

# **Corporate Presentation**

# May 2025



IVA NasdaqListed



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# Management team with extensive global experience across all stages of drug development and commercialization



# Lanifibranor well positioned to become the leading oral therapy for MASH patients with advanced fibrosis, particularly those with Type 2 Diabetes

### **Best in Class Oral Efficacy Data**

Phase 2b demonstrated **18% fibrosis placebo**adjusted improvement at 6 months (42% lanifibranor vs 24% placebo, p=0.01)

Differentiated profile that has been observed to improve cardiovascular, glycemic and metabolic markers and reduce insulin resistance

### **Differentiated pan-PPAR Agonist**

Balanced pan-PPAR agonist activity, once-daily dosing, IP protection through 2040

### **Differentiated Safety & Tolerability Profile**

Differentiated safety profile in the PPAR class

**Non-overlapping AE profile** with incretin agonists, allowing for combination therapy

### **Blinded Phase 3 Data Mimics Phase 2**

Blinded analysis of Phase 3 data show similar improvements in key hepatic and metabolic biomarkers and a stronger effect on fibrosis markers and glycemic biomarkers as the Phase 2b study

A multi-tranche equity financing of \$400M+ secured in October 2024 led by New Enterprise Associates, BVF Partners and Samsara BioCapital capitalized Inventiva to execute on the clinical trial through NDA<sup>(1)</sup>

(1) In October 2024, Inventiva announced a multi-tranche equity financing of up to €348 million, subject to conditions, and up to \$30 million in milestone payments.

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### Lanifibranor: a pan-PPAR agonist with differentiated profile

A new chemical entity: not a fibrate, not a TZD

### Moderate and balanced pan-PPAR agonist activity



- Small molecule that activates all three PPAR isoforms in humans
- Balanced activity across the three human PPAR isoforms
- Differentiated chemical structure: not a fibrate or a TZD
- Once daily oral administration
- FDA confirmation that the non-clinical toxicology package is complete and acceptable for NDA filing
- In 2020, FDA granted lanifibranor breakthrough therapy and fast track designation for the treatment of MASH
- IP protection through 2040

### Pan-PPAR activity likely required for efficacy across MASH disease drivers

METABOLISM	STEATOSIS	INFLAMMATION AND BALLOONING	FIBROSIS	VASCULAR
ΡΡΑRα ΡΡΑRδ ΡΡΑRγ	PPARy	ΡΡΑΖα ΡΡΑΖδ ΡΡΑΖγ	ΡΡΑRδ ΡΡΑRγ	PPARα PPARγ
<ul> <li>Insulin sensitivity</li> <li>HDLc</li> <li>Triglycerides</li> </ul>	<ul> <li>FA uptake</li> <li>FA catabolism</li> <li>Lipogenesis</li> </ul>	<ul> <li>NFkB-dependent gene activation</li> <li>Inflammasome</li> <li>Ballooning</li> </ul>	<ul> <li>Stellate cell</li> <li>proliferation and activation</li> <li>Collagen and fibronectin production</li> </ul>	<ul> <li>Portal pressure</li> <li>LSEC capillarization</li> <li>Intrahepatic vascular resistance</li> </ul>
TZD: Thiazolidinediones Corporate Presentation   May 2025		inventiva		Property of Inventiva

# Balanced PPAR activity with differential binding/target engagement

Lanifibranor did not lead to the adverse events and toxicity previously seen in single/dual PPAR agonists

### Moderate pan-PPAR agonist activity...

Compound	PPARα EC50 (nM)	PPARδ EC50 (nM)	PPARγ EC50 (nM)
Lanifibranor*	1630	850	230
Fenofibrate	2400	-	-
Pioglitazone	-	-	263
Rosiglitazone	-	-	13
Elafibranor**	10	100	-
Seladelpar <sup>^</sup>	-	2	-

### ... that engages PPARy differently



Induces different coactivator recruitment<sup>^^</sup>

# Adverse events and toxicity previously seen in other single and dual PPAR agonists have not been observed with lanifibranor in preclinical studies

Orga	in	Isoforms activated	Reported PPAR side effects	Lanifibranor effects
Ğ	HEART	PPARy	Fluid retention Cardiac hypertrophy	
	SKELETAL MUSCLE	ΡΡΑΖα	Myofiber degeneration	toxicity of single / dual
CP)	KIDNEY	ΡΡΑΖα	> 50% increases in creatinine, degenerative changes in renal tubules	observed in primate
Y	URINARY BLADDER	PPARy	Proliferative changes in bladder epithelium	and rouellt studies

Source: \* Company data \*\* Hanf R et al, Diabetes & Vascular Dis Res 2014 ^ Cymabay company presentation ^^ J Med Chem. 2018 Feb 15. doi: 10.1021/acs.jmedchem.7b01285

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# **Clinicians and industry have recognized the value of PPAR agonists**

Prescriptions and M&A support the potential of this class of drugs

# Physicians continue to prescribe pioglitazone with close to 6M scrips written in 2024 in the U.S.

Pioglitazone U.S. Annual TRx

	2022	2023	2024
ACTOPLUS MET	369	259	225
ACTOPLUS MET XR	1	1	-
ACTOS	1,941	1,340	1,001
AVANDIA	7	1	1
DUETACT	35	16	4
PIOGLIT/GLIMEPIRID	11,361	10,660	9,840
PIOGLIT/METFORMIN	139,794	119,237	106,172
PIOGLITAZONE HCL	6,025,851	5,882,329	5,703,614
TOTAL	6,179,359	6,013,843	5,820,857

Pioglitazone is one of the recommended diabetes pharmacotherapy for patients with MASLD F0 to compensated cirrhosis<sup>(1)</sup>

"It is my opinion that PPAR gamma activation remains most effective in repletion of adiponectin levels and adiponectin is the missing link that connects the health of visceral adipose depot to systemic inflammation."

– Kris Kowdley, Director at Liver Institute Northwest, Washington.

# In 2024, the FDA liver division has approved two PPARs in PBC





Gilead acquires Cymabay for \$4.3B in February 2024



- Cymabay was developing seladelpar, a PPARδagonist in PBC, an orphan chronic liver indication
- At time of Cymabay acquisition, results of the Phase 3 had been published but seladelpar was not yet approved by FDA nor EMA

Source: IQVIA Script Data; KOL Interviews; Inventiva Analysis; (1) 2025 ADA Standard of care

# NATIVE Phase 2b Study of lanifibranor in MASH

# The Phase 2b NATIVE trial published in NEJM

Evaluated 800 and 1200mg, oral, once-daily, 247 patients





Main inclusion criteria: patients with biopsy-proven MASH confirmed by central reader having Steatosis-Activity-Fibrosis (SAF) scores of 1-3 for steatosis, 3-4 for activity, and <4 for fibrosis</p>

Results published in the New England Journal of Medicine<sup>(1)</sup> and additional analysis in Nature Communications<sup>(2)</sup>



A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

nature communications	ම
Article	https://doi.org/10.1038/s41467-024-47919-5
The pan-PPAR agonis	t laninbranor improves

(1) A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH, N Engl J Med 2021;385:1547-1558 (2) The pan-PPAR agonist lanifibranor improves cardiometabolic health in patients with metabolic dysfunction-associated steatohepatitis | Nature Communications



Parameters (unit) n (%) or mean ± SD	Placebo - N = 81	lanifibranor 800 mg/day N = 83	lanifibranor 1200 mg/day N = 83	Overall - N = 247			
Demographics							
Female	41 (51%)	54 (65%)	49 (59%)	144 (58%)			
Age (years)	$53.4 \pm 13.1$	$55.0 \pm 10.4$	$52.2\pm13.8$	$53.6 \pm 12.5$			
White	74 (91%)	80 (96%)	78 (94%)	232 (94%)			
Weight (kg)	$95.1 \pm 17.3$	$91.6 \pm 19.3$	$93.0\pm19.9$	93.2 ± 18.9			
Body Mass Index (kg/m²)	$\textbf{32.8} \pm \textbf{5.1}$	$32.5\pm5.5$	$33.3\pm5.5$	$\textbf{32.9} \pm \textbf{5.4}$			
Type 2 diabetes	35 (43%)	33 (40%)	35 (42%)	103 (42%)			
Liver biopsy characteristics							
SAF Activity score (inflammation + ballooning)	$3.3\pm0.5$	$3.2\pm0.5$	$3.3\pm 0.5$	$3.3\pm0.5$			
NAFLD Activity Score (NAS) ≥6	56 (69.1%)	63 (75.9%)	61 (73.5%)	180 (72.9%)			
Fibrosis stage F2/F3	57 (70.4%)	68 (81.9%)	63 (75.9%)	188 (76.1%)			





Parameters (unit) mean ± SD	Placebo - N = 81	lanifibranor 800 mg/day N = 83	lanifibranor 1200 mg/day N = 83
Liver enzymes			
Alanine aminotransferase, ALT (UI/L)	$56.9 \pm 31.6$	$64.1\pm41.4$	$63.6\pm43.4$
Aspartate aminotransferase, AST (UI/L)	$43.3\pm24.1$	$53.9 \pm 43.4$	$43.9\pm24.8$
Gamma glutamyl transferase, GGT (UI/L)	$67.9 \pm 80.4$	$101.6 \pm 146.1$	67.1 ± 93.1
Plasma lipid levels			
HDL-Cholesterol (mmol/L)	$1.2\pm0.3$	$1.3\pm0.3$	$1.2\pm0.3$
Triglycerides (mmol/L)	$2.0\pm0.8$	$1.9\pm0.9$	$2.0\pm0.9$
Glucose metabolism for patients with T2D (n= 103)			
Fasting Glucose (mmol/L)	$6.9 \pm 2.0$	$7.3\pm2.2$	6.6 ±1.2
HbA1c (%)	$6.5 \pm 0.7$	$6.7 \pm 0.8$	$6.6\pm0.7$
Insulin (pmol/L)	$222.7 \pm 186.5$	$246.3 \pm 213.4$	$278.5 \pm 233.5$

# Resolution of MASH and fibrosis improvement ≥ least 1 stage

Compares favourably to other oral and injectable compounds





#### No head-to-head clinical trials have been conducted; results obtained from different trials, with different designs, endpoints and patient populations. Results may not be comparable.

\*Effect size was 26% in the 1200 mg arm in patients with T2D \*\*Resmetirom has been approved under accelerated approval by the FDA.

Source: lanifibranor native results; Efruxifermin Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, Phase IIb trial. Lancet Gastroenterology October 2023 ; Semaglutide Phase III ESSENCE trial of semaglutide 2.4mg in participants with non-cirrhotic non-alcoholic steatohepatitis; Newsome et al.; Resmetirom MAESTRO MASH top-line results webcast Dec. 19 2022, pg 10 and EASL 2023 presentation pg. 8; Efruxifermin EASL 2023 presentation pg. 8, corporate presentation of March 2024 pg 22; Survodutide A Phase II randomized trial for Survodutide in MASH and fibrosis, The NEJM DOI: 10.1056/NEJMoa2401755; Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis, The NEJM DOI: 10.1056/NEJMoa2401943

## Fibrosis improvement ≥1 stage with no worsening of MASH

Compares favourably to other oral and injectable compounds





No head-to-head clinical trials have been conducted; results obtained from different trials, with different designs, endpoints and patient populations. Results may not be comparable.

\* Resmetirom has been approved under accelerated approval by the FDA.

Source: lanifibranor native results;; resmetirom MAESTRO NASH top-line results webcast Dec. 19 2022, pg 10; resmetirom : Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6 Efruxifermin Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, Phase IIb trial. Lancet Gastroenterology October 2023; corporate presentation of March 2024 pg 15; Semaglutide Phase III ESSENCE trial of semaglutide 2.4mg in participants with non-cirrhotic non-alcoholic steatohepatitis; Newsome et al.; Pegozafermin, 89Bio Phase IIb ENLIVEN Topline Results presentation; Survodutide A Phase II randomized trial for Survodutide in MASH and fibrosis, The NEJM DOI: 10.1056/NEJMoa2401755 ; Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis, The NEJM DOI: 10.1056/NEJMoa2401943

# MASH resolution with no worsening of fibrosis

Compares favourably to other oral and injectable compounds





No head-to-head clinical trials have been conducted; results obtained from different trials, with different designs, endpoints and patient populations. Results may not be comparable.

\* Resmetirom has been approved under accelerated approval by the FDA.

Source: lanifibranor native results;; resmetirom MAESTRO NASH top-line results webcast Dec. 19 2022, pg 10; resmetirom : Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6 Efruxifermin Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, Phase IIb trial. Lancet Gastroenterology October 2023; corporate presentation of March 2024 pg 15; Semaglutide Phase III ESSENCE trial of semaglutide 2.4mg in participants with non-cirrhotic non-alcoholic steatohepatitis; Newsome et al.; Pegozafermin, 89Bio Phase IIb ENLIVEN Topline Results presentation; Survodutide A Phase II randomized trial for Survodutide in MASH and fibrosis, The NEJM DOI: 10.1056/NEJMoa2401755 ; Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with liver Fibrosis, The NEJM DOI: 10.1056/NEJMoa2401943

# **Reduction in Steatosis measured by MRI-PDFF**

Compares favourably to other oral and injectable compounds



No head-to-head clinical trials have been conducted; results obtained from different trials, with different designs, endpoints and patient populations. Results may not be comparable.

\* Resmetirom has been approved under accelerated approval by the FDA

\*\* Results reported among completers

\*\*\*Reductions reported only for subset of patients with liver fat content ≥10 at baseline

Efruxifermin – Akero's Phase IIb Harmony Study Results presentation (sept. 2022), Pegozafermin - 89Bio' Corporate Presentation (May 2023); Resmetirom – Madrigal's corporate presentation (May 2023); Semaglutide - Flint A, Andersen G, Hockings P, Johansson L, Morsing A, Sundby Palle M, Vogl T, Loomba R, Plum-Mörschel L. Randomised clinical trial: semaglutide versus placebo reduced liver statosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. Aliment Pharmacol Ther. 2021 Nov;54(9):1150-1161. doi: 10.1111/apt.16608. Epub 2021 Sep 27. PMID: 34570916; PMCID: PMC9292692; Survodutide A Phase II randomized trial for Survodutide in MASH and fibrosis, The NEJM DOI: 10.1056/NEJMoa2401755 ; Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis, The NEJM DOI: 10.1056/NEJMoa2401943

# Statistically significant decrease in liver enzymes

Liver biomarkers show rapid and sustained improvement



### Other secondary endpoints in ITT (N = 247)



Improvements in HDL-cholesterol & triglycerides without a change in LDL-cholesterol



W24

### Other secondary endpoints in ITT (N = 247)

#### \* p<0.01 \*\*p<0.001



### Absolute change from baseline in HDL-C

### Absolute change from baseline in triglycerides

\*\*

W14



No change in LDL-cholesterol

cholesterol

# **Clear benefit in MASH patients with T2D, across multiple studies**

Significant reductions in HbA1c and fasting glucose



### Secondary endpoints in patients with NASH/MASH and T2D (N = 103)



SECONDARY ENDPOINTS

# Significant improvements in hepatic and muscular insulin sensitivity<sup>(1)</sup>

Strong benefit has been observed across multiple studies



(1) Data from the clinical study conducted by Dr. Kenneth Cusi from the University of Florida, evaluating lanifibranor (800mg/day) in patients with NAFLD and type 2 diabetes mellitus (T2D) for 24 weeks

Increasing use of biomarkers to measure MASH/fibrosis in clinical practice

Data from Phase 2b NATIVE clinical trial evaluating lanifibranor (800mg/day and 1200mg/day) in patients with MASH for 24 weeks

	Median relative change (%)     Placebo		lanifibranor (Two doses pooled)	Pvalue	
		Pro-C3	(4.1%)	(13.9%)	p= 0.005*
012006	Fibrosis	Pro-C3 >14 at baseline <sup>(1)</sup>	(12.8%)	(20.5%)	p= 0.017*
		Ratio TIMP-1/MMP-2	(4.6%)	(22.5%)	p < 0.001*
00100	Apoptosis	CK18-M30	0.5%	(41.1%)	p < 0.001*
VIIIIO	lufference (fere	Ferritin	(9.1%)	(29.4%)	p < 0.001*
	Inflammation	hs-CRP	13.0%	(35.5%)	p < 0.001*

(1) Level where it is estimated that fibrogenesis is active and corresponding to F2/F3 patients

FAS (Full Analysis Set) population with available data at baseline and at week 24

\* Statistically significant

NATIVE



N (%) patients reporting Adverse Event (AE)	Placebo (N = 81)	800 mg (N = 83)	1200 mg (N = 83)
Any Treatment-Emergent AE (TEAE)	50 (61.7%)	59 (71.1%)	62 (74.7%)
Drug-related TEAE	19 (23.5%)	25 (30.1%)	23 (27.7%)
Any TEAE leading to drug withdrawal	3 (3.7%)	4 (4.8%)	3 (3.6%)
Drug-related TEAE leading to drug withdrawal	2 (2.5%)	1 (1.2%) <sup>(1)</sup>	2 (2.4%) <sup>(2)</sup>
Any Serious TEAE	3 (3.7%)	3 (3.6%)	Focus of next slide 7 (8.4%)
Drug-related Serious TEAE	2 (2.5%) <sup>(3)</sup>		

(1) One patient with moderate diarrhea; (2) One patient with mild cardiac failure; one patient with mild diarrhea, abdominal pain, dizziness; (3) 2 SUSARs in the placebo arm: one patient with mild cardiac failure; one patient with moderate urticaria

Consistent with known insulin sensitizing pharmacology, a mean weight increase from baseline of 2.4 kg (2.6%) at the 800 mg/day dose and 2.7 kg (3.1%) at the 1200 mg/day dose was observed.

	Placebo (N = 81)	800 mg (N = 83)	1200 mg (N = 81)
Peripheral edema	2 (2.5%)	5 (6.0%)	7* (8.4%)
Drug-related peripheral edema	-	2 (2.4%)	2 (2.4%)

Peripheral edema (bilateral ankle edema): usually mild, in most cases no treatment was required, a few patients received diuretics. 4 cases were considered study drug related by the investigator (2 at 800 and 1200 mg each). One case of severe intensity, which resolved by stopping treatment (lanifibranor 1200mg) for 12 days, without reoccurrence when the study treatment was resumed. All were female patients.

# A limited number of serious TEAEs occurred



Patients reporting treatment-emergent Serious AE (SAE); N (%)	Placebo (N = 81)	800 mg (N = 83)	1200 mg (N = 83)		
Total	3 (3.7%)	3 (3.6%)	7 (8.4%)		
Treatment-Emergent Serious AE linked to biopsy procedure					
Post-procedural haematoma/haemorrhage	-	1 (1.2%)	1 (1.2%)		
Post-procedural pain	-	-	1 (1.2%)		
Pneumobilia (post-procedural)	-	-	1 (1.2%)		
Other Treatment-Emergent Serious AE					
Wrist fracture	1 (1.2%)	-	-		
Angina unstable	-	-	1 (1.2%)		
Cardiac failure	1 (1.2%)	-	-		
Gastroenteritis	-	-	1 (1.2%)		
Pyelonephritis	-	-	1 (1.2%)		
Pancreatitis	-	1 (1.2%)	-		
Undifferentiated connective tissue disease	-	1 (1.2%)	-		
Urticaria	1 (1.2%)	-	-		
Foot operation	-	-	1 (1.2%)		
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# Weight changes at end of treatment (week 24) in patients treated with lanifibranor versus placebo



Source: MP. Cooreman, Lanifibranor improves markers of cardio-metabolic health in NASH patients independent of weight change – EASL 2022

# Weight gain comes with improvements in metabolic, cardiometabolic, or liver markers (I/II)



Source: MP. Cooreman, Lanifibranor improves markers of cardio-metabolic health in NASH patients independent of weight change – EASL 2022

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NATIV

# Weight gain comes with improvements in metabolic, cardiometabolic, or liver markers (II/II)



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NATI

# Lanifibranor alone and in combination with empagliflozin leads to a shift towards metabolically healthy adipose tissue



#### Ratio VAT/SAT, N=23

LS Mean Relative change (%) from Baseline to Week 24



SAT=Subcutaneous Adipose Tissue, VAT=Visceral Adipose Tissue \* p=0.08, \*\*p<0.05, versus placebo (ANCOVA)

Sixteen patients were not considered in the FAS because of no VAT/SAT values available at Week 24:

- 5 patients under placebo and 1 patient under lani+empa who prematurely stopped before Week 24

- 2 patients under placebo / 3 patients under lanifibranor / 5 patients under lani+empa with missing values at Week 24

## Lanifibranor has a differentiated weight gain profile relative to pioglitazone

Weight gain plateaus with lanifibranor after 24-36 weeks



In the interim blinded data of the main cohort from NATiV3, lanifibranor shows a distinct plateau after week 24-36, consistent with prior data



- In PIVENS study, a 96-week randomized trial of pioglitazone vs vitamin E in nondiabetic adults with MASH, mean weight increased 4.7kg
- Continuous weight gain seen over the full 96 weeks

While not conclusive, data suggests that lanifibranor weight gain stops after 24-36 weeks

*"If you can get PPAR activation without the liabilities it could be a best-in-class drug" – Kris Kowdley* 

Source: Tan MH et al. Diabetes Care 28:544 – 550, 2005; KOL Interviews; Inventiva Analysis.

# SGLT2 inhibitor empagliflozin mitigates lanifibranor weight gain

Meta-analysis data suggest that GLP-1s have a similar effect when combined with PPARs



In the LEGEND trial, albeit with a small n, results suggested that empagliflozin, an SGLT2i, completely mitigated the lanifibranor weight gain profile over 24 weeks



Recently published meta-analyses suggested that pioglitazone with GLP1 or SGLT2i is associated with increased weight loss and reduced risk of heart failure compared with monotherapy

Source: Anson. 2024. Diabetes, Obesity, and Metabolism; KOL Interviews; Inventiva Analysis.

# LEGEND Study of lanifibranor in Combination with SGLT2 inhibitor



Strong mechanistic rationale for combination of lanifibranor with an SGLT2 inhibitor agent

Lanifibranor in Combination with the SGLT2 Inhibitor empagliflozin in patients with MASH and Type 2 Diabetes LEGEND Trial

- Clinical data suggest that lanifibranor improves insulin sensitivity, lipid and glucose metabolism, inflammation, liver tissue injury (MASH activity) and fibrosis.
- Empagliflozin improves glycaemia, insulin sensitivity, has weight reducing and diuretic effects.
- The combination of lanifibranor + empagliflozin may
  - Add additional metabolic benefits
  - Address metabolically healthy weight gain observed in some patients on lanifibranor





Parameters (unit) n (%) or mean ± SD	Lanifibranor 800 mg N=12	Lanifibranor + Empagliflozin N=13	Placebo N=14	Total N=39		
Disposition						
24-week completed	12 (100%)	12 (92%)	9 (64%)	33 (85%)		
Prematurely discontinued	0 (0%)	1 (8%)	5 (36%)	6 (15%)		
Demographics						
Female	6 (50%)	8 (62%)	7 (50%)	21 (54%)		
Age (years)	55.1 ± 11.4	$54.2 \pm 13.5$	$54.7 \pm 13.0$	$54.6 \pm 12.4$		
White	10 (91%)	10 (77%)	9 (69%)	29 (78%)		
Weight (kg)	$93.3 \pm 11.6$	$103.3\pm12.4$	$94.5\pm21.3$	$97.1 \pm 16.2$		
Body Mass Index (kg/m²)	$33.3\pm2.3$	$\textbf{37.6} \pm \textbf{4.3}$	$34.5 \pm 5.4$	$35.2 \pm 4.6$		
MASH diagnosis						
Based on LiverMultiScan® (cT1 >= 875 ms or cT1 >= 825 ms and MRI-PDFF≥ 10%)	12 (100%)	12 (92%)	13 (93%)	37 (95%)		





Parameters (unit) mean ± SD	Lanifibranor 800 mg N=12	Lanifibranor + Empagliflozin N=13	Placebo N=14	Total N=39		
Liver enzymes						
Alanine aminotransferase, ALT (UI/L)	$54.0\pm36.9$	$54.8\pm40.5$	$\textbf{38.9} \pm \textbf{22.2}$	$48.8\pm33.7$		
Aspartate aminotransferase, AST (UI/L)	$37.3 \pm 24.8$	$35.2\pm20.5$	$31.1 \pm 15.6$	$34.4\pm20.0$		
Gamma glutamyl transferase, GGT (UI/L)	$44.9\pm26.4$	$54.9\pm31.0$	$63.3 \pm 66.1$	$54.8 \pm 45.4$		
Plasma lipid levels						
HDL-Cholesterol (mmol/L)	$1.1 \pm 0.3$	$1.1\pm0.3$	$1.1\pm0.3$	1.1 ± 0.3		
Triglycerides (mmol/L)	$3.0\pm2.6$	$2.0\pm0.9$	$2.2\pm1.3$	$\textbf{2.4} \pm \textbf{1.7}$		
Glucose metabolism for patients with T2D (n= 103)						
Fasting Glucose (mmol/L)	$8.8\pm2.7$	$8.7 \pm 1.7$	$9.5\pm5.0$	$9.0\pm3.4$		
HbA1c (%)	8.0 ± 1.1	$8.2\pm1.0$	$8.1 \pm 1.2$	8.1 ± 1.1		
Insulin (pmol/L)	$174.0\pm86.3$	$285.2\pm175.4$	$280.6\pm169.0$	$249.3 \pm 155.7$		

Statistically significant reduction in HbA1c with lanifibranor alone and in combination



### HbA1c (%) – FAS N=37

LS Mean Absolute Change from Baseline to Week 24

# 7



<sup>\*</sup>p<0.05, \*\*p<0.01, \*\*\*p<0.001, versus placebo (Mixed Model Repeated Measure [MMRM])

Two patients were not considered in the FAS because not having post-treatment values available:

- 1 patient under placebo who prematurely stopped before Week 4
- 1 patient under lanifibranor who received 'Metformin' as a rescue medication (intercurrent event) before Week 4 (Results were similar including this patient in a sensitivity analysis).

### HbA1c < 6.5% Completers, N=30

HbA1c absolute decrease ≥1% Completers, N=30



Percentage of responders at Week 24

Nine patients were not considered in the Completers set:

- 5 patients under placebo who prematurely stopped before Week 24
- 1 patient under lanifibranor who received 'Metformin' as a rescue medication (intercurrent event) before Week 4
- 1 patient under lani+empa who prematurely stopped before Week 24,1 patient with missing data at Week 24, and 1 patient under lani+empa who significantly modified his/her diet (intercurrent event) before Week 24

# Insulin sensitivity was improved, consistent with other studies

Additional improvement was observed in combination with empagliflozin

# LEGEND

### Insulin – FAS N=37

#### LS Mean Relative change (%) from Baseline to Week 24



<sup>\*</sup>p<0.1, \*\*p<0.05, versus placebo (MMRM)

Two patients were not considered in the FAS because not having post-treatment values available:

- 1 patient under placebo who prematurely stopped before Week 4
- 1 patient under lanifibranor who received 'Metformin' as a rescue medication (intercurrent event) before Week 4

### HOMA-IR – FAS N=37

### LS Mean Relative change (%) from Baseline to Week 24



\*p<0.1, \*\*p<0.05, versus placebo (MMRM)

Two patients were not considered in the FAS because not having post-treatment values available:

- 1 patient under placebo who prematurely stopped before Week 4
- 1 patient under lanifibranor who received 'Metformin' as a rescue medication (intercurrent event) before Week 4

# Markers of liver injury were significantly improved

Improvement was solely driven by lanifibranor; empagliflozin did not add any additional benefit

ALT – FAS N=38

LS Mean Relative change (%) from Baseline to Week 24



\*p<0.05, \*\*p<0.01, \*\*\*p<0.001, versus placebo (MMRM)

One patient under placebo was not considered in the FAS because no post-treatment values available (Premature discontinuation before Week 4)

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001, versus placebo (MMRM)

One patient under placebo was not considered in the FAS because no post-treatment values available (Premature discontinuation before Week 4)

AST – FAS N=38

#### LS Mean Relative change (%) from Baseline to Week 24



\*\*\*

Improvement was observed with lanifibranor alone and in combination with empagliflozin

### Liver fat measured by MRI-PDFF, N=32 from Baseline at Week 24



LS Mean Relative change (%)

20 -20 -40 -60 Placebo Lani -80 Lani + Empa -100 Lanifibranor + Percentage of responders Lanifibranor Placebo (n=9) empagliflozin at Week 24

0%

11%

(n=12)

83%

67%

Individual Relative changes (%)

\*p<0.05, \*\*p<0.01 versus placebo (ANCOVA – Analysis of Covariance) Seven patients were not considered in the FAS because no MRI-PDFF values available at Week 24:

- 5 patients under placebo who prematurely stopped before Week 24
- 1 patient under lani+empa who prematurely stopped before Week 24, and 1 patient under lani+empa who significantly modified his/her diet (intercurrent event) before Week 24

Relative reduction  $\geq 30\%$ 

Absolute reduction of  $\geq$  5%

(n=11)

64%

64%

### Markers of inflammation and fibrosis measured by cT1 were improved LEGEND

100

Improvement were similar with lanifibranor alone or in combination with empagliflozin

#### Changes in Inflammation and Fibrosis measured by cT1, N=31 LS Mean Absolute change (ms) from Baseline to Week 24

### cT1 Absolute Reduction of >80 ms Percentage of responders at Week 24





n=12

n= 8

Eight patients were not considered in the FAS because of no cT1 values available at Week 24:

5 patients under placebo who prematurely stopped before Week 24 and 1 patient under placebo with a missing value at Week 24

1 patient under lani+empa who prematurely stopped before Week 24, and 1 patient under lani+empa who significantly modified his/her diet (intercurrent event) before Week 24

n= 11

Improvement were similar with lanifibranor alone or in combination with empagliflozin



### HDL-C, N=38 LS Mean Relative change (%) from Baseline to Week 24



\*p<0.10, versus placebo (MMRM) + p<0.01, versus baseline (MMRM)

One patient under placebo was not considered in the FAS because of no post-treatment HDL-C values available (premature discontinuation before Week 4)

### Adiponectin, N=37 LS Mean Fold change from Baseline to Week 24



\*\*p<0.01, versus placebo (MMRM)

Two patients were not considered in the FAS because not having post-treatment adiponectin values available:

- 1 patient under placebo who prematurely stopped before Week 4

1 patient under lanifibranor who received 'Metformin' as rescue medication (intercurrent event) before Week 4

# SGLT2 inhibitor empagliflozin mitigates lanifibranor weight gain

Meta-analysis data suggest that GLP-1s have a similar effect when combined with PPARs



In the LEGEND trial, albeit with a small n, results suggested that empagliflozin, an SGLT2i, completely mitigated the lanifibranor weight gain profile over 24 weeks



Recently published meta-analyses suggested that pioglitazone with GLP1 or SGLT2i is associated with increased weight loss and reduced risk of heart failure compared with monotherapy

Source: Anson. 2024. Diabetes, Obesity, and Metabolism; KOL Interviews; Inventiva Analysis.

# Lanifibranor alone and in combination with empagliflozin leads to a shift towards metabolically healthy adipose tissue



#### Ratio VAT/SAT, N=23

LS Mean Relative change (%) from Baseline to Week 24



SAT=Subcutaneous Adipose Tissue, VAT=Visceral Adipose Tissue \* p=0.08, \*\*p<0.05, versus placebo (ANCOVA)

Sixteen patients were not considered in the FAS because of no VAT/SAT values available at Week 24:

- 5 patients under placebo and 1 patient under lani+empa who prematurely stopped before Week 24

- 2 patients under placebo / 3 patients under lanifibranor / 5 patients under lani+empa with missing values at Week 24

# Lanifibranor for the Treatment of MASH

## MASH with advanced fibrosis represents a high unmet medical need

Patients with MASH and type 2 diabetes are at higher risk



### Despite Rezdiffra approval, treatment needs still exist for patients with advanced fibrosis...

- ▶ Rezdiffra<sup>TM</sup> 's published rates of fibrosis improvement are indirect and at best modest with 12% effect size
- ► Rezdiffra<sup>TM</sup> has no impact on glycemic parameters
- ▶ Rezdiffra<sup>TM</sup> does not appear to synergize with incretins, where use is growing in obesity
- Pipeline agents targeting FGF21 are injectable and have an unfavorable GI AE profile
- MASH patients need more than one oral option available to them

Source: Estes. 2018. Hepatology; Sanyal. EASL. 2024; Lomanoco Diabetes Care 2021;44(2):399–406; Angulo P, et al. Gastroenterology. 2015;149:389-397. 2. Loomba R, Adams L. Hepatology. 2019;70(6):1885-1888; Noureddin et al. AASLD 2024; KOL Interviews; Inventiva Analysis.

NAFLD: Nonalcoholic fatty liver disease; MASH: Metabolic dysfunction-associated steatohepatitis

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# Lanifibranor is well-positioned in the MASH market

Multiple competitive advantages vs. other therapies

	inventiva	Madrigal MIKING	ak≡ro 89bio	Boehringer Ingelheim
	pan-PPAR	THR-β	FGF-21	GLP-1
Route of administration	Oral	Oral	Injectable	Injectable
Fibrosis improvement	Direct activity seen at 6 months	Indirect seen after 12 months	Direct activity seen at 6 months	Indirect seen with sema. after 18 month. Reported by BI & Lilly after 12 months
MASH resolution	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$
Insulin resistance	$\checkmark$	X	$\checkmark$	$\checkmark$
Tolerability	Limited dropout Limited GI side effects	Limited dropout GI side effects on initiation	High dropout due to GI side-effects & injections	High dropout due to GI side-effects & injections

### Lanifibranor

Data suggests fibrosis improvement, MASH resolution and cardiometabolic benefits

Balanced pan-PPAR agonists have a favorable insulin sensitivity profile, manageable AEs and oral route of administration making them a promising candidate for patients with advanced fibrosis and/or for combination therapy, particularly in patients with comorbid T2D

# Lanifibranor could play a key role in several high unmet need segments in MASH

Priority patient segment based on KOL feedback at time of lanifibranor launch



### Lanifibranor: well positioned in MASH, especially in patients with T2D

Based on patient type, can be used as a monotherapy or in combination with anti-diabetic agents

### **Lanifibranor Profile**

Improvements observed in Fibrosis, CV, and Metabolic Markers	<ul> <li>Superior fibrosis improvement to Rezdiffra<sup>TM*</sup></li> <li>Oral dosing differentiates from FGF21 and incretin agents</li> <li>Sustained improvements in hepatic, CV, and glycaemic biomarkers</li> <li>Synergy with SGLTs agents</li> </ul>	Comprehensive impact on MASH and associated cardiometabolic morbidities
Balanced Safety Profile Without GLP-1 overlapping AEs	<ul> <li>Manageable safety and tolerability issues and no carry-over of AEs and toxicity associated with single and dual PPAR agonists</li> <li>Weight gain is limited to one-third of patients with lanifibranor, plateaus after 6-8 months, and did not impact efficacy or metabolic parameters</li> <li>Limited overlap of AEs associated with GLP-1s</li> </ul>	<i>Clinical results suggest a positive risk-benefit profile</i>
Top-Line Results targeted H2 2026	<ul> <li>\$375M multi-tranche financing from existing and new investors in 2024 marks the largest financing of a French biotech and will fully fund Inventiva through NATiV3 TLR if all tranches close</li> <li>Phase 3 fully enrolled in H1 2025 and Top-Line Data in H2 2026</li> </ul>	Lanifibranor could be the second liver- directed therapy approved for MASH

\*Not a head to head comparison

Source: KOL Interviews; Inventiva Analysis.

# NATiV3 Phase 3 Study of lanifibranor in MASH

# **NATiV3 fully recruited**

### Trial design mirrors the successful Phase 2b study





- Primary endpoint: Composite endpoint of patients having both MASH resolution and one stage fibrosis improvement
- Key secondary endpoints: MASH resolution and no worsening of fibrosis, Fibrosis improvement and no worsening of MASH
- **GLP1**: Patients under a stable dose of GLP1-RA for at least 3 months prior to screening can be included
- Statistical powering: 90% considered for sample size calculations
- Stratification by fibrosis stage and diabetic status
- NATiV3 fully recruited with 1009 patients in the main cohort and 410 in the exploratory cohort
- In a blinded analysis conducted comparing Phase 2b and NATiV3, baseline values and magnitude of changes in relevant biomarkers are consistent

# **Baseline characteristics of NATiV3 versus NATIVE Phase 2b are aligned** with expectations

		Exploratory N=261	Main N=798	Randomized N=1059	NATIVE N=247
Actual	N	259	795	1054	247
Diabetic status	No	152 (59%)	355 (45%)	507 (48%)	144 (58%)
(eCRF)	Yes	107 (41%)	440 (55%)	547 (52%)	103 (42%)
Actual	N	260	798	1058	-
Fibrosis stage (Perspectum)	1-3	190 (73%)	7 (1%)	197 (19%)	F0: 6 (2%) F1: 53 (22%)
	2	1 (0%)	243 (30%)	244 (23%)	102 (41%)
	3	1 (0%)	547 (69%)	548 (52%)	86 (35%)
	4	68 (26%)	1 (0%)	69 (7%)	0 (0%)
GLP-1	N	261	798	1059	-
concomitant to	No	228 (87%)	692 (87%)	920 (87%)	-
Baseline	Yes	33 (13%)	106 (13%)	139 (13%)	-
GLP-1	N	261	798	1059	-
post Baseline	No	252 (97%)	742 (93%)	994 (94%)	-
	Yes	9 (3%)	56 (7%)	65 (6%)	-
SGLT2i	N	261	798	1059	247
concomitant to Baseline	No	233 (89%)	725 (91%)	958 (90%)	240 (97%)
	Yes	28 (11%)	73 (9%)	101 (10%)	7 (3%)
SGLT2i	N	261	798	1059	-
post Baseline	No	259 (99%)	781 (98%)	1040 (98%)	-
	Yes	2 (1%)	17 (2%)	19 (2%)	_

### Status September 10, 2024

		Exploratory N=261	Main N=798	Randomized N=1059	NATIVE N=247
Weight (kg)	N	261	798	1059	247
	Mean ± SD	94.9 ± 21.3	98.7 ± 23.6	97.8 ± 23.1	93.3 ± 18.8
	Median	95	96	95	92
	Min; Max	44; 163	46; 249	44; 249	50; 147
BMI (kg/m2)	N	260	798	1058	247
	Mean ± SD	34.2 ± 7.0	35.3 ± 7.0	35.0 ± 7.0	32.9 ± 5.4
	Median	33	34	34	32
	Min; Max	20; 64	21; 77	20; 77	21; 45
BMI class	Non obese	65 (25%)	175 (22%)	240 (23%)	86 (35%)
	Obese	195 (75%)	623 (78%)	818 (77%)	161 (65%)

- Higher percentage of patients with T2D in the Phase 3 versus the Phase 2b: 55% vs 42%. The effect size of lanifibranor in the Phase 2b on the primary efficacy endpoint of NATiV3 (MASH resolution and fibrosis improvement) was higher in patients with T2D: 21% and 26% for lanifibranor 800 and 1200 mg/day in patients with T2D versus 7% and 22% in patients who did not have diabetes
- NATiV3 expected to generate data of lanifibranor in combination with GLP1 and with SGLT2 inhibitors
- Blinded analyses of Phase 3 data suggest preliminary biomarkers in line with Phase 2b NATIVE study results

## NATiV3 data expected in H2 2026

Lanifibranor could be the second oral liver-directed agent for the treatment of MASH if approved

### **Targeted timeline for anticipated catalysts**



Financing	Targeted Timeline to Potential Launch
A \$400M+ Financing in October 2024 capitalized Inventiva to execute on the clinical trial through to NDA <sup>1</sup>	Lanifibranor could be the second oral, liver- targeted agent on the market in 2028 if NDA is filed and approved. Best-in-class fibrosis, cardiovascular, and metabolic benefits.

(1) In October 2024, Inventiva announced a multi-tranche equity financing of up to €348 million, subject to conditions, and up to \$30 million in milestone payments \* Announced on April 2, 2025

Corporate Presentation | May 2025

### Contacts

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