 (0.07) ***	-0.49 (0.07) ***
Lipid metabolism and apolipoprotein levels		
Tryglycerides (mmol/L)	-0.55 (0.13) ***	-0.50 (0.12) ***
HDL-C (mmol/L)	0.16 (0.03) ***	0.10 (0.03) **
APO-B (mg/dL)	-9.7 (2.9) ***	-9.8 (2.9) ***
APO-B/APO-A1	-0.08 (0.03) **	-0.06 (0.02) *
APO-C3 (ug/mL)	-18 (6) ***	-20 (6) ***
Systemic inflammation		
hs-CRP (mg/L)	-2.2 (0.7) ***	-1.5 (0.7) *
Ferritin (µg/L)	-84 (21) ***	-72 (21) ***
Liver tests		
ALT (U/L)	-25 (5) ***	-23 (5) ***
AST (U/L)	-15 (5) ***	-12 (5) **
GGT (U/L)	-48 (8) ***	-32 (8) ***
Blood pressure		
Diastolic blood pressure (mmHg)	-3.9 (1.5) *	-2.5 (1.5)
Steatosis		
CAP™ (dB/m)	-16 (9) *	-23 (9) *

*p≤0.1 **p≤0.01 ***p≤0.001 versus placebo

[+]Patients treated with sulphonylureas were removed from HOMA-IR related analyses. Resulting from Mixed Model for Repeated Measures (MMRM) models using change from baseline as endpoint, the time, treatment, the diabetic status, the interaction (treatment*time) and the baseline value as fixed effects, a time repeated measure within each subject and an unstructured variance covariance matrix; no adjustment for multiple comparisons was performed.

APO=apolipoprotein, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CAP™=controlled attenuation parameter, EOT=end of treatment, GGT=gamma glutamyl transferase, HbA1c=hemoglobin A1c, HDL=high density lipoprotein, HOMA IR=homeostatic model assessment of insulin resistance, hs CRP=high-sensitivity C-reactive protein, LDL=low density lipoprotein, SE=standard error

Publication details

Publication title:	*"The pan-PPAR agonist lanifibranor improves cardiometabolic health in patients with metabolic dysfunction-associated steatohepatitis"*
Date of publication:	May 10, 2024
Authors:	Michael P. Cooreman, Javed Butler, Robert P. Giugliano, Faiez Zannad, Lucile Dzen, Philippe Huot-Marchand, Martine Baudin, Daniel R. Beard, Jean-Louis Junien, Pierre Broqua, Manal F. Abdelmalek, Sven M. Francque.
Online version:	https://www.nature.com/articles/s41467-024-47919-9

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 for the treatment of MASH/NASH. 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 MASH/NASH.

About the NATIVE Phase IIb trial

The NATIVE Phase IIb (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 MASH/NASH. The primary 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 MASH/NASH resolution. To be considered for inclusion, patients were required to have: a diagnosis of MASH/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 MASH/NASH resolution, improvements in each of the steatosis, inflammation, ballooning and fibrosis scores from baseline and fibrosis stage scoring, improvements in various other fibrosis measures, improvements in several metabolic markers, and safety. The trial randomized 247 patients with MASH/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 research and development of oral small molecule therapies for the treatment of patients with MASH/NASH and other diseases with significant unmet medical need. The Company benefits from a strong expertise and experience in the domain of compounds targeting nuclear receptors, transcription factors and epigenetic modulation. Inventiva is currently advancing one

clinical candidate, has a pipeline of two preclinical programs and continues to explore other development opportunities to add to its pipeline.

Inventiva's lead product candidate, lanifibranor, is currently in a pivotal Phase III clinical trial, NATiV3, for the treatment of adult patients with MASH/NASH, a common and progressive chronic liver disease for which there are currently no approved therapies.

Inventiva's pipeline also includes odiparcil, a drug candidate for the treatment of adult MPS VI patients. As part of Inventiva's decision to focus clinical efforts on the development of lanifibranor, it suspended its clinical efforts relating to odiparcil and is reviewing available options with respect to its potential further development. Inventiva is also in the process of selecting a candidate for its Hippo signaling pathway program.

The Company has a scientific team of approximately 90 people with deep expertise in the fields of biology, medicinal and computational chemistry, pharmacokinetics and pharmacology, and clinical development. It 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 B 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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Important Notice

This press release contains "forward-looking statements" within the meaning of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, included in this press release are forward-looking statements.

These statements include, but are not limited to, forecasts and estimates with respect to Inventiva's pre-clinical programs and clinical trials, including design, duration, timing, recruitment costs, screening and enrollment for those trials, including the ongoing NATiV3 Phase III clinical trial with lanifibranor in MASH/NASH, clinical trial data releases and publications, the information, insights and impacts that may be gathered from clinical trials, the potential therapeutic benefits, including glycemic control (HbA1c), reduction in hepatic steatosis, lipid metabolism (triglycerides, HDL-C, APO-B, APO-B/APO-A1), insulin resistance (HOMA-IR), adiponectin, systemic inflammation (hs-CRP, ferritin) and diastolic blood pressure, of Inventiva's product candidates, including lanifibranor, the impact of lanifibranor on markers of cardiometabolic health and cardiovascular risk, potential regulatory submissions, approvals and commercialization, Inventiva's pipeline and preclinical and clinical development plans, the expected benefit of having received Breakthrough Therapy Designation, including its impact on the development and review timeline of Inventiva's product candidates, the potential development of and regulatory pathway for odiparcil, and future activities, expectations, plans, growth and prospects of Inventiva and its partners. Certain of these statements, forecasts and estimates can be recognized by the use of words such as, without limitation, "believes", "anticipates", "expects", "intends", "plans", "seeks", "estimates", "may", "will", "would", "could", "might",

"should", "designed", "hopefully", "target", "potential", "opportunity", "possible", "aim", and "continue" and similar expressions. Such statements are not historical facts but rather are statements of future expectations and other forward-looking statements that are based on management's beliefs. These statements reflect such views and assumptions prevailing as of the date of the statements and involve known and unknown risks and uncertainties that could cause future results, performance, or future events to differ materially from those expressed or implied in such statements. Actual events are difficult to predict and may depend upon factors that are beyond Inventiva's control. There can be no guarantees with respect to pipeline product candidates that the clinical trial results will be available on their anticipated timeline, that future clinical trials will be initiated as anticipated, that product candidates will receive the necessary regulatory approvals, or that any of the anticipated milestones by Inventiva or its partners will be reached on their expected timeline, or at all. Future results may turn out to be materially different from the anticipated future results, performance or achievements expressed or implied by such statements, forecasts and estimates, due to a number of factors, including that Inventiva cannot provide assurance on the impacts of the Suspected Unexpected Serious Adverse Reaction (SUSAR) on enrollment or the ultimate impact on the results or timing of the NATiV3 trial or regulatory matters with respect thereto, that Inventiva is a clinical-stage company with no approved products and no historical product revenues, Inventiva has incurred significant losses since inception, Inventiva has a limited operating history and has never generated any revenue from product sales, Inventiva will require additional capital to finance its operations, in the absence of which, Inventiva may be required to significantly curtail, delay or discontinue one or more of its research or development programs or be unable to expand its operations or otherwise capitalize on its business opportunities and may be unable to continue as a going concern, Inventiva's ability to obtain financing and to enter into potential transactions, 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 and its partners' clinical trials may not support Inventiva's and its partners' product candidate claims, Inventiva's expectations with respect to its clinical trials may prove to be wrong and regulatory authorities may require holds and/or amendments to Inventiva's clinical trials, Inventiva's expectations with respect to the clinical development plan for lanifibranor for the treatment of MASH/NASH may not be realized and may not support the approval of a New Drug Application, Inventiva and its partners may encounter substantial delays beyond expectations in their clinical trials or fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities, the ability of Inventiva and its partners to recruit and retain patients in clinical studies, 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 and its partners' 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 and its partners' business, and preclinical studies and clinical development programs and timelines, its financial condition and results of operations could be materially and adversely affected by geopolitical events, such as the conflict between Russia and Ukraine and related sanctions, impacts and potential impacts on the initiation, enrollment and completion of Inventiva's and its partners' clinical trials on anticipated timelines and the state of war between Israel and Hamas and the related risk of a larger conflict, health epidemics, and macroeconomic conditions, including global inflation, rising interest rates, uncertain financial markets and disruptions in banking systems. 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, 2023, filed with the Autorité des Marchés Financiers on April 3, 2024, and the Annual Report on Form 20-F for the year ended December 31, 2023, filed with the Securities and Exchange Commission on April 3, 2024. Other risks and uncertainties of which Inventiva is not currently aware may also affect its forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. All information in this press release is as of the date of the release. 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.