Developing breakthrough therapies in NASH and MPS

Corporate Presentation
May 2020

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Inventiva: highlights

- Clinical stage biotech with focus on **oral small molecules for high unmet need** in fibrosis, lysosomal storage disorders and oncology

- **Two unencumbered late stage assets** in two high value indications
  - **Lanifibranor** – only pan-PPAR agonist in clinical development for NASH, Phase IIb data due in June
  - **Odiparcil** – first orally available therapy for MPS

- **A clinical stage partnership with AbbVie**
  - **ABBV-157 RORγ program** with blockbuster potential in several auto-immune indications currently in clinical development in patients with psoriasis
  - Inventiva eligible to milestone payments and sales royalties

- **Compelling early stage pipeline**
  - YAP-TEAD program in late pre-clinical stage approaching clinical candidate selection

- **State of the art R&D capabilities** including wholly owned 'pharma scale' discovery facilities with a **discovery engine** focused on nuclear receptors, transcription factors and epigenetic targets
  - 240,000 compound library, 60% of which are proprietary

- **Strong US and European shareholder base and experienced senior management** team with a track record of operational and scientific excellence

- Cash position allowing a **runway until end of Q2 2021**

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

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

- Wide expertise within the areas of research, development, marketing, strategy and commercial operations
- Held senior positions at Abbott, Fournier, Solvay Pharma and The Boston Consulting Group
- Former member of both Fournier and Solvay Pharma Executive Committees

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

- Has successfully managed numerous research programs leading to the discovery, development and commercialization of innovative compounds, including lanifibranor and Ferring's GnRH antagonist Degarelix/ Firmagon®
- Held several senior research positions at Fournier, Solvay Pharma and Abbott

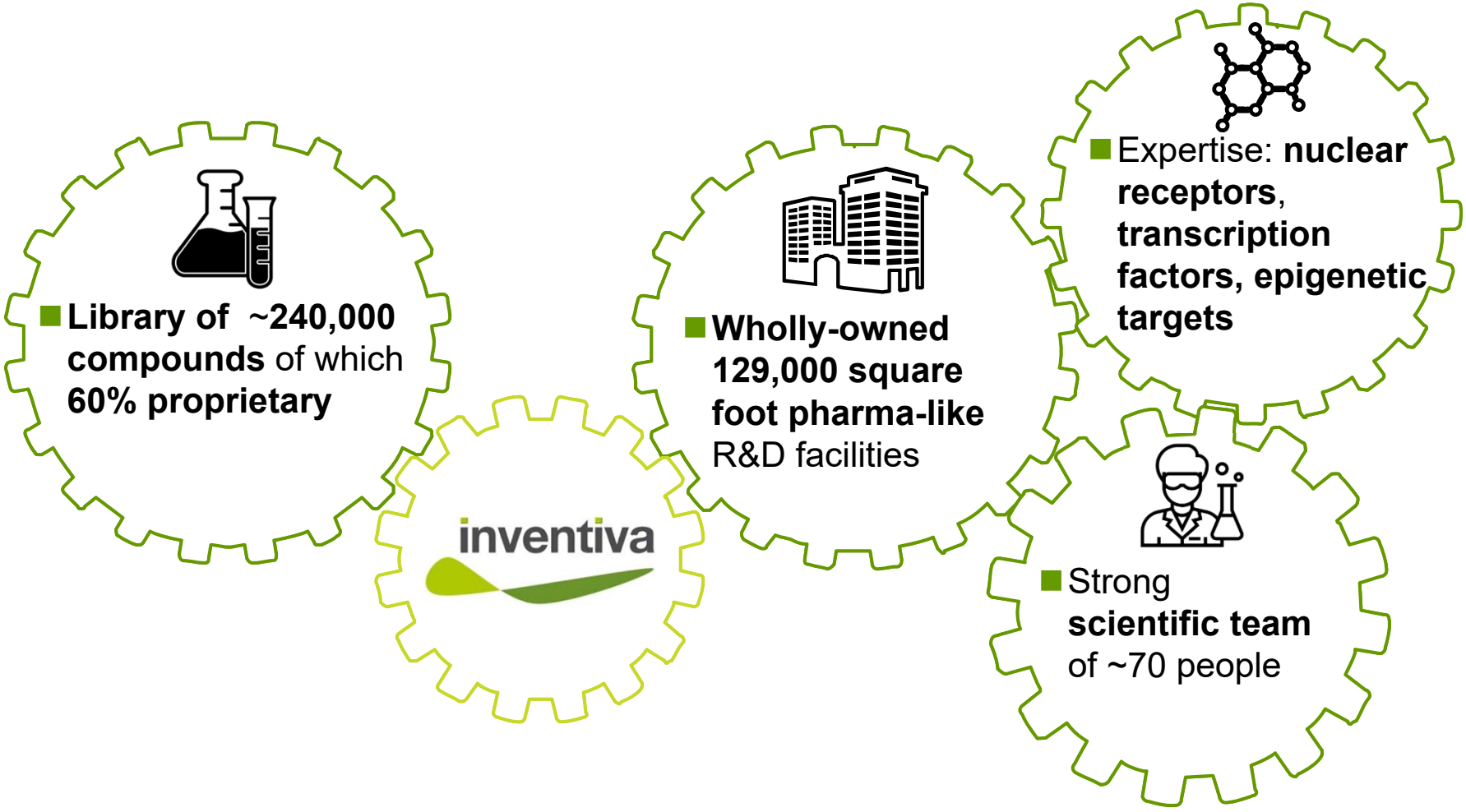
Jean Volatier, MA, CFO

- Started his career with PwC in Paris and Philadelphia
- Former Head of controlling at URGO & Financial Director International Operations of Fournier
- Held various positions as CFO with Soufflet and Naos groups

Marie-Paule Richard, MD, CMO

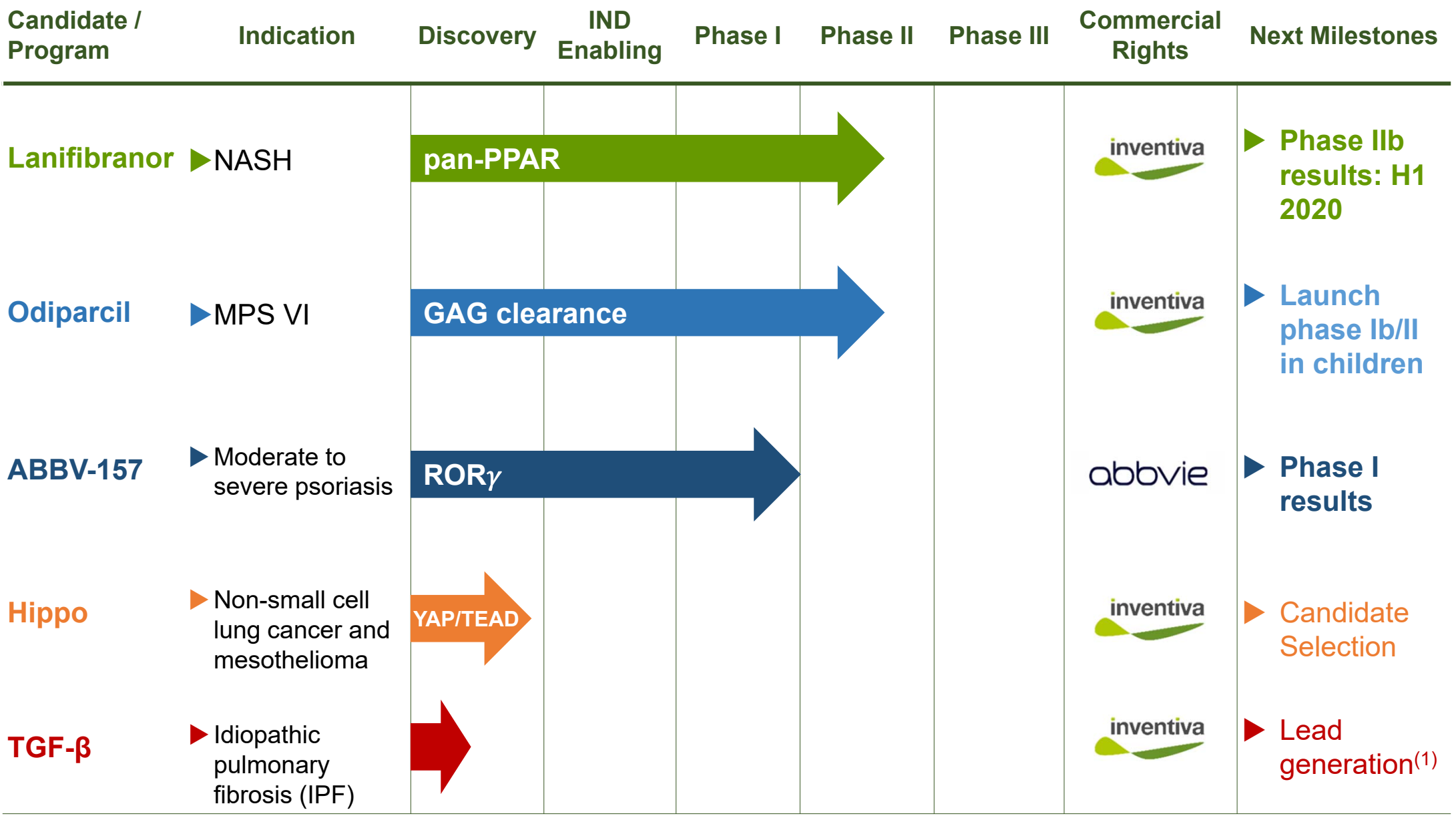
- Long and diverse international experience acquired with large pharmaceutical organizations such as GSK, Aventis, Sanofi Pasteur as well as biotech in CMO roles
- Former CMO of Belgium biotech Tigenix, recently acquired by Takeda

Validated oral small molecule-focused discovery engine targeting nuclear receptors, transcription factors and epigenetic modulation



Power of discovery engine underpins deep pipeline of clinical and discovery stage assets

Deep pipeline approaching major near term value inflection points



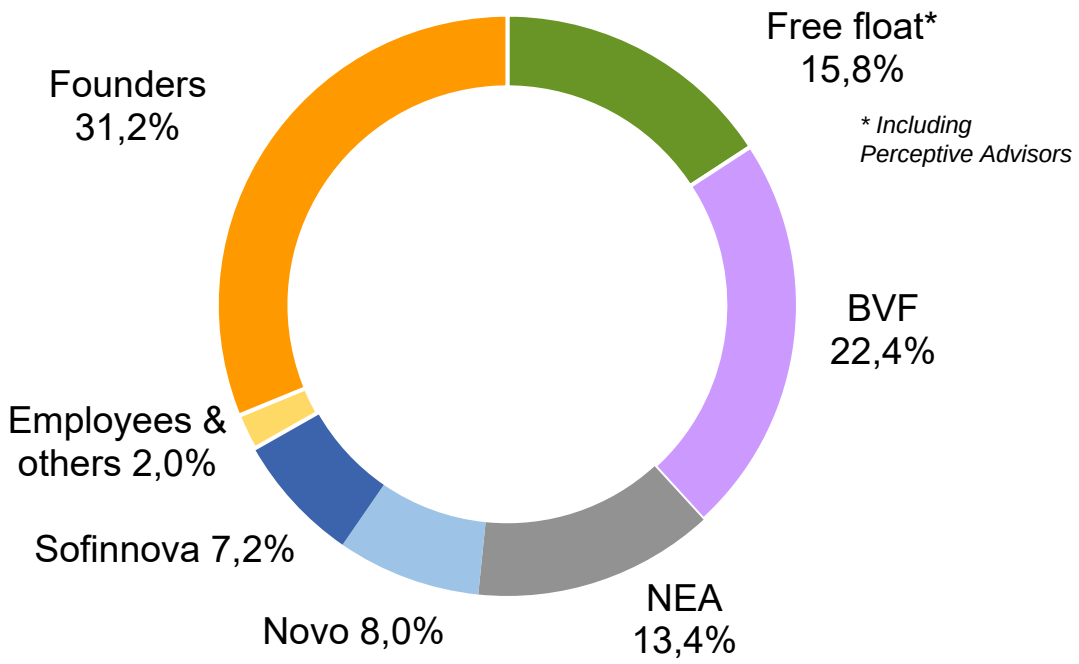
(1) Lead generation means identifying molecules in anticipation of selecting candidates

Key financials and shareholder base

Key financials

ISIN code	FR0013233012
Market	Euronext Paris
Shares outstanding	30.687.750
Market cap (May 5 2020)	€132m
Cash position (Dec. 31 2020)[1]	€35,8m compared to €56,7m as of December 2018. Runway mid-2021
Revenues in 2019 (Dec. 31, 2020)[1]	€7,1m compared to €3,2m in 2018
R&D expenditures in H1 2019 (June 30, 2019)	€19,6m compared to €15,9m in H1 2018

Shareholder base *(incl. capital increase)*



Analyst coverage

HC Wainwright	Ed Arce
LifeSci Capital	Patrick Dolezal
Jefferies	Peter Welford
KBC	Lenny Van Steenhuyse
Société Générale	Delphine Le Louët
Gilbert Dupont	Jamila El Bougrini

(1) unaudited

Lanifibranor in Nonalcoholic Steatohepatitis (NASH)

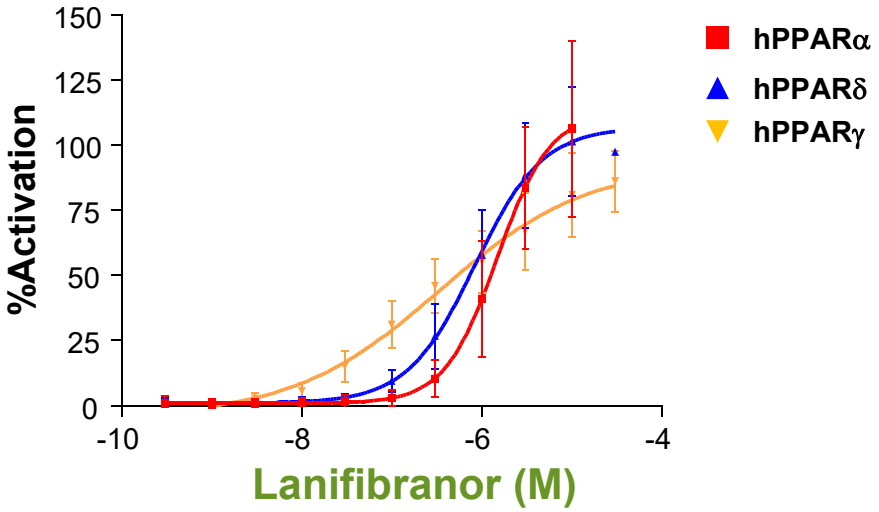
Lanifibranor: the only pan-PPAR agonist in clinical development for the treatment of NASH

- **Moderate and balanced pan-PPAR agonist activity** (PPARα, PPARγ and PPARδ) with differentiated chemical structure
- **Once daily oral administration**
- **Efficacy demonstrated** 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 safety profile** demonstrated in:
  - 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 study with **47** TD2M patients
  - Approximately **250** patients have been treated for 24 or 48 weeks in our ongoing and completed Phase IIb clinical trials
  - In connection with these trials, lanifibranor has undergone a total of **7 positive DSMB reviews**
- Composition of matter patent delivered in 59 countries and method of use patent granted in the US, China and in the EU: **limit of exclusivity 2035**
- **FAST Track** designation granted by FDA

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

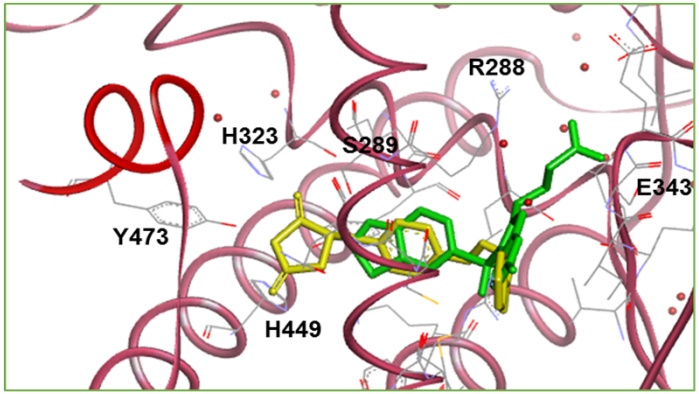
Lanifibranor is a differentiated pan-PPAR agonist with moderate and well balanced activity on the 3 PPAR isoforms

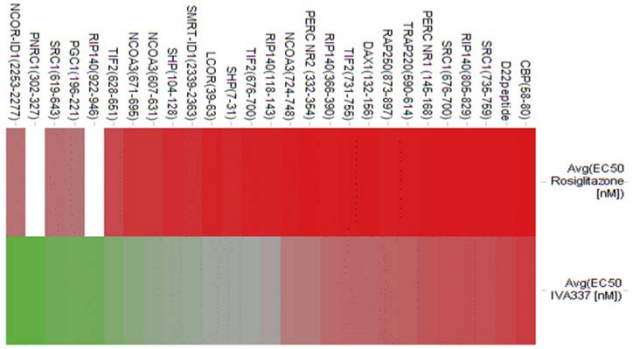
Lanifibranor human dose response curves and EC50s for various PPAR agonists



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]





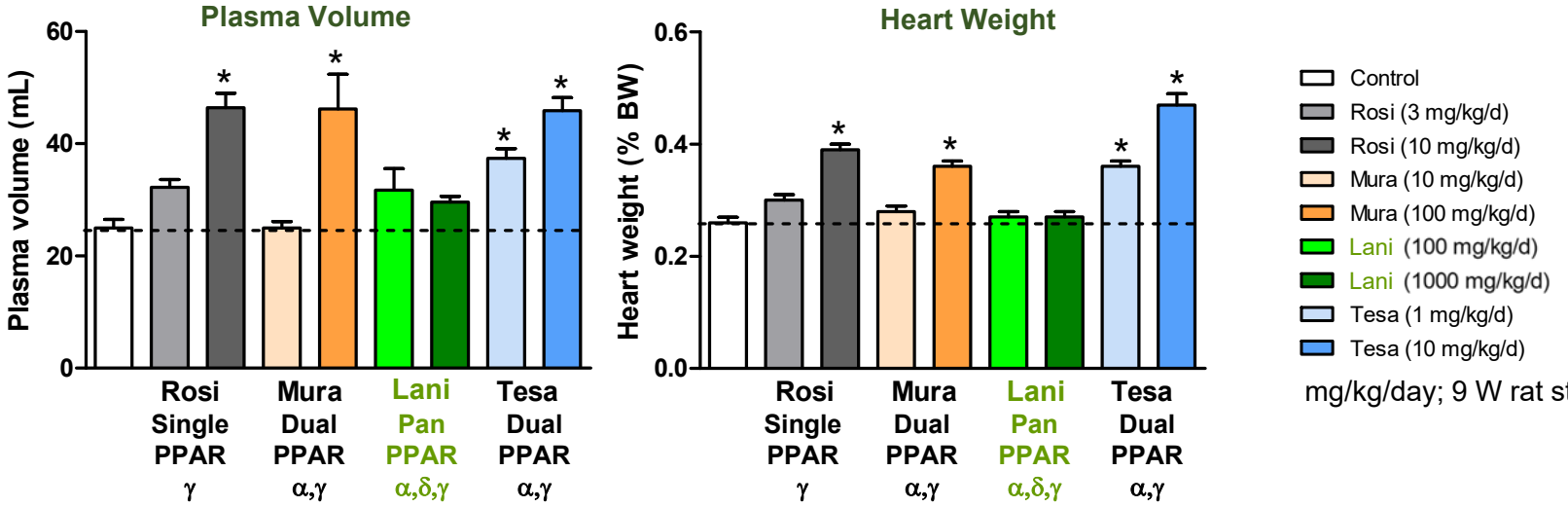
Potency scale: red 10 nM; grey: 500 nM; green 5 000 nM

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

Favorable safety profile differing from previously developed PPARs

Organ	PPAR isoforms activated	Reported PPAR liabilities	Lanifibranor effects
Heart	▶ PPARγ	▶ Fluid retention ▶ Cardiac hypertrophy	**Not observed**
Skeletal muscle	▶ PPARα	▶ Myofiber degeneration	**Not observed**
Kidney	▶ PPARα	▶ > 50% increases in creatinine, degenerative changes in renal tubules	**Not observed**
Urinary bladder	▶ PPARγ	▶ Proliferative changes in bladder epithelium	**Not observed**

Plasma volume and heart weight after administration of PPAR agonists



Lanifibranor not associated with plasma volume expansion or heart weight increase

Source: Company data

In long-term toxicological studies lanifibranor presents a safe and 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

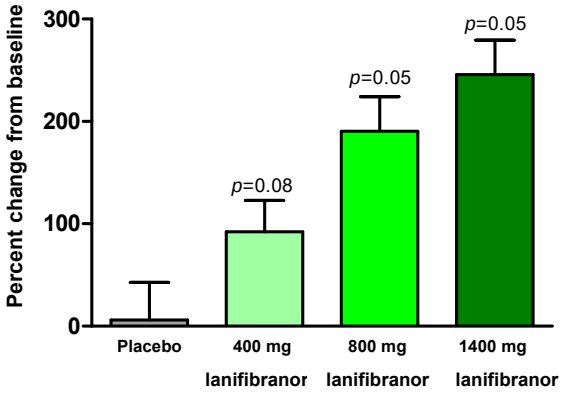
- Lanifibranor shows a very favorable profile in 12 month monkey study …
  - No adverse clinical signs were observed at any dose-level tested
  - No effects on body weight and heart weight, no haemodilution or creatinine increase
  - Electrocardiography and clinical pathology investigations did not reveal 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

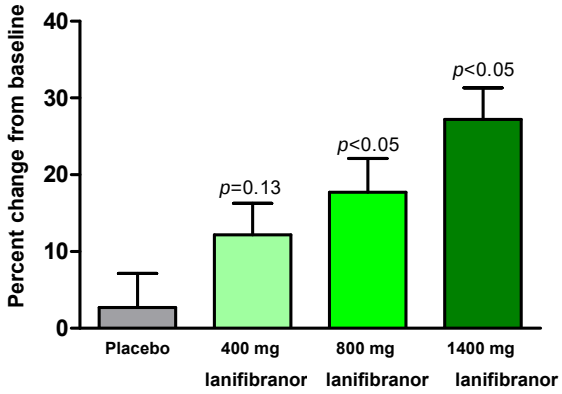
Phase I and Phase IIa clinical studies(1) demonstrated lanifibranor beneficial effects on key metabolic markers

Lanifibranor has beneficial effects on key metabolic markers in type II diabetic patients

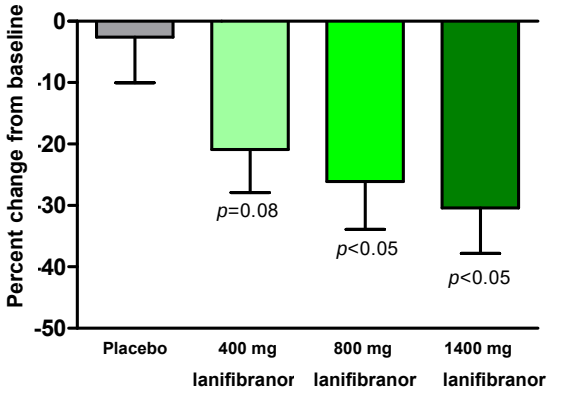
Adiponectin (PPARγ)



HDL Cholesterol (PPARα/δ)



Triglycerides (PPARα/δ)



Adiponectin fold:

- Lanifibranor (800/1400mg): +2.8/+3.2
- Pioglitazone(2) (45mg): +2.3

Homa-IR:

- Lanifibranor (800/1400mg): -20%/-44%

HDL increase:

- Lanifibranor (800/1400mg): +18%/28%
- Elafibranor(3) (80mg): +7,8%
- Seladelpar(4) (50mg): +9,9%

TG decrease:

- Lanifibranor (800/1400mg): -24%/28%
- Elafibranor (80mg)(3): -16,7%
- Seladelpar(4) (50mg): -32,4%

Source: Company data ; (1) Conducted by Abbott

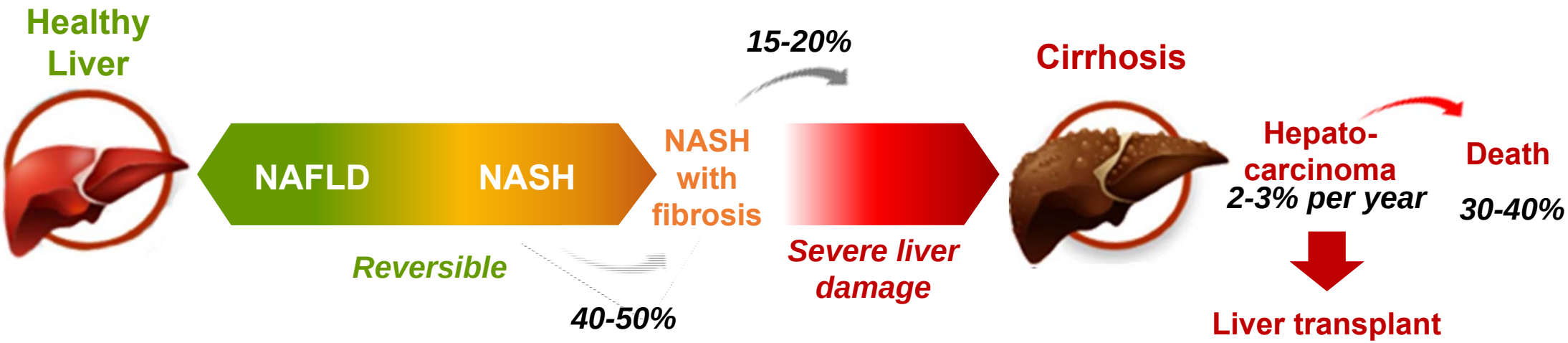
(2) A placebo controlled trial of Pioglitazone in subjects with nonalcoholic steatohepatitis Belfort et Al; N Engl J Med 355;22 November 30, 2006; 6 month treatment

(3) Effects of the new dual PPAR α/δ agonist GFT505 on lipid and glucose homeostasis in abdominally obese patients with combined dyslipidemia or impaired glucose metabolism *; Diabetes Care. 2011 Sep;34(9):2008-14. doi: 10.2337/dc11-0093. Epub 2011 Aug 4. 4 week treatment study 1*

(4) A Novel Peroxisome Proliferator Receptor-δ Agonist: Lipid and Other Metabolic Effects in Dyslipidemic Overweight Patients Treated with and without Atorvastatin *The Journal of Clinical Endocrinology & Metabolism, Volume 96, Issue 9, 1 September 2011, Pages 2889–2897, https://doi.org/10.1210/jc.2011-1061; 8 week treatment*

NASH overview

A severe disease with no currently approved treatment



The overall NASH prevalence in the adult population of the United States is believed to be approximately 12%

Source: NASH Market, Allied Market Research 2016 ; Deutsche Bank Markets Research; Intercept website.; Epidemiology and natural history of non-alcoholic steatohepatitis.Clinical Liver Disease 2009 Nov;13(4):511-31.

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

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

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

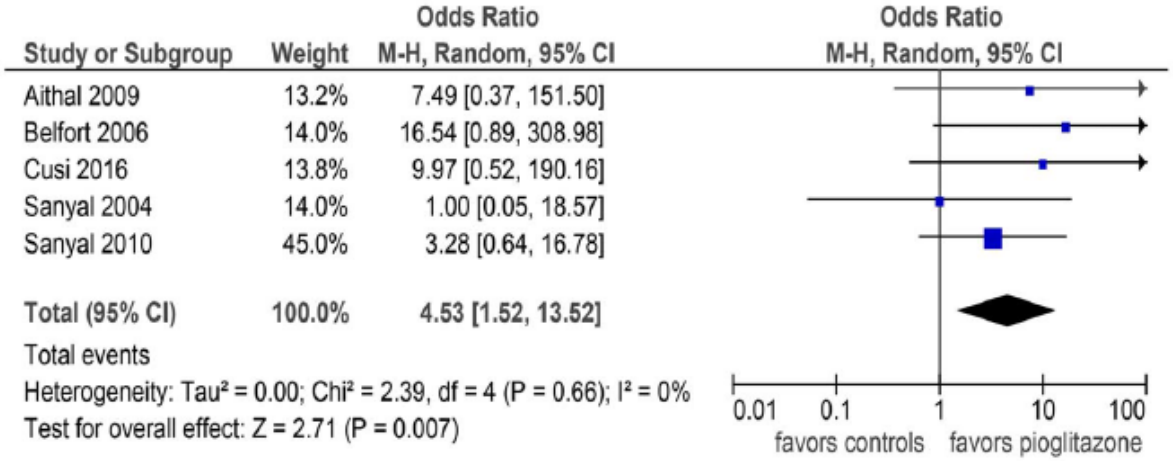
PPARγ efficacy is well established in NASH

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

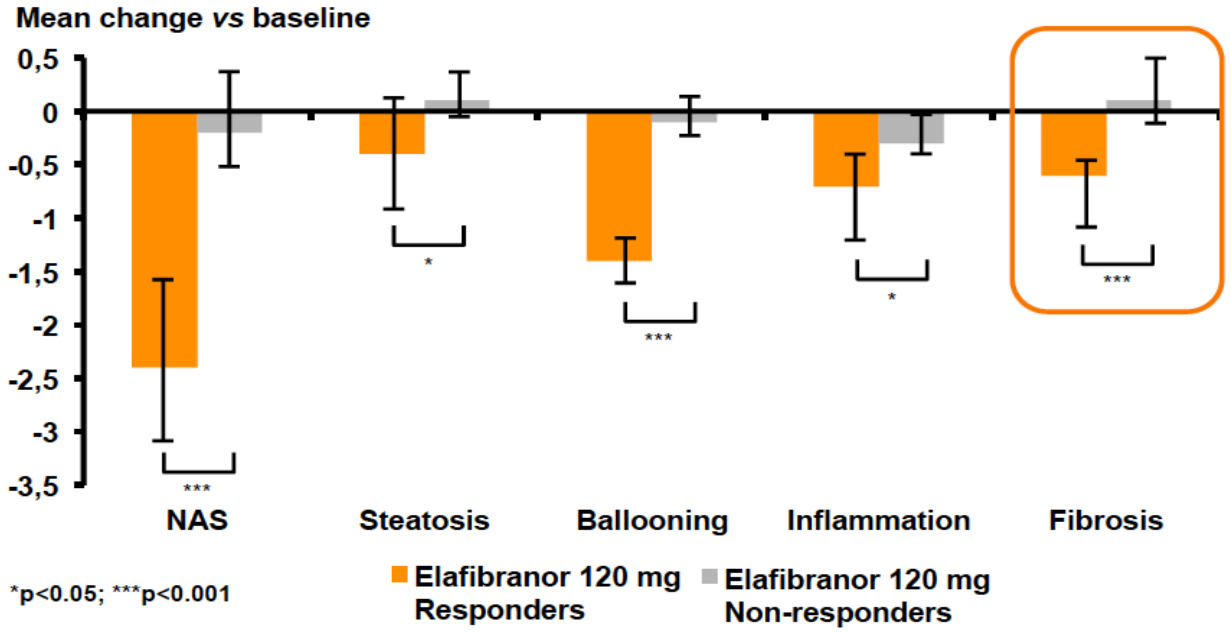
Source: Corey KE and Malhi H, Hepatology 2016. Note: clinical trial not conducted by Inventiva

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

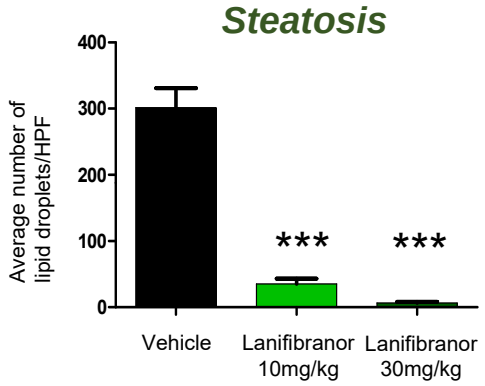
- Portal pressure
- Established fibrosis

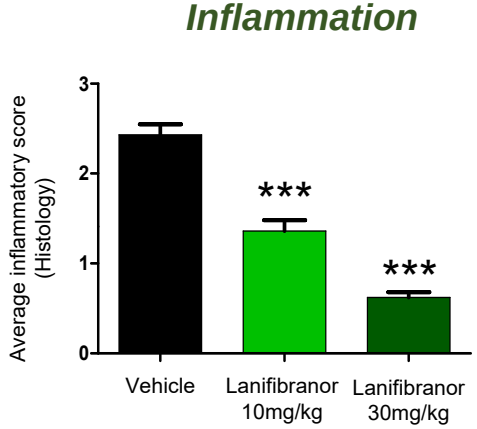
In Vivo

In Vitro

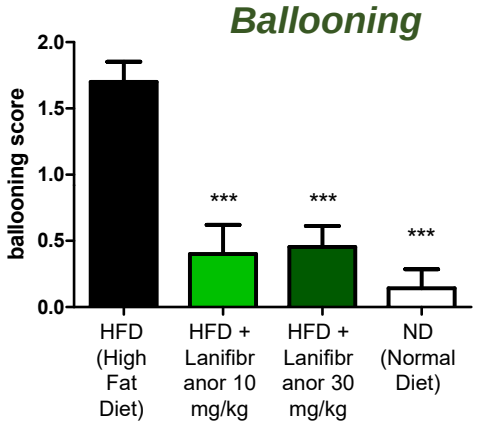
Lanifibranor significantly reduces steatosis, inflammation, ballooning and fibrosis in preclinical models

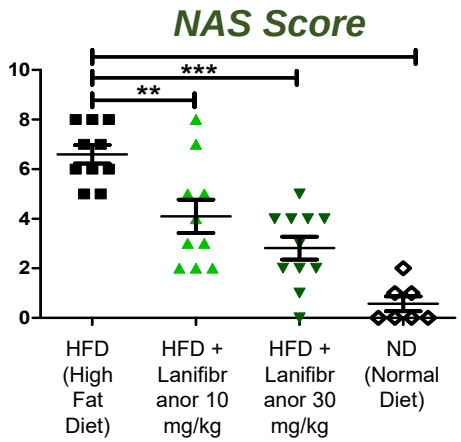
Lanifibranor inhibits steatosis and inflammation in the mice MCD model



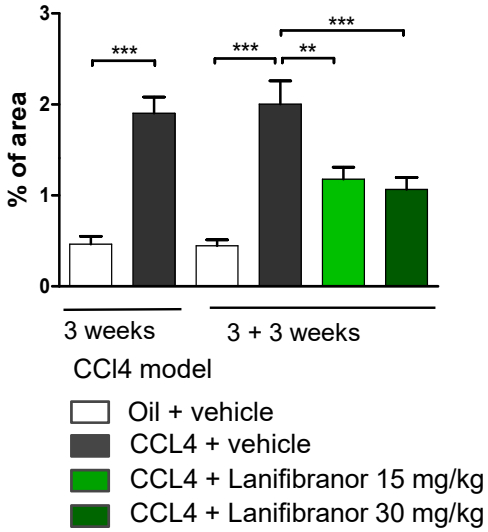


Lanifibranor significantly reduces ballooning and the NAS score in the foz/foz model





Lanifibranor reverses established liver fibrosis in mice CCL4 models



Lanifibranor associated with beneficial effects on all NASH-relevant liver features

Source: Company data; The new-generation Pan-Peroxisome Proliferator-Activated Receptor Agonist IVA337 Protects the Liver From Metabolic Disorders and Fibrosis; Hepatology Communications, June 2017

Lanifibranor improves portal hypertension and hepatic fibrosis in a model of advanced chronic liver disease

AASLD THE LIVER MEETING® NOVEMBER 8-12 2019 BOSTON

Lanifibranor leads to marked amelioration in fibrosis and portal hypertension

Objective:

The present project aimed at characterizing the effects of the pan-PPAR agonist lanifibranor on the systemic and hepatic hemodynamics, inflammation, sinusoidal cells phenotype, and fibrosis in a pre-clinical model of advanced chronic liver disease.

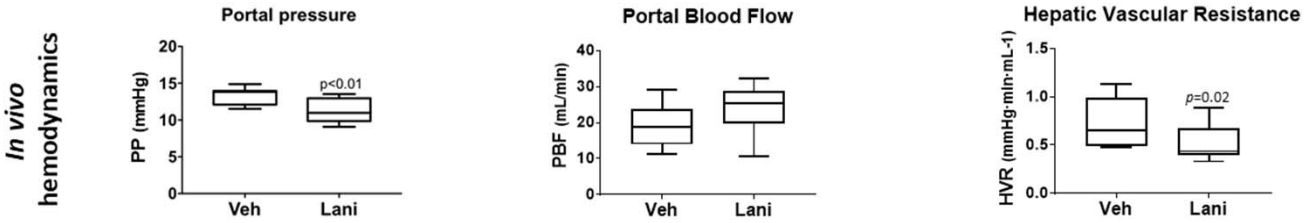
Methods:

Cirrhotic rats randomly received lanifibranor or vehicle for 14 days before evaluating *in vivo* systemic and hepatic hemodynamics (MAP, PP, PBF, HVR), serum AST, ascites degree (0-III), liver inflammation (IL-6 & IL-10), fibrosis (Sirius red staining, collagen I, MMPs & TIMPs), hepatic stellate cells activation (a-SMA, p-moesin and desmin) and, liver sinusoidal endothelial cells de-differentiation (ICAM-1, VCAM-1, E-Sel, and sinusoidal porosity).

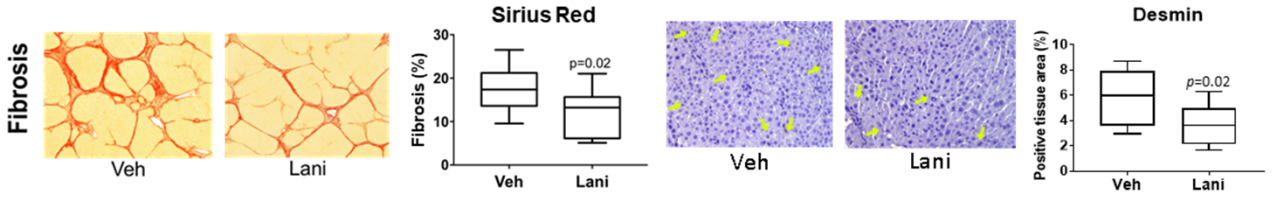
Conclusions:

Lanifibranor exerts clear beneficial effects in a pre-clinical model of decompensated cirrhosis, which lead to marked amelioration in fibrosis and portal hypertension.

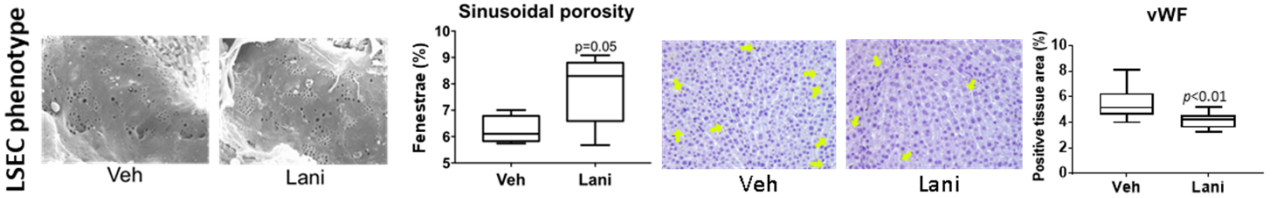
Aristu P, et al., Abstract 63



Cirrhotic rats receiving lanifibranor showed significantly lower PP than vehicle-treated animals (11.2±0.5 Vs 13.1±0.4 mmHg; -14%;) with no significant changes in PBF, thus indicating improved HVR (0.53±0.06 Vs 0.75±0.1 mmHg·min·mL^{-1}; -30%).



Animals treated with lanifibranor showed a significant fibrosis regression and improvement of hepatic stellate cells phenotype.



Lanifibranor-treated rats showed improvement in liver sinusoidal endothelial cells phenotype.

NATIVE: a phase III enabling study

Trial design

Principal investigators

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

Inclusion criteria

- Severe patients with an inflammation and ballooning score of 3 or 4
- Steatosis score ≥ 1 and fibrosis score < 4 (no cirrhosis)

Randomisation

- 1/1/1, stratification on T2DM patients
- Study powered with 75 patients per group
- Central reading

Clinicaltrials.gov identifier

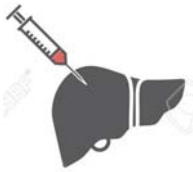
- NCT03008070

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

Double blind randomized placebo controlled

Screening

- Liver biopsy



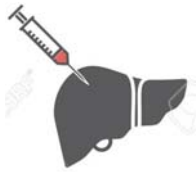
Placebo, 75 patients

Lanifibranor, 800 mg once daily, 75 patients

Lanifibranor, 1200 mg once daily, 75 patients

End of treatment

- Liver biopsy



Primary endpoint

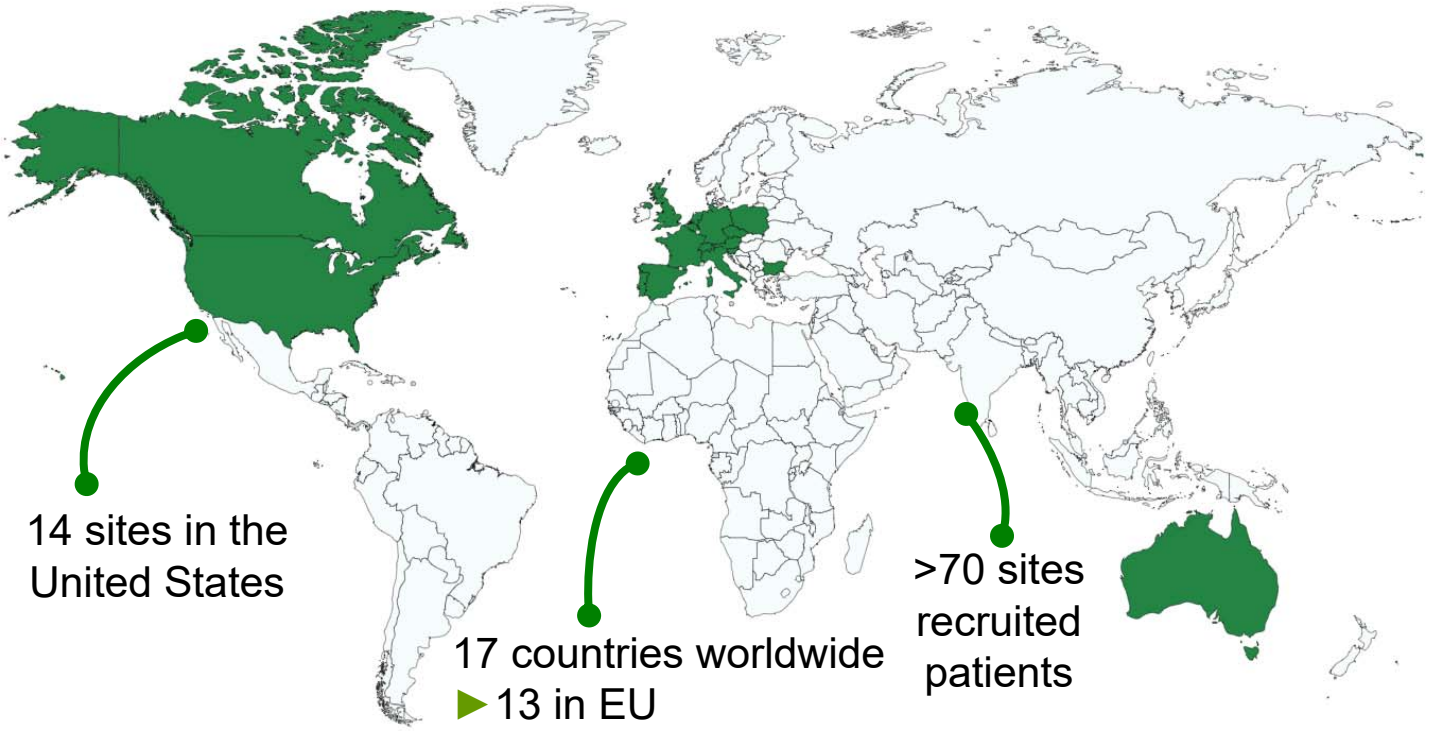
- Decrease from baseline ≥ 2 points of the inflammation and ballooning score without worsening of fibrosis

Key secondary endpoints

- Decrease of at least 2 points in NAS
- Resolution of NASH (to NAFLD: steatosis ± mild inflammation)
- Change in fibrosis score, liver enzymes, inflammatory markers, glucose metabolism parameters, plasma lipids parameters, adiponectin, …
- Safety

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

247 patients randomized exceeding the initial target of 225 patients



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

Results expected for June 2020

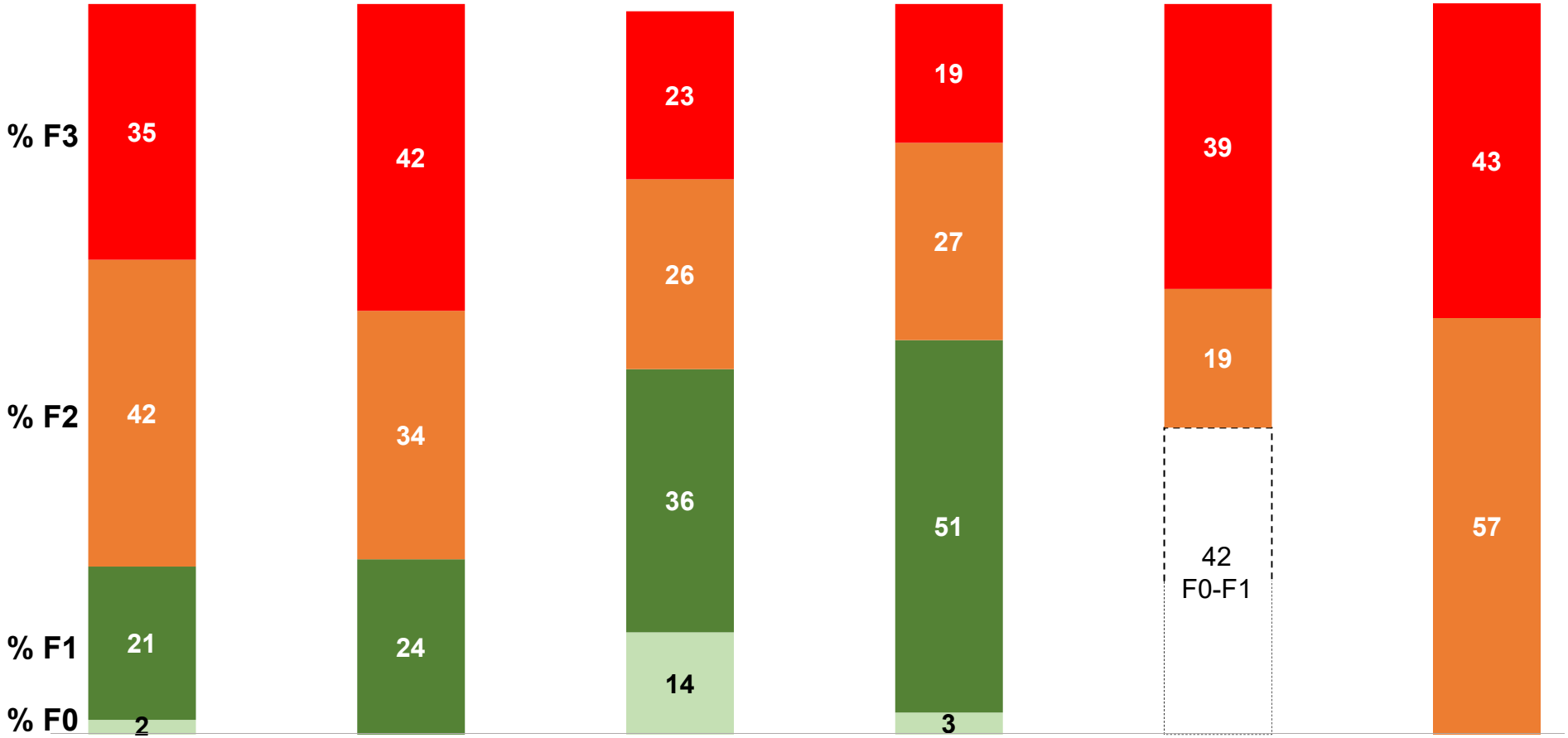
(1) Database extraction January 2020

Baseline characteristics

Parameters		Patients without diabetes (N = 145 ; 59%)	Patients with diabetes (N = 102 ; 41%)	Total (N = 247 ; 100%)
Gender	Female	57%	60%	58%
	Male	43%	40%	42%
Age	Mean ± SD	51.7 ± 13.6	56.2 ± 10.4	53.6 ± 12.5
	Min ; Max	20 ; 76	28 ; 77	20 ; 77
Weight (kg)	Mean ± SD	93.1 ± 19.0	93,8 ± 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%)

NATIVE patient fibrosis score distribution similar to Intercept phase III trial

Patient distribution according to fibrosis scoring (%)

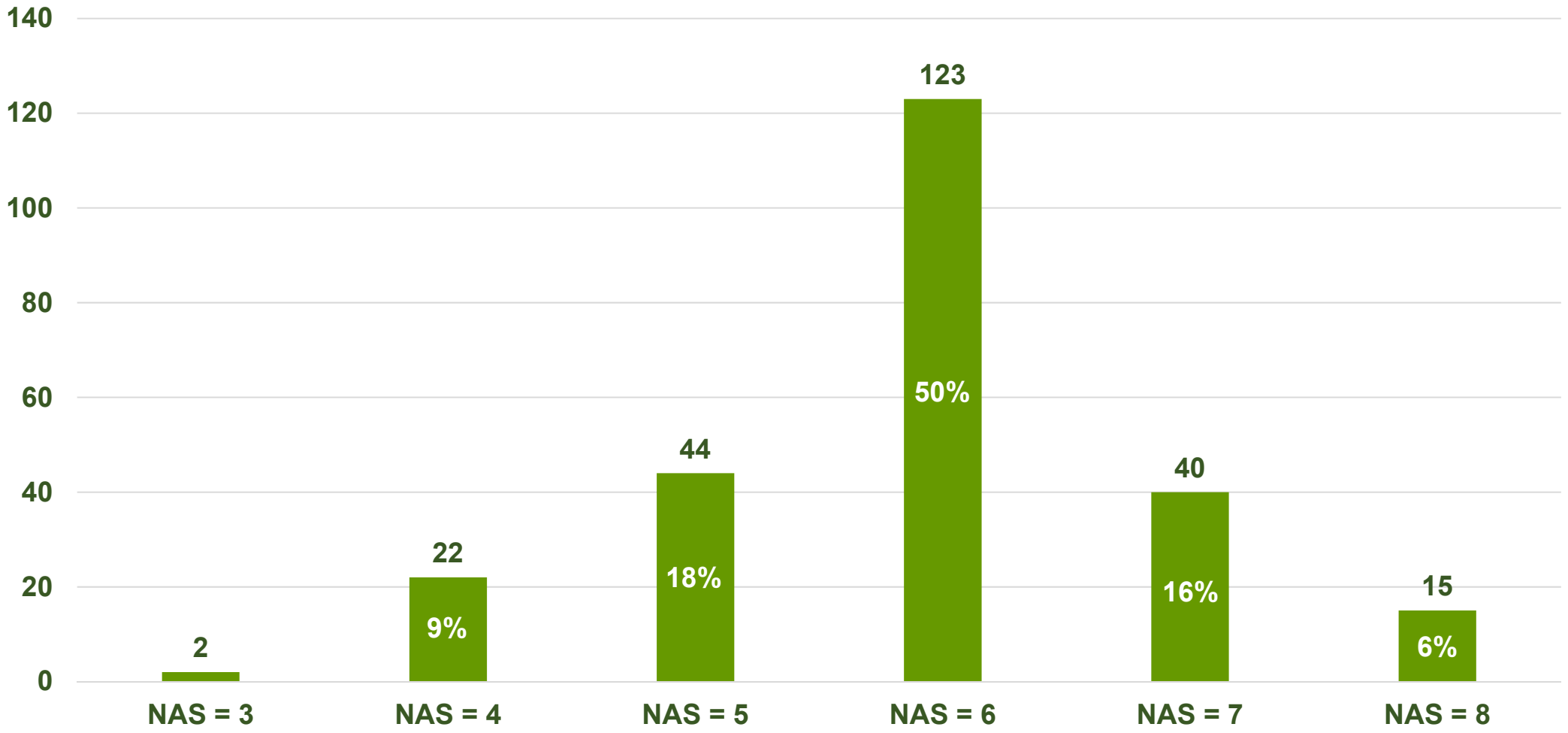


Source: ocaliva: Younossi et al, Lancet 2019; 394:2184-96 / Ocaliva EASLD-AASLD 2019 presentations ; elafibranor: Ratziu et al, Gastorenterology 2016; 150:1147-1159 ; resmetirom: Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6; Aramchol AASLD 2018 presentation; Aldafermin 2020 NGM biopharmaceuticals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

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

NATiVE
NASH TRIAL TO VALIDATE IVA337 EFFICACY

Patient distribution according to the NAS score



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	✓	✓	✓	✓

Ongoing Phase II trial in type 2 diabetes patients with NAFLD evaluating the effect of lanifibranor on hepatic insulin sensitivity

Trial design

Principal investigator

- Prof. Kenneth Cusi (University of Florida)

Randomisation

- Randomized (1:1), double-blind, placebo-controlled
- Non-obese subject control group for the metabolic and imaging procedures
- N=64 calculated assuming a 35% relative reduction of IHGT(1)

Status

- ☑ IND approved
- ☑ First Patient First Visit: August 2018
- **Results expected 2021**

Primary endpoint

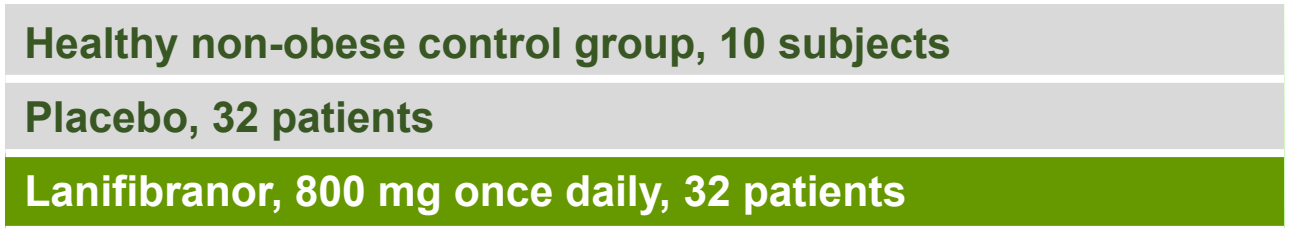
- Change from baseline to week 24 in IHTG

Key secondary endpoints

- Proportion of responders (IHTG, NAFLD resolution)
- Change in hepatic fibrosis (MRE(2), biomarkers)
- Change in metabolic outcomes (insulin sensitivity, DNL(3), glycemic control, lipids)
- Safety

Clinicaltrials.gov identifier: NCT03459079

64 patients
24 week treatment
Double blind randomized placebo controlled



Lanifibranor could be the drug of choice for NASH patients with TD2M: ~48% of NASH patients have TD2M(4)

(1) Intrahepatic triglycerides (2) Magnetic resonance elastography (3) De-novo lipogenesis ; (4) Levin J., EASL 2018. Bril, F & Cusi, K, 2017 Diabetes Care, 40:419-430. Younossi, Z., et al, 2018. Nat Rev Gastroenterol Hepatol, 15(1): 11-20

PanNASH Initiative: a group of well recognized international experts working to promote NASH and the role of PPARs

- Inventiva created panNASH™, a committee of international independent experts aiming to developing and disseminating their NASH expertise among the scientific community, patients and other key stakeholders.
- The committee includes European and American medical experts in areas related to NASH such as hepatology, diabetes and cardiology
- More information available at: https://pannash.org/

Member	Specialty	Country	Affiliation
Pr. Sven Francque	Hepatology	Belgium	Antwerp University Hospital
Pr. Frank Tacke	Hepatology	Germany	University Hospital Aachen
Pr. Jean-François Dufour	Hepatology	Switzerland	University Clinic Bern
Pr. Manal Abdelmalek	Hepatology	United States	Duke University
Pr. Gyongyi Szabo	Hepatology	United States	University of Massachusetts
Pr. Michael Roden	Diabetology	Germany	Heinrich Heine University
Pr. Kenneth Cusi	Diabetology	United States	University of Florida
Pr. Christopher Byrne	Cardiology	UK	University of Southampton
Pr. Frank Sacks	Cardiology	United States	Harvard T.H. Chan School of Public Health

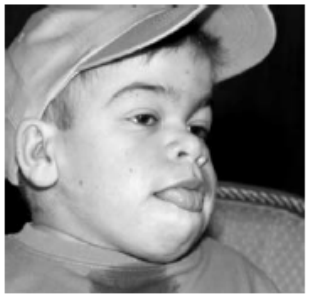
Odiparcil – MPS

Mucopolysaccharidoses (MPS) are devastating diseases with high unmet medical needs

MPS is a group of inherited lysosomal storage disorders

- Lysosomes function as the primary digestive units within cells: enzymes within lysosomes break down or digest particular nutrients, such as certain carbohydrates and fats
- The absence or malfunctioning of lysosomal enzymes are responsible of metabolic disorders caused by the abnormal degradation of glycosaminoglycans (GAGs) or mucopolysaccharides
- MPS symptoms are first shown during early childhood and patient's life expectancy depends on the severity of symptoms: without treatment, severely affected individuals may survive only a few years, those with milder forms of the disorder usually live into adulthood, although their life expectancy may be reduced
- The prevalence of all forms of MPS combined is estimated to be 1 / 25 000 births: however as MPS, especially the milder forms often go unrecognized, these disorders are under-diagnosed or misdiagnosed

Kathleen (MPS I)



Scotty (MPS II)

Karima (MPS VI)

MPS has devastating clinical consequences: example MPS I, II and VI

- The progressive accumulation of GAGs in the lysosomes causes progressive damage throughout the body, including the heart, eyes, bones, joints, respiratory system and central nervous system

Consequences	MPS I	MPS II	MPS VI
Mental retardation	☑	☑	
Coarse facies, short stature	☑	☑	☑
Dysostosis multiplex	☑	☑	☑
Joint stiffness	☑	☑	☑
Spinal cord compression	☑	☑	☑
Organomegaly	☑	☑	☑
Poor vision (corneal clouding)	☑	☑(1)	☑
Hearing loss	☑	☑	☑
Cardiac/respiratory disease	☑	☑	☑
		Pebbled skin	Odontoid hypoplasia
		Diarrhoea	Kyphoscoliosis, genu valgum

(1) Retinal degeneration with no corneal clouding

Source: (1) Source: Rheumatology 2011 Therapy for mucopolysaccharodises; Vassili Valayannopoulos and Frits A. Wijburg

Despite enzyme replacement therapies (ERT) being commercially successful, many unmet medical needs remain

Enzyme replacement therapies are standard of care in MPS

- Recombinant human enzymes, **requiring a once a week intravenous infusion over 4 hours**
- **Approximately 50% of patients experience infusion reactions** initially, some can be life threatening
- **Limited penetration into protected or poorly vascularized tissues** such as cornea or cartilage, where MPS symptoms often manifest

Product	Company	MPS	Est. yearly cost	2019 sales
Aldurazyme (laronidase)	genzyme	MPS I	$ 217K	€ 224M
elaprase (idursulfase)	Takeda	MPS II	$ 522K	$ 634M(1)
Vimizim (elosulfase alfa)	BIOMARIN	MPS IVA	$ 578K	$ 544M
Naglazyme (GALSULFASE - rch)	BIOMARIN	MPS VI	$ 476K	$ 374M
Mepsevii (vestronidase alfa-vjbk) injection, for intravenous use	ultragenyx pharmaceutical	MPS VII	$ 550K	$ 12,6M

Source: Sales - Full year 2019 press-release; WAC without discounts for a 25-kg patient - BioCentury "Making of MEPSEVII" Dec 11, 2017; (1) 2018 sales

ERT is expensive and usually requires outpatient administration. Significant unmet need remains in addressing symptoms in organs where ERT fails to penetrate

Source: H. Noh, J. I. Lee; Current and potential therapeutic strategies for mucopolysaccharidoses; Journal of Clinical Pharmacy

Odiparcil: an orally available small molecule substrate reduction therapy to treat several forms of MPS

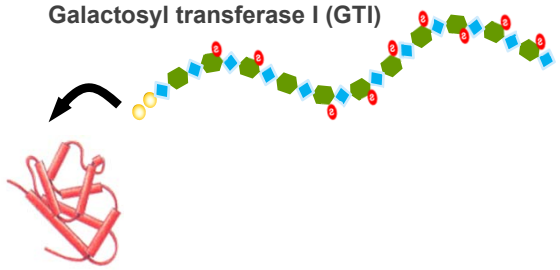
- **Decreases lysosomal accumulation** of GAGs by promoting formation of soluble DS / CS which can be excreted in the urine
- **Oral administration** and **distribution** in tissues that are poorly penetrated by enzyme replacement therapy
- Potential to be prescribed in **combination with ERT and as monotherapy**
- Odiparcil-mediated reduction of intracellular GAG accumulation **demonstrated in *in vitro* and *in vivo* models**
- **Positive phase IIa study in MPS VI adult patients** with good safety and efficacy. Study in children in preparation
- **Low toxicity** *in vivo and* **favorable safety and tolerability** profile **in multiple Phase I and Phase II clinical studies** in unrelated indication(1) (administered to >1,800 subjects)
- Method of use patent granted in the United-States and in Europe with **LOE(2) 2039 including 5-year extension**
- MPS VI **Orphan Drug Designation granted in the US and in the EU** and **Rare Pediatric Disease Designation** in MPS VI granted in the US

(1) Trial conducted by GSK prior to Inventiva's founding (2) LOE: Loss of exclusivity

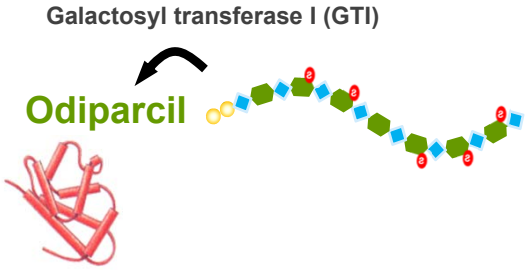
Unique mechanism of action potentially synergistic with ERT

Odiparcil diverts endogenous protein-bound GAG synthesis to soluble odiparcil-bound chondroitin sulfate (CS) and dermatan sulfate (DS) synthesis

Synthesis of proteoglycans (HS, CS, DS)



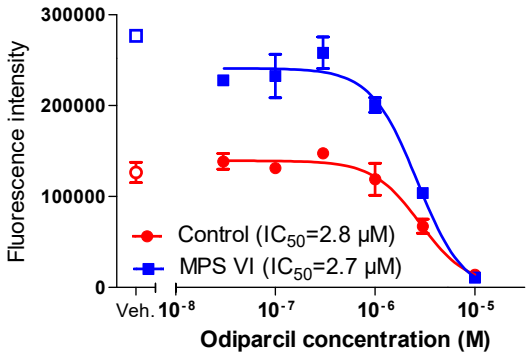
GTI activity	
Substrate	Vm/Km
D-xylose	0.8
Odiparcil	1857

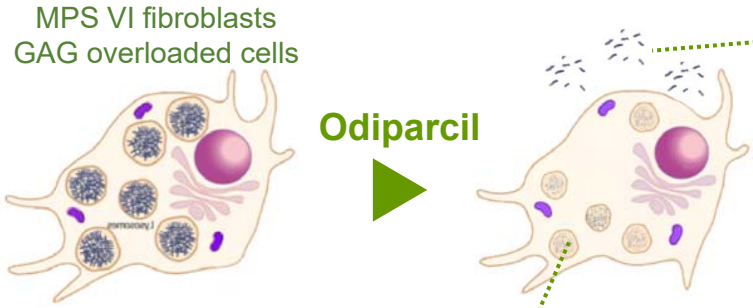


Synthesis of soluble DS and CS

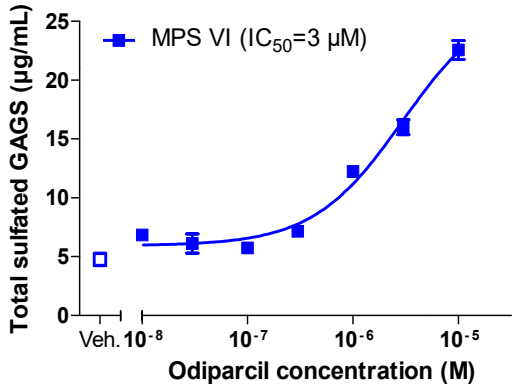
Odiparcil decreases intracellular GAG accumulation *in vitro* in MPS VI patient cells

Intracellular CS storage





Extracellular GAG



Odiparcil observed to reduce GAG accumulation in MPS VI patient cells

Source: H. Noh, J. I. Lee; Current and potential therapeutic strategies for mucopolysaccharidoses; Journal of Clinical Pharmacy, company data

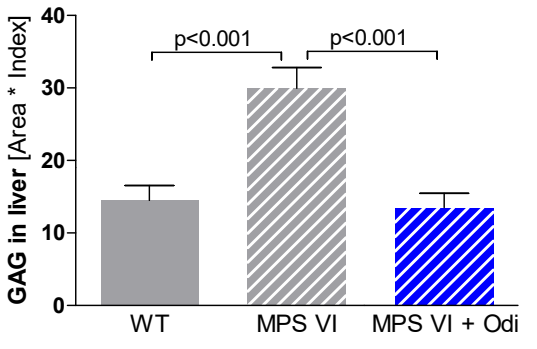
By producing soluble dermatan and chondroitin sulfates, odiparcil can address several types of MPS

MPS Type	Frequency	DS	CS	HS	KS
MPS I-H		✓		✓	
MPS I-S	1/100,000	✓			
MPS I-H/S		✓		✓	
MPS II Types A & B	1/100,000	✓		✓	
MPS IV Type A	1/40,000 to 1/200,000		✓		✓
MPS VI	1/240,000 to 1/400,000	✓	✓		
MPS VII	Very rare	✓	✓	✓	

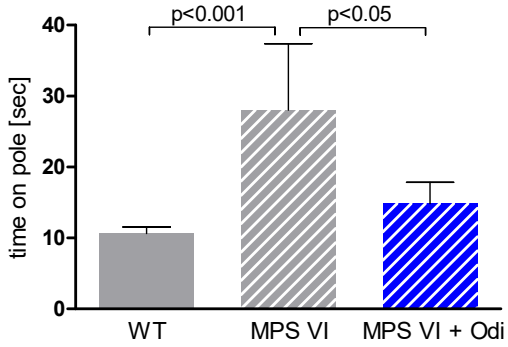
Source:Rheumatology 2011 Therapy for mucopolysaccharodises; Vassili Valayannopoulos and Frits A. Wijburg

Odiparcil GAG clearance mechanism of action observed in MPS VI mice

Odiparcil decreases GAG accumulation in tissues

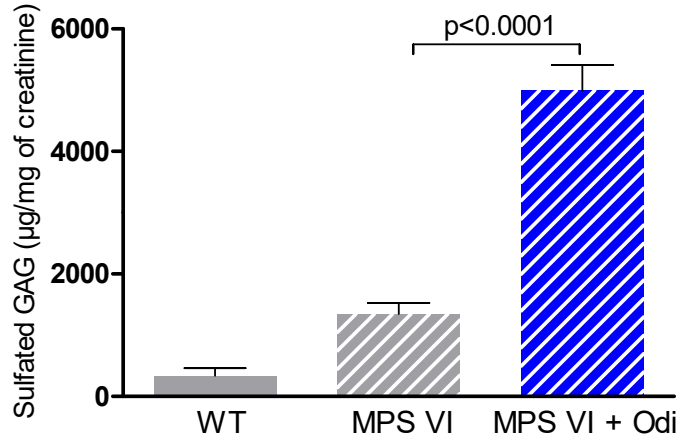


Odiparcil restores mobility



Wild-type and MPS VI mice

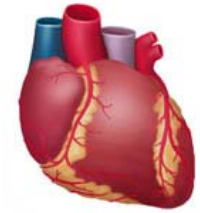
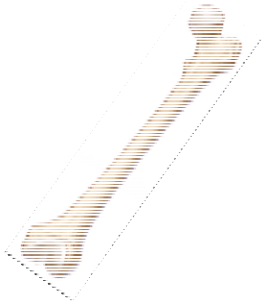
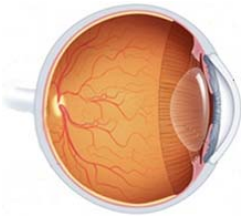
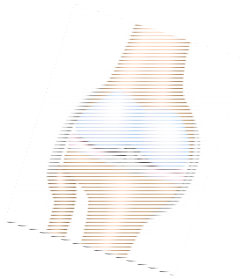
Soluble GAGs produced from odiparcil are excreted in urine



Source: Company data

Odiparcil penetrates tissues that ERT cannot reach

Odiparcil is well distributed in tissues and organs poorly penetrated by recombinant enzymes

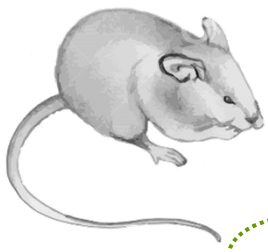
	Heart	Bone	Cornea	Cartilage
				
Odiparcil[1]	✓	✓	✓	✓
rhASB[2]	✓	**Not tested**	**Not detected**	**Not detected**

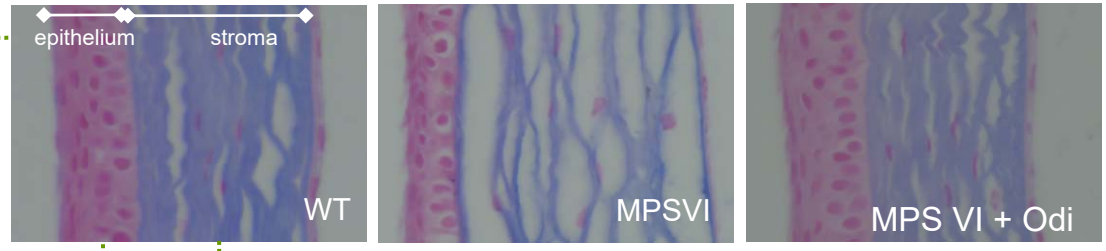
Meaningful concentrations of odiparcil observed also in tissues that are poorly vascularized or protected by a barrier: bone, corneal tissue and cartilage

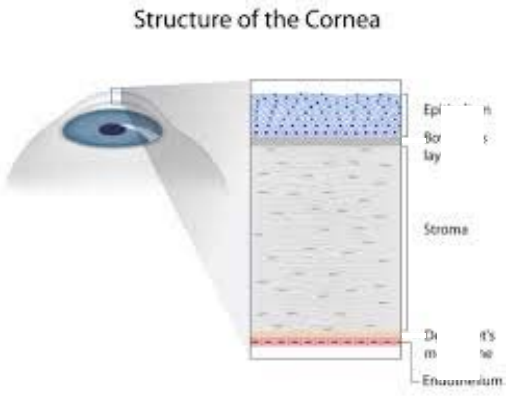
Source: (1) Odiparcil: tissue distribution following 25mg/kg oral administration , TID for 5 days; (2) Recombinant human ARB: Expressed as ratio of ARSB enzyme activity in the liver in MPS VI cats after repeat infusion (conditions: preliminary trial, Trial A and Trial B from Auclair et al. 2003)

Odiparcil reverses corneal impairment in MPS VI mice

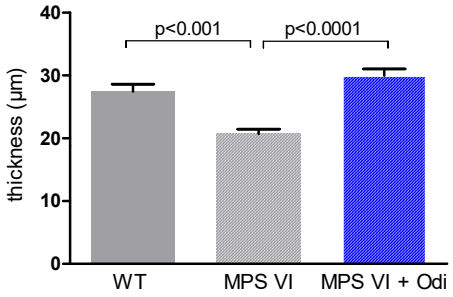
Odiparcil restores an healthy corneal structure and decreases corneal GAG storage





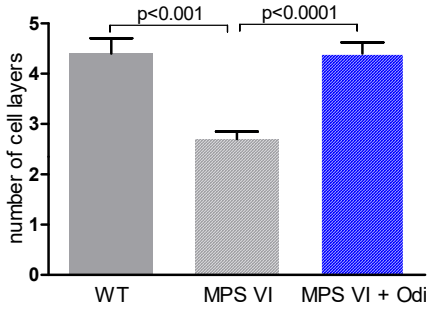


Odiparcil restores corneal epithelium thickness



N=10 for all groups

Odiparcil restores corneal epithelium cell layers



Odiparcil decreases GAG storage in corneal stroma

Blinded corneal stroma vacuolation scoring

WT	0.0
MPS VI	2.9
MPS VI + Odi	0.5

scale (0-3)

0. no detectable vacuolation, no GAG accumulation
1. some large vacuolation with some distended cells
2. extensive area of large vacuolation with GAG accumulation
3. extensive area of large vacuolation with GAG accumulation and separate collagen fibers

Source: Company data

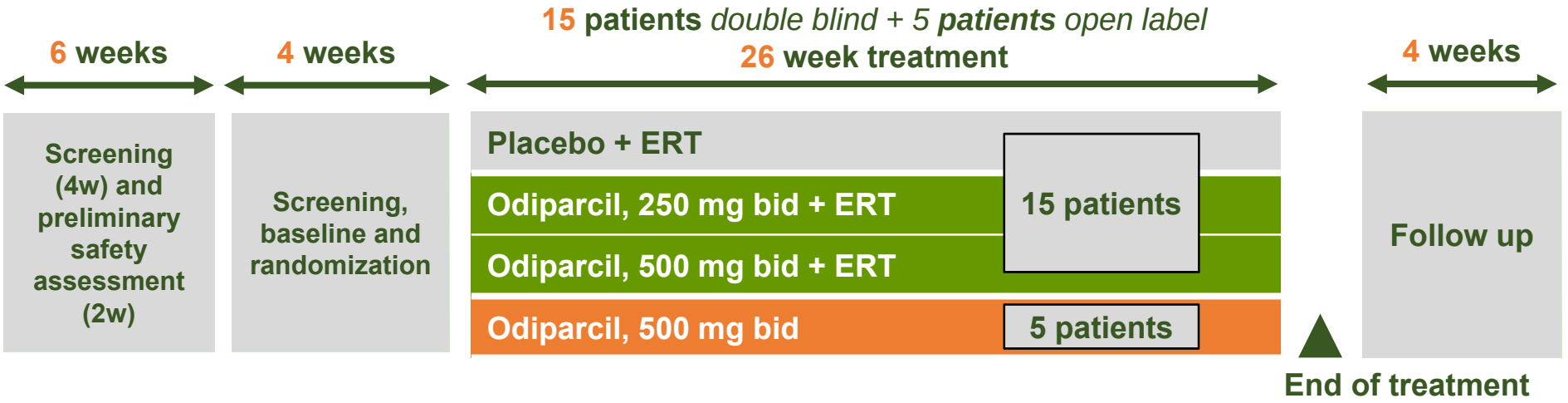
iMProveS Phase IIa trial of odiparcil in MPS VI

Phase IIa

- Phase III enabling study with evidence for dose selection and PK / PD response characterization
- **Clinicaltrials.gov identifier:** NCT03370653

Population

≥ 16yo



Endpoints

Safety

- Clinical and biological assessments (standard tests)

Pharmacokinetics

- Odiparcil plasma levels

Efficacy

- Leukocyte, skin and urinary GAG content
- Activity and mobility tests (6 minute walk test, upper limb function, shoulder mobility range)
- Cardiac, vascular and respiratory functions
- Eye impairment, hearing capacity, pain assessment, quality of life questionnaires

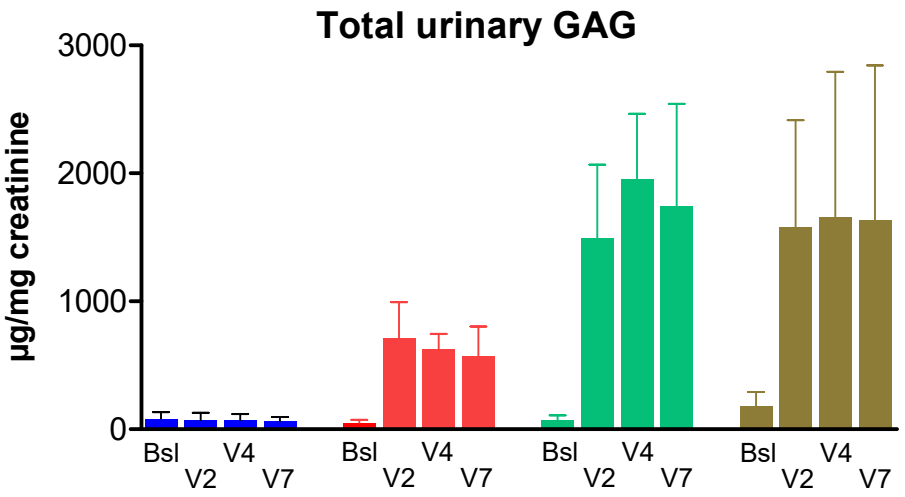
More information on: http://www.improves-mpsvi-trial.com/

Safety

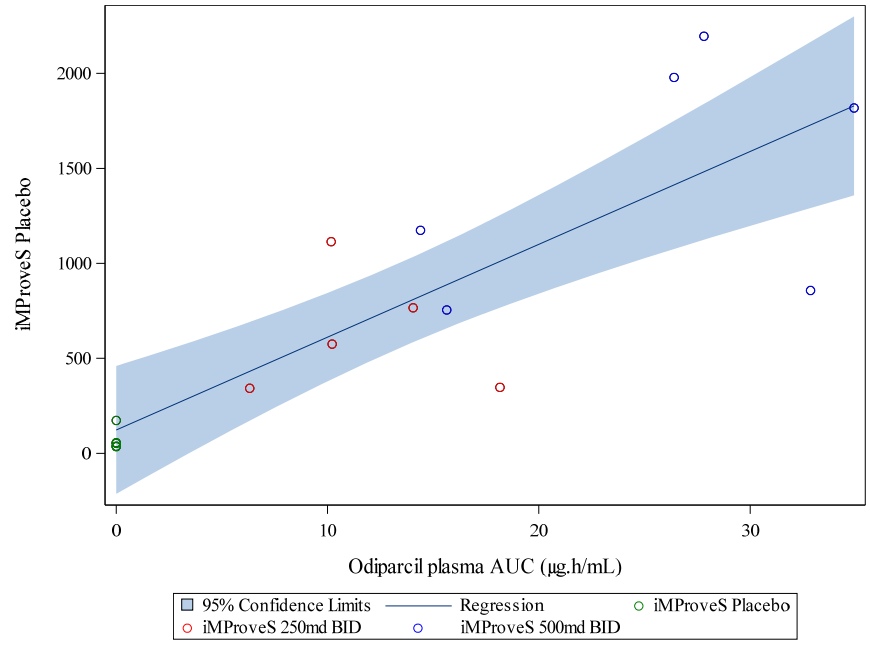
- The **clinical study met its safety primary objective** further supporting the good overall safety profile of odiparcil already observed in previous Phase I and Phase II clinical studies
- **All 4 European investigators** of the iMProveS study **reported positive experience** with odiparcil in terms of safety
- The majority of adverse events were **mild or moderate**
- One death occurred in the placebo group
- Three serious adverse events (SAEs) were assessed as treatment-related in patients in the odiparcil groups.
  - Two SAEs were biological findings qualified as laboratory false-positive
  - One SAE was a skin reaction, which is frequently observed in MPS patients
- Compared to previous Phase I and II clinical studies conducted with odiparcil for the prevention of thrombosis, **no new safety findings were observed**

Odiparcil pharmacodynamics: total GAG levels in urine and PK/PD correlation

A dose-dependent urinary GAGs clearance, used as an activity biomarker, was clearly demonstrated in the entire odiparcil treated patient population



- uGAG (total) is increased after 4 week of odiparcil
- uGAG increase reaches a steady state after 4 weeks of treatment
- At 1000 mg/day the increase is comparable in ERT and non-ERT cohorts



- Urinary GAG (total) is correlated with odiparcil exposure in plasma

ERT + placebo ERT + odiparcil 500mg ERT + odiparcil 1000mg Non-ERT, odiparcil 1000mg

- The PK profile obtained in MPS VI patients treated with odiparcil is not impacted by ERT and is consistent with profiles previously observed in other Phase I and Phase II studies in prevention of thrombosis

Efficacy

Partially addressed by ERT

Endurance and mobility
- 6-minute walk test (6MWT)
- 9 hole peg test (9HPT)
- Range of motion of left and right shoulders (S-ROM)

Respiratory function
- Forced vital capacity (FVC)
- Forced expiratory volume in 1 second (FEV1)

- Number of evaluable patients at Visit 7 (26w) N=13
- Efficacy parameters assessed at baseline and end-of-treatment (EOT)
- Two efficacy analyses
  - Statistical approach
  - Interpretation of blinded individual results by experts

Not addressed by ERT (hard-to-reach tissues)

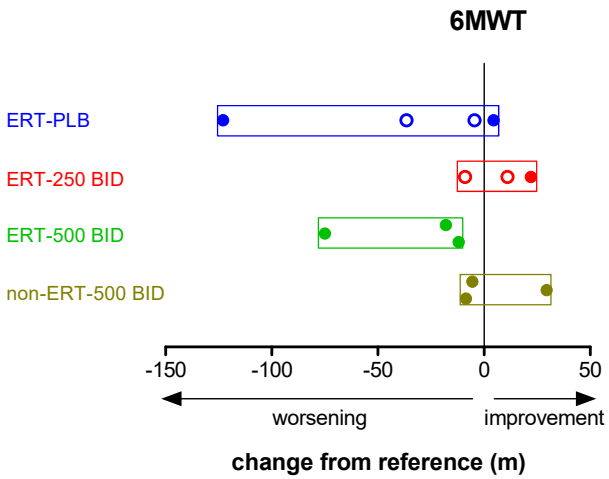
Cardiac and vascular system
- ECG, Echocardiogram
- Carotid intima media thickness (CIMT)

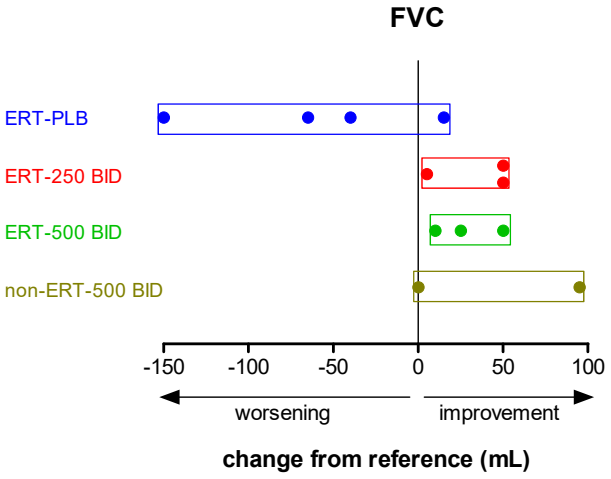
Ophthalmology
- Visual acuity
- Corneal clouding
  - Subjective evaluation (slit lamp)
  - Quantitative measurement (iris camera: corneal opacity measure (COM))

Pain assessment
- Brief Pain Inventory (BPI) questionnaire
  - 'Intensity' dimension
  - 'Interferences' dimension

Audiology
- Pure tone audiometry (PTA)

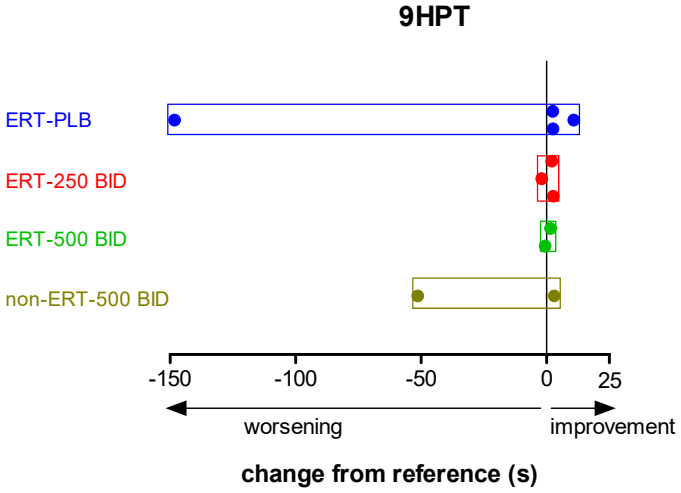
Efficacy: trends of improvement on 6MWT and FVC

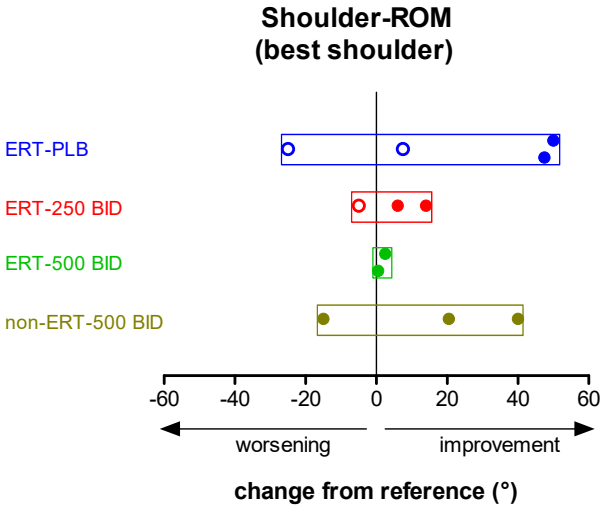




Trends for improvement in ERT-250 BID and non-ERT-500 BID compared to ERT-placebo

Improvement in all odiparcil treated groups compared to ERT-PI





No significant differences between groups are observed

Efficacy: several patients treated by ERT and odiparcil demonstrated improvements in one or several parameters

iMProveS
IMPROVE MPS TREATMENT

Treatment (N=10)	Respiratory (FVC)	Ophthalmology (COM left eye, right eye)	Cardiology
Placebo + ERT (N=4)	**0**	**1** (slightly improved) Patient A: +4, +11 -	**1** (slightly improved) - Patient B: ↓ 30% LVMI
Odiparcil + ERT (N=6)	**3** (slightly improved) **250mg bid** Patient C: + 5% - **500mg bid** Patient E: + 4% Patient F: +9% -	**2** (improved) **250mg bid** - Patient D: +11, +14 **500mg bid** - Patient F: +13(1) -	**4** (3 slightly improved + 1 improved) **250mg bid** Patient C: ↓ 17% LVMI Patient D: no longer mitral regurgitation **500mg bid** - Patient F: ↓ severity mitral regurgitation Patient G: ↓ 14.5% LVMI, ↓ severity aortic regurgitation, ↓ CIMT both carotids

(1) Corneal transplant of the other eye; LVMI: left ventricular mass index (echocardiogram); CIMT: carotida intima media thickness

Efficacy: signals of efficacy were also detected in patients only treated with odiparcil

iMProveS
IMPROVE MPS TREATMENT

Odiparcil 500mg Bid (N=3)	Respiratory (FVC)	Ophthalmology	Cardiology	Range of Motion	Other
Patient H	Improved FVC by +18%	NA	Stable	Improved range of motion on both shoulders (+17,8%/+21,0%)	Pain improved
Patient I	Stable	Stable	Slightly Worsened	Improved range of motion on both shoulders (+8,1%/+8,5%)	Pain improved
Patient J • Severe patient hospitalized • Poor compliance	NA	Stable	Worsening	Worsening	Pain improved

Odiparcil: clinical development path for approval in MPS VI

Completed

Phase IIa (6-m treatment)
MPS VI adults (16y+)
- Add on to ERT, n=15
- Not receiving ERT, n=5

iMProveS
IMPROVE MPS TREATMENT

- Safety
- PK, PD (uGAG) and BM (leukoGAG, skinGAG)
- Exploratory assessment of efficacy

Planned

Open-label (iMProveS Extension)
Completers of iMProveS study
- Add on to ERT, n=10
- Not receiving ERT, n=3

iMProveS extension
IMPROVE MPS TREATMENT

- Safety
- Efficacy

Planned

Phase Ib/II (6-m treatment)
MPS VI children (5y to 15y)
- Add on to ERT, n=24

Safe-KIDDS

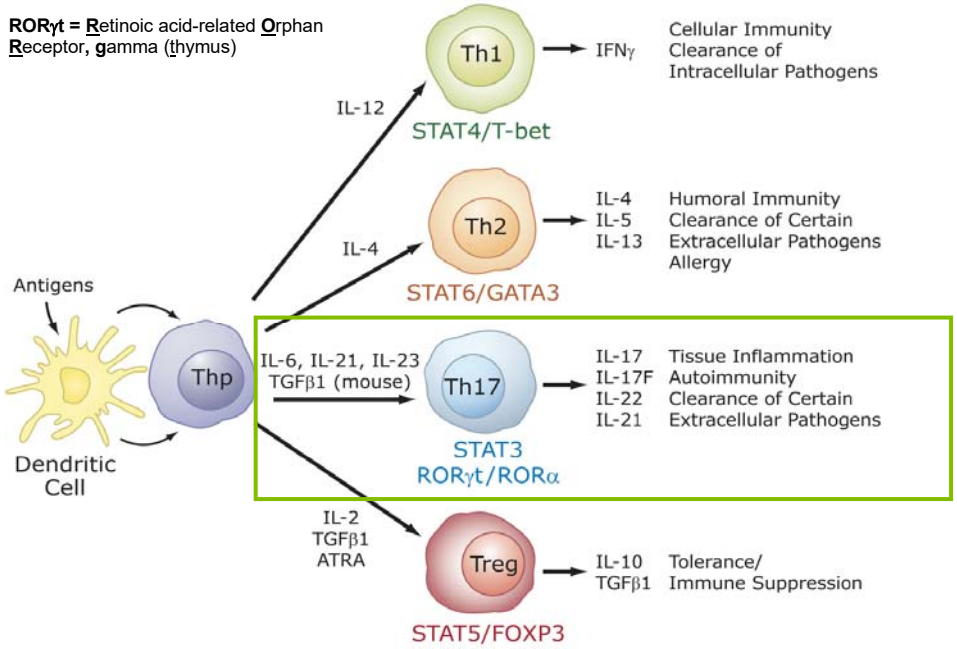
- Safety
- PK / PD
- Efficacy

Phase III
MPS VI patients (5y to adult)

ABBV-157

ABBV-157, a clinical compound co-discovered by Inventiva, has block-buster potential in several auto-immune diseases

RORγ is a master regulator of Th17 differentiation and IL-17 expression



IL-17 / 23 approach has been validated by several successful biologics

Brand Name	Company	Target	Sales (2019, B$)[1]
Stelara	Janssen	IL-12 and IL-23	6,3
Cosentyx	Novartis	IL-17A	3,5
Taltz	Eli Lilly	IL-17A	1,4

- Target Product Profile: **Humira in a pill + oral + better safety**
- ABBV-157, a potent RORγ, addresses large markets dominated by biologics: psoriasis, rheumatoid arthritis, multiple sclerosis, IBD, uveitis, …

ABBV-157 POC expected in 2020

- **Single ascending dose and multiple ascending dose** studies in healthy volunteers **completed**
- **Second clinical study initiated**: a randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the pharmacokinetics, safety and tolerability of ABBV-157 in 60 healthy volunteers and **patients with chronic plaque psoriasis** (clinicaltrials.gov identifier: NCT03922607)
  - Study start date: June 2019 / Study completion: October 2020[2]

Inventiva eligible to milestone payments and sales royalties

Source: (1) 2019 full year press-relese; (2) clinicaltrials.gov

YAP-TEAD

YAP-TEAD program: significant progress achieved

- Novel cancer pathway involved in drug resistance, immune evasion, tumor progression and metastases
- Relevant in multiple, commercially attractive cancer indications

- Proprietary chemistry
- Lead and back-up compounds available
- IP protected

First in class YAP-TEAD program

- Preclinical candidate screening ongoing
- Clinical candidate selection in 2020
- Phase I/II start planned in 2021

- *In vitro* evidence for synergies with standard of care and suppression of tumor resistance
- *In vivo* efficacy shown (alone and in combination with standard of care)

Recent and upcoming catalysts

Recent and upcoming key milestones

Lanifibranor

- Results: phase IIb NASH - **June 2020**

Odiparcil

- ☑ Positive results of the phase IIa in MPS VI
- Launch of a Phase Ib/II clinical trial of odiparcil in a pediatric population with MPS VI
- Initiate a Phase IIa extension study in patients who completed the prior phase IIa trial

ABBV-157

abbvie

- ☑ ABBV-157 milestone received for the first psoriatic patient treated: **3,5M€ in Q4 2019**
- ABBV-157 clinical POC

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