Update on NATIVE Phase IIb trial evaluating lanifibranor in Nonalcoholic Steatohepatitis (NASH)

KOL Meeting
May 4, 2020

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Today’s speakers

Frédéric Cren, MA/MBA, Chairman, CEO and Co-Founder

Pierre Broqua, Ph.D., CSO and Co-Founder

Prof. Sven Francque, MD
University Hospital Antwerp, Native Principal Investigator

Prof. Pierre Bedossa, MD
University Paris Diderot, pathologist and Native Central reader

Agenda

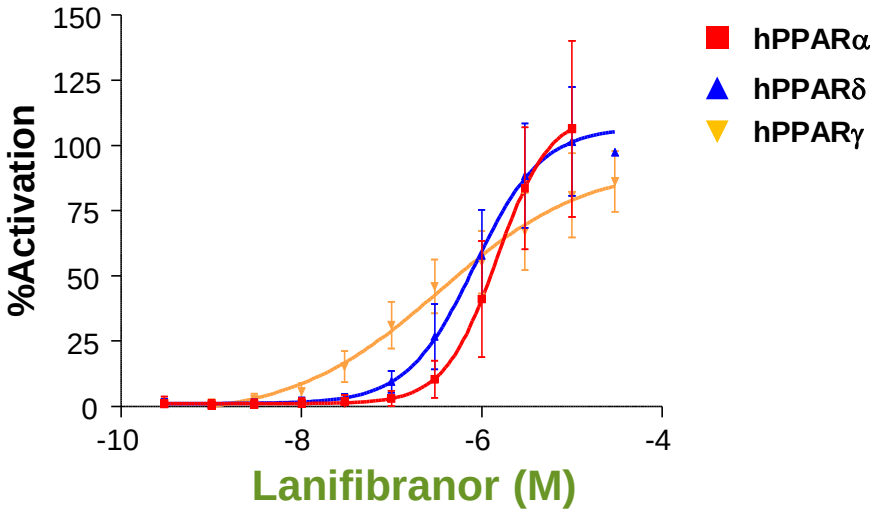
- **Lanifibranor in NASH**
- **SAF scoring and biopsy reading in NASH**
- **Native phase 2b trial update**
- **Q&A**

Lanifibranor in NASH

Pierre Broqua, Ph.D., CSO and Co-Founder

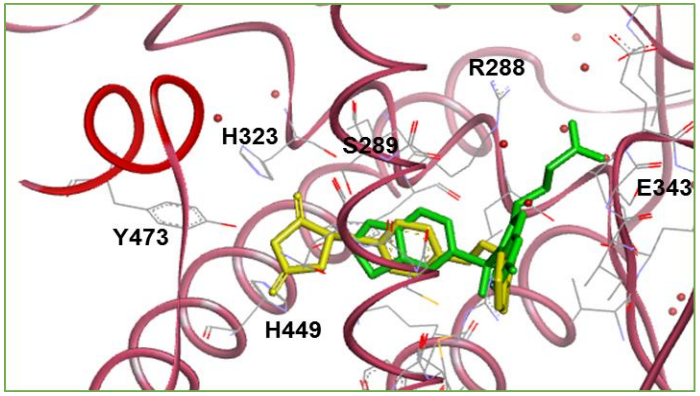
Lanifibranor is a differentiated pan-PPAR agonist with moderate and well balanced activity on the 3 PPAR isoforms

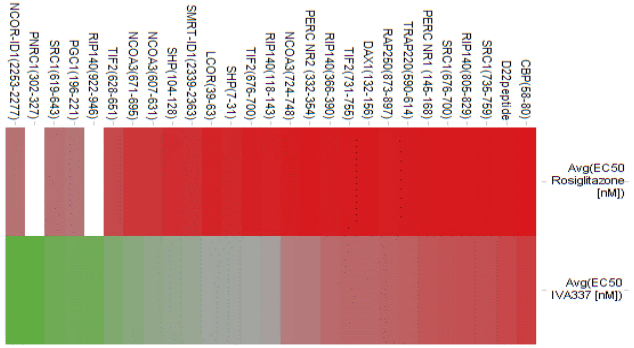
Lanifibranor human dose response curves and EC50s for various PPAR agonists



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	-

Lanifibranor binds differently than rosiglitazone to PPARγ inducing different coactivator recruitment[4]

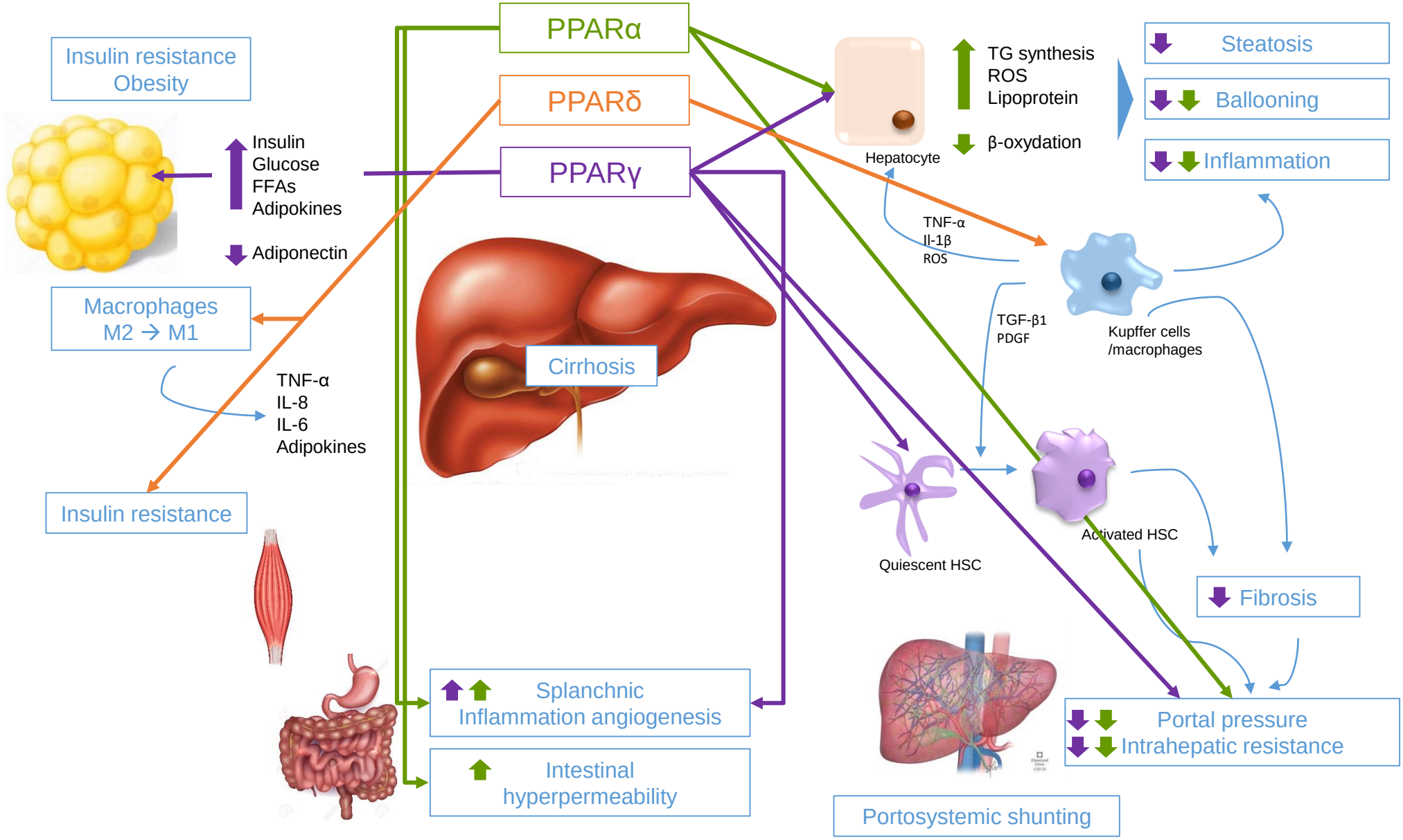




Potency scale: red 10 nM; grey: 500 nM; green 5 000 nM

Source: (1) Company data (2) Hanf R et al, Diabetes & Vascular Dis Res 2014 (3) Cymabay company presentation (4) J Med Chem. 2018 Feb 15. doi: 10.1021/acs.jmedchem.7b01285

All three PPAR isoforms are needed for an optimal activity in NASH and for fibrosis improvement



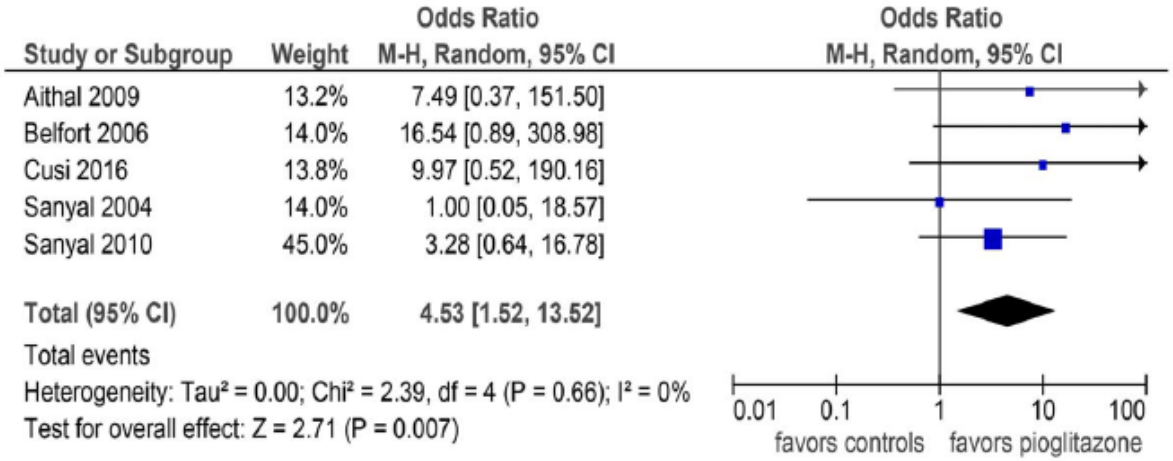
PPARγ efficacy is well established in NASH

Compound	PPARα EC50 (nM)	PPARδ EC50 (nM)	PPARγ EC50 (nM)
▶ Lanifibranor	1630	850	230
▶ Pioglitazone	-	-	263

PPARγ activation by pioglitazone improves steatosis, ballooning, inflammation and metabolic markers in NASH patients after 6 months or 18 months of treatment

Pioglitazone (PPARγ)	Belfort NASH study 6 month treatment			Cusi NASH study 18 month treatment		
	Placebo	Pio	P	Placebo	Pio	P
Steatosis (% patients improved)	38%	65%	0.001	26%	71%	< 0.001
Inflammation (% patients improved)	29%	65%	0.001	22%	49%	= 0,004
Ballooning (% patients improved)	24%	54%	0.001	24%	51%	= 0,004
NASH resolution (% patients)	-	NA	-	19%	51%	< 0.001
Fibrosis (mean change in score)	-	NS	-	0	- 0.5	= 0.039

Pioglitazone improves advanced fibrosis



▶ **Pioglitazone improves advanced fibrosis** (stage F3-F4) as indicated by an increase in the number of NASH patients whose fibrosis stage changed from F3-F4 to F0-F2 at the end of treatment

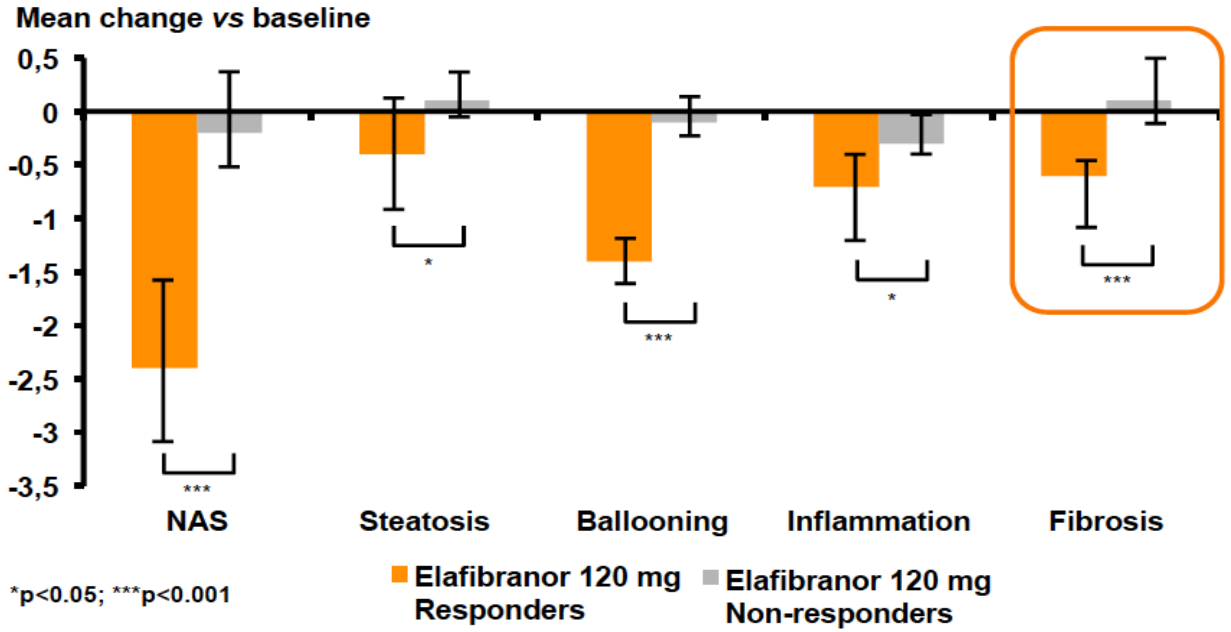
Source: Corey KE and Malhi H, Hepatology 2016. Note: clinical trial not conducted by Inventiva

PPARγ activity can also be reinforced by PPARα and δ efficacy

Compound	PPARα EC50 (nM)	PPARδ EC50 (nM)	PPARγ EC50 (nM)
Lanifibranor	1630	850	230
Elafibranor	10	100	-

- **PPARα/δ** activation by elafibranor 120mg/day **leads to significant improvement of ballooning and inflammation** as well as metabolic markers in NASH patients vs. placebo after 12 months of treatment
  - NASH resolution in ITT: 19% vs 12%, p = 0.045 (elafibranor 120mg, n=89; placebo, n=92)
  - In a sub-analysis of patients with NAS≥4 and randomized in centers that included in each treatment arm patients with decrease of at least 1 point (elafibranor 120mg, n=31; placebo, n=39)
    - Steatosis: 35% vs 18%, p = 0.10
    - **Inflammation:** 55% vs 33%, p < 0.05
    - **Ballooning:** 45% vs 23%, p = 0.02

- **Patients who resolved NASH showed significant reduction in liver fibrosis** while non-responders did not show any change from baseline (elafibranor 120mg, responders, n=17; non-responders, n=61)



Source: Ratziu V, et al. Gastroenterology 2016. Note: (1) GOLDEN 505 study conducted by Genfit

Lanifibranor shows consistent improvements in metabolic parameters and liver histology while displaying anti-fibrotic activity

Metabolic models	NASH & NAFLD models	Fibrosis models	Cirrhosis models
Diet induced obesity high fat / high sucrose	Methionine Choline Deficient diet (MCD)	Carbon tetrachloride (CCL4)	Thiocetamide (TAA)
Foz / Foz			
	Choline-deficient amino-acid and high fat diet		
Hepatoma and muscle cells biology	Macrophages biology	HSC biology	
			Endothelial biology

Lanifibranor improves

- Insulin resistance
- Non fasting glucose
- Homa-IR
- Lipid profile

Lanifibranor maintains body weight

Lanifibranor reduces

- Steatosis
- Inflammation
- Ballooning

Lanifibranor improves NAS score

Lanifibranor reduces fibrosis

Lanifibranor inhibits stellate cell activation

Lanifibranor reverses NASH

Lanifibranor reduces

- Portal pressure
- Established fibrosis

In Vivo

In Vitro

In long-term toxicological studies lanifibranor presents a differentiating profile

No identified concerns in safety pharmacology

- Lanifibranor is devoid of:
  - Effects on central and autonomic nervous system, respiratory functions, selected electrocardiographic and cardiovascular parameters
  - Mutagenic, genotoxic and clastogenic potential
  - Reprotoxicity concerns at predicted therapeutic exposures
- Safety margins established at NOAELs in all species explored

No carcinogenic effect relevant to humans, contrasting with some other PPARγ and PPARα/γ agonists

- Lanifibranor shows a very favorable profile in 12 month monkey study …
  - No adverse clinical signs were observed at any dose-level tested
  - No effects on body weight and heart weight, no haemodilution or creatinine increase
  - Electrocardiography and clinical pathology investigations did not reveal any undesirable effects
- … and in two-year carcinogenicity studies performed in rat and mice
  - Rat: no neoplastic change and increase in tumor types commonly associated with single PPARγ and dual PPARα/γ agonists: liver, adipose, bladder, renal and skin
  - Mice: no neoplastic changes and increase in tumor types of human relevance

After review of carcinogenicity studies, FDA has lifted PPAR class clinical hold and allowed long-term clinical studies in NASH with lanifibranor

Lanifibranor's mechanism of action addresses all the key features of NASH

Metabolism

PPARα,δ,γ

- ↑ Insulin sensitivity
- ↑ HDLc
- ↓ TG

Steatosis

PPARγ

- ↓ FA uptake
- ↑ FA catabolism
- ↓ Lipogenesis

Inflammation and Ballooning

PPARα,δ,γ

- ↓ NFkB-dependent gene activation
- ↓ Inflammasome
- ↓ Ballooning

Fibrosis

PPARγ

- ↓ Stellate cell proliferation and activation
- ↓ Collagen and fibronectin production

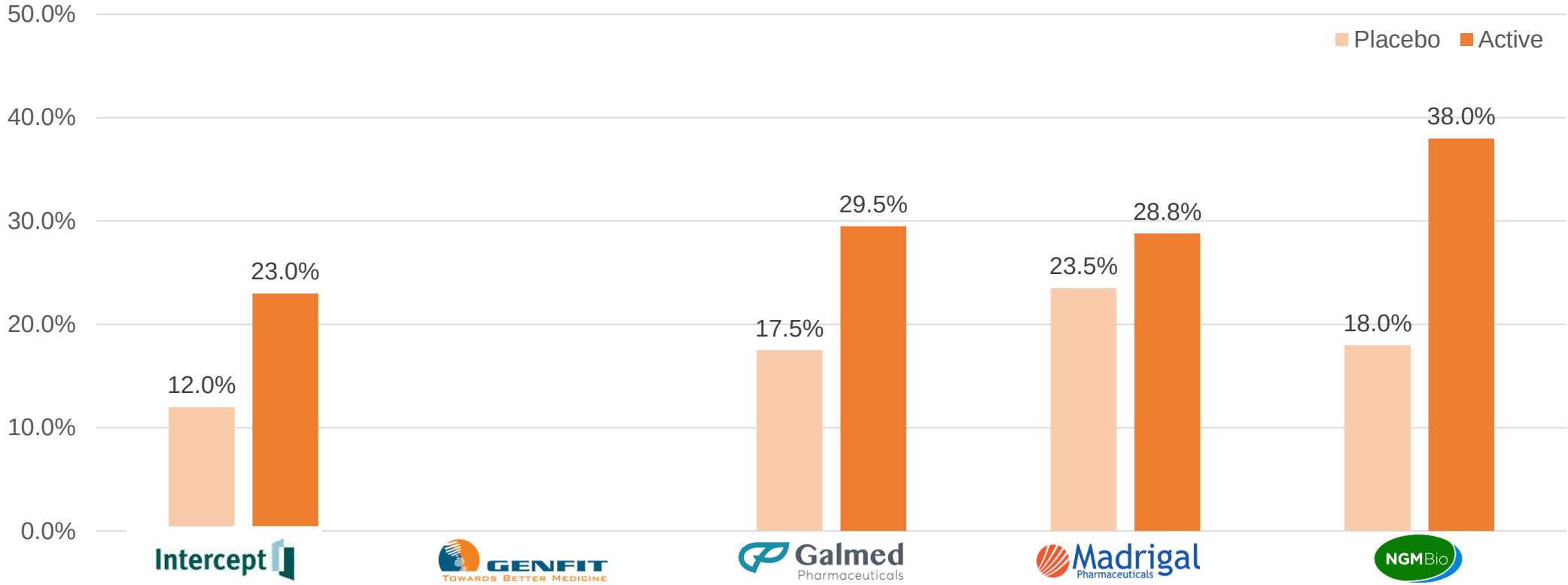
Vascular

PPARα,γ

- ↓ Portal pressure
- ↓ LSEC capillarization
- ↓ Intrahepatic vascular resistance

Results by key competitors show room for improvement (I/II)

Fibrosis improvement without worsening of NASH[(1)]

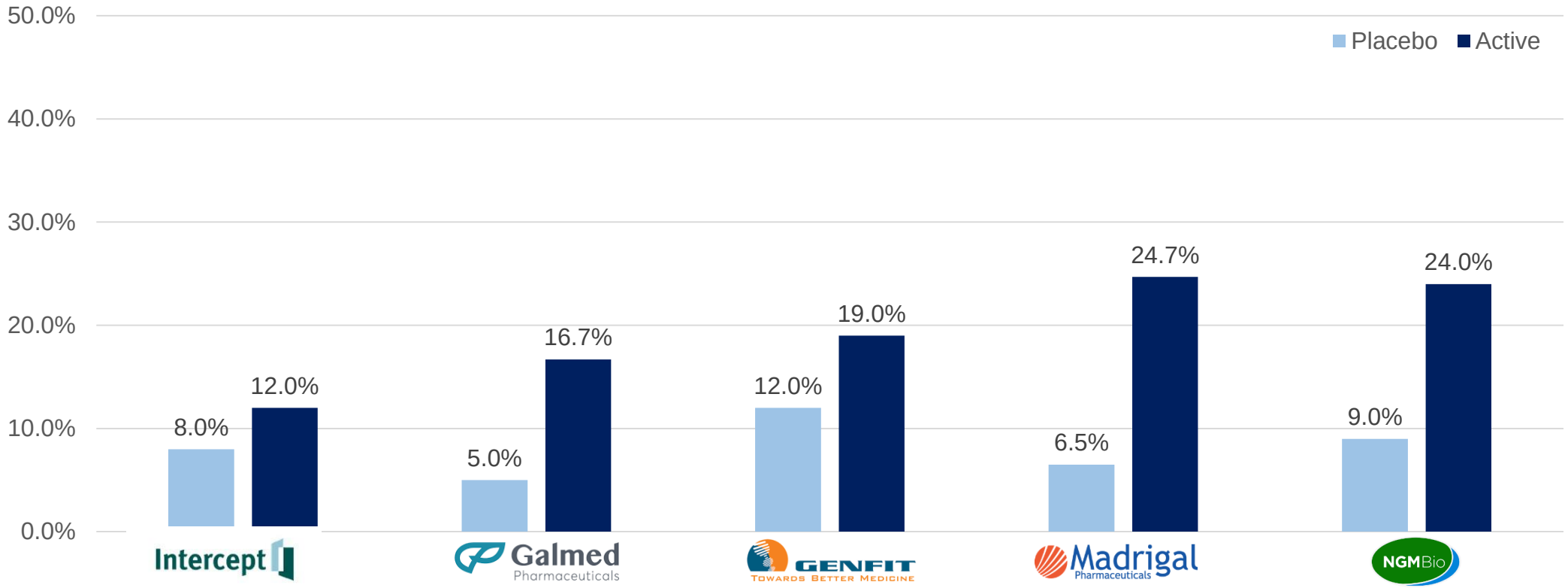


	Ocaliva	Elafibranor	Aramchol	Resmetirom	Aldafermin
	Phase III	Phase II	Phase II	Phase II	Phase II
N	931	276	247	125	78
P	0,0002		0,21	No stats reported	No stats reported

Source: ocaliva 25mg: Younossi et al, Lancet 2019; 394:2184-96 / Ocaliva EASLD-AASLD 2019 presentations ; 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; Aldafermin 1mg: 2020 NGM biopharmaceuticals presentation

Results by key competitors show room for improvement (II/II)

NASH resolution without worsening of fibrosis



	Ocaliva	Aramchol	Elafibranor	Resmetirom	Aldafermin
	Phase III	Phase II	Phase II	Phase II	Phase II
N	931	247	276	125	78
P	0,13	0,051	0,045	0,03	No stats reported

Source: ocaliva 25mg: Younossi et al, Lancet 2019; 394:2184-96 / Ocaliva EASLD-AASLD 2019 presentations ; 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; Aldafermin 1mg: 2020 NGM biopharmaceuticals presentation

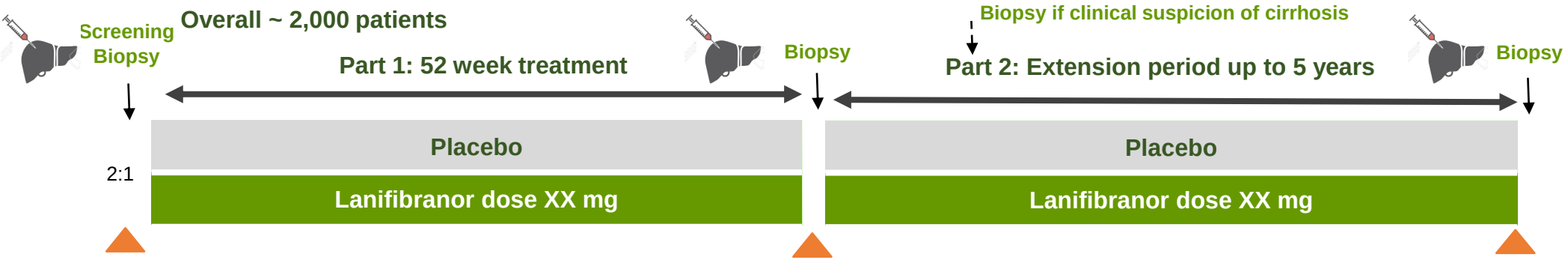
Lanifibranor: differentiated potential to address all features of NASH in safe and efficacious manner

	Lanifibranor	Ocaliva	Elafibranor	Cenicriviroc	Resmetirom	Aldafermin	Aramchol
	inventiva	Intercept	GENFIT Towards Better Medicine	Allergan	Madrigal Pharmaceuticals	NGM Bio	Galmed Pharmaceuticals
Insulino-resistance	✓	✗	✓	✗	✗	Unclear	✗
Steatosis	✓	✗	✗	✗	✓	✓	✓
Necro-inflammation	✓	✗	✓	✗	✓	✓	Unclear
Fibrosis	✓	✓	Unclear	✓	Unclear	✓	✗

Source: company estimates and evaluation

Lanifibranor: Phase III design – work in progress

A randomized, double-blind, placebo-controlled, multicentre, phase 3 study evaluating long-term efficacy and safety of lanifibranor in adult patients with NASH with liver fibrosis



Main inclusion criteria

- Adults ≥18 years of age
- Patients with biopsy-proven NASH
  - Steatosis score ≥ 1
  - NAFLD activity score (NAS) ≥5, with at least 1 point for inflammation and 1 point for ballooning OR NAS score of ≥4 with at least 2 points for either inflammation or ballooning
  - Fibrosis score F2-F3
- Stratification on T2DM
- Stratification on F2/F3

Interim primary endpoints n~1,000 patients

- Histology improvement at Week 52:
  - NASH resolution with no worsening of fibrosis OR
  - ≥1 stage reduction of fibrosis with no worsening of NASH

Key secondary endpoints

- Week 24 in patients with T2DM at baseline and HbA1c ≥7%, proportion of patients with HbA1c <7%

Other secondary endpoints

- Weeks 52 and yearly: in non-diabetic patients, time to T2DM (newly diagnosed/treated)
- Change in liver enzymes, inflammatory and fibrosis markers, glucose and lipid metabolism parameters, adiponectin
- PRO-QoL
- Safety

Hard clinical endpoints

- Histological progression to cirrhosis F4
- All cause mortality
- Hepatic decompensation events
  - Hepatic encephalopathy
  - Variceal bleeding
  - New onset ascites requiring treatment
  - Spontaneous bacterial peritonitis
- MELD score ≥15
- Liver transplant

Synopsis and protocol currently being drafted

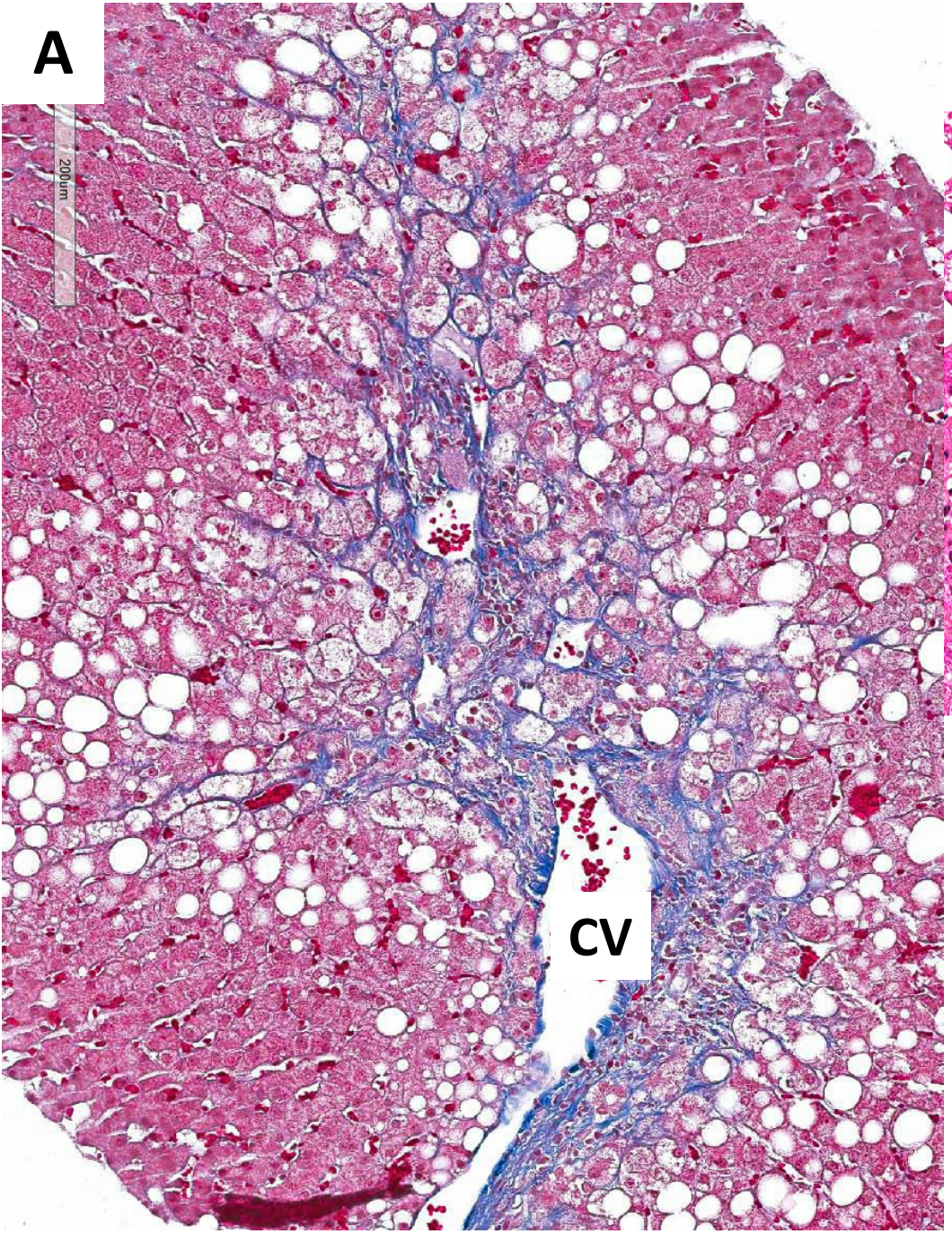
Lanifibranor: NASH key milestones

- Native phase IIb head-line results publication: **June 2020**
- Finalization of phase III synopsis and protocol: **ongoing**
- End of phase IIb meeting with FDA: **Q4 2020**
- Finalization of phase II study in NAFLD patients with TD2M conducted by Pr. Cusi
- Launch of pivotal phase III study in NASH

SAF scoring and biopsy reading in NASH trials

Prof. Pierre Bedossa, MD

University Paris Diderot, pathologist and Native Central reader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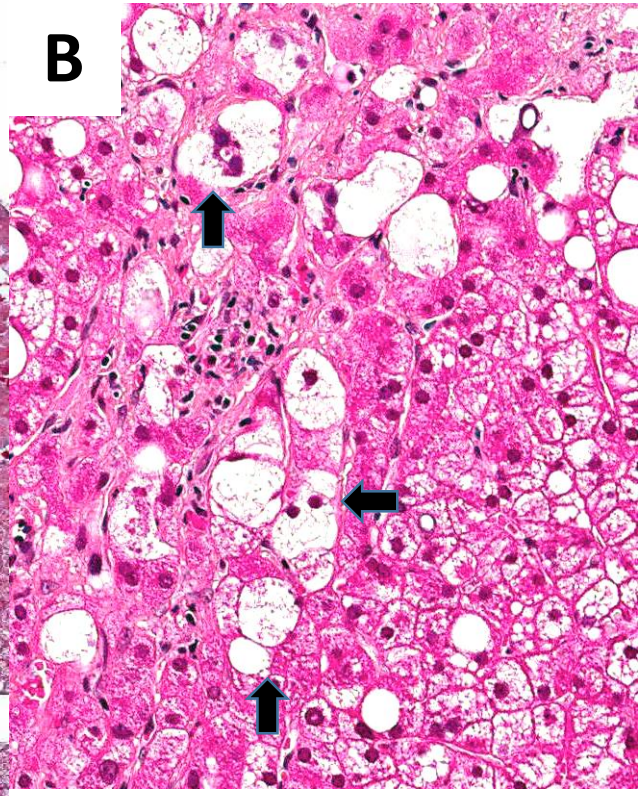
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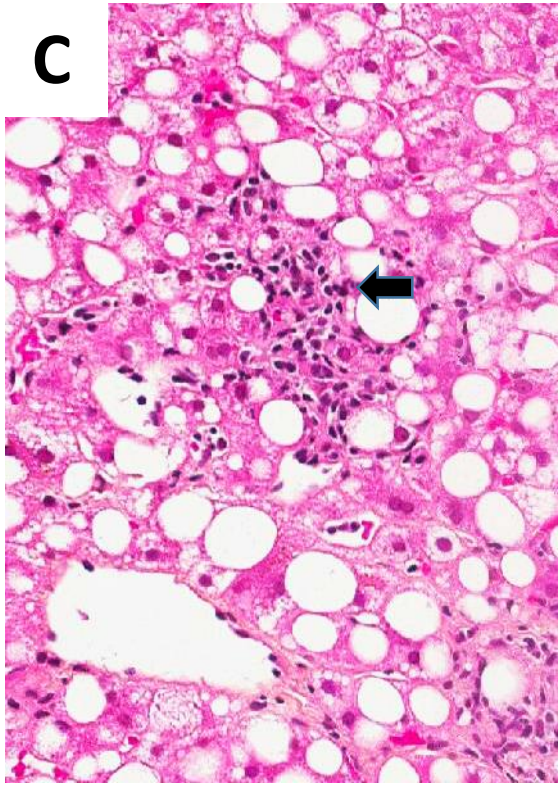
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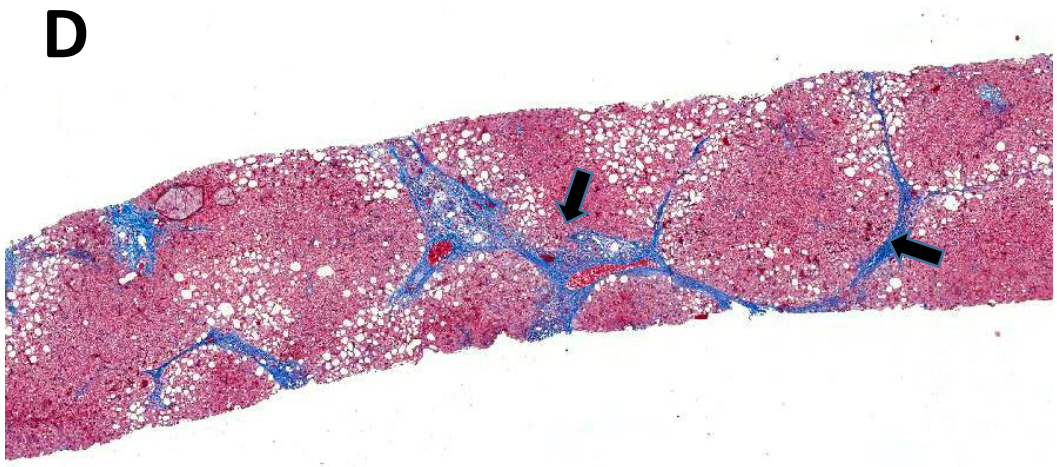
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The NAFLD Activity Score (NAS) (Kleiner 2005)

TROUBLES WITH NAS

Conceptual mistakes:

- Steatosis not a marker of activity (steatosis not a driver of fibrosis)
- Ballooning underweighted in NAS (2 points vs 3 for inflammation and steatosis), max 2 out of 8 points

Scoring not accurate enough:

- Inflammation and ballooning grading moderatly reproducible

Consequences

- NAS has never been demonstrated a prognosis value
- Significant interobserver variability in scoring, a challenge in clinical trials

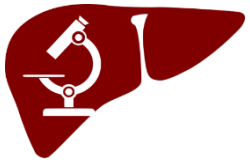
The NAFLD Activity Score (NAS) (Kleiner 2005)

Reference	NASH Diagnosis	Steatosis	Inflammation	Ballooning
Inter-observer variability (Kappa)				
Younossi 1998	0.5	0.64	0.33	0.50
Kleiner 2005	0.61	0.79	0.45	0.56
Bedossa 2014	0.54	0.61	0.41	0.52
Kleiner 2019	0.66	0.77	0.46	0.54

- High inter-observer variability in grading of ballooning and inflammation
- Explained by vague or inaccurate definition criteria

Ballooning: 0=none, 1=few, 2=many

The S.A.F. score (Steatosis-Activity-Fibrosis)



- Steatosis (0 - 3) as for NASH CRN
- ACTIVITY (0 - 4) = BALLOONING (0-2) + LOBULAR INFLAMMATION (0-2)
- Fibrosis (0 - 4) as for NASH CRN

$$S_{0\text{-}3}A_{0\text{-}4}F_{0\text{-}4}$$

Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K. Hepatology. 2012 Nov;56(5):1751-9

From NAS to SAF

NAS

SAF (Activity)

Hepatocyte ballooning

- Round shape **AND** clear, pale or reticulated cytoplasm
- Scoring of ballooning:

0: normal hepatocytes with cuboidal shape, sharp angles and pink eosinophilic cytoplasm or rounded hepatocytes without cytoplasmic clearing

1: presence of clusters of hepatocytes with round shape and pale cytoplasm, usually reticulated. Although the cell shape is different, the size is similar to that of normal hepatocytes

2: as for score 1, but where there is also at least one enlarged ballooned hepatocyte (at least twice the size [2x] of a normal hepatocyte, within a cluster of hepatocytes with score 1 ballooning)

*Bedossa P, FLIP Pathology Consortium. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of non-alcoholic fatty liver disease. Hepatology 2014; 60:565-575.

SAF score: inter-observer variation

κ score		
Steatosis (0 1 2 3)	κ = 0.61	Substantial
Activity **Ballooning (0 1 2)** **Lob. Infl (0 1 2)**	**κ = 0.75** **κ = 0.8** **κ = 0.72**	**Substantial**
Fibrosis (1-2-3-4)	κ = 0.83	Perfect

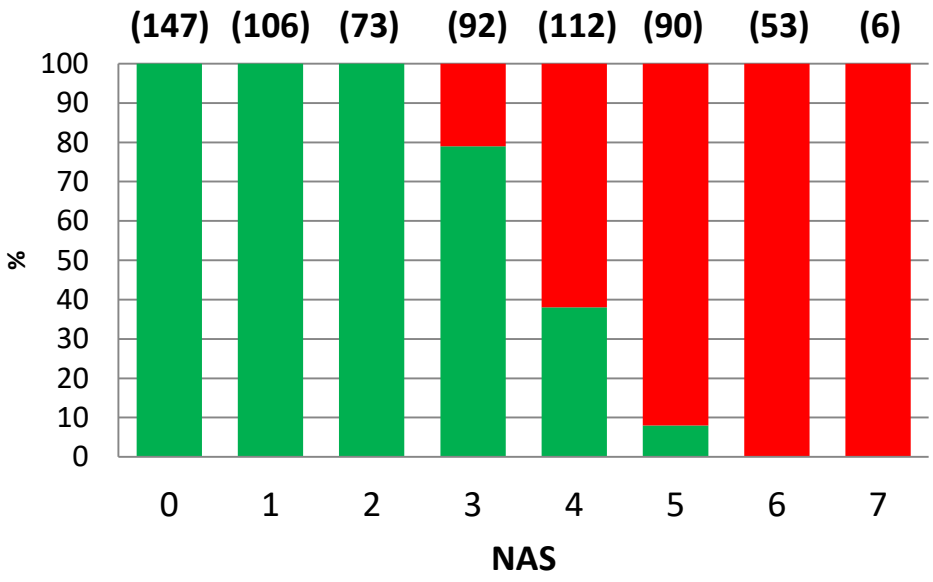
SAF score : highly reproducible semiquantitative features

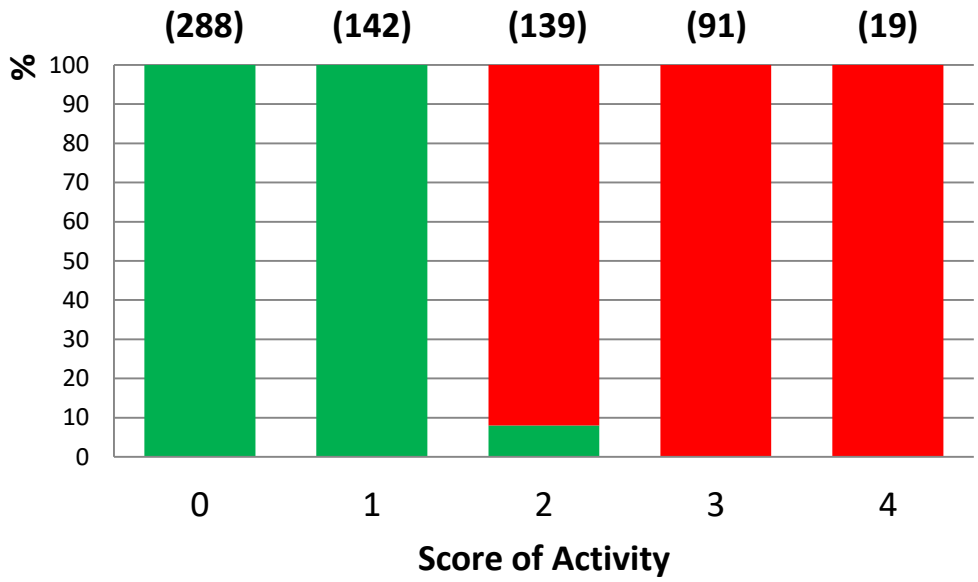
Hepatology 2012, Hepatology 2014,

Distribution of NAS and activity according to SAF according to presence of NASH (algorithmic definition)

In green, % of cases without NASH, in red, % of cases with NASH

(morbidly obese, n=860)





Hepatology 2014, Hepatology 2016, Gut 2016

WORKFLOW of BIOPSIES

Hepatologist / Radiologist → Adequate sample

↓

Local Pathologist
(8 unstained slides) → Adequate sections

↓

Central Lab (blinding, staining)

↓

Central Pathologist → Robust evaluation

↓

Eligibility

↓

ENROLMENT

REASONS FOR FAILURE TO ENROLMENT (BIOPSY)

1 INADEQUATE SAMPLE

2 INADEQUATE SECTIONS

3 HISTOLOGICAL CRITERIA NOT MET

ADEQUACY OF BIOPSY SAMPLE

Biopsy performed by different centers around the world

Providing recommendations

- Criteria for adequacy : > 20 mm length, not badly fragmented
- Hepatologist / Radiologist trained to liver biopsy procedure
- Adequate material : 16 gauge needle
- Cutting (Tru-cut) / Aspiration (Menghini) needle
- Repeat passages if needed
  - ➢ Careful processing in pathology laboratory
  - ➢ Sensitize (valorize) your pathologist !

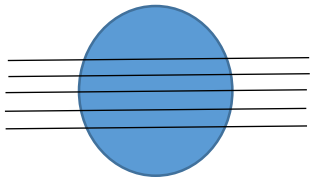
ADEQUACY OF BIOPSY : THE ROLE OF CENTRAL PATHOLOGY LAB

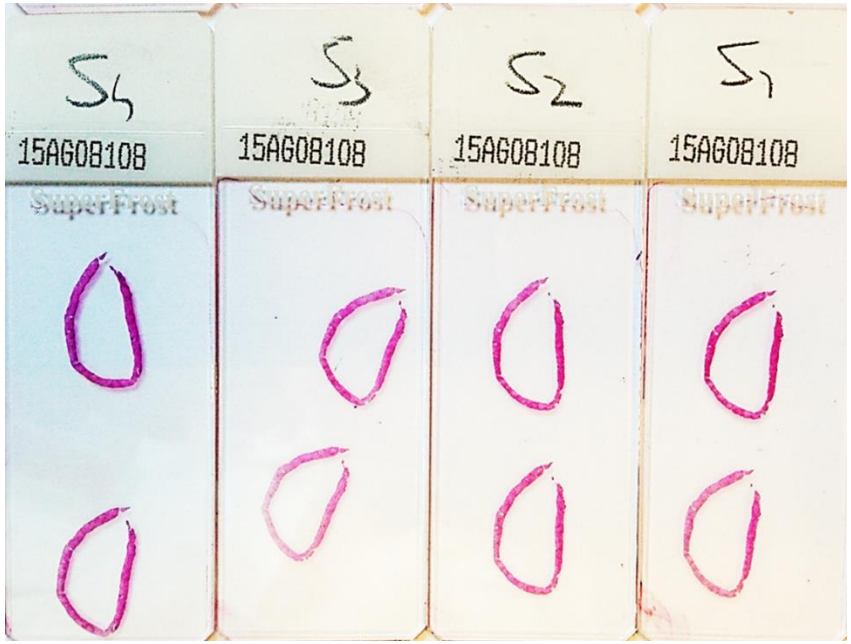
Use of central laboratory for histotechnology

- Careful processing in pathology lab by trained histotechnologist
- Reliable staining methods (H&E and Masson Trichrome)
- QC in the central pathology lab by expert in liver pathology
- Limited turn-around-time

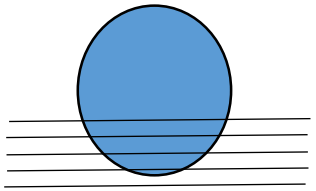
ADEQUACY OF BIOPSY : THE ROLE OF CENTRAL PATHOLOGY LAB

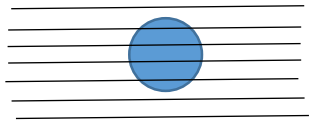
16 gauge needle

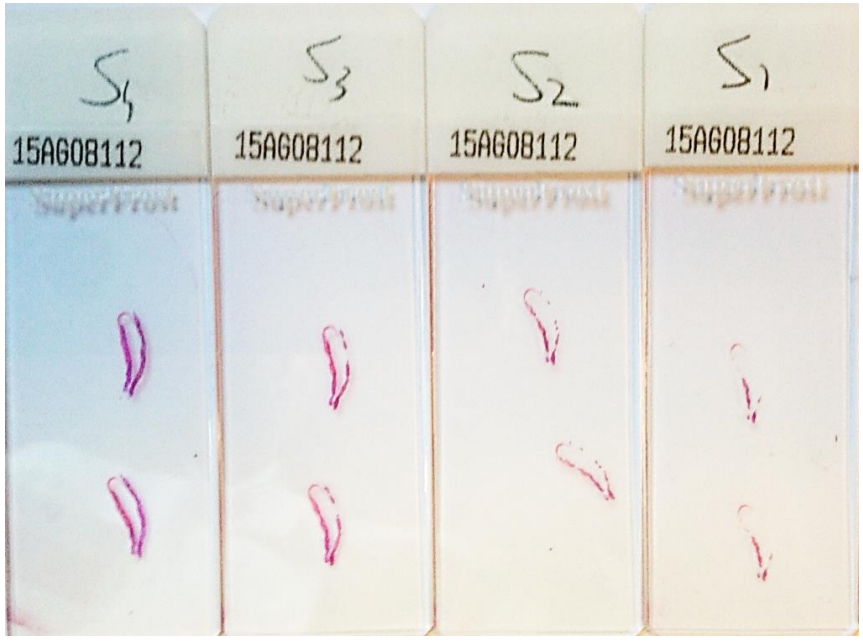




16 gauge needle **20 gauge needle**







Reading biopies: the need of a central pathologist

- Highly experienced in clinical trials and NASH pathology
- Low intra-observer variability
- Using same diagnostic criteria during all the study
- Adequate scoring sheet
- Limited turn-around-time

Native phase 2B trial update

Prof. Sven Francque, MD

University Hospital Antwerp, Native Principal Investigator

NATIVE: a Phase III enabling study in NASH

Trial design

A randomized, double-blind, placebo-controlled, multicenter, dose-range, proof-of-concept, 24-week treatment study of lanifibranor in adult subjects with nonalcoholic steatohepatitis (NASH)

Principal investigators

- Prof. Sven Francque (Antwerp University, Belgium)
- Prof. Manal Abdelmalek (Duke University, USA)

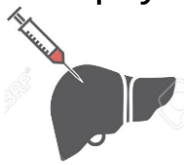
Inclusion criteria

- Biopsy confirmed NASH patients with an inflammation and ballooning score of 3 or 4 according to SAF scoring
- Steatosis score ≥ 1 and fibrosis score < 4 (no cirrhosis)

225 patients treated for 24 weeks + 4-week safety follow-up

Double blind, randomized, placebo-controlled

Screening
- Liver biopsy

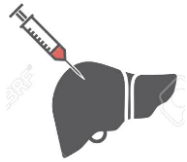


Placebo, ± 75 patients

Lanifibranor, 800 mg once daily, ± 75 patients

Lanifibranor, 1200 mg once daily, ± 75 patients

End of treatment
- Liver biopsy



More information on: http://www.native-trial.com/ ; clinicaltrials.gov identifier: NCT03008070

Primary efficacy endpoint

Primary endpoint

Decrease from baseline to week 24 of at least 2 points of the SAF activity score (inflammation and ballooning) without worsening of fibrosis

- Central reading (Prof. Pierre Bedossa)
- Statistical hypotheses based on:
  - 72 evaluable patients per arm
  - 10% responders on placebo
  - Excess rate of 20% considered clinically relevant
- Main analysis: evaluation of treatment effect
  - 1200mg versus placebo
  - 800mg versus placebo
- Analyses by sub-groups
  - Diabetic versus non-diabetic
- Evaluation of dose effect: 1200mg versus 800mg

Secondary endpoints

Key secondary endpoints

- NASH resolution with no worsening of fibrosis
- Improvement of fibrosis by at least 1 stage without no worsening of NASH
- NASH improvers
  - Decrease from baseline to week 24 of at least 2 points of the NAS CRN score with no worsening of fibrosis

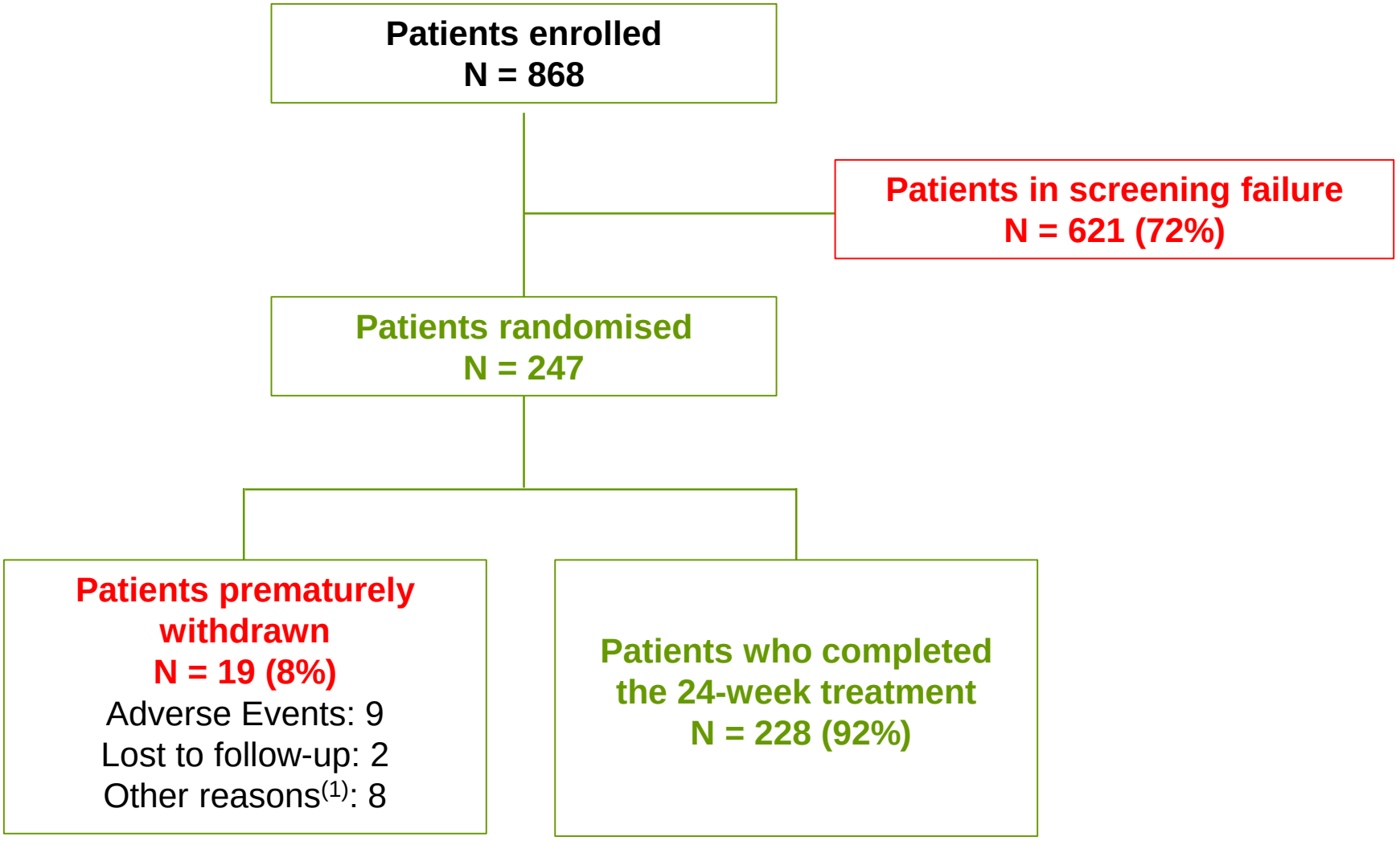
Other secondary endpoints

- Resolution of NASH and improvement of fibrosis by at least 1 stage
- Resolution of NASH with no worsening of fibrosis and NASH improvers
- Improvement of fibrosis by at least 2 stages without worsening of NASH
- Change in glucose metabolism parameters (fasting glucose, insulin, HOMA index, HbA1c, …)
- Change in liver function tests (ALT, AST, GGT, Alkaline Phosphatase, Total Bilirubin)
- Change in main plasma lipid parameters (TC, HDL-C, calculated LDL-C, TG,…)
- Change in efficacy inflammatory markers (fibrinogen, hs-CRP, alpha2 macroglobulin, haptoglobin,…)
- Change in efficacy fibrosis markers (TIMP-1, TIMP-2, Hyaluronic acid, P3NP, NFS, FIB-4 score, ELF score, Pro-C3,…)

NATIVE trial: confirmation of lanifibranor's good safety profile by four positive DSMBs

Parameters	DSMB # 1	DSMB # 2	DSMB # 3	DSMB # 4
Date of DSMB meeting	June 2018	October 2018	March 2019	**September 2019**
# patients reviewed / % of total patients in the study	52 / 21%	94 / 38%	156 / 63%	**227 / 92%**
# patients having finished the study / % of total patients in the study	18 / 7%	36 / 15%	86 / 35%	**139 / 57%**
DSMB conclusion: continuation of the study as planned	✓	✓	✓	✓

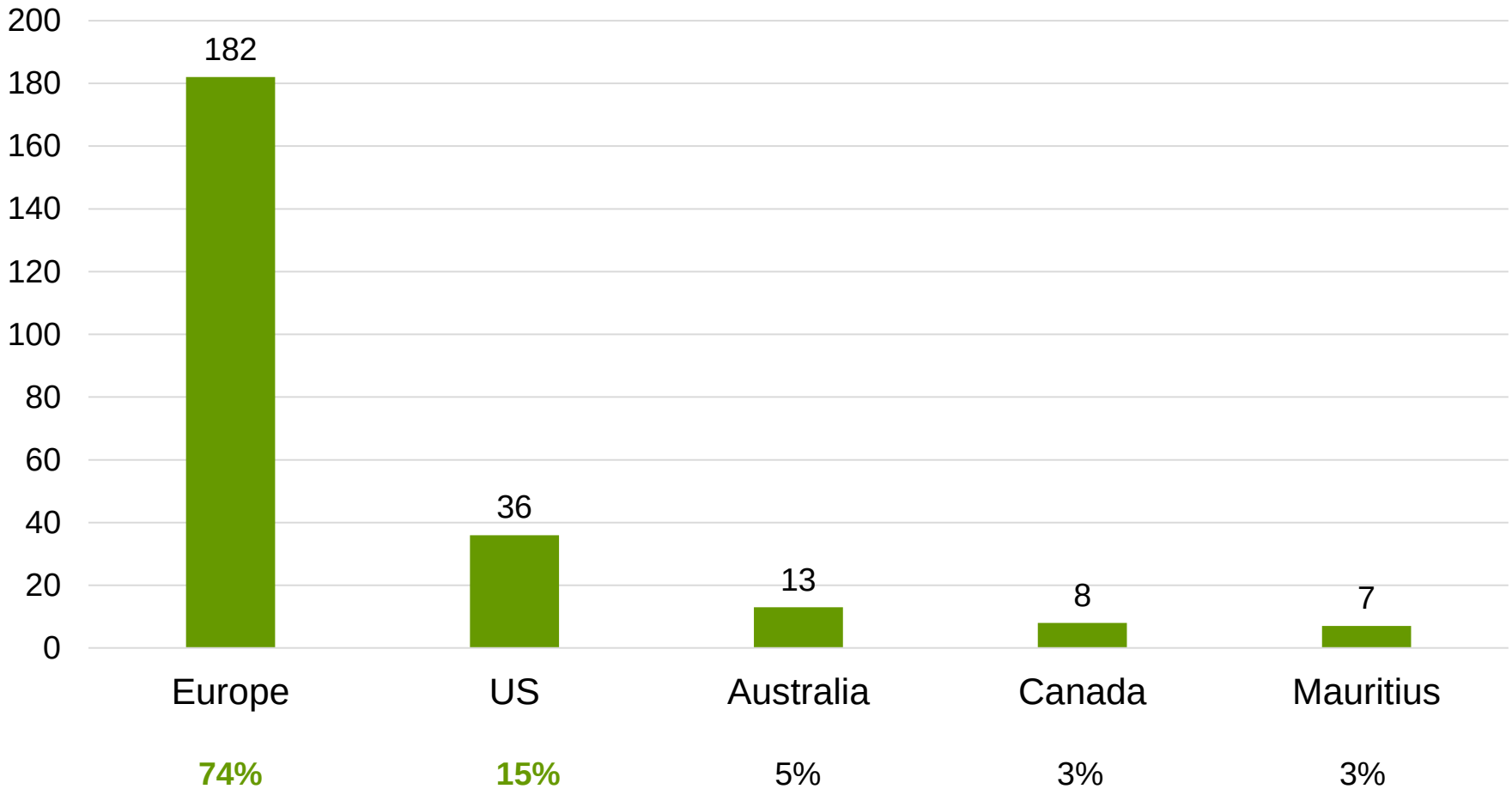
Patient disposition



(1) Withdrawal by patient (n=5); Forbidden concomitant treatment (n=2); Non-compliance to study schedule (n=1)

Patient distribution: ~90% of patients from Europe and the United-States

Number of patients randomized by region



Baseline characteristics (I/II)

		Absence of T2DM	Presence of T2DM	Overall
		N = 145	N = 102	N = 247
Sex	Female	83 (57%)	61 (60%)	144 (58%)
	Male	62 (43%)	41 (40%)	103 (42%)
Age (years)	Mean ± SD	51.7 ± 13.6	56.2 ± 10.4	53.6 ± 12.5
	Min ; Max	20 ; 76	28 ; 77	20 ; 77
Age in categories	< 65 yrs old	120 (83%)	79 (77%)	199 (81%)
	≥ 65 yrs old	25 (17%)	23 (23%)	48 (19%)
Race	Caucasian	133 (92%)	98 (96%)	231 (94%)

Baseline characteristics (II/II)

		Absence of T2DM	Presence of T2DM	Overall
		N=145	N=102	N=247
Weight (kg)	Mean ± SD	93.1 ± 19.0	93.3 ± 18.8	93.2 ± 18.9
	Min ; Max	51 ; 142	55 ; 145	51 ; 145
BMI (kg/m²)	Mean ± SD	32.6 ± 5.4	33.2 ± 5.4	32.9 ± 5.4
	Min ; Max	21 ; 45	23 ; 44	21 ; 45
BMI in class	Normal	7 (5%)	7 (7%)	14 (6%)
	Overweight	46 (32%)	26 (25%)	72 (29%)
	Obese class I	51 (35%)	33 (32%)	84 (34%)
	Obese class II	41 (28%)	36 (35%)	77 (31%)

Normal: 18.5 ≤ BMI < 25 kg/m² ; Overweight: 25 ≤ BMI < 30 kg/m² ; Obese class I (moderate): 30 ≤ BMI < 35 kg/m² ;
Obese class II (severe): 35 ≤ BMI < 40 kg/m² ; Obese class III (morbid): BMI ≥ 40 kg/m²

Metabolic syndrome

	Absence of T2DM N=145	Presence of T2DM N=102	Overall N=247
Waist Circumference ≥94 (M)/80 (F) cm	135 (93%)	98 (97%)	233 (95%)
Hypertension	78 (54%)	77 (75%)	155 (63%)
Type 2 diabetes or Fasting Glucose ≥5.6 mmol/L	51 (35%)	102 (100%)	153 (62%)
Triglycerides > 1.7 mmol/L or hypertriglyceridemia	78 (54%)	76 (75%)	154 (62%)
HDL <1.0 (M) / 1.3 (F) mmol/L	66 (46%)	49 (48%)	115 (47%)
Metabolic syndrome	**82 (57%)**	**90 (88%)**	**172 (70%)**
Number of features of the metabolic syndrome			
0	3 (2%)	0 (0%)	3 (1%)
1	19 (13%)	2 (2%)	21 (9%)
2	41 (28%)	10 (10%)	51 (21%)
3	**46 (32%)**	**24 (24%)**	**70 (28%)**
4	**23 (16%)**	**36 (35%)**	**59 (24%)**
5	**13 (9%)**	**30 (29%)**	**43 (17%)**

Liver Biopsy at screening

NAS scoring

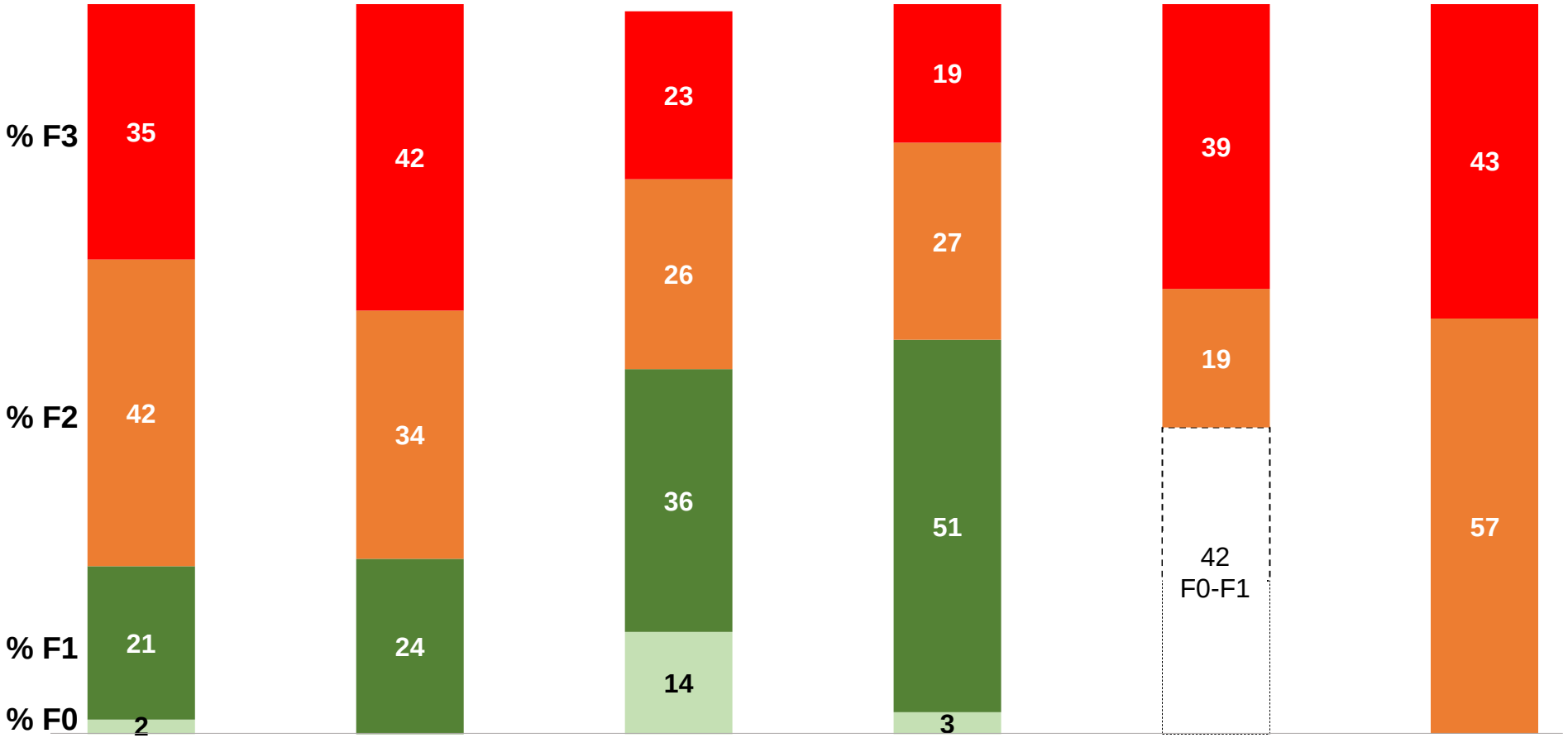
		Absence of T2DM N = 145	Presence of T2DM N = 102	Overall N = 247
Steatosis	Mean ± SD	2.5 ± 0.7	2.6 ± 0.6	2.5 ± 0.7
Inflammation	Mean ± SD	1.6 ± 0.6	1.6 ± 0.6	1.6 ± 0.6
Ballooning	Mean ± SD	1.7 ± 0.4	1.8 ± 0.4	1.8 ± 0.4
NAS score	Mean ± SD	5.8 ± 1.0	6.0 ± 1.0	5.9 ± 1.0

SAF scoring

		Absence of T2DM N = 145	Presence of T2DM N = 102	Overall N = 247
Steatosis	Mean ± SD	2.5 ± 0.7	2.6 ± 0.6	2.5 ± 0.7
Inflammation	Mean ± SD	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5
Ballooning	Mean ± SD	1.7 ± 0.4	1.8 ± 0.4	1.8 ± 0.4
Activity	Mean ± SD	3.2 ± 0.5	3.3 ± 0.5	3.3 ± 0.5
Fibrosis	Mean ± SD	2.0 ± 0.8	2.2 ± 0.8	2.1 ± 0.8

NATIVE patient fibrosis score distribution similar to Intercept phase III trial

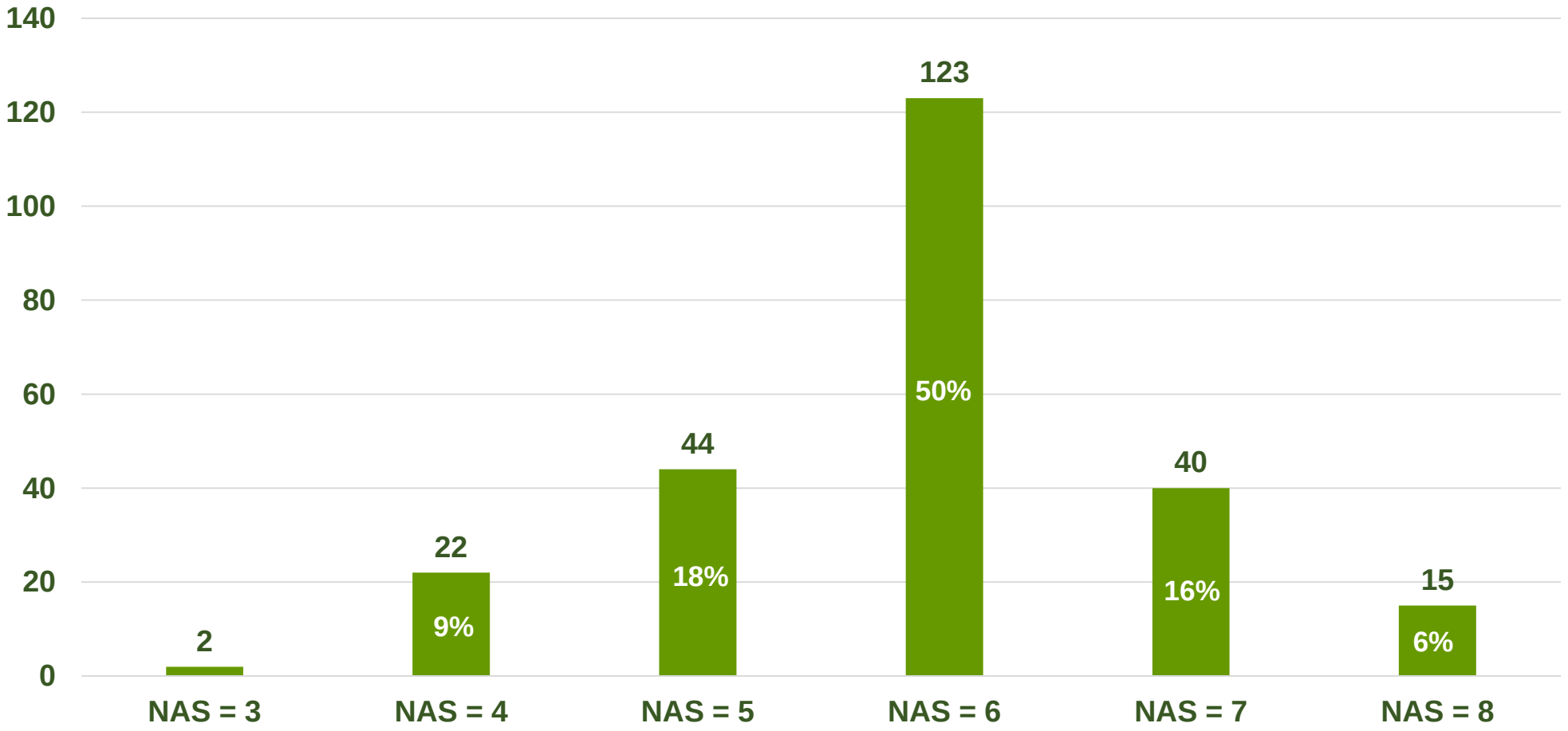
Patient distribution according to fibrosis scoring (%)



Source: ocaliva: Younossi et al, Lancet 2019; 394:2184-96 / Ocaliva EASLD-AASLD 2019 presentations ; elafibranor: Ratziu et al, Gastorenterology 2016; 150:1147-1159 ; resmetirom: Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6; Aramchol AASLD 2018 presentation; Aldafermin 2020 NGM biopharmaceuticals presentation ; lanifibranor company data

The screening strategy has successfully led to the recruitment of severe patients

NATIVE patient distribution according to the NAS score



NATIVE NAS score compares favorably with other phase II or III trials

	Lanifibranor	Ocaliva	Elafibranor	Resmetirom	Aramchol	Aldafermin
	Phase II	Phase II	Phase III	Phase II	Phase II	Phase II	Phase II
# of patients	247	283	1218	276	125	247	78
Inclusion criteria	SAF ≥ 3 Steatosis ≥ 1 F0, F1, F2, F3	NAS ≥ 4	NAS ≥ 4 F1a, 1b with risk factors, F2, F3	NAS ≥ 3	NAS ≥ 4 F1,F2, F3	NAS ≥ 4	NAS ≥ 4 F2 or F3
Mean NAS	5,9	5,2	NA	5,0	4,9	5,1	5,6
NAS%	72% NAS≥ 6	NA	64% NAS ≥ 6	34% NAS≥ 6	46-58% NAS ≥ 5(1)	NA	NA
Mean Fibrosis	2,1	1,8	NA	1,6	NA	2,0	NA

Source: ocaliva: Neuschwander et al, Lancet 2015;385:958-65 / Younossi et al, Lancet 2019; 394:2184-96 / Ocaliva EASLD-AASLD 2019 presentations ; elafibranor: Ratziu et al, Gastorenterology 2016; 150:1147-1159 ; resmetirom: Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6; Aramchol AASLD 2018 presentation; Aldafermin 2020 NGM biopharmaceuticals presentation ; lanifibranor company data; (1) placebo vs treatment

Conclusions

Native trial is a well-thought and designed trial including the most up-to date NASH end-points:

- NASH resolution, fibrosis score, NASH improvers,….

The trial has run smoothly with 92% of the 247 patients randomized completing the study

- 4 DSMB took place during the trial period, recommending each time to continue with no change to the protocol

Baseline characteristics are in-line with other NASH trials

- More than 40% of patients randomized have TD2M, stratified in each arm and allowing to run sub-analysis

The screening strategy has allowed to include patient with an elevated score of fibrosis and NAS

- 77% are F2 or F3 patients
- 73% have a NAS ≥ 6

Results will be communicated in June

Q & A