Lanifibranor in Nonalcoholic Steatohepatitis (NASH)

NATIVE Phase IIb Topline Results

June 16, 2020

IVA LISTED EURONEXT

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Today’s speakers

Frédéric Cren, MA/MBA, Chairman, CEO and cofounder

Pierre Broqua, Ph.D., CSO and cofounder

Marie-Paule Richard, MD, CMO

Prof. Sven Francque, MD

University Hospital Antwerp, Principal Investigator of NATIVE trial

Prof. Manal Abdelmalek, MD

Division of Gastroenterology and Hepatology at Duke University, Principal Investigator of NATIVE trial

Highlights of topline results

- **Lanifibranor (1,200 mg) met the primary endpoint** with a statistically significant reduction **after 6 months of treatment** 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)[1] and Per Protocol (PP)[2] populations

- **Lanifibranor also met key secondary endpoints** including NASH resolution with no worsening of fibrosis and, at the 1,200 mg dose, improvement of liver fibrosis with no worsening of NASH in both ITT and PP populations

- **Lanifibranor is the first drug candidate to achieve statistically significant effects on the FDA and EMA primary endpoints relevant for seeking accelerated approval:**
  - NASH resolution with no worsening of fibrosis
  - Improvement of fibrosis with no worsening of NASH

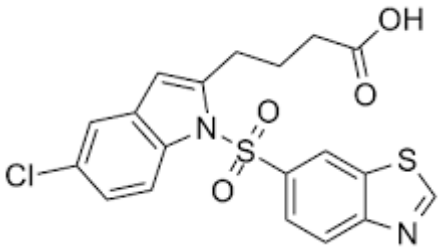
- Lanifibranor continued to show a **favorable tolerability profile**

- Positive topline results support Inventiva's decision to move forward with the clinical development of lanifibranor and **enter into pivotal Phase III development**

[1] ITT: includes all patients randomized in the trial.
[2] PP: includes all patients with paired biopsies and without deviation impacting efficacy assessment.

Lanifibranor: the only pan-PPAR agonist in clinical development for the treatment of NASH

Moderate and balanced pan-PPAR agonist activity



- **Differentiated chemical structure**
- **Once daily oral administration**

- Composition of matter patent granted in 55 countries and method of use patent granted in the US, China and in the EU: **limit of exclusivity in the US is 2035**
- **FAST Track** designation granted by FDA

Compound	PPARα EC50 (nM)	PPARδ EC50 (nM)	PPARγ EC50 (nM)
Lanifibranor(1)	**1630**	**850**	**230**
Fenofibrate	2400	-	-
Pioglitazone	-	-	263
Rosiglitazone	-	-	13
Elafibranor(2)	10	100	-
Seladelpar(3)	-	2	-

Results justifying a NASH development

- **Effects observed** on insulin-sensitivity, dyslipidemia, steatosis, ballooning, inflammation, hepatic fibrosis and cirrhosis in preclinical models
- **Phase IIa(1) trial demonstrated pan-PPAR agonist activity,** supporting dose selection for NASH clinical trial

Favorable tolerability profile

- 24-months rodent and 12-month monkey studies leading to **PPAR class clinical hold lifted** by FDA
- Phase I trials with more than **200** healthy volunteers(2) and Phase IIa trial with **47** TD2M patients
- Approximately **250** patients treated for 24 or 48 weeks in Inventiva's completed Phase IIb clinical trials
- In connection with these trials, lanifibranor has undergone a total of **7 DSMB reviews without recommendations of protocol change**

(1) Conducted by Abbott prior to our founding; (2) Including 125 healthy volunteers in the phase I conducted by Abbott prior to our founding.

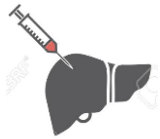
Trial design

Clinicaltrials.gov identifier: NCT03008070

Screening
- **Liver biopsy**

24-week treatment + 4-week follow-up
Double blind, randomized, placebo-controlled

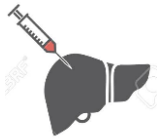
End of treatment
- **Liver biopsy**



Placebo

Lanifibranor, 800 mg once daily

Lanifibranor, 1200 mg once daily



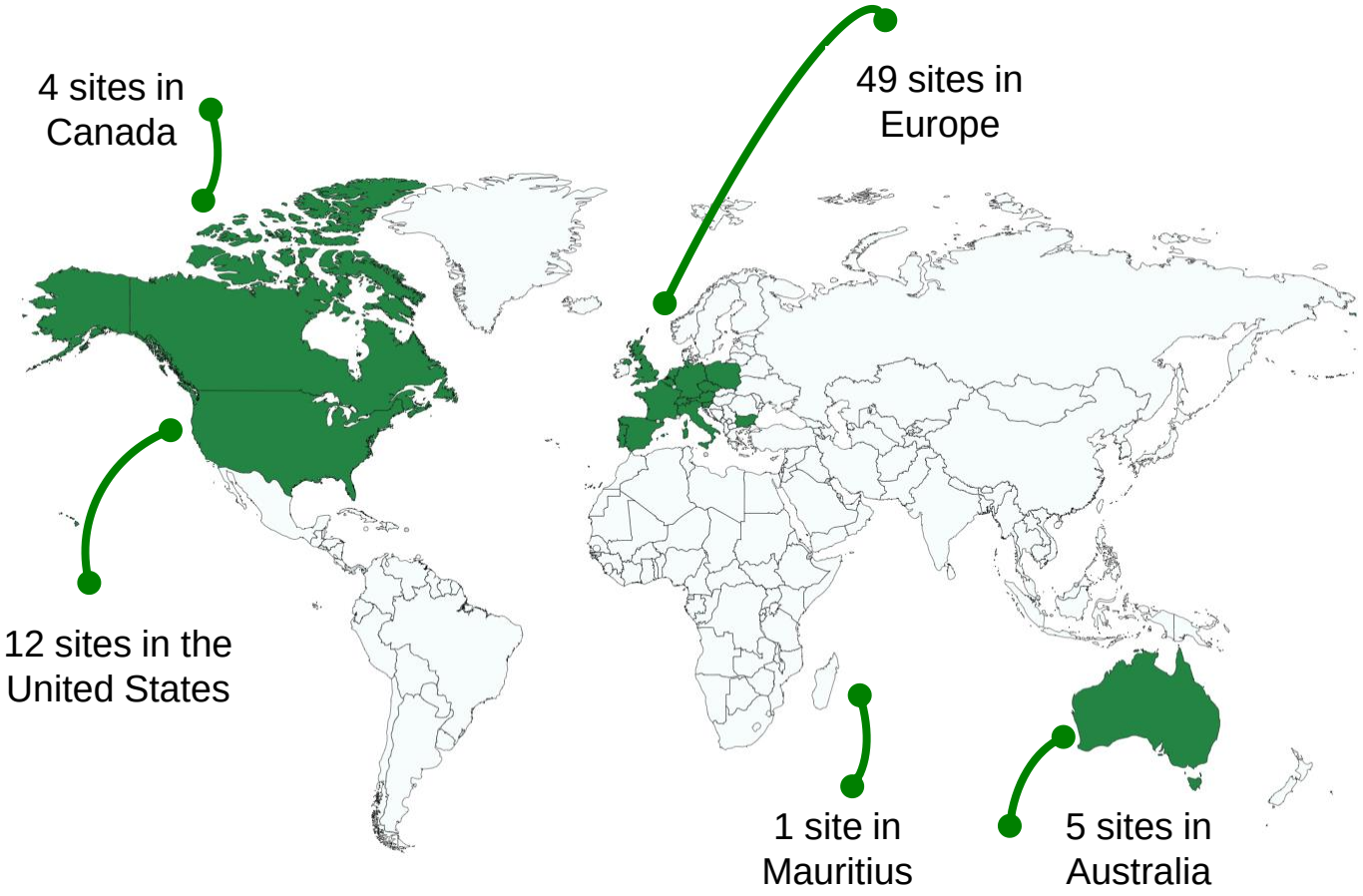
- Randomisation 1/1/1
- Stratification on type 2 diabetes mellitus (T2DM)

Patient population	# patients	Definition
Safety / Intention-to-Treat (ITT)	247	Patients randomized having received at least one dose of lanifibranor/placebo
Per Protocol (PP)	194	Patients with paired biopsies and without deviation impacting efficacy results

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

More information on: http://www.native-trial.com/

247 patients randomized in 71 sites worldwide



Country	Patients randomized
Europe	183 (74%)
US	36 (15%)
Australia	13 (5%)
Canada	8 (3%)
Mauritius	7 (3%)
Total	247 (100%)

17 countries worldwide (number of sites having randomized at least 1 patient)

- Europe: Austria (1), Belgium (5), Bulgaria (5), Czech Republic (3), France (13), Germany (5), Italy (4), Poland (3), Slovenia (1), Spain (4), Switzerland (2), United Kingdom (3)
- North America: United States (12), Canada (4)
- Australia (5)
- Mauritius (1)

Efficacy endpoints

Primary endpoint

- Decrease from baseline to week 24 of at least 2 points of inflammation and ballooning and no worsening of fibrosis (as measured by SAF activity score)

Secondary endpoints

- Resolution of NASH and no worsening of fibrosis
- Improvement of fibrosis by at least 1 stage and no worsening of NASH
- Decrease from baseline to week 24 of at least 2 points of the NAS CRN score and no worsening of fibrosis
- Resolution of NASH and improvement of fibrosis by at least 1 stage
- Change in glucose metabolism parameters (fasting glucose, insulin, HOMA index, HbA1c, …)
- Change in liver enzymes tests (ALT, AST, GGT, Alkaline Phosphatase, Total Bilirubin)
- Change in main plasma lipid parameters (TC, HDL-C, calculated LDL-C, TG,…)

Other outcome measures

- Change in inflammatory markers (fibrinogen, hs-CRP, alpha2 macroglobulin, haptoglobin,…)
- Change in fibrosis markers (TIMP-1, TIMP-2, Hyaluronic acid, P3NP, NFS, FIB-4 score, ELF score, Pro-C3,…)

NATIVE endpoints use both SAF and NAS scoring

- The severity of hepatocellular ballooning and inflammation is a strong predictor for the presence of hepatic fibrosis and the risk for fibrosis progression
- NATIVE primary endpoint is a reduction of ≥ 2 points of the SAF activity score, which excludes steatosis and focuses on inflammation and ballooning
- Other key endpoints assess disease progression using both biopsy scoring measurements: SAF and NAS

SAF Steatosis-Activity-Fibrosis		NAS NAFLD Activity Score
0 - 3	**Steatosis**	**0 - 3**
0 - 2	**Inflammation**	**0 - 3**
0 - 2	**Ballooning**	**0 - 2**
0 - 4	**Fibrosis**	**0 - 4**

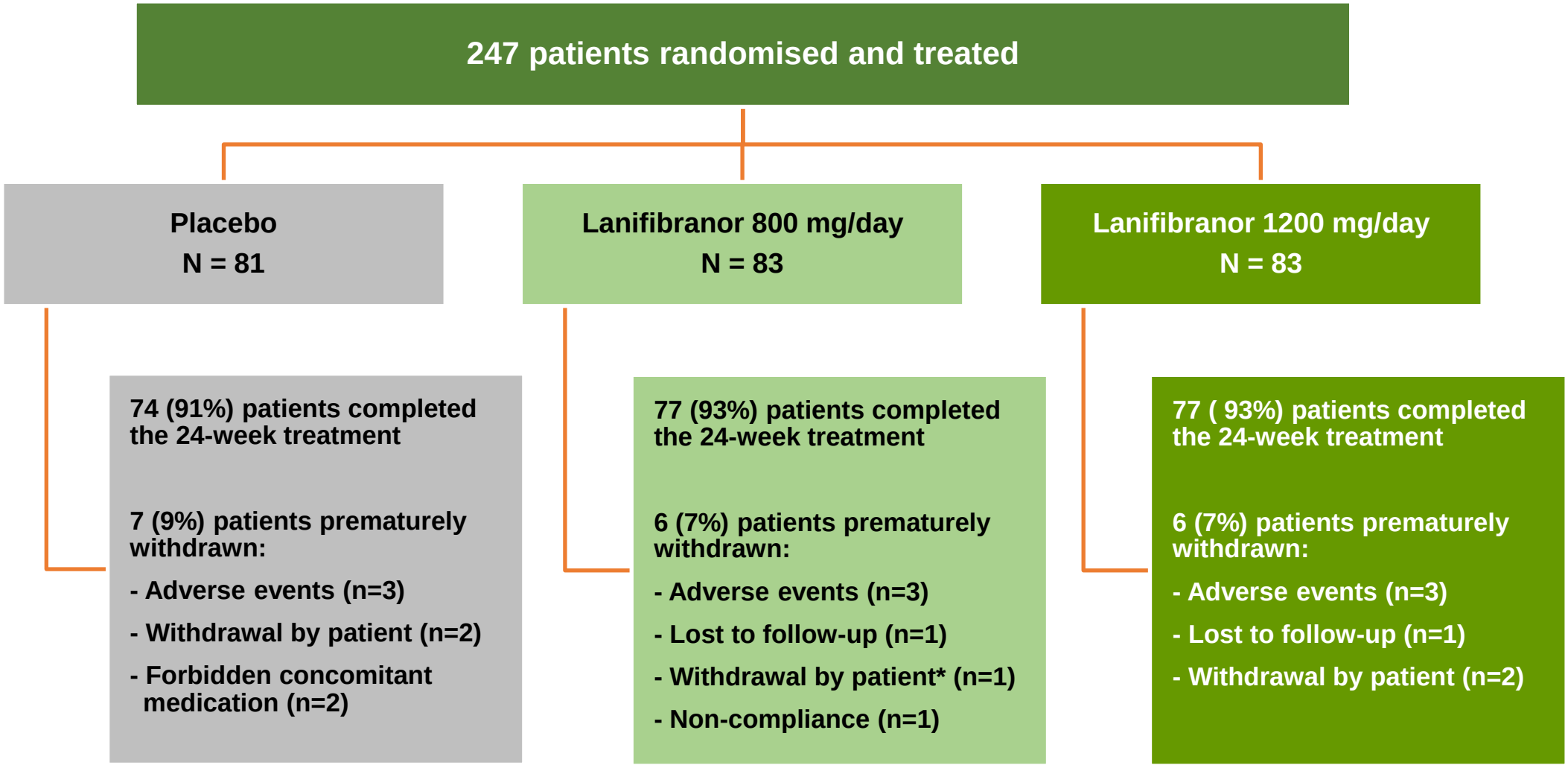
Decrease of ≥ 2 points of SAF activity score

NASH resolution

≥ 2 points reduction of NAS score

Fibrosis improvement

Patient disposition (N = 247)



* and adverse event as secondary reason

Patient Baseline Demographics and Characteristics (I/II)

ITT (N = 247)

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 ± 13.1	55.0 ± 10.4	52.2 ± 13.8	53.6 ± 12.5
White	74 (91%)	80 (96%)	78 (94%)	232 (94%)
Weight (kg)	95.1 ± 17.3	91.6 ± 19.3	93.0 ± 19.9	93.2 ± 18.9
Body Mass Index (kg/m²)	32.8 ± 5.1	32.5 ± 5.5	33.3 ± 5.5	32.9 ± 5.4
Type 2 diabetes	35 (43%)	33 (40%)	35 (42%)	103 (42%)
Liver biopsy characteristics				
SAF Activity score (inflammation + ballooning)	3.3 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	3.3 ± 0.5
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%)

Patient Baseline Demographics and Characteristics (II/II)

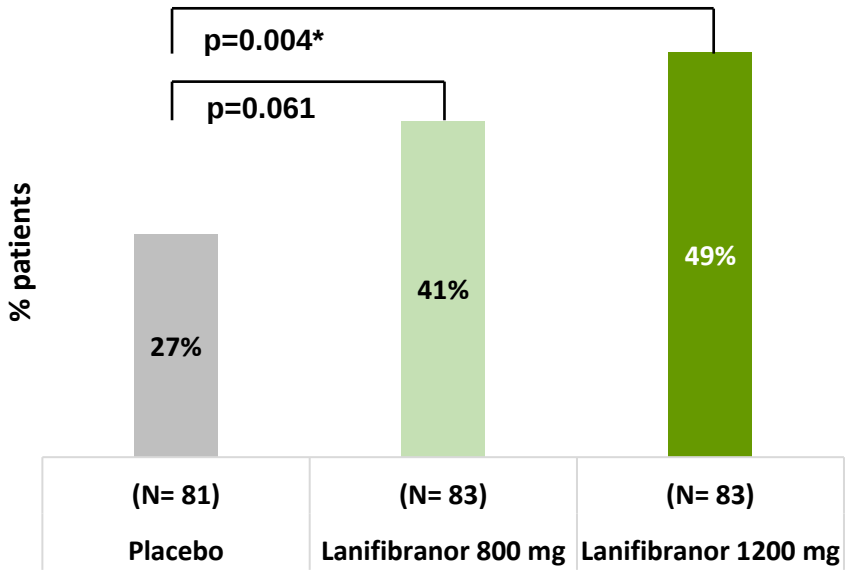
ITT (N = 247)

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 ± 31.6	64.1 ± 41.4	63.6 ± 43.4
Aspartate aminotransferase, AST (UI/L)	43.3 ± 24.1	53.9 ± 43.4	43.9 ± 24.8
Gamma glutamyl transferase, GGT (UI/L)	67.9 ± 80.4	101.6 ± 146.1	67.1 ± 93.1
Plasma lipids levels			
HDL-Cholesterol (mmol/L)	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3
Triglycerides (mmol/L)	2.0 ± 0.8	1.9 ± 0.9	2.0 ± 0.9
Glucose metabolism for diabetic patients (n= 103)			
Fasting Glucose (mmol/L)	6.9 ± 2.0	7.3 ± 2.2	6.6 ±1.2
HbA1c (%)	6.5 ± 0.7	6.7 ± 0.8	6.6 ± 0.7
Insulin (pmol/L)	222.7 ± 186.5	246.3 ± 213.4	278.5 ± 233.5

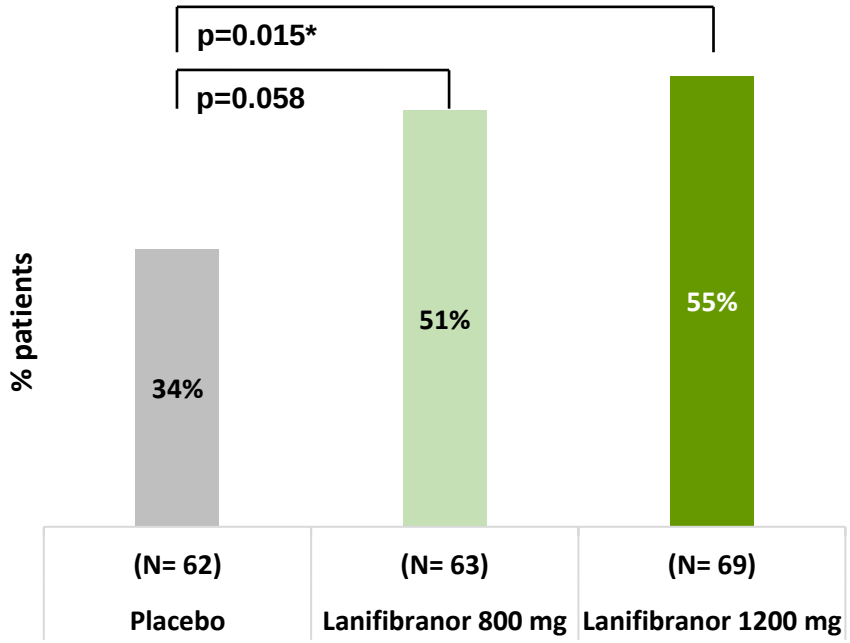
Dose-dependent and statistically significant (1200 mg) reduction of 2 points of inflammation and ballooning (SAF Activity Score) and no worsening of fibrosis

Primary Efficacy Endpoint

ITT Population (N = 247)



Per Protocol Population (N = 194)



* Statistically significant in accordance to the statistical analysis plan (SAP)

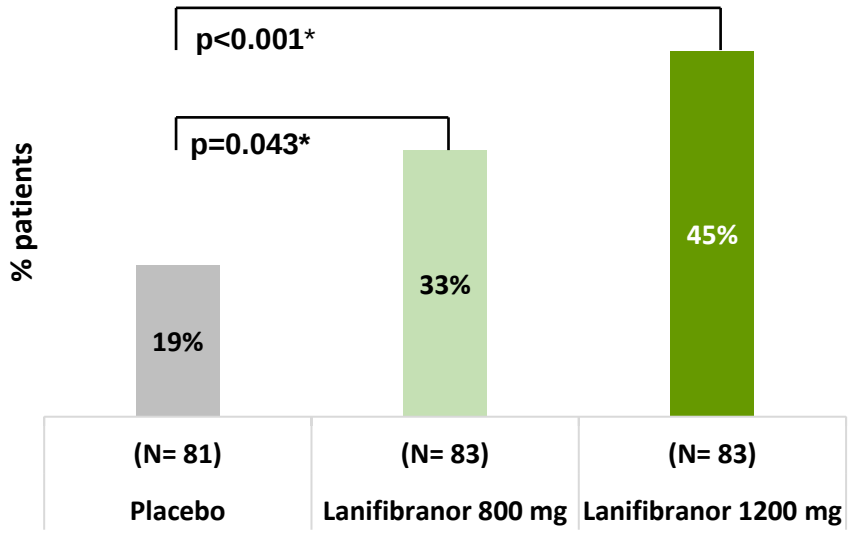
▶ **Lanifibranor (1200 mg) met the primary endpoint in both ITT and PP populations**

Primary efficacy endpoint: Response is defined as a decrease from baseline to week 24 of at least 2 points of the SAF Activity score (SAF-A) and no worsening of the CRN Fibrosis score (CRN-F). No worsening means that the score remains stable or decreases.

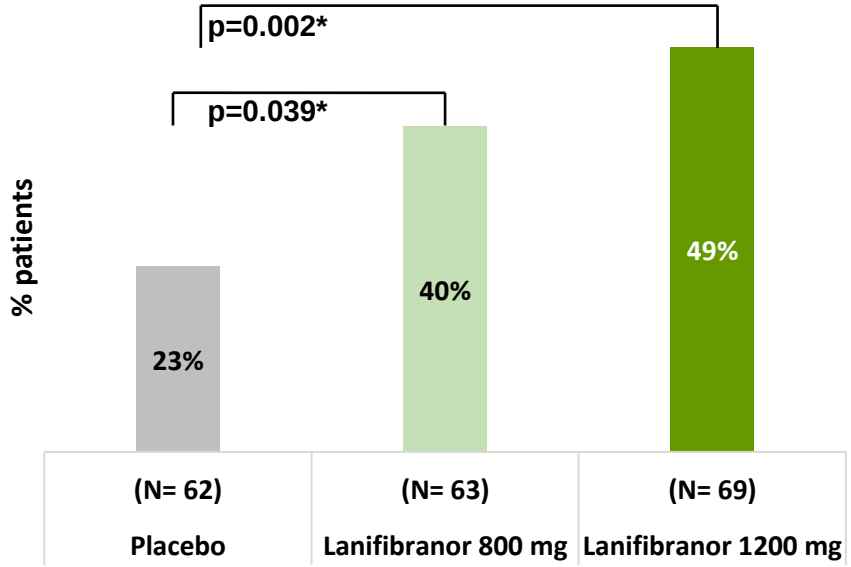
Dose-dependent and statistically significant results in resolution of NASH and no worsening of fibrosis

Secondary endpoint

ITT Population (N = 247)



Per Protocol Population (N = 194)



* Statistically significant in accordance to the statistical analysis plan (SAP)

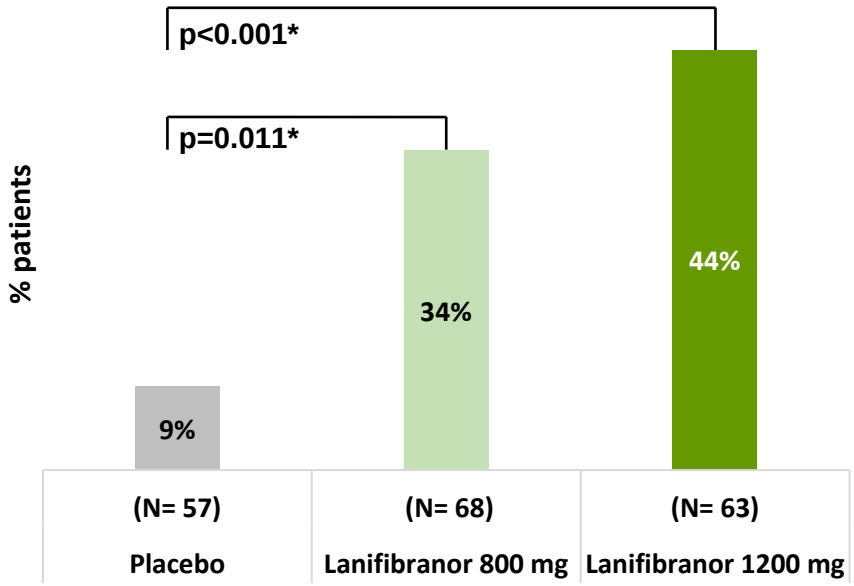
- **Both lanifibranor dose groups met resolution of NASH and no worsening of fibrosis in both ITT and PP populations**
- **49% of patients treated with lanifibranor 1200mg daily in the PP population had their NASH resolved**

Resolution of NASH and no worsening of fibrosis at week 24: CRN-I = 0 or 1, CRN-B = 0 and no worsening of CRN-F from baseline.

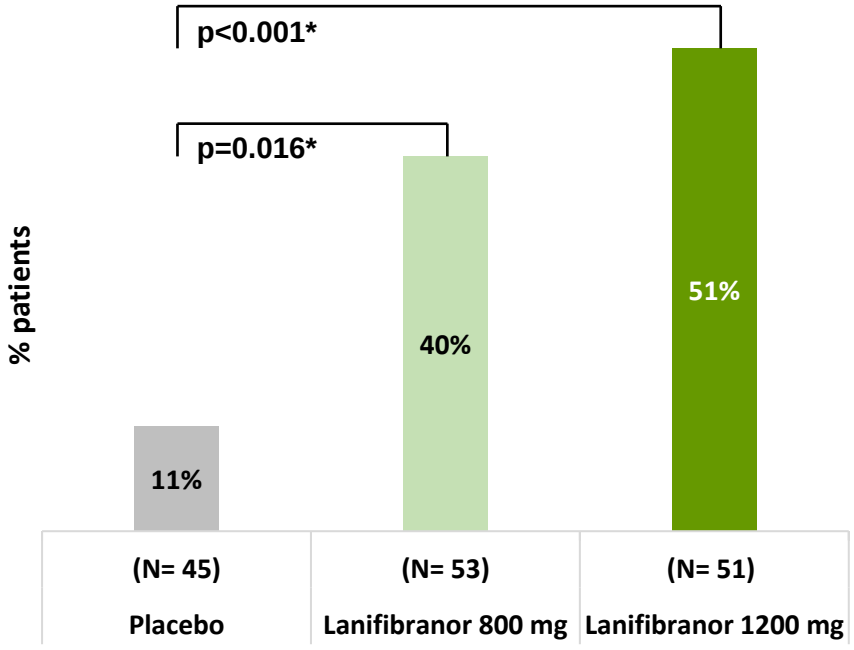
Dose-dependent and statistically significant results in resolution of NASH and no worsening of fibrosis in F2/F3 patients in both ITT and PP populations

Secondary endpoint in F2/F3 patients

ITT Population in F2/F3 (N = 188)



Per Protocol Population in F2/F3 (N = 149)



* Statistically significant in accordance to the statistical analysis plan (SAP)

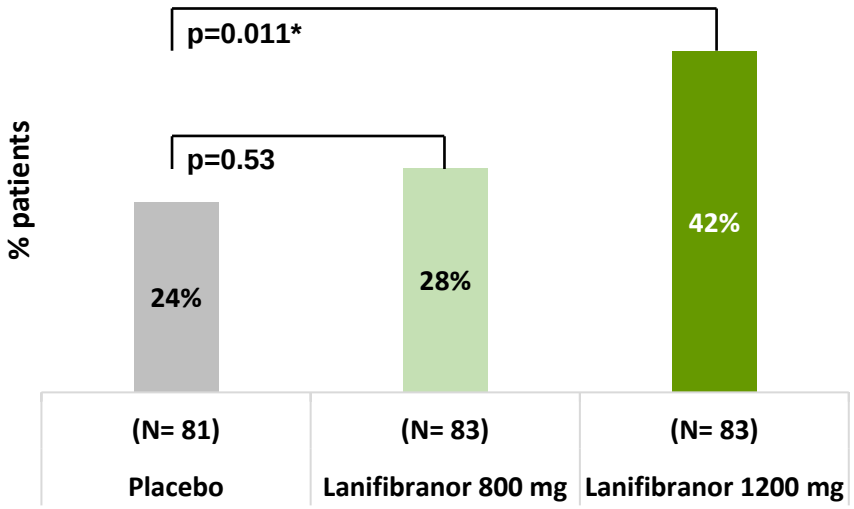
- **In the ITT population, approximately four times and five times more patients in the 800mg/day dose and 1200mg/day group respectively met the secondary endpoint compared to placebo**

Resolution of NASH and no worsening of fibrosis at week 24: CRN-I = 0 or 1, CRN-B = 0 and no worsening of CRN-F from baseline.

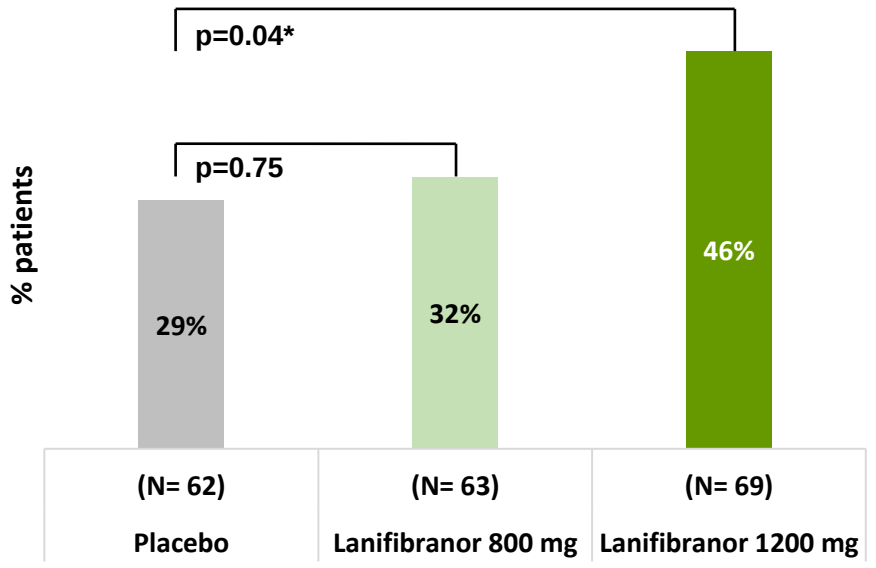
Dose-dependent and statistically significant (1200 mg) improvement of fibrosis and no worsening of NASH

Secondary endpoint

ITT Population (N = 247)



Per Protocol Population (N = 194)



* Statistically significant in accordance to the statistical analysis plan (SAP)

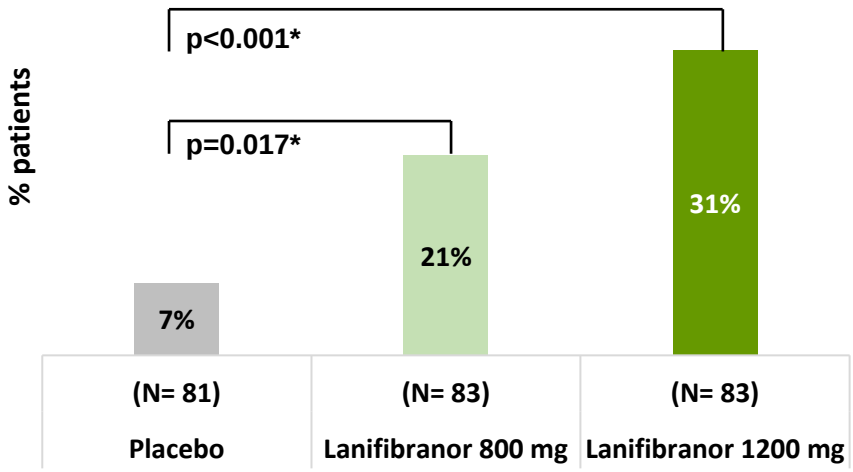
- **Lanifibranor 1200 mg group met improvement of fibrosis and no worsening of NASH in both ITT and PP populations**
- **46% of patients treated with lanifibranor 1200mg daily in the PP population had their fibrosis reduced in 6 months**

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.

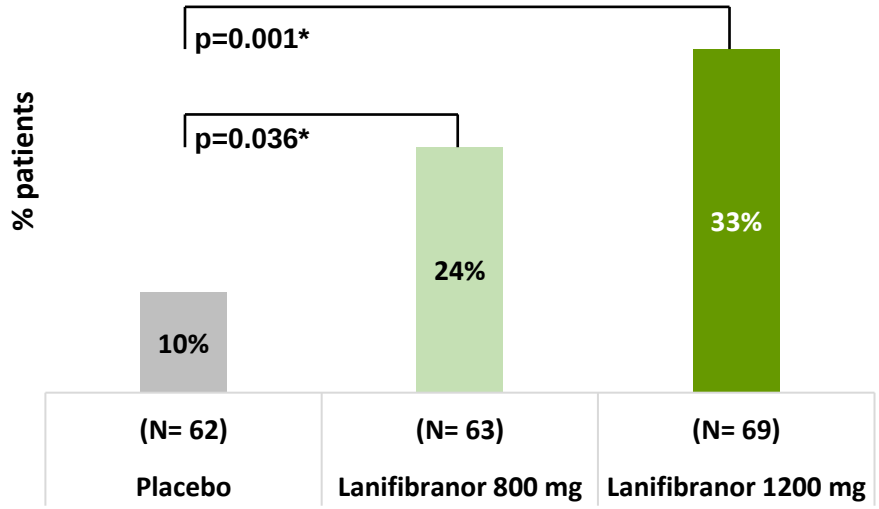
Dose-dependent and statistically significant results on both resolution of NASH and fibrosis improvement

Secondary endpoint

ITT Population (N = 247)



Per Protocol Population (N = 194)



* Statistically significant in accordance to the statistical analysis plan (SAP)

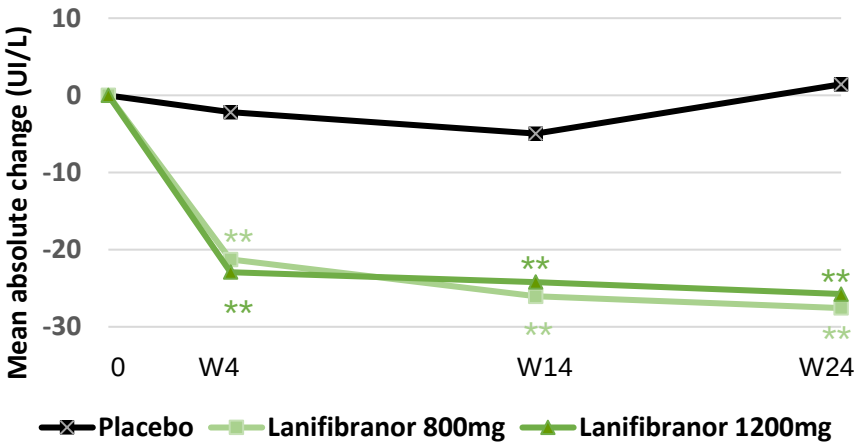
- **Both lanifibranor dose groups met resolution of NASH and fibrosis improvement in both ITT and PP populations**
- **In the ITT population, three times and four times more patients in the 800mg/day dose and 1200mg/day group respectively met the secondary endpoint compared to placebo**

Resolution of NASH and Improvement of liver fibrosis ≥ 1 stage at week 24: CRN-I = 0 or 1, CRN-B = 0 and Improvement of CRN-F ≥ 1 stage.

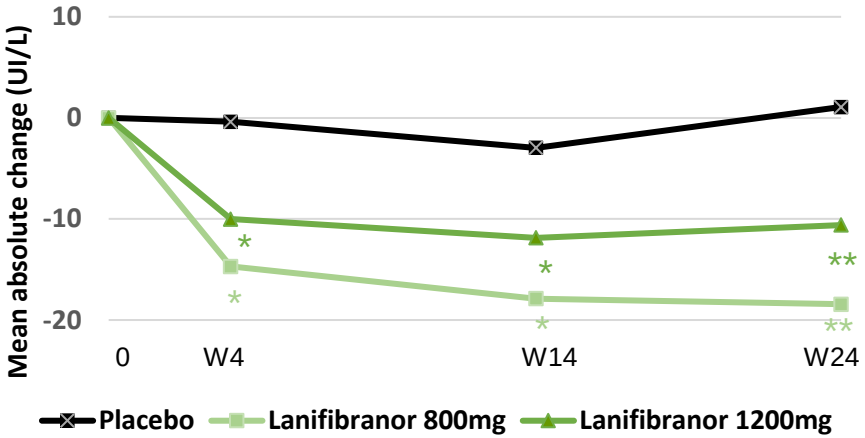
Statistically significant decrease in liver enzymes

Other secondary endpoints in ITT (N = 247)

Absolute change from baseline in ALT

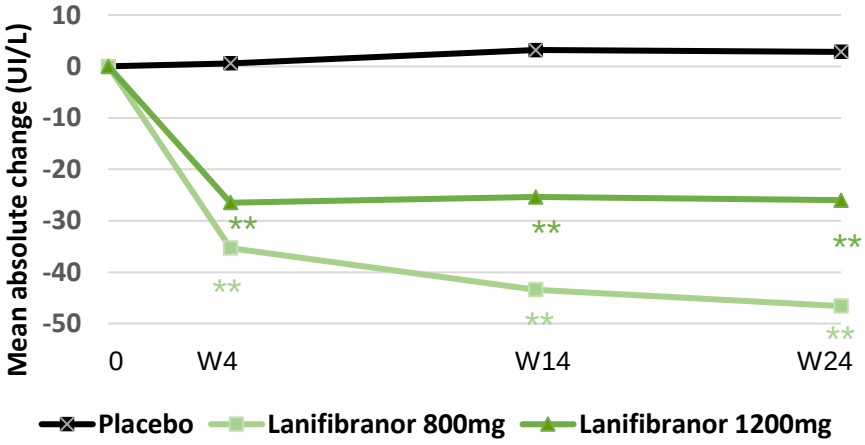


Absolute change from baseline in AST



*** p<0.01 **p<0.001**

Absolute change from baseline in GGT

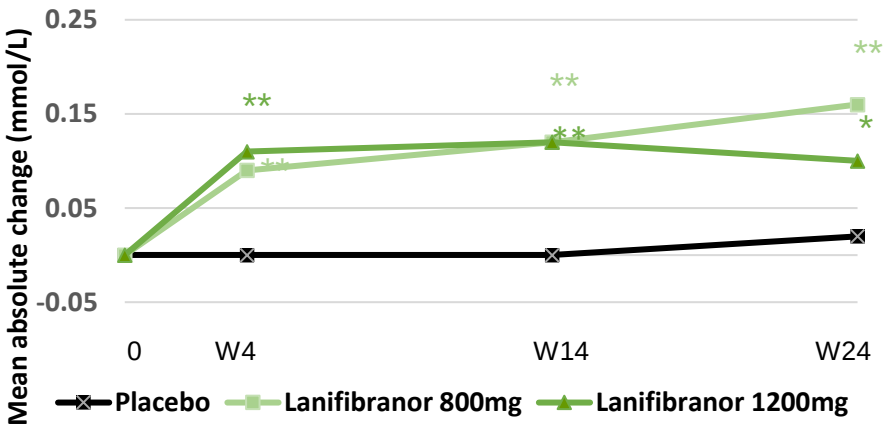


- **Statistically significant decrease of ALT, AST and GGT in both lanifibranor dose groups observed beginning after 4 weeks**

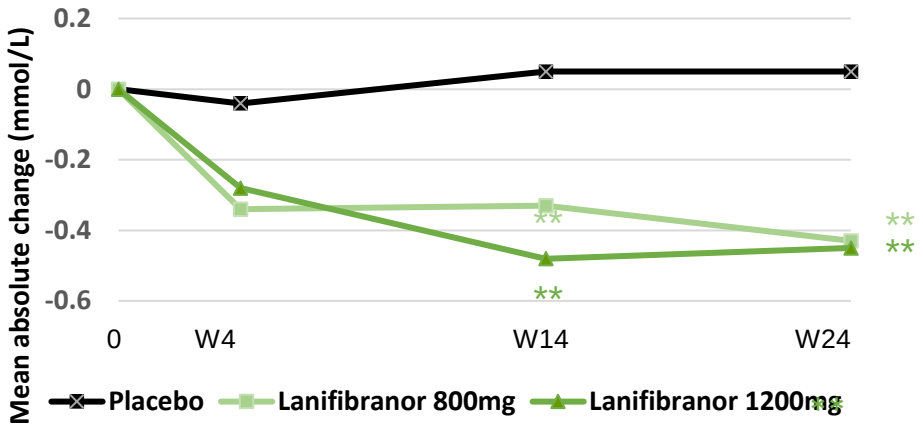
Statistically significant change in HDL-cholesterol and triglycerides

Other secondary endpoints in ITT (N = 247)

Absolute change from baseline in HDL-C



Absolute change from baseline in triglycerides



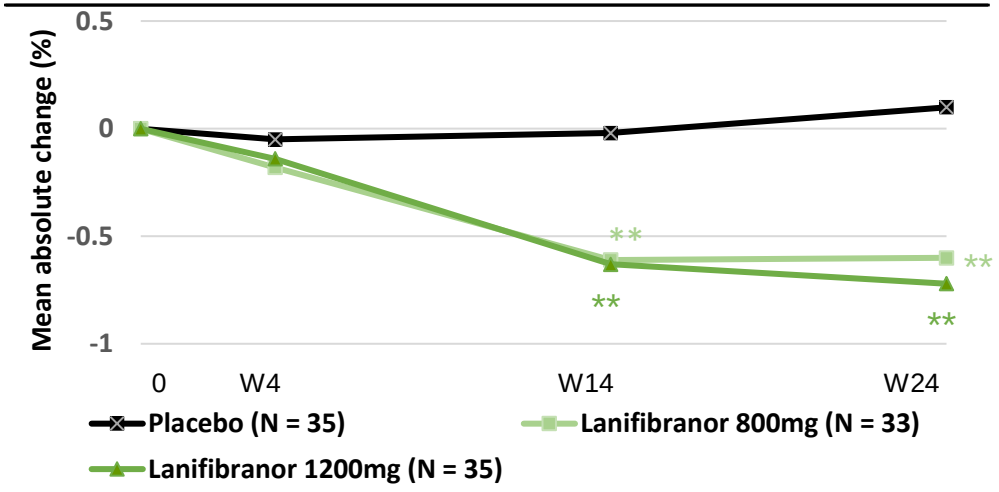
*** p<0.01 **p<0.001**

▶ **No change in LDL-cholesterol**

Statistically significant reductions of fasting glucose and insulin, HbA1c in type 2 diabetes (T2DM) patients with NASH

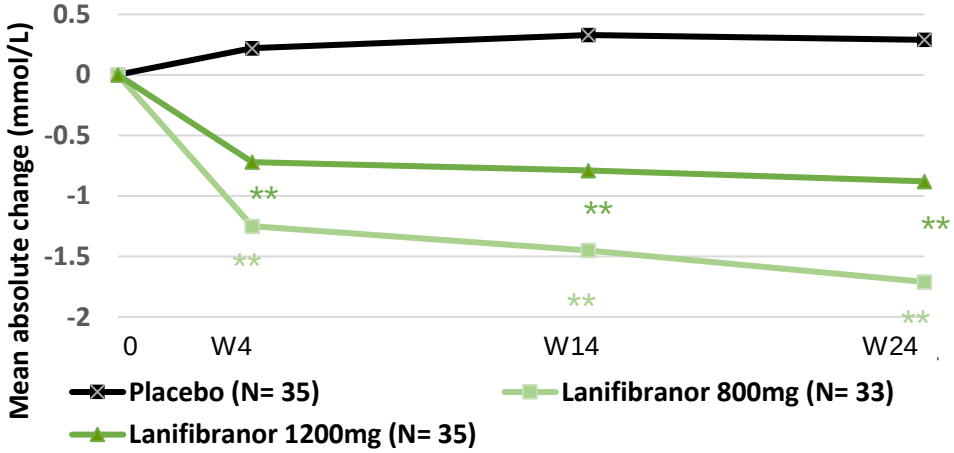
Secondary endpoints in T2DM patients with NASH (N = 103)

Absolute change from baseline in HbA1c

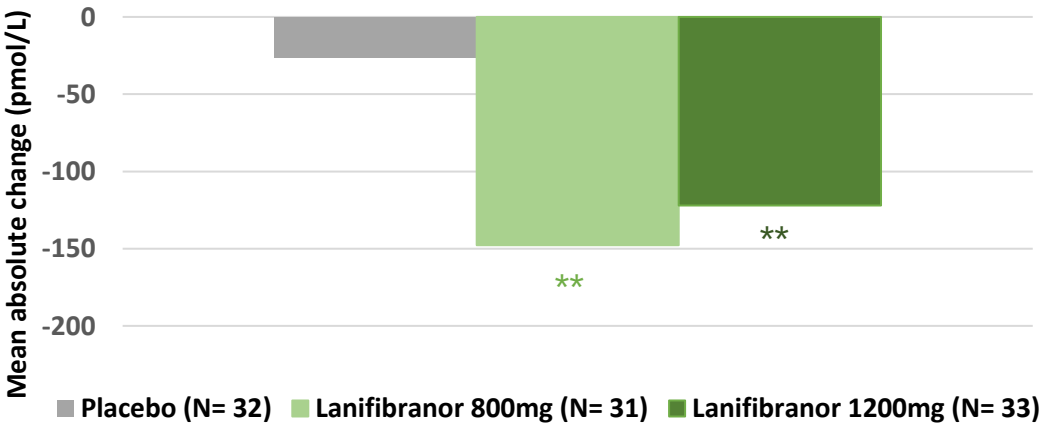


**p<0.001

Absolute change from baseline in fasting glucose



Absolute change from baseline in insulin at W24



- **Lanifibranor improves insulin sensitivity and glycemic control in NASH patients**

Lanifibranor: a continued favorable tolerability profile (I/II)

Safety population N = 247

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%)(1)	2 (2.4%)(2)
Any Serious TEAE	3 (3.7%)	3 (3.6%)	7 (8.4%)
- Drug-related Serious TEAE	2 (2.5%)(3)	-	-

(1) One patient with moderate diarrhea

(2) One patient with mild cardiac failure; one patient with mild diarrhea, abdominal pain, dizziness

(3) 2 SUSARs: 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%)

* One AE of severe intensity

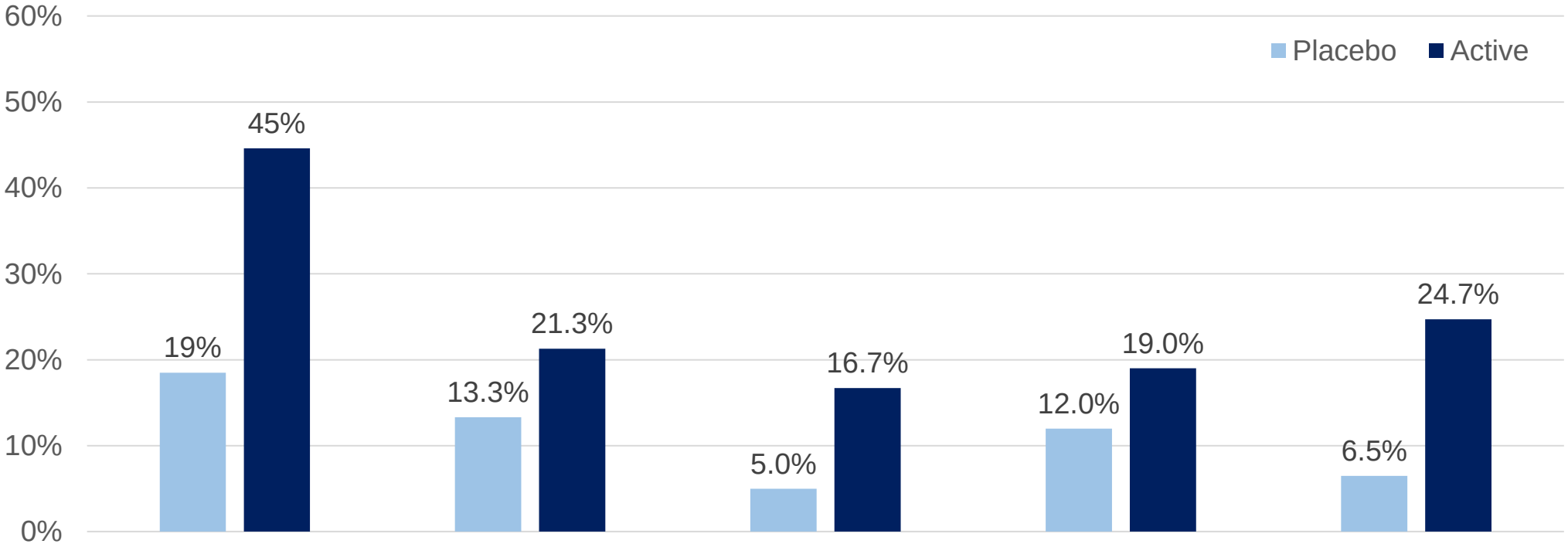
Lanifibranor: a continued favorable tolerability profile (II/II)

Safety population N = 247

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%)

Lanifibranor NATIVE results and other oral NASH drug candidates (I/II)

Phase II results of orally available drug candidates: NASH resolution without worsening of fibrosis



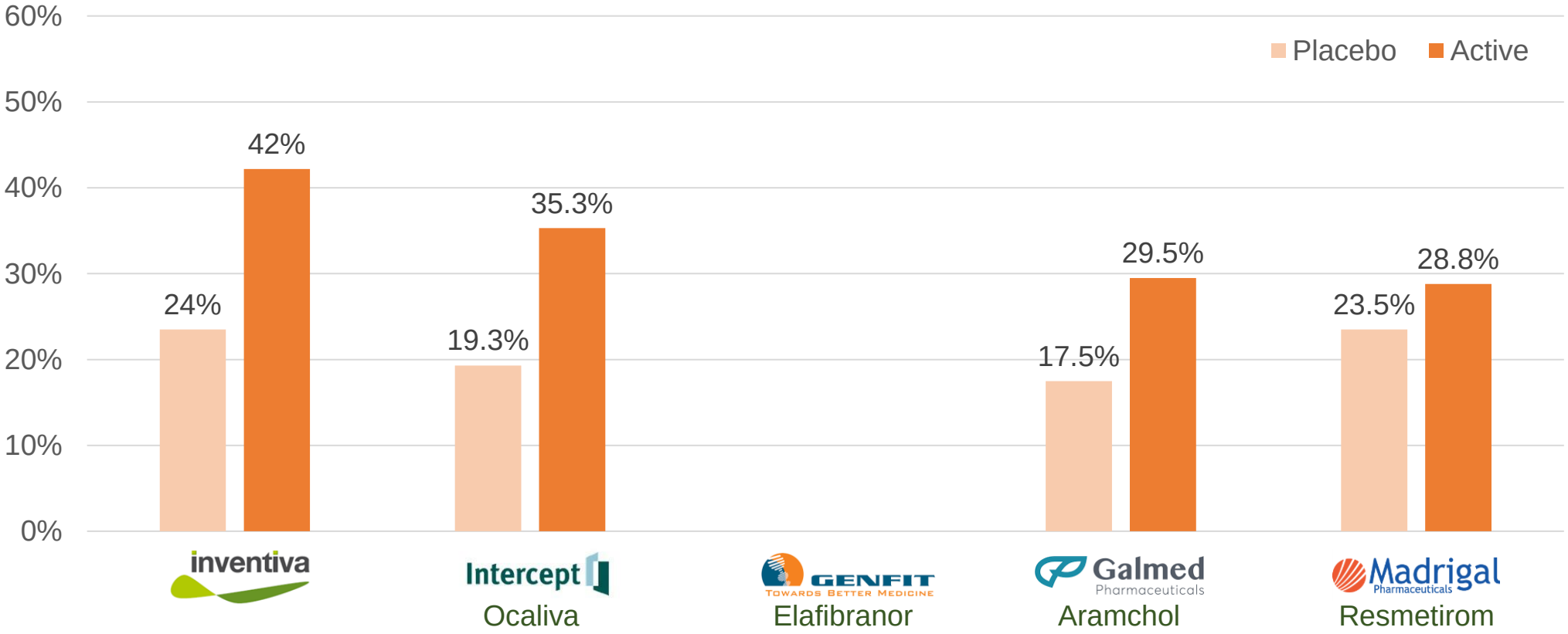
	Phase II 6 months	Ocaliva Phase II 18 months	Aramchol Phase II 12 months	Elafibranor Phase II 12 months	Resmetirom Phase II 9 months
N =	**247**	283	247	276	125
P =	**<0,001**	0,08	0,051	0,045	0,03

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.

Source: lanifibranor native results 1200 mg/day, ITT population; ocaliva 25mg : Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial The Lancer November 6 2014; elafibranor 120mg: Ratziu et al, Gastorenterology 2016; 150:1147-1159 ; resmetirom 80mg ± 20mg: Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6; Aramchol 600mg :AASLD 2018 presentation

Lanifibranor NATIVE results and other oral NASH drug candidates (II/II)

Phase II results of orally available drug candidates: fibrosis improvement without worsening of NASH[1]



	inventiva	Ocaliva	Elafibranor	Aramchol	Resmetirom
	Phase II 6 months	Phase II 18 months	Phase II 12 months	Phase II 12 months	Phase II 9 months
N =	**247**	283	276	247	125
P =	**0,011**	0,004	N/A	0,21	*No stats reported*

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.

Source: lanifibranor native results 1200 mg/day, ITT population; ocaliva 25mg: Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial The Lancer November 6 2014; elafibranor 120mg: Ratziu et al, Gastorenterology 2016; 150:1147-1159 ; resmetirom 80mg ± 20mg: Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6; Aramchol 600mg :AASLD 2018 presentation.

Conclusion

- **Lanifibranor (1,200 mg) met the primary endpoint** with a statistically significant reduction **after 6 months of treatment** 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)[1] and Per Protocol (PP)[2] populations

- **Lanifibranor also met key secondary endpoints** including NASH resolution with no worsening of fibrosis and, at the 1,200 mg dose, improvement of liver fibrosis with no worsening of NASH in both ITT and PP populations

- **Lanifibranor is the first drug candidate to achieve statistically significant effects on the FDA and EMA primary endpoints relevant for seeking accelerated approval:**
  - NASH resolution with no worsening of fibrosis
  - Improvement of fibrosis with no worsening of NASH

- Lanifibranor continued to show a **favorable tolerability profile**

- Positive topline results support Inventiva's decision to move forward with the clinical development of lanifibranor and **enter into pivotal Phase III development**

[1] *ITT: includes all patients randomized in the trial.*
[2] *PP: includes all patients with paired biopsies and without deviation impacting efficacy assessment.*

Lanifibranor: NASH key milestones

- Finalization of Phase III synopsis and protocol: **ongoing**
- End of Phase IIb meeting with FDA: **expected in Q4 2020**
- Scientific advice meeting with EMA: **expected in Q4 2020**
- Finalization of Phase II trial in NAFLD patients with TD2M conducted by Pr. Cusi
- Launch of pivotal Phase III trial in NASH

Q & A