Developing innovative therapies in NASH

Corporate Presentation

April 2023

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DISCLAIMER

This presentation contains “forward-looking statements” within the meaning of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, included in this presentation are forward-looking statements. These statements include, but are not limited to, forecasts, targets and estimates with respect to Inventiva’s pre-clinical programs and clinical trials, including design, duration, objectives and key dates, selection, activation and performance of clinical sites, screen failure rates, expectations regarding patient recruitment, screening, enrollment and randomization, the benefits of the central review process and protocol amendments, for those trials and the timing thereof, including the NATiV3 Phase III clinical trial with lanifibranor in NASH, the LEGEND Phase IIa combination trial with lanifibranor and empagliflozin in patients with NASH and type 2 diabetes, and the Phase II clinical study evaluating lanifibranor for the treatment of NAFLD in patients with T2D, the potential benefits of the modification of the Phase III NATiV3 trial evaluating lanifibranor in NASH, the potential development of and regulatory pathway for odiparcil including potential partnership, clinical trial data releases and publications, including the LEGEND Phase IIa combination trial with lanifibranor and empagliflozin in patients with NASH and type 2 diabetes, and the Phase II clinical study evaluating lanifibranor for the treatment of NAFLD in patients with T2D, the information, insights and impacts that may be gathered from clinical trials, the potential therapeutic benefits of Inventiva’s product candidates, including lanifibranor, potential regulatory submissions and approvals, Inventiva’s pipeline and pre-clinical and clinical development plans, the design of trials and the implementation of amendments to trial design and the anticipated benefits related thereto, expectations with respect to enrollment of patients in China in the NATiV3 trial, and future activities, expectations, plans, growth, and prospects of Inventiva, the potential receipt of the second tranche under the EIB loan and any potential transaction or receipt of additional funds, and the sufficiency of Inventiva’s cash resources and cash runway and the ability of the Company to continue as a going concern, competitive advantages and opportunities, including pipeline product development of Inventiva. Certain of these statements, forecasts and estimates can be recognized by the use of words such as, without limitation, “believes”, “anticipates”, “expects”, “intends”, “plans”, “seeks”, “estimates”, “may”, “will”, “would”, “could”, “might”, “should”, “plans”, “designed”, “hopefully”, “target”, “aim” and “continue” and similar expressions. Such statements are not historical facts but rather are statements of future expectations and other forward-looking statements that are based on management's beliefs. These statements reflect such views and assumptions prevailing as of the date of the statements and involve known and unknown risks and uncertainties that could cause future results, performance or future events to differ materially from those expressed or implied in such statements. Future events are difficult to predict and may depend upon factors that are beyond Inventiva's control. There can be no guarantees with respect to pipeline product candidates that the clinical trial results will be available on their anticipated timeline, that future clinical trials will be initiated as anticipated, that product candidates will receive the necessary regulatory approvals, or that any of the anticipated milestones by Inventiva or its partners will be reached on their expected timeline, or at all. Actual results may turn out to be materially different from the anticipated future results, performance or achievements expressed or implied by such statements, forecasts and estimates, due to a number of factors, including that Inventiva is a clinical-stage company with no approved products and no historical product revenues, Inventiva has incurred significant losses since inception, Inventiva has a limited operating history and has never generated any revenue from product sales, Inventiva will require additional capital to finance its operations, in the absence of which, Inventiva may be required to significantly curtail, delay or discontinue one or more of its research or development programs or be unable to expand its operations or otherwise capitalize on its business opportunities and may be unable to continue as a going concern, Inventiva's future success is dependent on the successful clinical development, regulatory approval and subsequent commercialization of current and any future product candidates, preclinical trials or earlier clinical trials are not necessarily predictive of future results and the results of Inventiva's clinical trials may not support Inventiva's product candidate claims, Inventiva’s expectations with respect to the changes to the clinical development plan for lanifibranor for the treatment of NASH may not be realized and may not support the approval of a New Drug Application, Inventiva may encounter substantial delays in its clinical trials or Inventiva may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities, the ability of Inventiva to recruit and retain patients in clinical studies, enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be made more difficult or rendered impossible by multiple factors outside Inventiva's control, Inventiva's product candidates may cause adverse drug reactions or have other properties that could delay or prevent their regulatory approval, or limit their commercial potential, Inventiva faces substantial competition and Inventiva’s business, and preclinical trials and clinical development programs and timelines, its financial condition and results of operations could be materially and adversely affected by the current COVID-19 pandemic and geopolitical events, such as the conflict between Russia and Ukraine, related sanctions and related impacts and potential impacts on the initiation, enrollment and completion of Inventiva’s clinical trials on anticipated timelines, and macroeconomic conditions, including global inflation, uncertain financial markets and disruptions in banking systems. Given these risks and uncertainties, no representations are made as to the accuracy or fairness of such forward-looking statements, forecasts and estimates. Furthermore, forward-looking statements, forecasts and estimates only speak as of the date of this presentation. Readers are cautioned not to place undue reliance on any of these forward-looking statements.

Please refer to the Universal Registration Document for the year ended December 31, 2022 filed with the Autorité des Marchés Financiers on March 30, 2023, the Annual Report on Form 20-F for the year ended December 31, 2022 filed with the Securities and Exchange Commission on March 30, 2023.

All information in this presentation is as of the date of the release. Except as required by law, Inventiva has no intention and is under no obligation to update or review the forward-looking statements referred to above.

Key take-aways

A Phase III asset in NASH

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

Positive Phase IIb results with statistically significant efficacy on histological NASH resolution and one stage fibrosis reduction

Mechanism of action addressing all key features of NASH

Breakthrough Therapy Designation granted by FDA

Pivotal Phase III initiated in Q3 2021 with topline results expected H2 2025

Two Phase 2 trials ongoing with results expected in mid-Q2 2023 and H2 2023

Licensing and commercialization agreement in Greater China with Sino Biopharm, one of the largest Chinese pharmaceutical groups

A Phase III ready program in MPS(1)

Odiparcil: a GAG reduction therapy to potentially treat several forms of MPS

Reduces GAG accumulation in multiple organs in MPS VI models. Well-tolerated in MPS VI patients and in 1000s of patients previously tested(2)

Functional improvements to mobility and respiratory function and clinical efficacy signals in both ERT treated patients and ERT-naïve MPS VI patients

MPS VI Orphan Drug Designation granted in the U.S. and in the EU. Rare Pediatric Disease Designation in MPS VI granted in the U.S.

Guidance on path to regulatory submission from FDA with a single Phase II/III trial

Inventiva continues to review potential options to further develop odiparcil which may include pursuing a partnership

R&D Capabilities and Cash Position

R&D capabilities including wholly-owned 'pharma scale' discovery facilities with a discovery engine focused on nuclear receptors, transcription factors and epigenetic targets

Clinical Ops team in place in Europe and the United States

Strong U.S. and European shareholder base and experienced senior management team

Cash position allowing a runway through Q4 2023, excluding the conditional(3) €25m second tranche of the bullet loan facility secured with the European Investment Bank (4)

(1) MPS: mucopolysaccharidosis ; (2) Trials conducted by GSK prior to Inventiva's founding; (3) The second tranche is subject to conditions that are not satisfied as of the date of this presentation; (4) This estimate is based on Inventiva's current business plan and excludes any potential milestones payable to or by Inventiva and any additional expenditures related to the potential continued development of the odiparcil program or resulting from the potential in-licensing or acquisition of additional product candidates or technologies, or any associated development Inventiva may pursue. Inventiva may have based this estimate on assumptions that are incorrect and Inventiva may end up using its resources sooner than anticipated.

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

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

- Wide expertise within the areas of R&D, 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

- Successfully managed numerous research programs leading to the discovery, development and commercialization of innovative compounds, including lanifibranor and Degarelix/ Firmagon®
- Held several senior research positions at Fournier, Solvay Pharma and Abbott

Jean Volatier, MA, CFO

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

Michael Cooreman, MD, CMO

- Gastroenterologist-hepatologist
- Held global roles in several companies including Takeda Pharmaceuticals, Merck, Mitsubishi Tanabe, ImmusanT and Novartis
- U.S. based

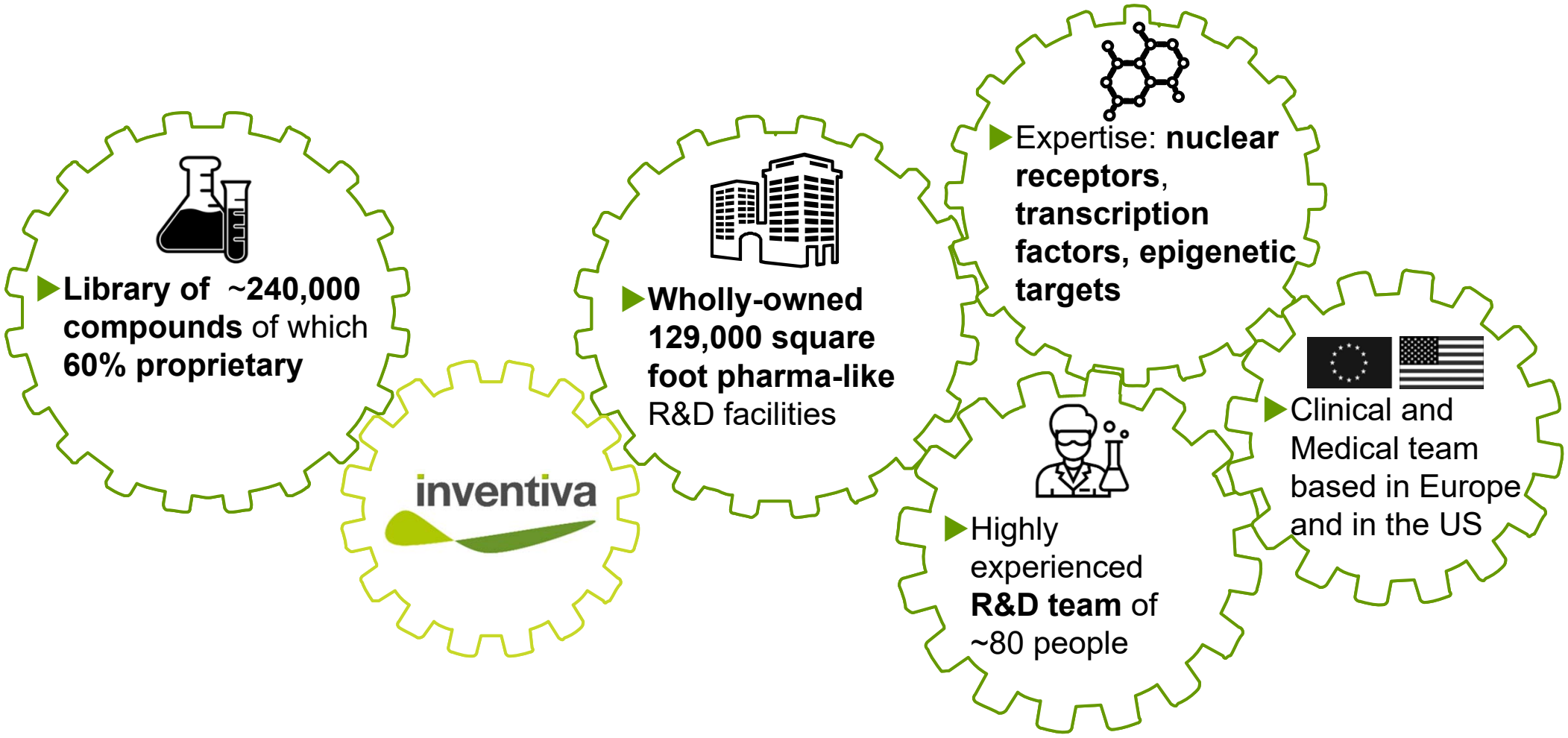
Alice Roudot-Ketelers, PharmD, COO

- Previously in charge of all drug development programs and cross-functional teams in Chemistry, CMC, non-clinical and clinical development up to Phase III at one of the major biotech companies in the NASH field

David Nikodem, Ph.D., VP U.S. Operations

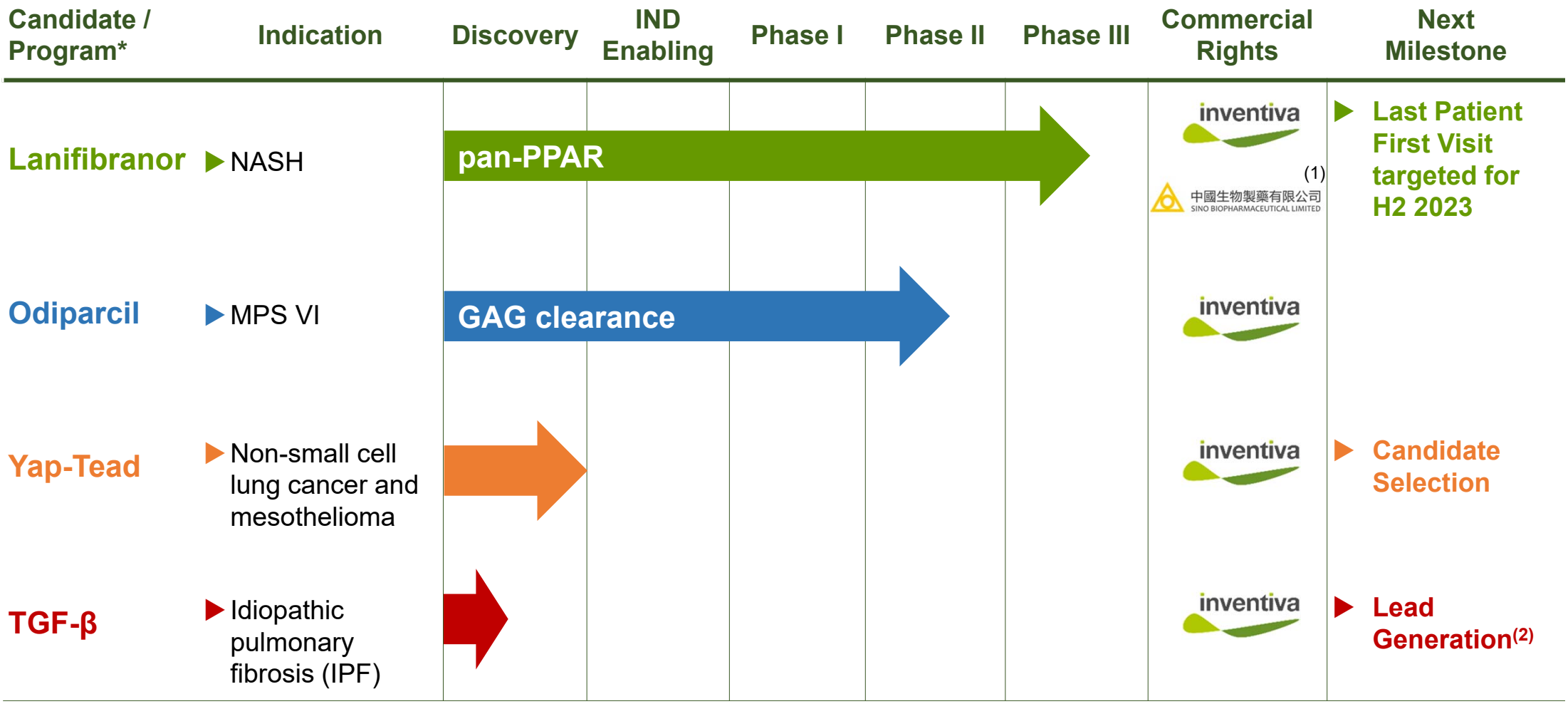
- Former buyside portfolio manager and analyst for +15 years in public equities and VC
- U.S. based

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



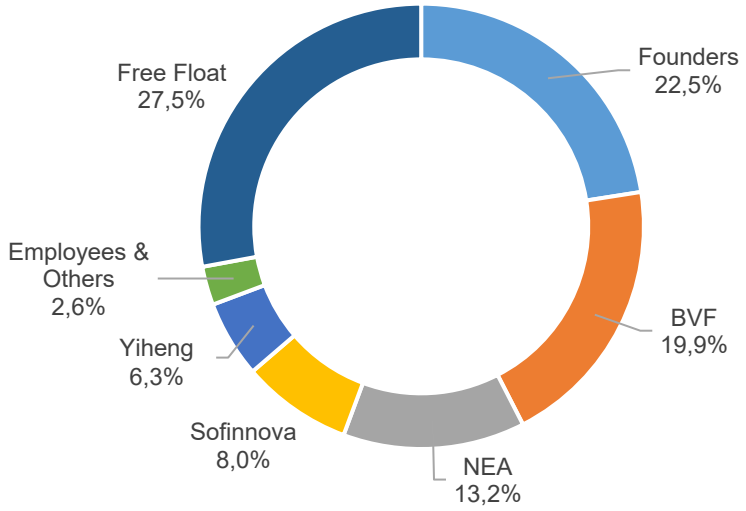
(1) Licensing agreement giving Chia Tai Tianqing Pharmaceutical Group, Co., LTD. ("CTTQ"), an affiliate of Sino Biopharm, exclusive rights to develop and commercialize in China, Hong-Kong, Macao and Taiwan (2) Lead generation means identifying molecules in anticipation of selecting candidates; (2) All MPS-related research and development activities were suspended in 2020. All options for potential further development of odiparcil for the treatment of MPS are continued to be evaluated

Key financials and shareholder base

Key financials

ISIN code	FR0013233012 / US46124U1079
Market	Euronext Paris / Nasdaq GM
Shares outstanding	42,134,169
Market cap (March 29, 2023)	Euronext Paris: €139m Nasdaq Global Market: $158m
Cash position (as of Dec. 31,2022)	€87.8m (vs €95.4m as of December 31, 2021)(1) Current expected cash runway until the end of Q4 2023(2)
Revenues (2022)	€12.2m compared to €4.2m in 2021
R&D expenditures (2022)	€60.5m compared to €48.5m in 2021

Shareholder base



Analyst coverage

Jefferies	L. Codrington / M. J. Yee
Guggenheim	S. Fernandez
HC Wainwright	E. Arce
Stifel	A. Samimy
KBC	J. Van den Bossche
Société Générale	D. Le Louët
Bryan Garnier	A. Cogut
Portzamparc	M. Kaabouni

(1) The cash position is defined as cash and cash equivalents as well as short-term deposits which are included statement of financial position for €1.0 million as of Dec. 31, 2022 and for €8.8 million as of December 31, 2021, considered by the Company as liquid and easily available

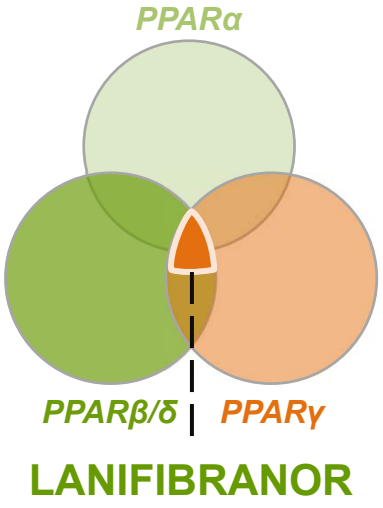
(2) This estimate is based on Inventiva's current business plan and excludes any potential milestones payable to or by Inventiva and any additional expenditures related to the potential continued development of the odiparcil program or resulting from the potential in licensing or acquisition of additional product candidates or technologies, or any associated development Inventiva may pursue, Inventiva may have based this estimate on assumptions that are incorrect and Inventiva may end up using its resources sooner than anticipated.

Lanifibranor in Nonalcoholic Steatohepatitis (NASH)

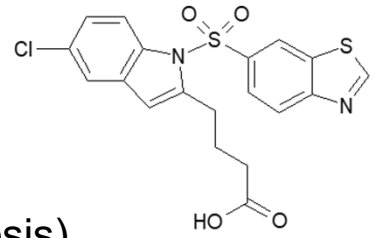
Lanifibranor: a pan-PPAR agonist in phase III development in NASH

LANIFIBRANOR

Moderate and balanced pan-PPAR agonist activity



LANIFIBRANOR



- Small molecule that activates all three PPAR isoforms in humans
- Differentiated chemical structure: not a fibrate or a TZD
- Once daily oral administration
- **Positive Phase IIb trial** topline results in NASH
- **FAST Track** (including in NASH patients with compensated cirrhosis) **and Breakthrough Therapy** designations granted by FDA
- **IP :**
  - Composition of matter patent: LOE(1) August 2026
  - Method of use patent: LOE(1) June 2035
  - 5-year extension can be added to composition or method of use patent

Favorable tolerability profile

- Phase I trials with more than **200** healthy volunteers 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
- **Thorough QT/QTc study** demonstrates no impact of the drug on QT intervals
- FDA confirmation that the **non-clinical toxicology package is complete and acceptable for NDA filing**

(1) LOE: Loss of exclusivity

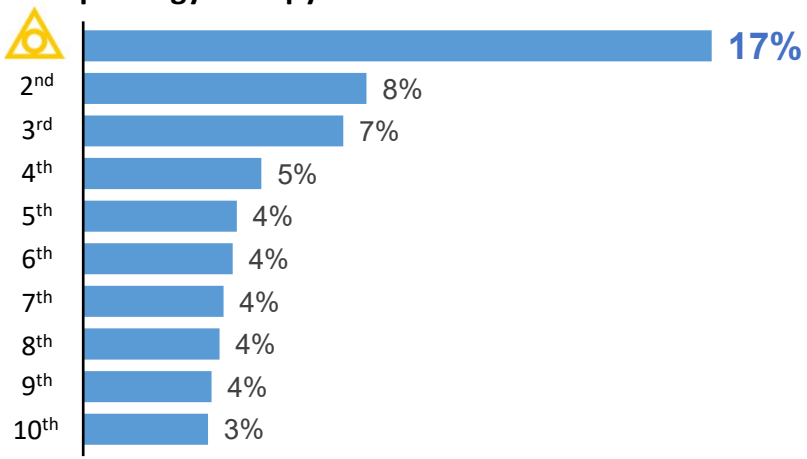
Lanifibranor: licensing and commercialization agreement in Greater China

中國生物製藥有限公司
SINO BIOPHARMACEUTICAL LIMITED

- Sino Biopharm is one of the largest Chinese pharmaceutical groups listed in Hong Kong Exchange (HSI composite) with a market cap of c.US$10bn(1) and c.US$4bn of revenue(2) and ranked top 40th pharma globally(3)
  - Through its subsidiaries, Sino Biopharm is a fully integrated pharma with R&D, manufacturing, marketing, sales and distribution capabilities
  - Sales organisation with 13,900+ reps, covering 32 provinces and more than 90% of hospitals in China, using both traditional sales and emerging online channels

The largest market share in China(4)

Hepatology therapy market share of China in 2021 (4)



Licensing key terms

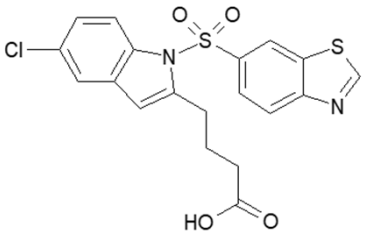
- Exclusive license to CTTQ to develop, manufacture and commercialize in China, Hong-Kong, Macao and Taiwan
- Inventiva received a **$12 million upfront payment** following the recent signing
- Additional **$5 million expected in the short-term** if certain clinical milestones are met
- Potential to receive up to **$290 million of clinical, regulatory and commercial milestone payments upon achievement of milestones**
- Subject to regulatory approval, **Inventiva has the right to receive tiered royalties** from high single-digit to mid-teen double digits of net sales made by Sino Biopharm in Greater China during the first three years of commercialization and from low to mid-teen double digits starting from year four.
- Depending on the multiple factors including Chinese regulatory authorities feedback, **CTTQ expected to either join the ongoing NATiV3 Phase III clinical trial of lanifibranor in NASH or run an independent study**. CTTQ will bear all costs associated with the trials conducted in Greater China.

(1) Information about Sino Biopharm, its business, operations and finances are based on third-party information and disclosures. Inventiva makes no representations regarding the accuracy of such information presented herein; (2) Market data as of Sept 2022 ; (3) Converted from RMB to USD ; (4) Based on IMS data

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

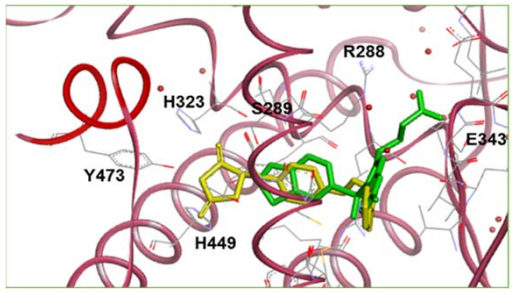
LANIFIBRANOR

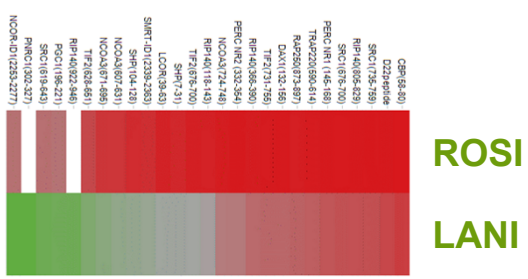
Differentiated oral small molecule …



- Small molecule that activates all three PPAR isoforms
- Differentiated chemical structure with once daily oral administration
- Offered in two dosage forms (800 mg, 1200 mg)

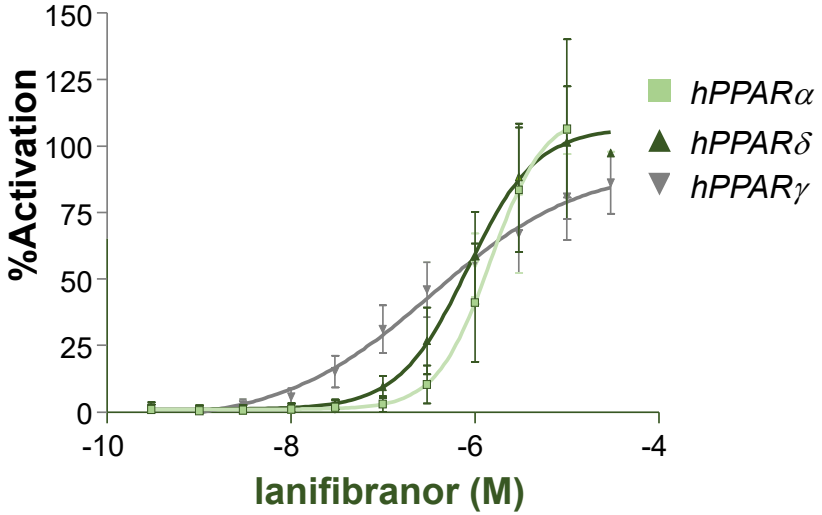
… that binds differently than glitazone to PPARγ





- Induces different coactivator recruitment^^

Moderate and balanced pan-PPAR agonist activity



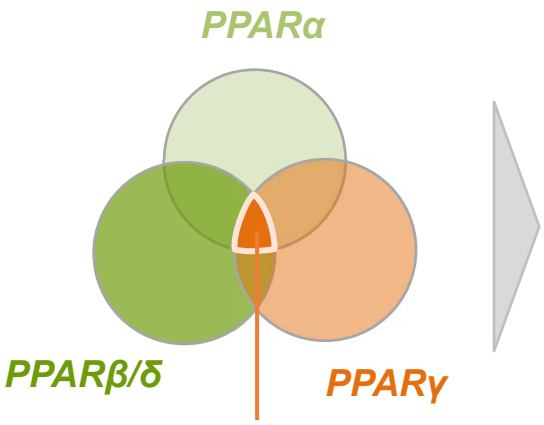
Compound	PPARα EC50 (nM)	PPARδ EC50 (nM)	PPARγ EC50 (nM)
Lanifibranor*	**1630**	**850**	**230**
Fenofibrate	*2400*	*-*	*-*
Pioglitazone	*-*	*-*	*263*
Rosiglitazone	*-*	*-*	*13*
*Elafibranor***	*10*	*100*	*-*
*Seladelpar^*	*-*	*2*	*-*

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

Lanifibranor's activation of the three PPAR isoforms addresses the key features of NASH

LANIFIBRANOR

Pan-PPAR activity expected to ensure improved efficacy



LANIFIBRANOR

METABOLISM

PPARα PPARδ PPARγ

- ↑ Insulin sensitivity
- ↑ HDLc
- ↓ Triglycerides

STEATOSIS

PPARγ

- ↓ FA uptake
- ↑ FA catabolism
- ↓ Lipogenesis

INFLAMMATION AND BALLOONING

PPARα PPARδ PPARγ

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

FIBROSIS

PPARδ PPARγ

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

VASCULAR

PPARα PPARγ

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

Adverse events and toxicity previously seen in other single and dual PPAR agonists have not been observed to date with lanifibranor

SAFETY

Organ	Isoforms activated	Reported PPAR side effects	lanifibranor effects
 HEART	*PPARγ*	▶ Fluid retention ▶ Cardiac hypertrophy	NOT OBSERVED TO DATE
 SKELETAL MUSCLE	*PPARα*	▶ Myofiber degeneration	
 KIDNEY	*PPARα*	▶ > 50% increases in creatinine, degenerative changes in renal tubules	
 URINARY BLADDER	*PPARγ*	▶ Proliferative changes in bladder epithelium	

Adverse events and toxicity of single / dual PPAR agonists not observed in primate and rodent studies

FAVOURABLE TOLERABILITY PROFILE in a 12-month monkey study …

- ▶ No adverse clinical signs observed at any dose-level tested
- ▶ No effects on body and heart weight, no haemodilution or creatinine increase
- ▶ Electrocardiography and clinical pathology investigations did not reveal any undesirable effects

… and in two-year **CARCINOGENITY STUDIES** performed in rat and mice

- ▶ Rat: no observed neoplastic change or increase in tumor types commonly associated with single PPARγ and dual PPARα/γ agonists (liver, adipose, bladder, renal and skin)
- ▶ Mice: no observed neoplastic changes of human relevance

Confirmation by FDA that the non-clinical toxicology package is complete and acceptable to support NDA filing in NASH

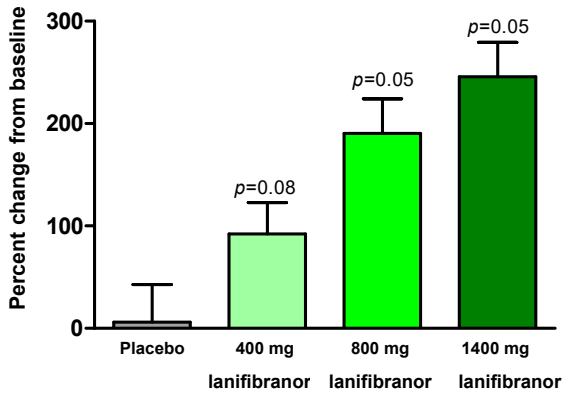
Source: Company data

Phase I and Phase IIa clinical trials* in type 2 diabetes (T2D) patients: beneficial changes in key metabolic markers

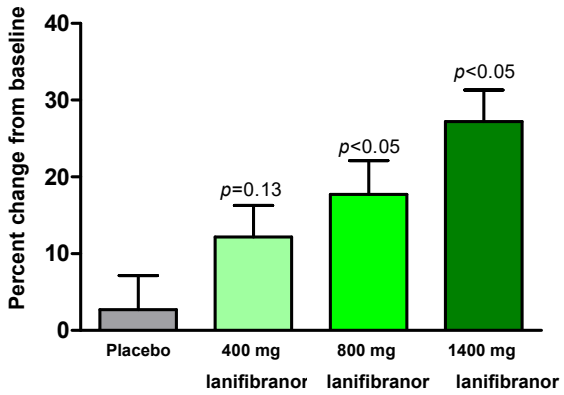
PHASE I AND IIa

Lanifibranor metabolic markers in patients with T2D

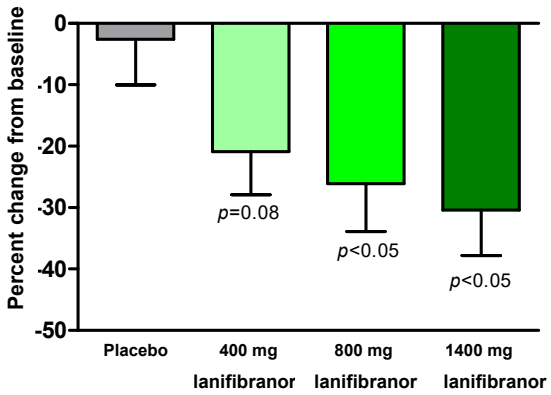
Adiponectin (PPARγ)**



HDL Cholesterol (PPARα/δ)^



Triglycerides (PPARα/δ) ^^



Phase I and IIa* clinical findings support the favorable tolerability of lanifibranor

- Phase I trials: > **200** healthy volunteers
- Phase IIa trial with **47** T2D patients
- Phase IIb: > **250** patients treated for 24 or 48 weeks
- Good overall tolerability and no major safety findings
- No increases of creatinine, LFTs, or CPK
- No changes in blood pressure, no signal of fluid overload or haemodilution
- No clinically relevant weight gain

Thorough QT/QTc study demonstrates no impact of the drug on QT intervals

- Study carried out in 2020 and 2021 to prepare the NDA package
- A randomized, double-blind, double-dummy, placebo, positive-controlled (400mg of moxifloxacin) and multiple-dose (1200mg and 2400mg as the supratherapeutic dose) cardiac safety study to evaluate the effect of lanifibranor on the QT interval in healthy adult subjects
- At doses of 1200 mg and 2400 mg, lanifibranor has no impact on QT intervals

Note: * Conducted by Abbott; ** Adiponectin is associated with PPARγ activation; ^ HDL-C is associated with PPARα and d activation; ^^ Triglycerides are associated with PPARα and δ activation
Source: Company data

Improvements in metabolic parameters and liver histology with anti-fibrotic activity have been demonstrated in animal models

LANIFIBRANOR

ANIMAL MODELS, BY MODEL TYPE

METABOLIC	NASH & NAFLD	FIBROSIS	CIRRHOSIS
Diet induced obesity high fat / high sucrose	Methionine Choline Deficient diet (MCD)	Carbon tetrachloride (CCL4)	Thiocetamide (TAA)
Foz / Foz model			
	Choline-deficient amino-acid and high fat diet		

In vivo models

Hepatoma and muscle cells biology	Macrophages biology	Hepatic Stellate Cells (HSC) biology	
			Endothelial biology

In vitro models

OBSERVED EFFECTS, BY MODEL TYPE

- Improvements in
  - Insulin resistance
  - Non fasting glucose
  - Homa-IR
  - Lipid profile
- Maintenance of body weight

- Improvements in
  - Steatosis
  - Inflammation
  - Ballooning
- Improvements in NAS score

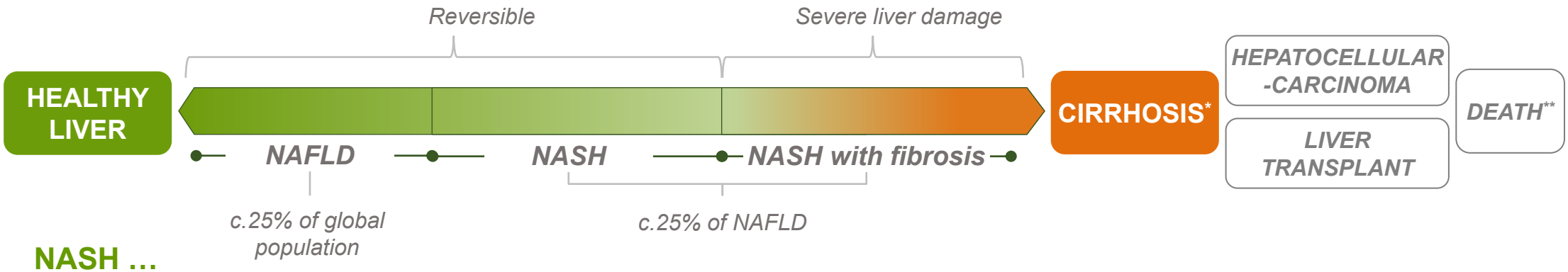
- Improvement of fibrosis
- Inhibition of stellate cell activation

- Reductions in
  - Portal pressure
  - Established fibrosis

NASH is a chronic progressive disease with no currently approved treatment options

NASH OVERVIEW

Chronic disease that may progress to cirrhosis



NASH …

… can be classified based on histologic features

FIBROSIS STAGE

F0 F1 F2 F3 F4

NAS SCORE

Reflects disease activity; composite of three features (steatosis, inflammation, ballooning)

SAF SCORE

Semi-quantitative score of steatosis, activity, fibrosis

… is associated with type 2 diabetes (T2D)

T2D patients tend to present with more severe and faster progressing NASH

… is currently mainly diagnosed through liver biopsy

Liver biopsy is currently the method of reference; broader adoption of non-invasive tests and launch of disease-modifying therapies may make diagnosis easier

… is characterised by high unmet needs

KEY UNMET NEED F2 F3

Treatment targeting both NASH resolution and fibrosis

KEY UNMET NEED F4

Treatment of cirrhosis

Note: * More than 20% of patients with NASH progress to cirrhosis within a decade of diagnosis; ** Compared to the general population patients with NASH have a ten-fold greater risk of liver-related mortality
Source: PanNASH; NASH Market, Allied Market Research 2016 ; Deutsche Bank Markets Research; HCV Trials; Duseja (2019) L.E.K. interviews, research, and analysis

Lanifibranor: clinical development plan

CLINICAL DEVELOPMENT

Phase I → **Phase IIa** → **Phase IIb (NATIVE)**

IIb DESIGN

- *24 weeks*
- *800 and 1200 mg Lanifibranor once-daily versus placebo*

IIb EFFICACY

- *First investigational compound to show robust efficacy on NASH resolution and fibrosis improvement – FDA and EMA endpoints for accelerated / conditional approval*

IIb SAFETY

- *Favourable safety profile*

Phase III in patients with NASH and fibrosis stages F2-F3

Potential accelerated approval

III OVERVIEW

- *Surrogate histological endpoints at 72 weeks*
- *72 weeks exploratory cohort*
- *≥ 48 weeks active treatment extension*

Phase III in patients with NASH and compensated cirrhosis

III OVERVIEW

- *Clinical outcome endpoints*
- *Event driven, up to 3 years*

Potential full approval

Phase II in NAFLD patients with T2D (*)

Lanifibranor + empagliflozin combination

Proof-of-Concept study in patients with NASH and T2D

Completed clinical trials

Ongoing clinical trials

Planned clinical trials

(*) Sponsor: University of Florida, dr Ken Cusi

The Phase IIb NATIVE trial evaluated 800 mg and 1200 mg once-daily lanifibranor versus placebo in 247 patients

PHASE IIb **DESIGN** **OVERVIEW**

NATIVE — NASH TRIAL TO VALIDATE IVA337 EFFICACY

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 (T2D)

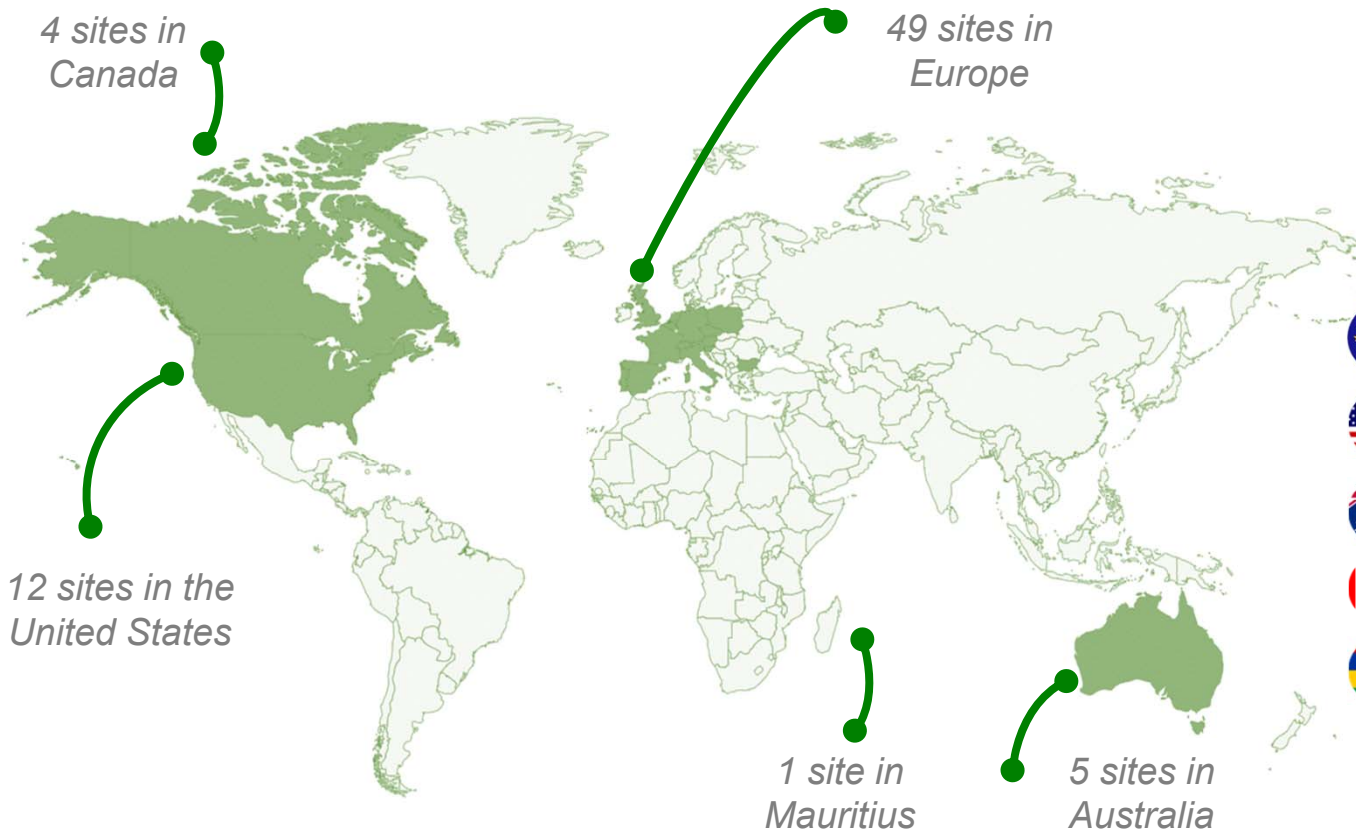
Patient population	# patients	Definition
Safety / Intention-to-Treat (ITT)	247	Patients randomized having received at least one dose of lanifibranor/placebo
Per Protocol (PP)	194	Patients with paired biopsies and without deviation impacting efficacy results

- **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
- **Results published in the New England Journal of Medicine**[1]:

(1) https://www.nejm.org/doi/full/10.1056/NEJMoa2036205

247 patients were randomised across 71 sites worldwide, with the majority of patients based in Europe

PHASE IIb | DESIGN | SITE SELECTION



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

16 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)

The majority of patients successfully completed the 24-week treatment

PHASE IIb | DESIGN | TREATMENT ARMS

247 patients randomised and treated

Placebo N = 81	lanifibranor 800 mg/day N = 83	lanifibranor 1200 mg/day N = 83
74 (91%) patients completed the 24-week treatment	77 (93%) patients completed the 24-week treatment	77 (93%) patients completed the 24-week treatment
7 (9%) patients prematurely withdrawn: - Adverse events (n=3) - Withdrawal by patient (n=2) - Forbidden concomitant medication (n=2)	6 (7%) patients prematurely withdrawn: - Adverse events (n=3) - Lost to follow-up (n=1) - Withdrawal by patient* (n=1) - Non-compliance (n=1)	6 (7%) patients prematurely withdrawn: - Adverse events (n=3) - Lost to follow-up (n=1) - Withdrawal by patient (n=2)

Note: * And adverse event as secondary reason

Patient population included 58% of female and 42% of patients with T2D

PHASE IIb | DESIGN | BASELINE

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%)

Several liver tests and markers of lipid and glucose metabolism were recorded

PHASE IIb | DESIGN | BASELINE

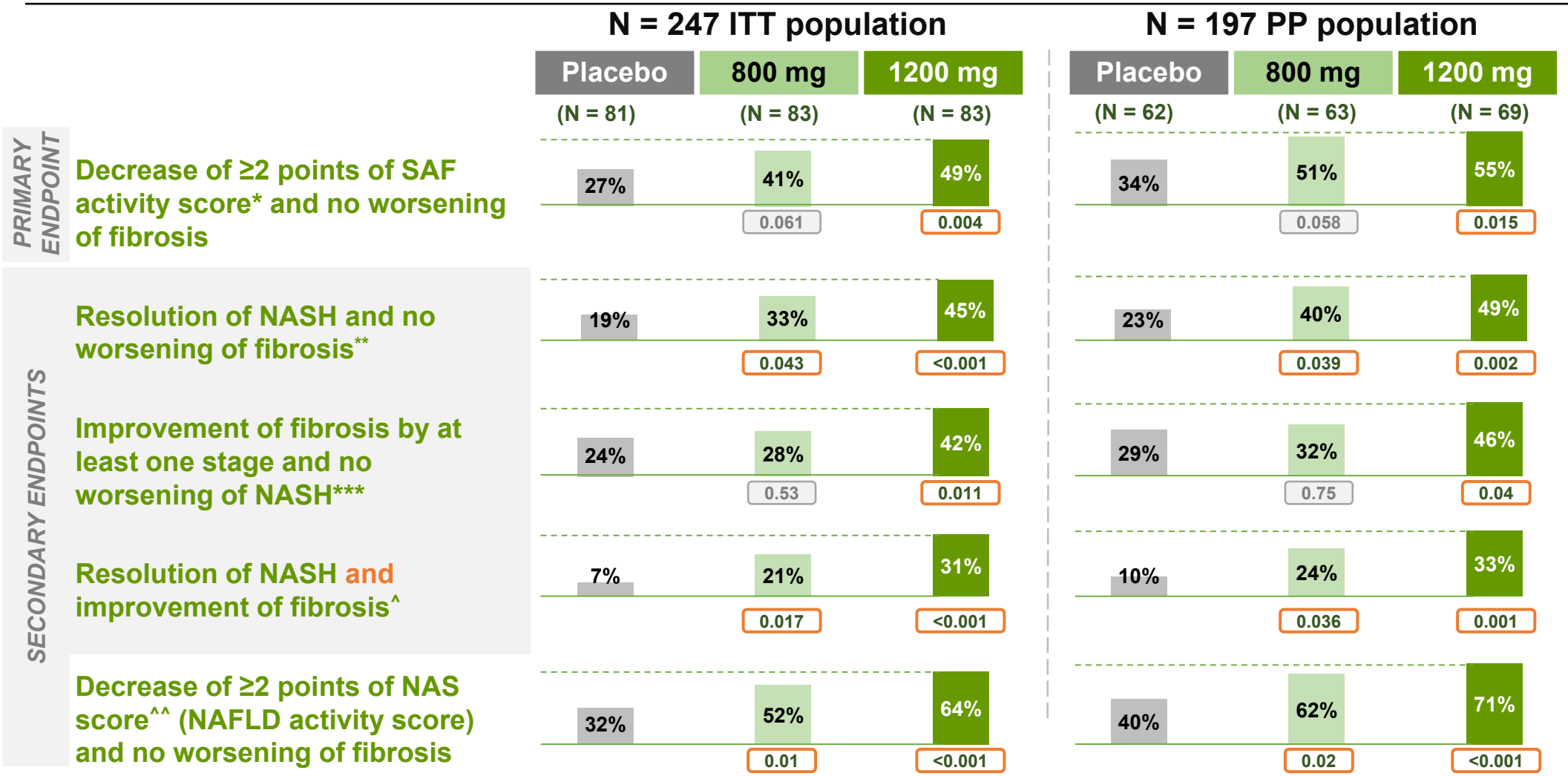
Parameters (unit) mean ± SD	Placebo - N = 81	lanifibranor 800 mg/day N = 83	lanifibranor 1200 mg/day N = 83
Liver enzymes			
Alanine aminotransferase, ALT (UI/L)	56.9 ± 31.6	64.1 ± 41.4	63.6 ± 43.4
Aspartate aminotransferase, AST (UI/L)	43.3 ± 24.1	53.9 ± 43.4	43.9 ± 24.8
Gamma glutamyl transferase, GGT (UI/L)	67.9 ± 80.4	101.6 ± 146.1	67.1 ± 93.1
Plasma lipid 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 patients with T2D (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

Lanifibranor demonstrated statistical significance on all histological endpoints in both ITT and PP populations

PHASE IIb | EFFICACY | KEY ENDPOINTS

xx Statistically significant xx Non-statistically significant

Key Phase IIb results by endpoint



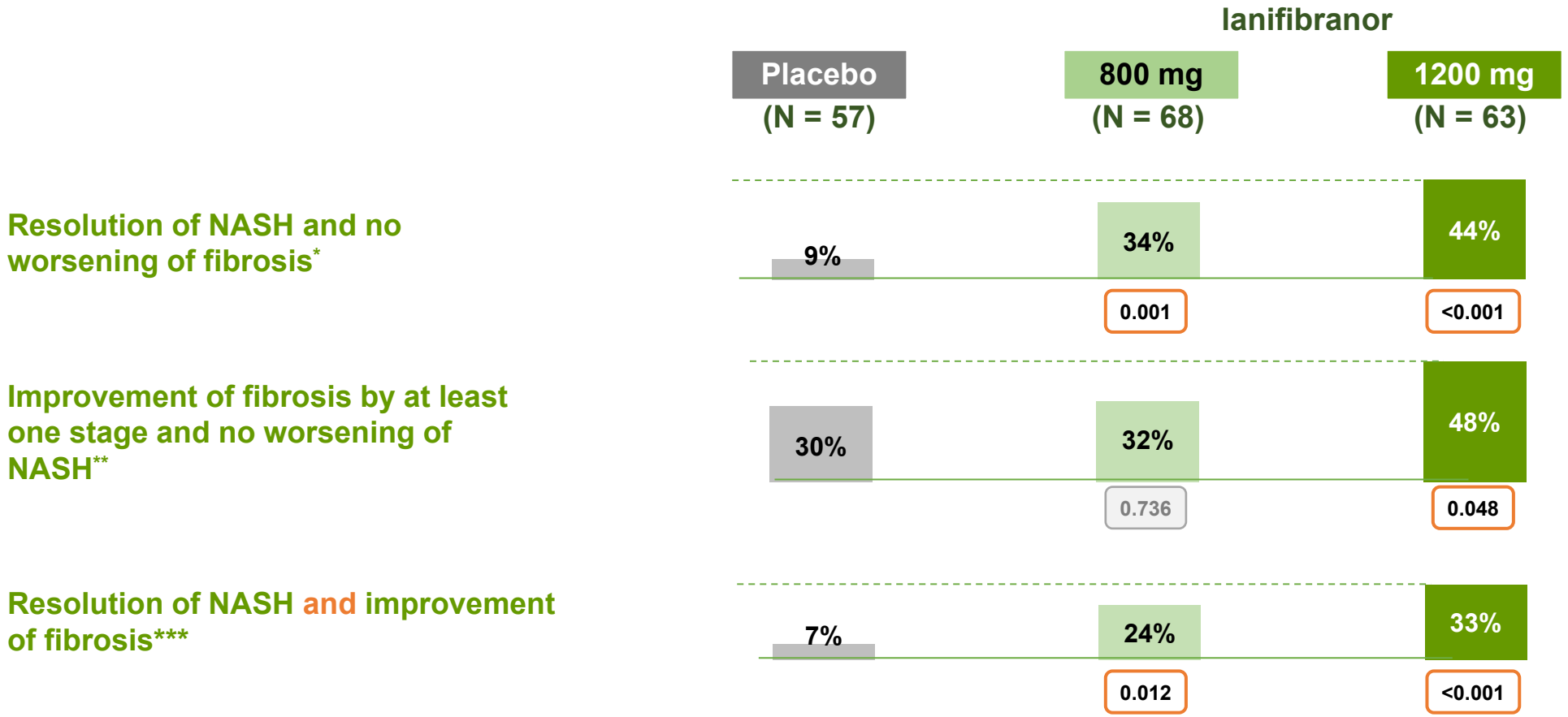
* Response is defined as a decrease from baseline to week 24 of at least 2 points of the SAF Activity score (SAF-A) with no worsening of the NAS Fibrosis score (NAS-F). No worsening means that score remains stable or decreases ; ** Resolution of NASH and no worsening of fibrosis at week 24: NAS-I = 0 or 1 (NAS-Inflammation), NAS-B = 0 (NAS-Ballooning) and no worsening of NAS-F from baseline; *** Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH at week 24; ^ Resolution of NASH and improvement of fibrosis at week 24: NAS-I = 0 or 1, NAS-B = 0 and an improvement of NAS-F ≥ 1 stage; ^^ NAS score is a commonly accepted, semi-quantitative evaluation of biopsy results that assesses the severity of steatosis, inflammation and ballooning in the liver.

Statistical significance was also demonstrated for the main key histological endpoints in patients with F2-F3 fibrosis stage

PHASE IIb | EFFICACY | F2-F3 POPULATION

xx Statistically significant xx Non-statistically significant

Key secondary endpoints in FAS F2-F3 patients (N=188)



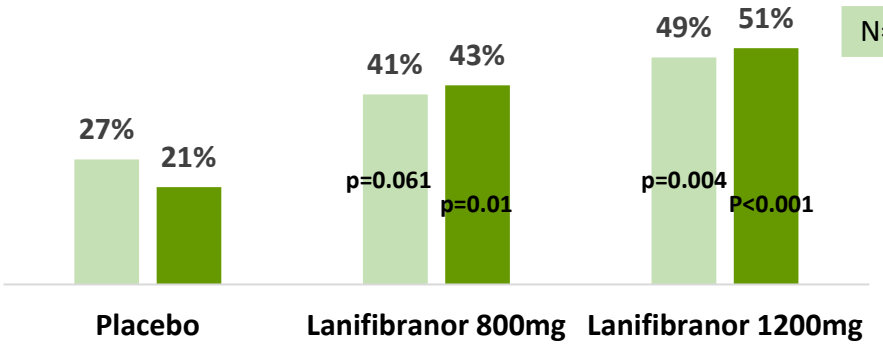
- Similar results in the PP population
- Consistent response in diabetic and non-diabetic patients

* Resolution of NASH and no worsening of fibrosis at week 24: NAS-I = 0 or 1 (NAS-Inflammation), NAS-B = 0 (NAS-Ballooning) and no worsening of NAS-F from baseline; ** Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH at week 24; *** Resolution of NASH and improvement of fibrosis at week 24: NAS-I = 0 or 1, NAS-B = 0 and an improvement of NAS-F ≥ 1 stage

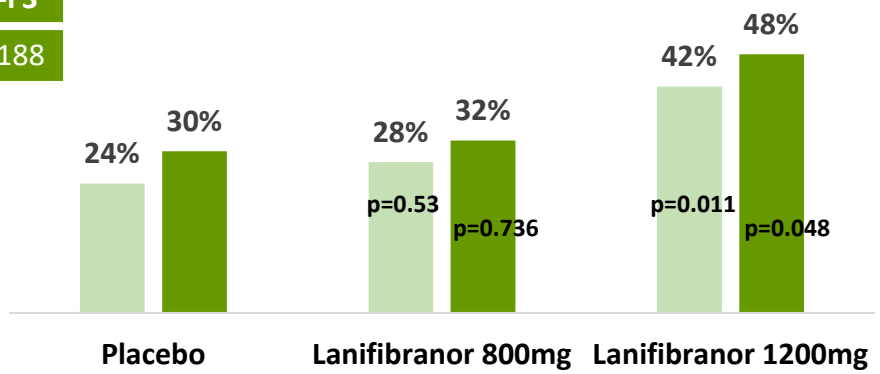
Effect of lanifibranor therapy on histological endpoints, in the overall population and the subgroup with F2-F3 fibrosis stage

Reduction of 2 points of SAF Activity Score and no worsening of fibrosis

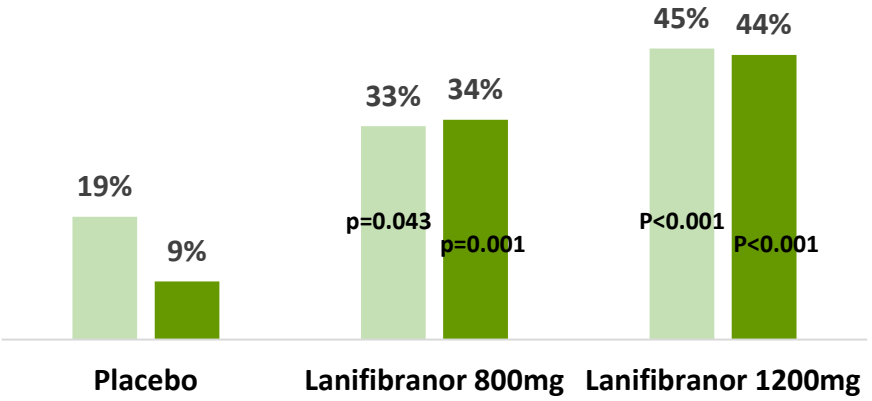
All	F2-F3
N=247	N=188



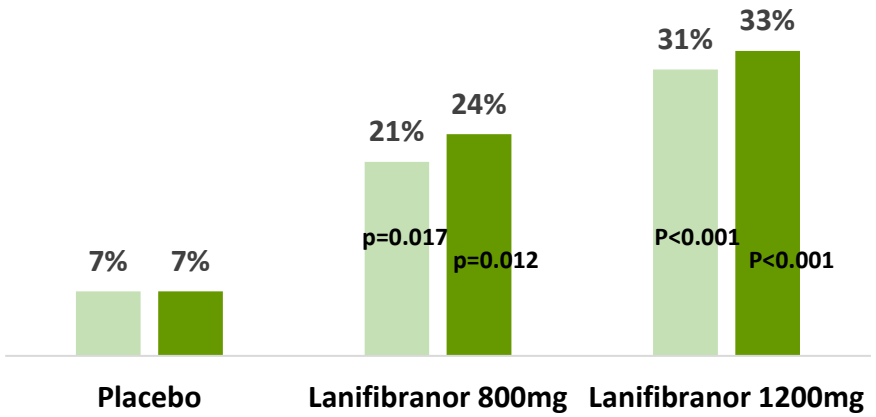
Fibrosis improvement w/o worsening of NASH



NASH resolution w/o worsening of fibrosis



NASH resolution AND Improvement of fibrosis



Effect is higher in the F2-F3 subpopulation

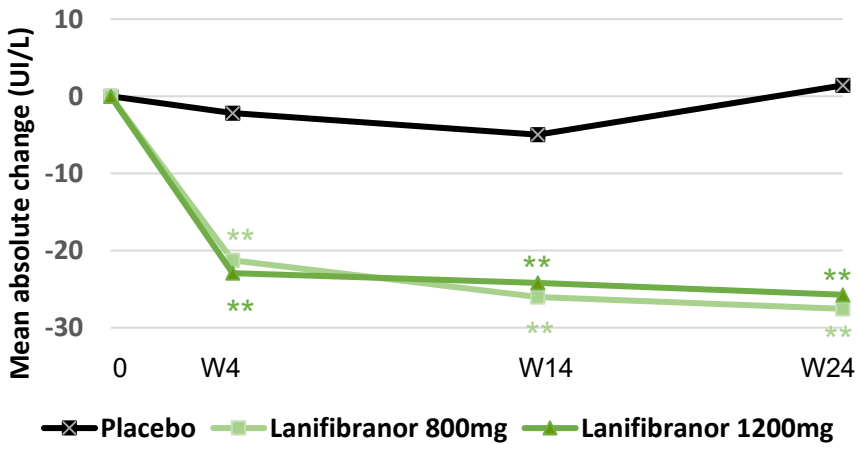
A statistically significant decrease in liver enzymes was observed

PHASE IIb | EFFICACY | OTHER

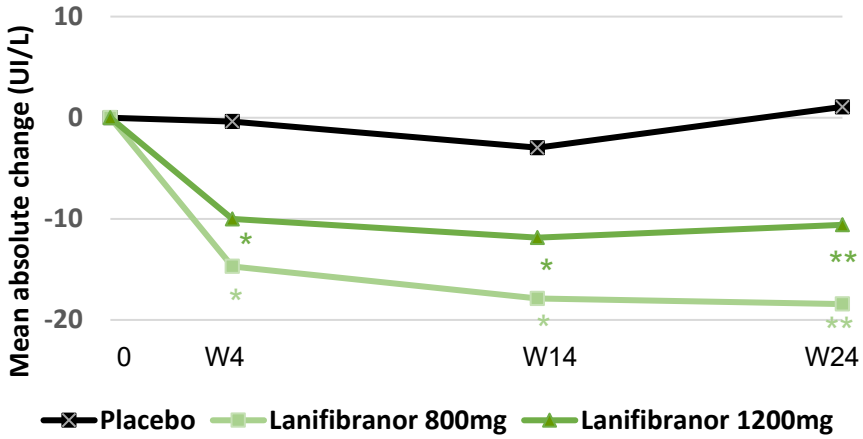
Other secondary endpoints in ITT (N = 247)

SECONDARY ENDPOINTS

Absolute change from baseline in ALT

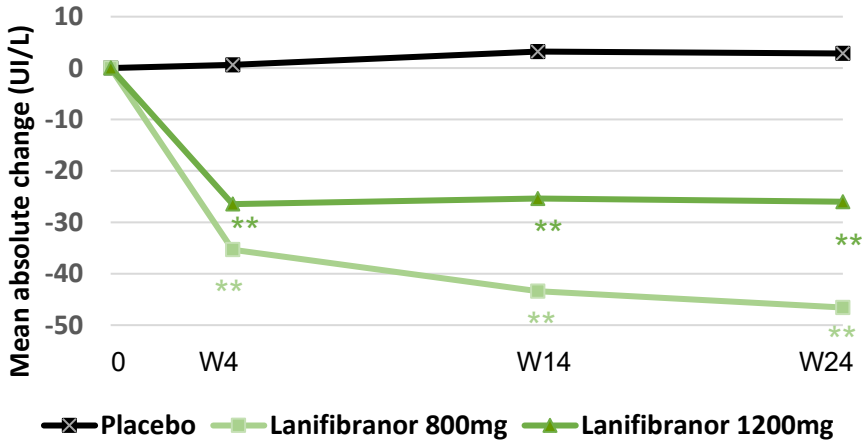


Absolute change from baseline in AST



* p<0.01 **p<0.001

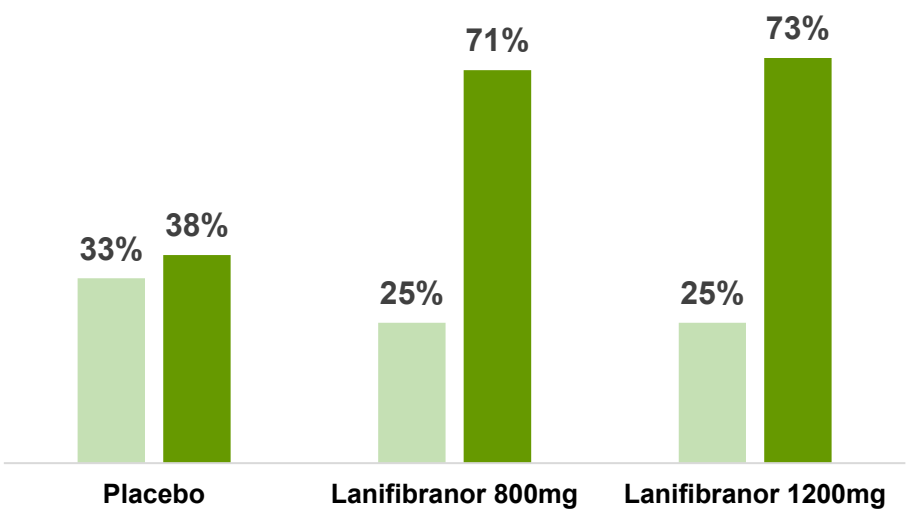
Absolute change from baseline in GGT



A statistically significant decrease of ALT, AST and GGT in both lanifibranor dose groups observed after 4 weeks

Effect of lanifibranor therapy on liver enzymes

Percentage of patients with normal ALT values

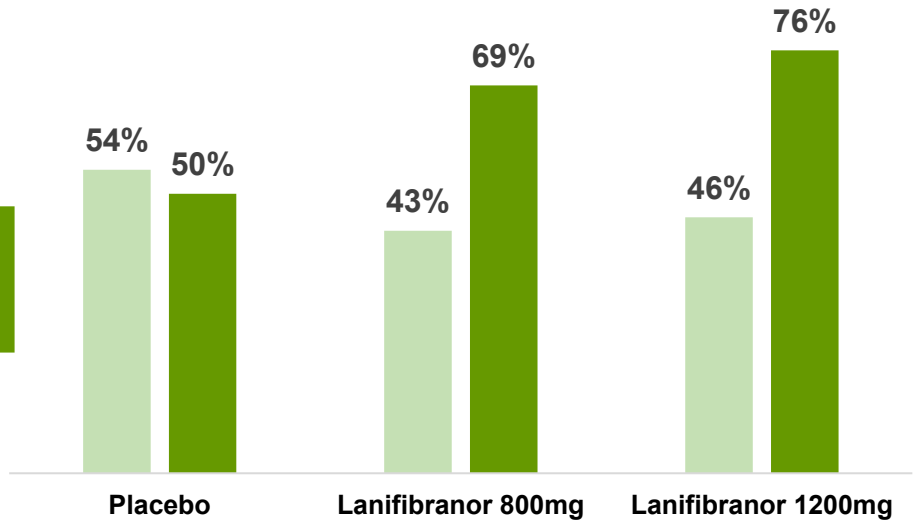


Lower Limit of Normal (LLN)= 0 U/L, Upper Limit of Normal (ULN)= 41 U/L for males, 33 U/L for females

Baseline

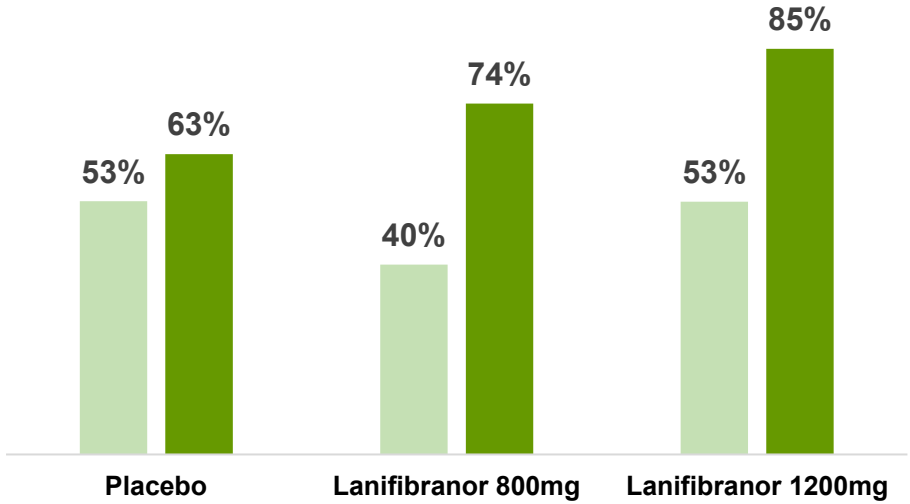
End of treatment (Week 24)

Percentage of patients with normal AST values



LLN= 0 U/L, ULN= 40 U/L for males, 32 U/L for females

Percentage of patients with normal GGT values



LLN= 8 U/L for males, 5 U/L for females; ULN= 61 U/L for males, 36 U/L for females

Significant higher percentage of patients under lanifibranor treatment reach normal liver enzymes at end of treatment

A statistically significant change in HDL-cholesterol and triglycerides was seen, without a change in LDL-cholesterol

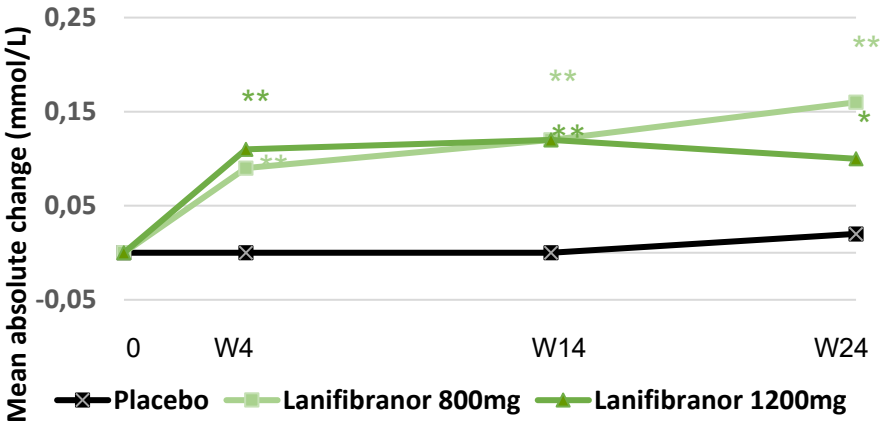
PHASE IIb | EFFICACY | OTHER

SECONDARY ENDPOINTS

Other secondary endpoints in ITT (N = 247)

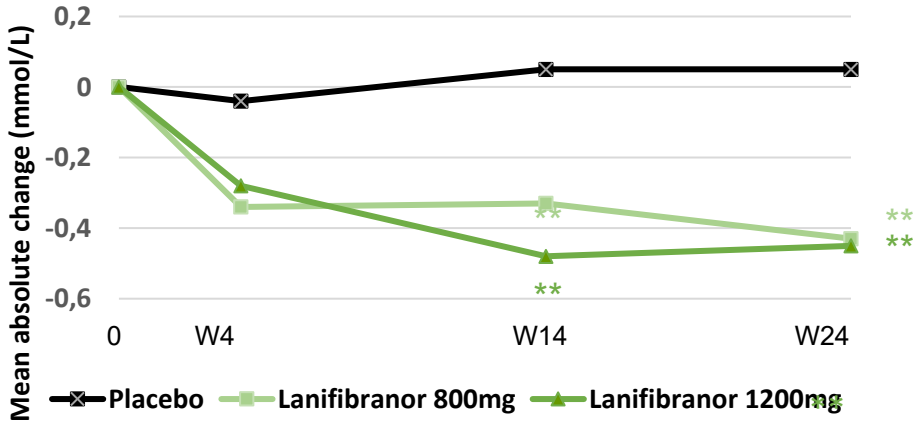
* p<0.01 **p<0.001

Absolute change from baseline in HDL-C



Statistically significant change in HDL-cholesterol

Absolute change from baseline in triglycerides



Statistically significant change in triglycerides

- No change in LDL-cholesterol

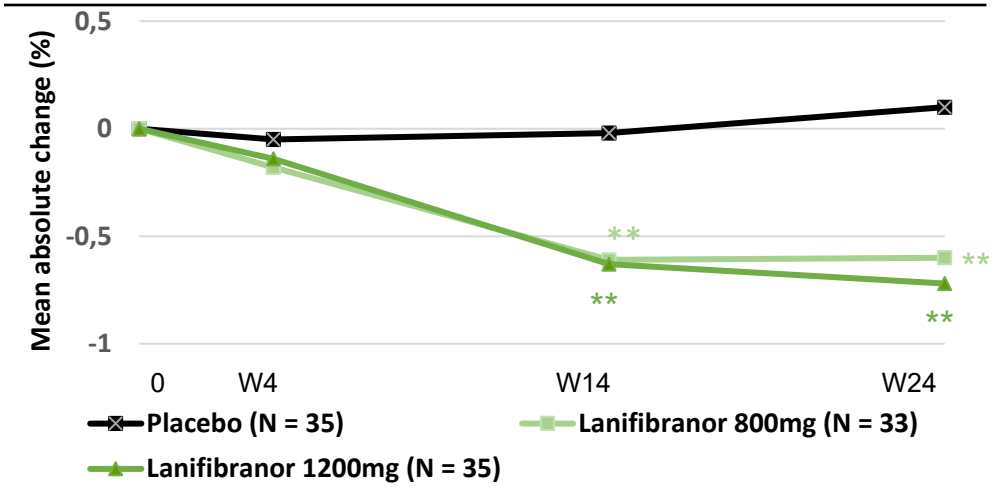
In patients with NASH and T2D, statistically significant reductions of fasting glucose and insulin, HbA1c were observed

PHASE IIb | EFFICACY | OTHER

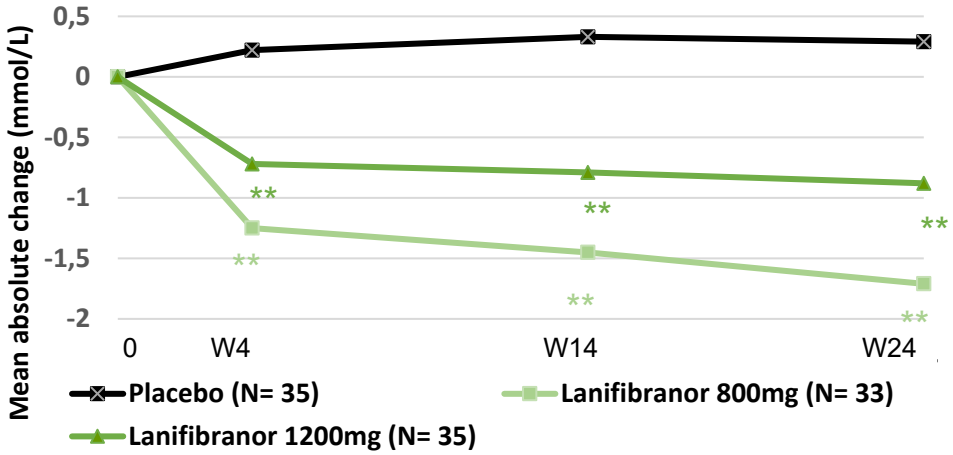
Secondary endpoints in patients with NASH and T2D (N = 103)

SECONDARY ENDPOINTS

Absolute change from baseline in HbA1c

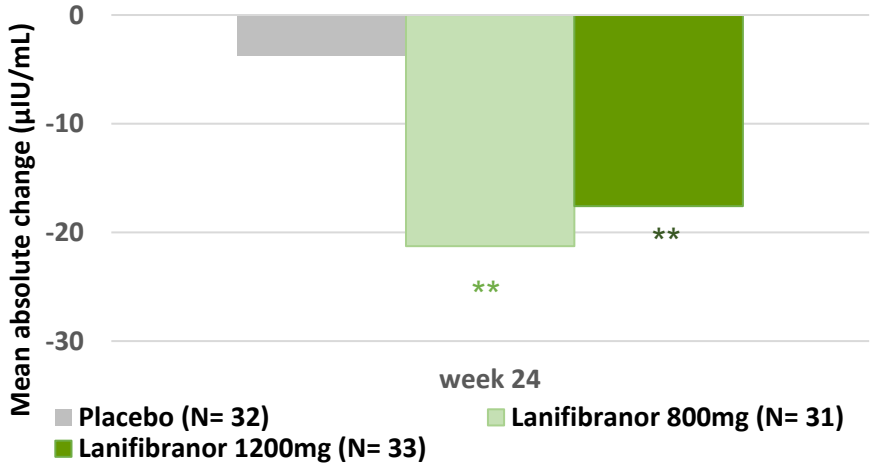


Absolute change from baseline in fasting glucose



**p<0.001

Absolute change from baseline in insulin at W24



Lanifibranor associated with improvements in insulin sensitivity and glycemic control in NASH patients

A significant decrease in circulating biomarkers was observed under lanifibranor treatment after 24-weeks

PHASE IIb | EFFICACY | OTHER

OTHER OUTCOME MEASURES

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

(1) Level where it is estimated that fibrogenesis is active and corresponding to F2/F3 patients
FAS (Full Analysis Set) population with available data at baseline and at week 24
* Statistically significant

Additional analyses of NATIVE results: lanifibranor improved markers of cardiometabolic health

Clinical data demonstrating a robust benefial effect on markers of cardiometabolic health

- Lanifibranor improved markers of glucose metabolism in prediabetic patients
  - The majority of patients who were prediabetic at study entry and received lanifibranor had normal fasting glucose levels at the end of therapy
- Lanifibranor reduced hepatic steatosis, quantified by ultrasound-based imaging (Fibroscan CAP(1))
- Glycemic control correlates with NASH severity. The improvement of metabolic markers of NASH and hepatic steatosis with lanifibranor treatment is consistent with its beneficial effect on glycemic control
- The beneficial effects of Lanifibranor on markers of cardiometabolic health were the same in patients with stable weight as in patients with weight increase

Clinical data on predictive markers – non-invasive and histological evaluations

- Following treatment with lanifibranor 'NASH resolution' responders were significantly more likely to also be 'fibrosis improvers' than non-responders
- Lanifibranor treatment improved the FibroScan-aspartate aminotransferase (Fast™) score, a promising non-invasive test (NIT) for active NASH with significant fibrosis
- Application of stringent statistical methods identified non-invasive markers predictive of histological response with Lanifibranor therapy
- Lanifibranor therapy led to a reduction in LSEC(2) capillarization, measured by CD34 immunostaining

Nonclinical data

- Lanifibranor improved NASH, fibrosis and diastolic dysfunction in a hamster model of diet-induced NASH and diastolic dysfunction

(1) CAP: Controlled Attenuation Parameter (2) *Liver Sinusoidal Endothelial Cell*

Lanifibranor has a favourable safety profile

PHASE IIb | SAFETY | OVERALL

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

Focus of next slide

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

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

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

* One AE of severe intensity

A limited number of serious TEAEs occurred

PHASE IIb | SAFETY | SERIOUS TEAE

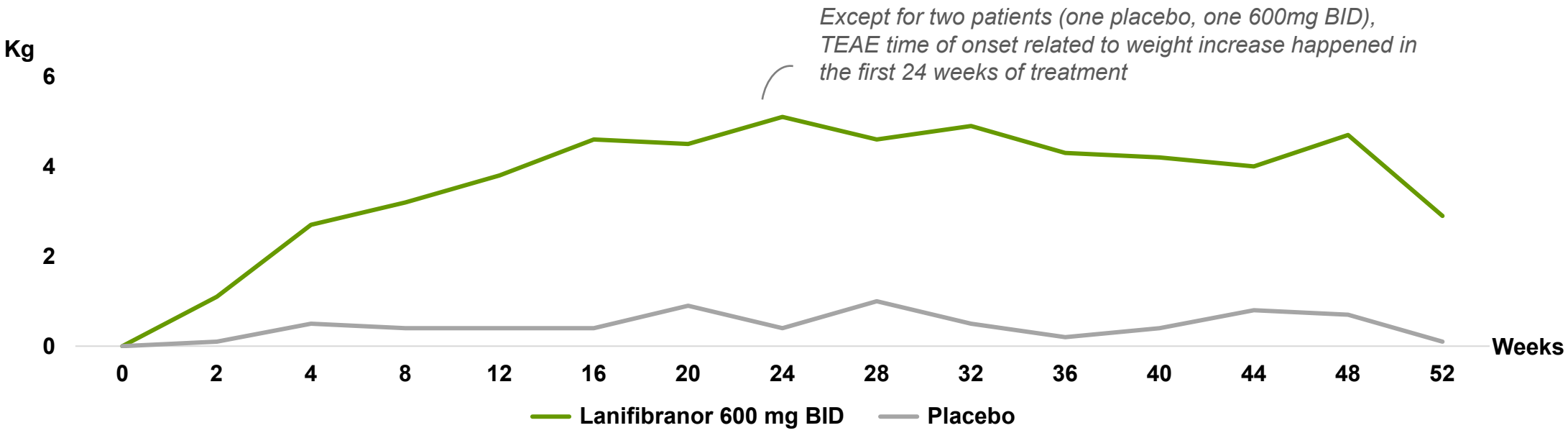
Patients reporting treatment-emergent Serious AE (SAE); N (%)	Placebo (N = 81)	800 mg (N = 83)	1200 mg (N = 83)
Total	3 (3.7%)	3 (3.6%)	7 (8.4%)
Treatment-Emergent Serious AE linked to biopsy procedure			
Post-procedural haematoma/haemorrhage	-	1 (1.2%)	1 (1.2%)
Post-procedural pain	-	-	1 (1.2%)
Pneumobilia (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%)

Phase II results have demonstrated modest weight increase with no impact on efficacy

PHASE IIb | SAFETY | WEIGHT GAIN

- **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
- According to a six month study with pioglitazone in patients * with NASH body weight gain is likely attributed to an **INCREASE IN ADIPOSE TISSUE** and **NOT WATER RETENTION**
- Based on a 52-week lanifibranor trial in systemic sclerosis (SSc) patient weight gain is expected **TO REACH A MAXIMUM BY WEEK 24**

SSc lanifibranor study: weight (kg) relative change from baseline over 52 weeks (Observed cases under treatment – FAS population)



Note: * Pioglitazone treatment increases whole body fat but not total body water in patients with non-alcoholiv steatohepatitis ; Balas, Belfort, Harrison et al. ; Journal of Hepatology 47 (2007) 565-570

Improvement of adipose tissue health and cardio-metabolic markers following a 24-weeks treatment with lanifibranor (I/II)

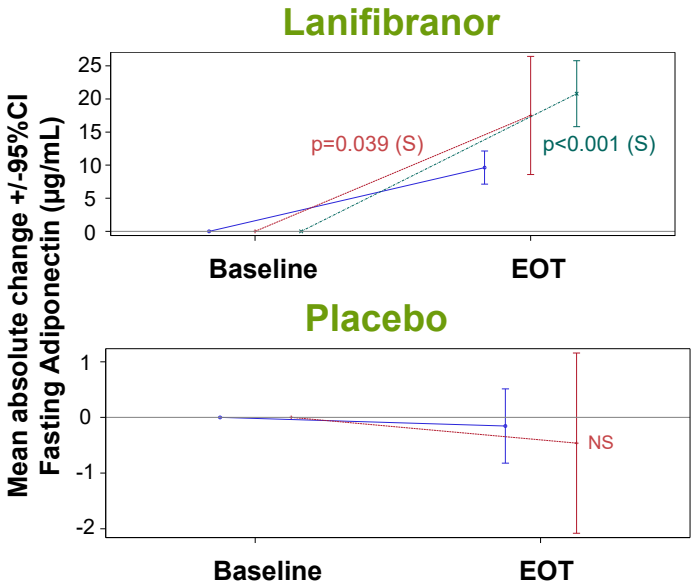
PHASE IIb | SAFETY | WEIGHT GAIN

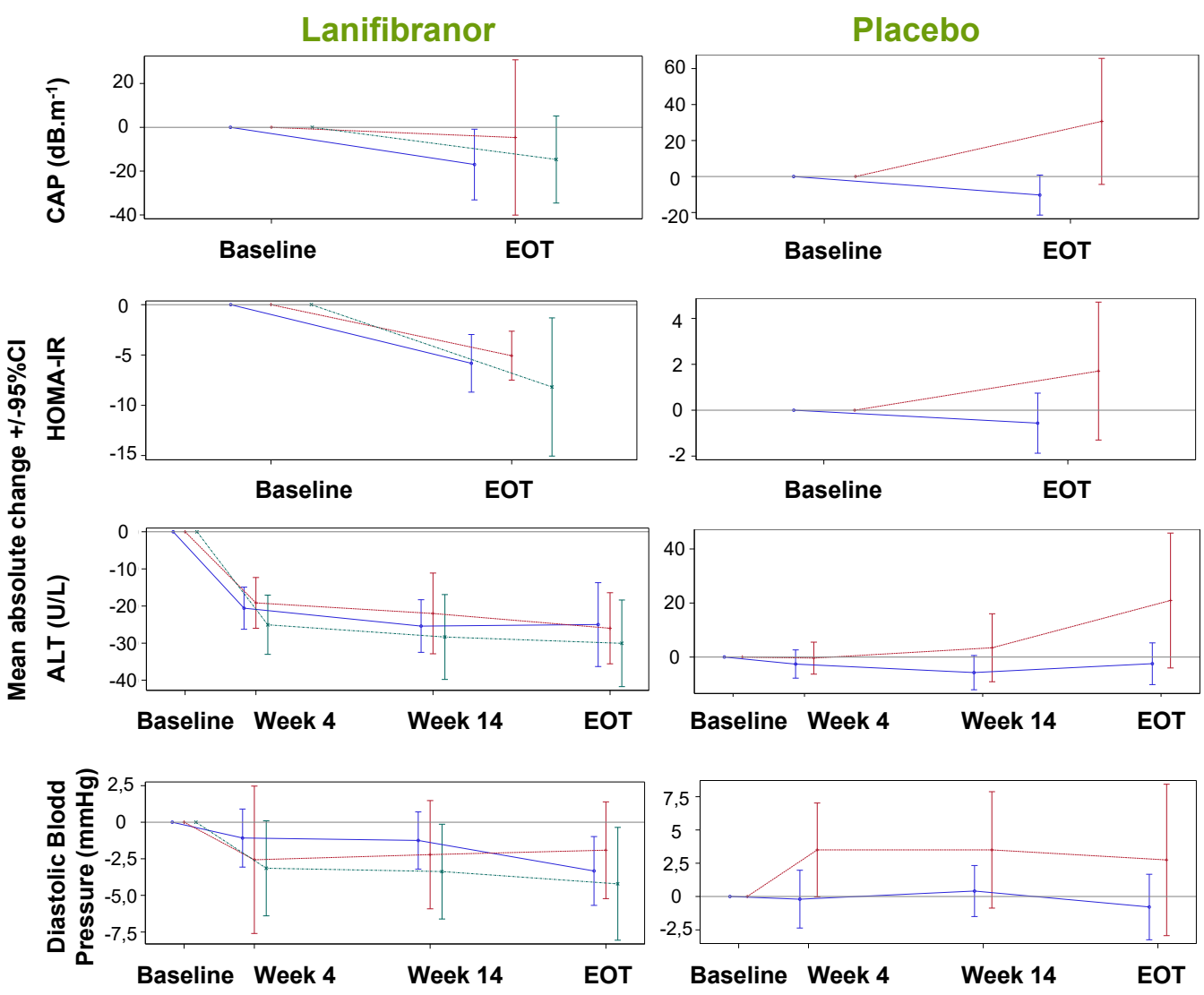
- NATIVE enrolled 247 patients with SAF activity score 3-4 and fibrosis stage F0-F3 in 3 arms: lanifibranor 800, 1200 mg/d and placebo for 24 weeks
- 217 (lanifibranor: 144, placebo: 73) patients who completed the trial with weight data at baseline and end of treatment (EOT) were included in the analyses
- Mean weight increase at EOT was 2.4 (2.6%) and 2.7 (3.1%) kg for 800 and 1200 mg lanifibranor, respectively
- Patients were divided in 3 groups according to % weight change

	Lanifibranor (800 or 1200mg)	Placebo
N	144	73
Stable weight (≤2.5%)	73 (51%)	61 (84%)
Moderate weight increase (2.5% - 5%)	23 (16%)	12 (16%)
Weight increase (>5%)	48 (33%)	-

Improvement of adipose tissue health and cardio-metabolic markers following a 24-weeks treatment with lanifibranor (II/II)

Adiponectin | Stable weight, Moderate weight increase, Weight Increase | **CAP, HOMA-IR, ALT and DBP**





- **Adiponectin**, a PPARγ downstream mediator, increased in ALL 3 weight change groups
  - Higher increase in the >2.5% weight increase groups
- **Focusing on steatosis (CAP), HOMA-IR, DBP and ALT, improvement of CMH markers at EOT** compared to baseline occurred to the same degree in the 3 weight change groups for the pooled lanifibranor arms
- Worsening of these parameters were observed in the placebo-treated patients with weight increased at EOT

Improvements of markers of cardio-metabolic health (CMH) at 24-weeks of treatment with lanifibranor

Change from baseline in CMH parameters at EOT Mean (standard deviation)	Weight change				
	Lanifibranor			Placebo	
	Stable N = 73	Moderate increase N = 23	Increase N = 48	Stable N = 61	Increase N = 12
Lipids					
HDL-cholesterol (mmol/L)	0.15 (0.23)	0.13 (0.23)	0.12 (0.20)	0.02 (0.20)	0.01 (0.14)
Triglycerides (mmol/L)	-0.42 (0.97)	-0.44 (0.57)	-0.45 (0.60)	0.03 (1.02)	0.12 (0.71)
APO-B (mg/dL)	-9.66 (15.76)	-13.04 (25.36)	-14.56 (24.12)	-2.58 (13.08)	-0.08 (30.21)
APO-B/APO-A1	-0.08 (0.12)	-0.06 (0.15)	-0.07 (0.21)	-0.01 (0.16)	-0.01 (0.20)
APO-C3 (µg/mL)	-10.72 (37.90)	-7.30 (36.80)	-9.33 (31.75)	8.85 (37.76)	19.08 (49.19)
Glucose Metabolism					
Fasting glucose (mmol/L)	-0.86 (1.34)	-0.86 (0.81)	-0.65 (1.76)	0.26 (0.91)	0.04 (0.87)
Insulin resistance					
Insulin (pmol/L)	-122.6 (226.2)	-98.1 (112.1)	-155.2 (352.9)	-24.8 (109.2)	46.9 (110.2)
Inflammation					
hs-CRP (mg/L)	-0.55 (4.82)	-4.13 (7.61)	-2.65 (4.57))	0.63 (3.85)	-0.08 (2.06)
Liver					
AST (U/L)	-10.9 (31.0)	-12.9 (21.3)	-21.0 (46.4)	-1.2 (22.0)	12.3 (20.6)
GGT (U/L)	-33.2 (68.4)	-28.0 (25.5)	-40.8 (48.7)	1.0 (22.1)	12.0 (19.3)

- **Improvement of cardio-metabolic health markers at EOT** compared to baseline occurred to the same degree in the 3 weight change groups for the pooled lanifibranor arms, where placebo-treated patients with a weight change at EOT had no improvement of CMH markers

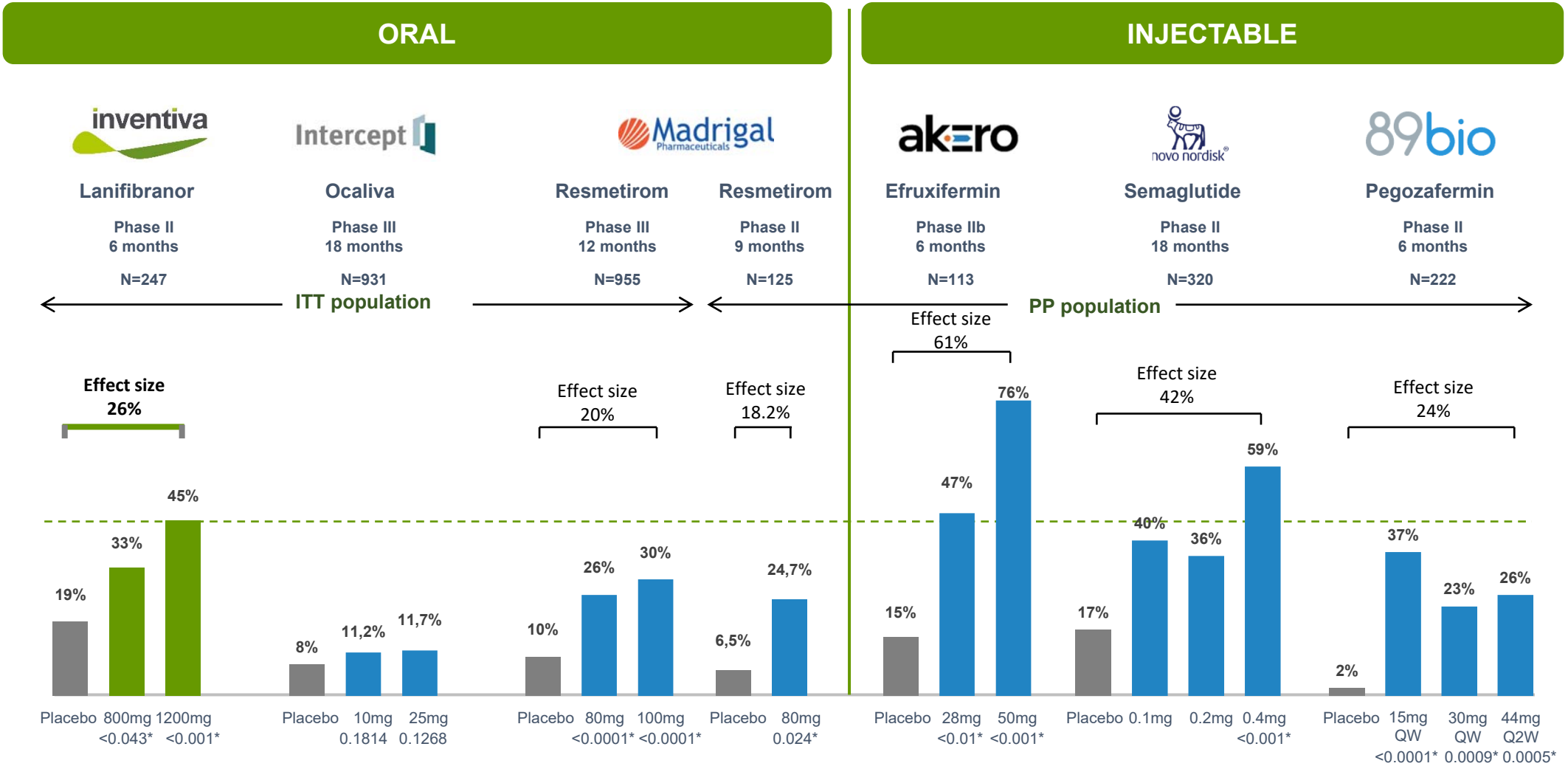
Lanifibranor is designed to address all key features of NASH

	Lanifibranor (PPAR)	Ocaliva (FXR)	Resmetirom (THR-β)	Efruxifermin (FGF)	Semaglutide (GLP-1)
STATUS	Phase III	CRL	Phase III	Phase II	Phase III
ROUTE OF ADMINISTRATION	Oral	Oral	Oral	Injectable	Injectable
INSULIN-RESISTANCE	✓	✗	✗	✓	✓
STEATOSIS	✓	✗	✓	✓	✓
NECRO-INFLAMMATION	✓	✗	✓	✓	✓
FIBROSIS	✓	✓	✓	✓	✗

Source: Newsome et al., 2020; Company websites

NASH competitive landscape

NASH resolution and no worsening of fibrosis

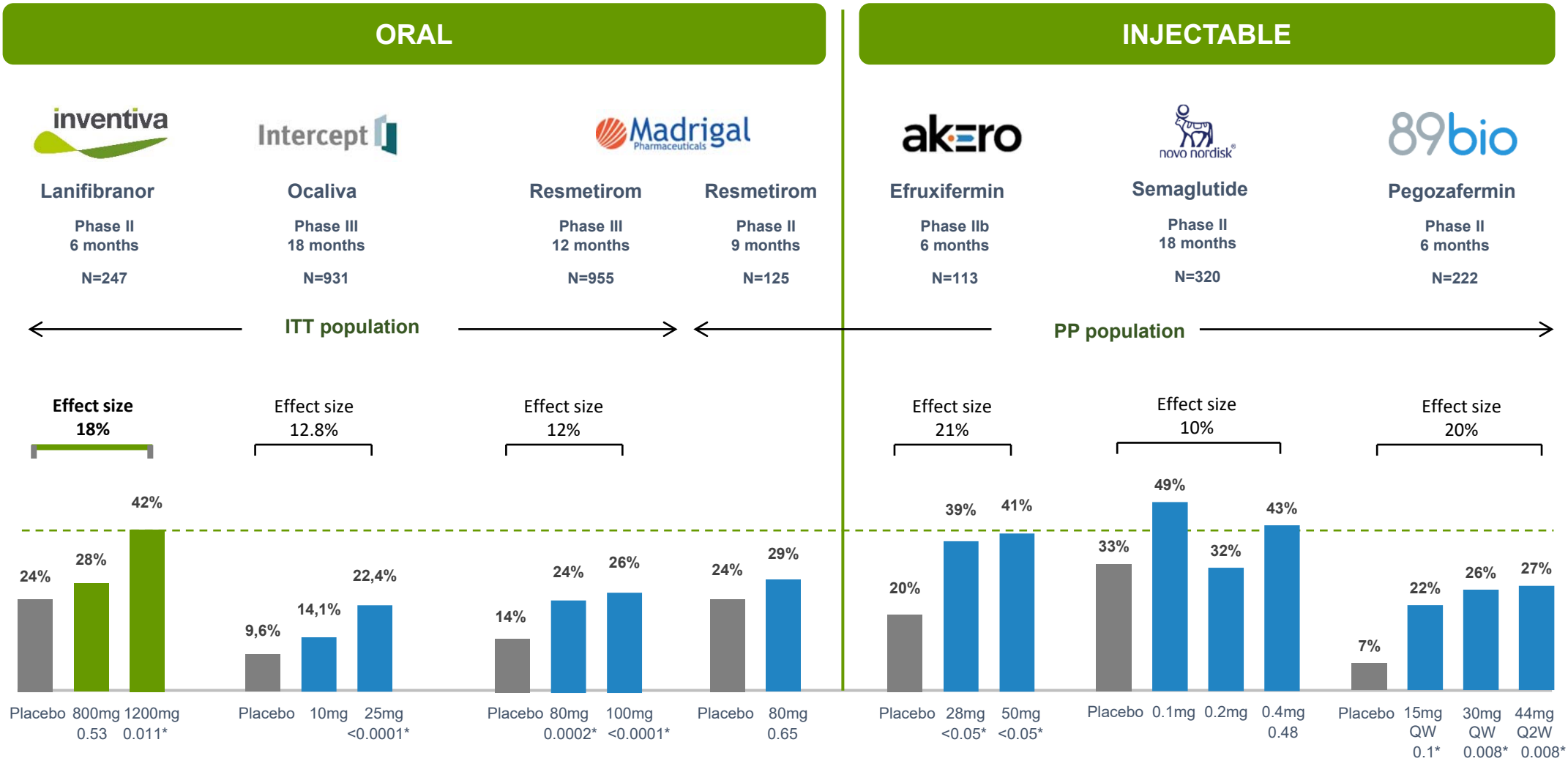


No head-to-head clinical trials have been conducted; results obtained from different trials, with different designs, endpoints and patient populations. Results may not be comparable.

Source: **lanifibranor** native results 1200 mg/day, ITT population; **ocaliva** 10mg and 25mg : REGENERATE Phase II trial: company press release February 19, 2019 https://ir.interceptpharma.com/news-releases/news-release-details/intercept-announces-positive-topline-results-pivotal-phase-3; Corporate presentation March 2023: *469e2d8e-22a1-4705-8245-ebd619c3417c (interceptpharma.com*; **resmetirom** 80mg and 100mg MAESTRO NASH top-line results webcast Dec. 19 2022, pg 10 *Phase 3 development of resmetirom, a liver-directed thyroid hormone receptor (THR)-β agonist for the treatment of patients with NASH and significant liver fibrosis (madrigalpharma.com)*; resmetirom 80mg ± 20mg : Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6; **Efruxifermin** 28mg and 50mg Akero Phase 2b HARMONY Readout Presentation – September 13, 2022 *PowerPoint Presentation (akerotx.com)* ; Semaglutide 0.1mg, 0.2mg, 0.4mg A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis; Newsome et al. NEJM 2021; 384:1113-1124 ; **Pegozafermin** 15mgQW, 30mg QW, 44mg Q2W, 89Bio Phase Iib ENLIVEN Topline Results presentation *Title Slide (89bio.com)*

NASH competitive landscape

≥1 Stage Fibrosis improvement and no worsening of NASH



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NASH competitive landscape

Resolution of NASH and improvement of fibrosis of at least 1 stage

ORAL

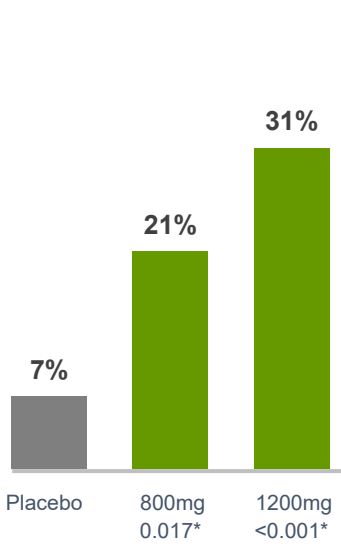
inventiva

Lanifibranor

Phase II
6 months

N=247

ITT population



INJECTABLE

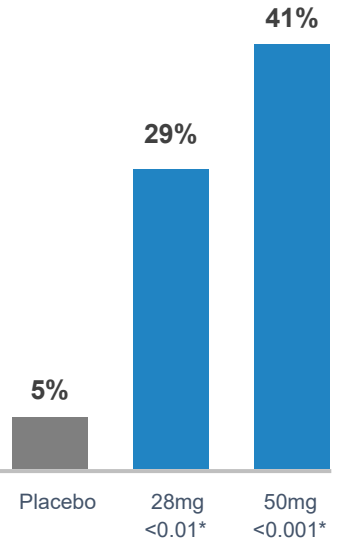
akero

Efruxifermin

Phase IIb
6 months

N=113

PP population



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Physicians are positive about lanifibranor's value proposition, noting its ability to target both fibrosis and NASH resolution

EFFICACY

Physicians valued Lanifibranor's efficacy on multiple endpoints

- **The benefits of a pan-PPAR targeting multiple isoforms are clear to most physicians**, who comment positively on lanifibranor's efficacy on fibrosis and NASH resolution whilst also improving glycaemic control and insulin sensitivity

"… This product is a dream come true, it targets all the things I would want it to; it resolves the NASH, the fibrosis and you get improvement of glycaemic control and insulin resistance …" Physician #1, US

"… You have to attack both NASH and fibrosis because if you reverse fibrosis and still have NASH, that's going to lead to more fibrosis …" Physician #2, US

"… It is attractive, I do like that it has an effect on HbAC1 as the most common co-morbidity is T2D …" Physician #3, US

- **Physicians confirm F2-F3 is a correct patient population** to target, noting lanifibranor's MoA (targeting multiple metabolic pathways) makes it highly suited to the F2-F3 population
  - clinicians also want to treat the disease at its asymptomatic stage prior to complications occurring; some prefer this population over F4, as the latter is considered irreversible
  - some also suggested they would like to use it in F0-1 if possible, in order to slow or prevent progression to F2-F3

A once a day oral is considered optimal

- Lanifibranor's oral administration is considered attractive, **highlighting a once-daily oral pill** will increase ease of use to the patient

"… It is a once a day oral drug so compliance will be as good as you can get. At this point it would all be about education – it is important to educate the patient that they need to take this product, even if they are asymptomatic …" Physician #5, US

Source: L.E.K. Interviews, research and analysis (dated August 2020)

Physicians perceive weight gain due to lanifibranor as manageable, with the risk profile viewed positively

SAFETY

Weight gain appears acceptable and manageable, with limited concerns expressed around edemas

- Physician express differing views on the importance of weight gain
  - the majority of physicians believed that given lanifibranor's efficacy profile the **risk-benefit ratio was acceptable**, and with proper patient counselling around weight loss some of the weight gain could be offset
  - some suggested combination therapy could be used to **manage or reduce weight gain** (e.g., GLP-1, SGLT2)

"…Weight increase can be limiting, but I don't think it be a problem if we can find something to use in combination to offset potential increase in fat tissue …" – Physician, U.S., August 2020

"… I am surprised by the weight gain but I do not see it as a big concern. It would only become an issue if the weight gains happens continuously, for example if you increase 2-3kgs every 2 months… Physician, DE, August 2020

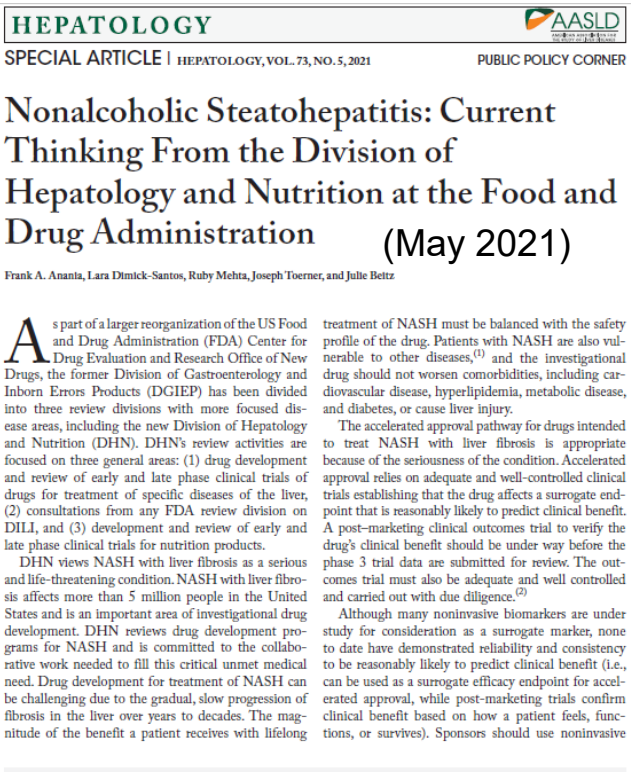
- Physicians express **less concern about oedema** noting the majority are mild

"… The mechanism of edema determines how bad it is, it is not alarming…" – Physician, FR, August 2020

"… edema is not relevant …" Physician, DE, August 2020

Source: L.E.K. Interviews, research and analysis (dated August 2020)

FDA's recent thinking on NASH



HEPATOLOGY

AASLD

SPECIAL ARTICLE | HEPATOLOGY, VOL. 73, NO. 5, 2021 PUBLIC POLICY CORNER

Nonalcoholic Steatohepatitis: Current Thinking From the Division of Hepatology and Nutrition at the Food and Drug Administration (May 2021)

Frank A. Ananta, Lara Dimick-Santos, Ruby Mehta, Joseph Toerner, and Julie Beitz

As part of a larger reorganization of the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research Office of New Drugs, the former Division of Gastroenterology and Inborn Errors Products (DGIEP) has been divided into three review divisions with more focused disease areas, including the new Division of Hepatology and Nutrition (DHN). DHN's review activities are focused on three general areas: (1) drug development and review of early and late phase clinical trials of drugs for treatment of specific diseases of the liver, (2) consultations from any FDA review division on DILI, and (3) development and review of early and late phase clinical trials for nutrition products.

DHN views NASH with liver fibrosis as a serious and life-threatening condition. NASH with liver fibrosis affects more than 5 million people in the United States and is an important area of investigational drug development. DHN reviews drug development programs for NASH and is committed to the collaborative work needed to fill this critical unmet medical need. Drug development for treatment of NASH can be challenging due to the gradual, slow progression of fibrosis in the liver over years to decades. The magnitude of the benefit a patient receives with lifelong treatment of NASH must be balanced with the safety profile of the drug. Patients with NASH are also vulnerable to other diseases,[1] and the investigational drug should not worsen comorbidities, including cardiovascular disease, hyperlipidemia, metabolic disease, and diabetes, or cause liver injury.

The accelerated approval pathway for drugs intended to treat NASH with liver fibrosis is appropriate because of the seriousness of the condition. Accelerated approval relies on adequate and well-controlled clinical trials establishing that the drug affects a surrogate endpoint that is reasonably likely to predict clinical benefit. A post–marketing clinical outcomes trial to verify the drug's clinical benefit should be under way before the phase 3 trial data are submitted for review. The outcomes trial must also be adequate and well controlled and carried out with due diligence.[2]

Although many noninvasive biomarkers are under study for consideration as a surrogate marker, none to date have demonstrated reliability and consistency to be reasonably likely to predict clinical benefit (i.e., can be used as a surrogate efficacy endpoint for accelerated approval, while post-marketing trials confirm clinical benefit based on how a patient feels, functions, or survives). Sponsors should use noninvasive

"The Division of Hepatology and Nutrition (DHN) at the FDA **views NASH with liver fibrosis as a serious and life-threatening condition."**

"Patients with NASH are also vulnerable to other diseases, and the **investigational drugs should not worsen other comorbidities, including cardiovascular disease, hyperlipidemia, metabolic disease and diabetes**"

"The accelerated approval pathway for drugs intended to treat NASH with liver fibrosis is appropriate because of the seriousness of the condition"

"Phase 3 studies demonstrating a **successful treatment difference on liver histology surrogate end-point(s) and an adequate safety profile can receive an accelerated approval with a requirement to verify and confirm clinical benefit after approval**"

FDA Webcast: Regulatory Perspectives for Development of Drugs for Treatment of NASH

A Phase III clinical trial based on surrogate histology endpoint in patients with non-cirrhotic NASH **AND** a **Phase III clinical outcome trial** in patients with compensated cirrhotic NASH **can support full approval**

"if **surrogate endpoint trial was completed sooner than the trial that is conducted in patients with compensated cirrhosis**, it is possible that the findings from the surrogate endpoint of the first trial would be the basis for an **accelerated approval.** The **confirmation of clinical benefit post marketing** could come from a **trial conducted and completed in the patients with compensated cirrhosis.**"

Source: FDA Webcast. "Regulatory Perspectives for Development of Drugs for Treatment of NASH." January 29, 2021. Available at https://www.fda.gov/drugs/news-events-human-drugs/regulatory-perspectives-development-drugs-treatment-nash-01292021-01292021

Lanifibranor: comprehensive impact on the histology and biology of NASH

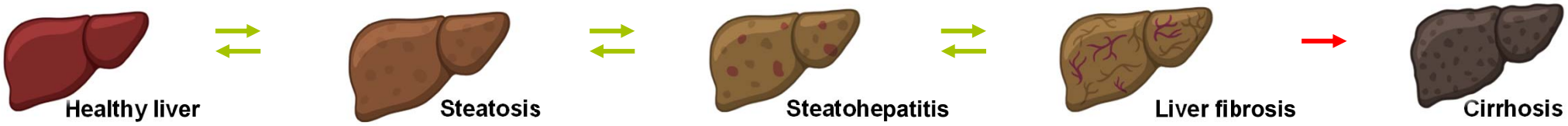
HISTOLOGY AND MARKERS

1 NASH resolution with no worsening of fibrosis

2 Fibrosis regression with no worsening of NASH (1200mg)

Responders were significantly more likely to also be fibrosis improvers

3 NASH resolution AND Fibrosis regression



- steatosis measured by CAP/Fibroscan
- circulating biomarkers of inflammation: Ferritin, hs-CRP and apoptosis: CK18-M30
- circulating biomarkers of fibrosis: Pro-C3, TIMP-1/MMP-2, MACK-3

LIVER ENZYMES

- ALT, AST, GGT

GLUCOSE METABOLISM MARKERS

Improves insulin sensitivity and glycemic control

- fasting glucose
- fasting insulin
- HbA1c
- HOMA-IR index

Improves markers of glucose metabolism in patients with prediabetes

CARDIOVASCULAR RISK MARKERS

Improves cardiovascular risk

- HDL-C
- Triglycerides levels
- LDL-cholesterol level
- Hs-CRP

Improves lipids metabolism

- APO-B
- APO-B/APO-A1
- APO-C3

- DBP

Lanifibranor improves markers of cardiometabolic health independently of weight gain which has been shown to be metabolically healthy

Ongoing Phase III NATiV3 new clinical trial design

Implementation ongoing with protocol cleared in key countries including U.S.

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

Surrogate endpoint trial

72 weeks treatment

N~ 950

Non-cirrhotic NASH & F2-F3 fibrosis

- Lanifibranor: 1200 mg once daily
- Lanifibranor: 800 mg once daily
- Placebo: Once daily

Exploratory Cohort

N~ 200

Exploratory Cohort screen failed patients with NASH and fibrosis

- Lanifibranor: 1200 mg once daily
- Lanifibranor: 800 mg once daily
- Placebo: Once daily

Active Treatment Extension

≥ 48 weeks EoT

- Lani.: 1200 mg once daily
- Lani.: 800 mg once daily

All patients who complete the surrogate endpoint trial or the exploratory cohort are expected to be eligible for active treatment extension study

NATIV3 Design recent improvements

2 biopsies instead of 3 biopsies

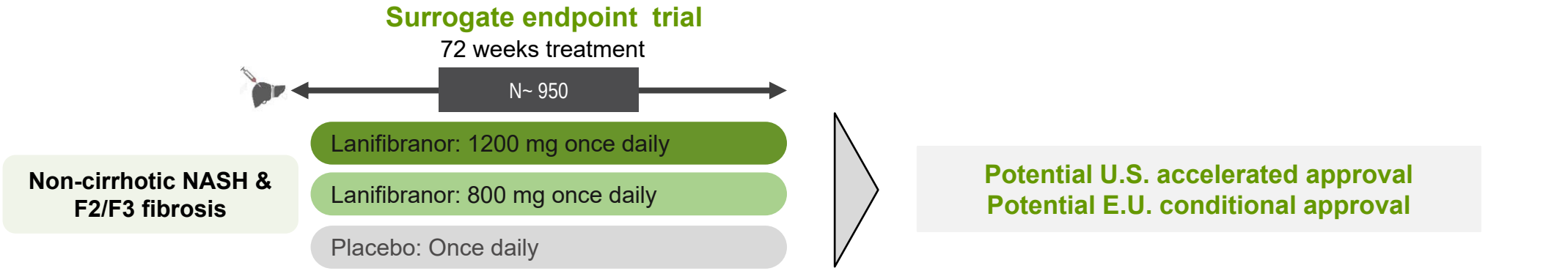
Patients to sign up for up to 120 weeks double-blind treatment consent form instead of 7 year

Possibility for 200 screen failed patients with NASH and fibrosis to join the exploratory cohort

All patients expected to be given access to lanifibranor treatment by joining the active treatment extension

Non invasive test results expected to be available from Part 1 AND from the exploratory cohort

Phase III NATiV3 clinical trial: anticipated regulatory approach for accelerated approval



PRINCIPAL INVESTIGATORS: **Dr. Sven Francque & Dr. Arun Sanyal**

MAIN INCLUSION CRITERIA: aligned to NATIVE Phase IIb trial

- Adults ≥18 years diagnosed with NASH using SAF scoring (steatosis ≥1, activity ≥3 and fibrosis score of F2-F3)

OTHER INCLUSION CRITERIA: Patients under a stable dose of GLP1-RA for at least 3 months prior to screening

RANDOMISATION AND STRATIFICATION: Randomisation 1:1:1 with stratification on T2DM and fibrosis stage

STATISTICAL POWERING: 90% considered for sample size calculations

CENTRAL BIOPSY READING: done by three expert pathologists

Potential regulatory approval based on:

PRIMARY ENDPOINT at week 72 on c.950 patients

- Composite endpoint of patients having both NASH resolution and fibrosis improvement of at least one stage

KEY SECONDARY ENDPOINTS

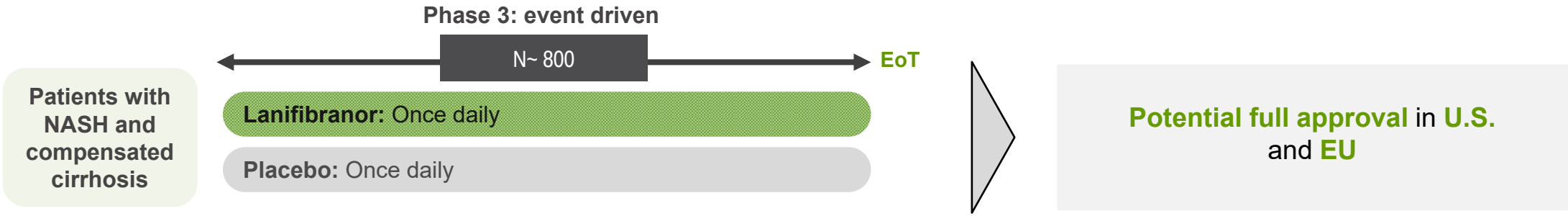
- NASH resolution and no worsening of fibrosis
- Improvement of fibrosis and no worsening of NASH

SAFETY: needs to demonstrate good safety and tolerability and favourable benefit-risk ratio

Phase III NATiV3 clinical trial confirmatory trial: anticipated expected design to support broader "full approval"

PHASE III **OVERVIEW**

Anticipated event driven trial in patients with NASH compensated cirrhosis



KEY ENDPOINTS *(non-exhaustive)*

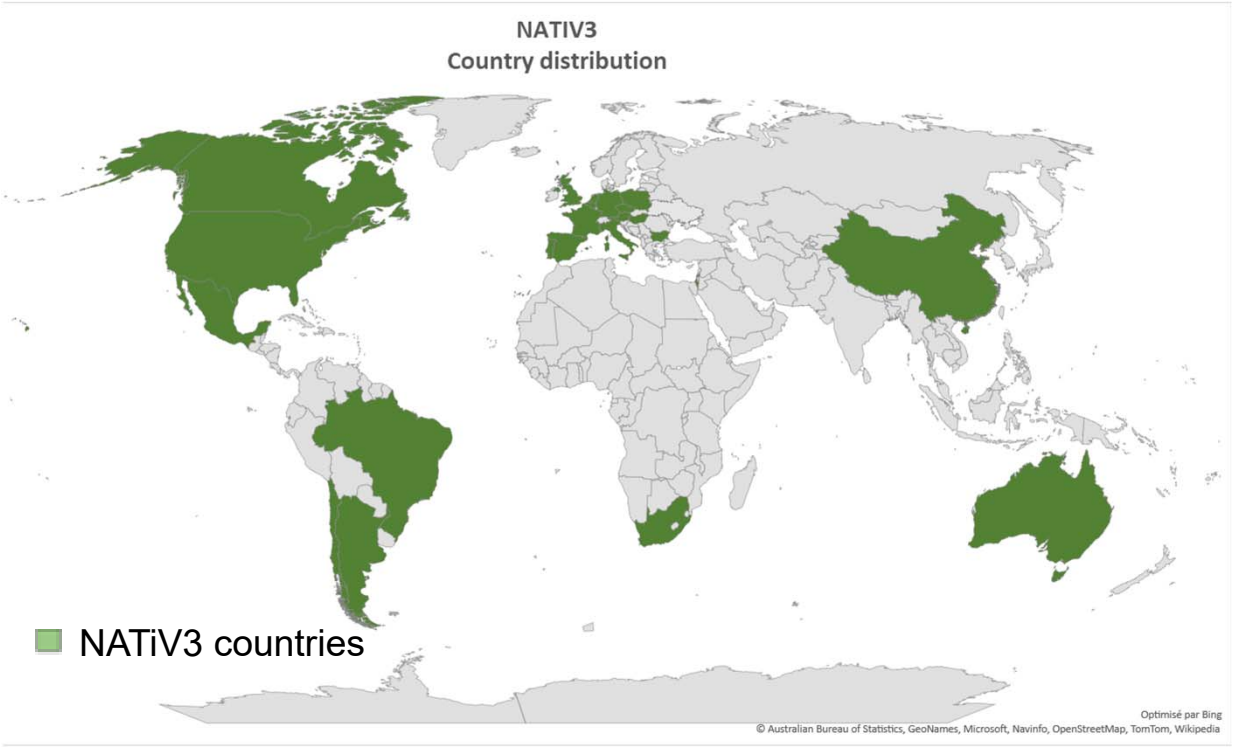
- Based on time to first clinical event on c.800 patients
  - all cause mortality
  - hepatic decompensation events
    - hepatic encephalopathy
    - variceal bleeding or progression to varices that require prophylactic treatment
    - new onset ascites requiring treatment
  - MELD score ≥15
  - liver transplantation

TRIAL END DATE

- Trial expected to last up to 3 years

Approximately 400 sites and 23 countries involved in NATIV3

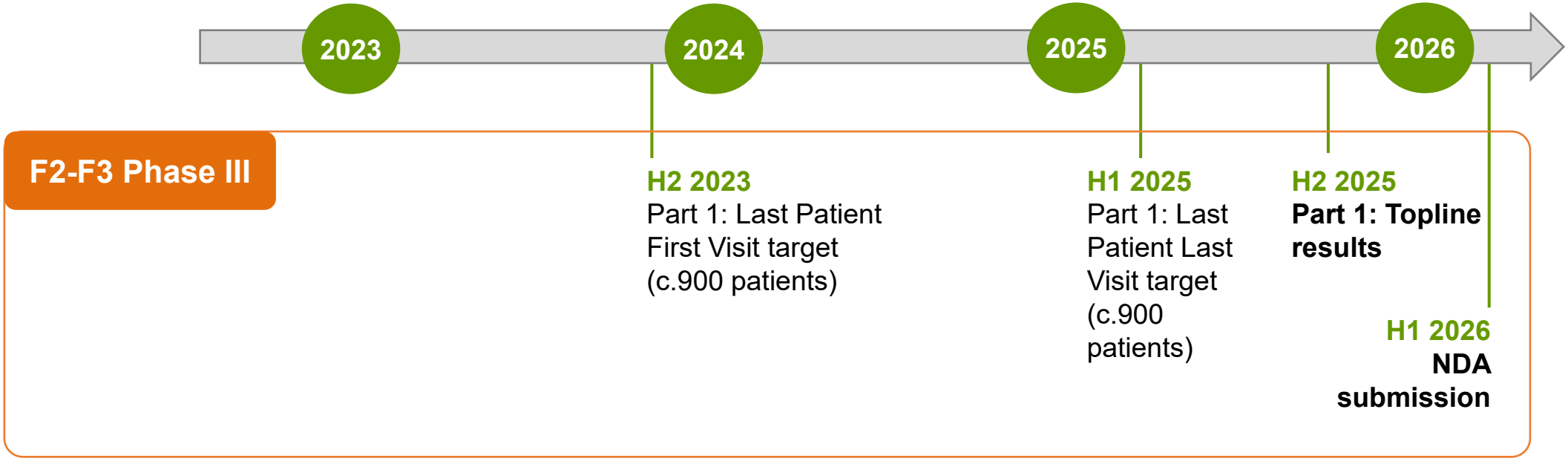
PHASE III | **DESIGN** | **SITE SELECTION**



- 23 countries included (removed Russia and Ukraine) of which 22 countries with full regulatory approval → pending potential addition of China
- 369 sites activated in 23 countries (status at end of March 2023)
- Continued improvement of screen failure rate and sites activation
- New design submitted and already approved in key countries including in the U.S.
- Target to complete enrollment in the second half of 2023
- **China**: in the event CTTQ decides to join NATIV3, 80 sites are expected to be qualified in China

Key milestones of the Phase III study in NASH

PHASE III **MILESTONES**



Lanifibranor clinical trial in patients with NAFLD and T2D

PHASE II **NAFLD T2D TRIAL**

Objective: Establish safety, efficacy and mechanism of action of lanifibranor in patients with T2D and NAFLD. Specifically determine if lanifibranor decreases IHTG(1), improves hepatic insulin sensitivity, endogenous (hepatic) glucose production, gluconeogenesis and DNL(2)

Principal investigator and sponsor

- Prof. Kenneth Cusi (University of Florida)
- ClinicalTrials.gov Identifier: NCT03459079

Randomisation

- Randomized (1:1), double-blind, placebo-controlled
- N=34 and 10 healthy non-obese as "normal" controls for all the metabolic and imaging tests
- Sample calculated assuming a 35% relative reduction of IHGT

Status

- **Topline results expected middle Q2 2023**

Primary endpoint

- Change in IHTG quantified by H-MRS(3) from baseline to week 24

Key secondary endpoints

- Proportion of responders (patients with a IHTG decrease ≥ 30%)
- NAFLD resolution (patients with IHTG ≤ 5%)
- Change in hepatic fibrosis (MRE(4), fibroscan, biomarkers)
- Change in metabolic outcomes (insulin sensitivity, DNL(3), glycemic control/HbA1c, lipids)
- Safety

30 patients; 24 week treatment

Double blind randomized placebo controlled

Healthy non-obese control group, ~10 subjects

Placebo, ~15 patients

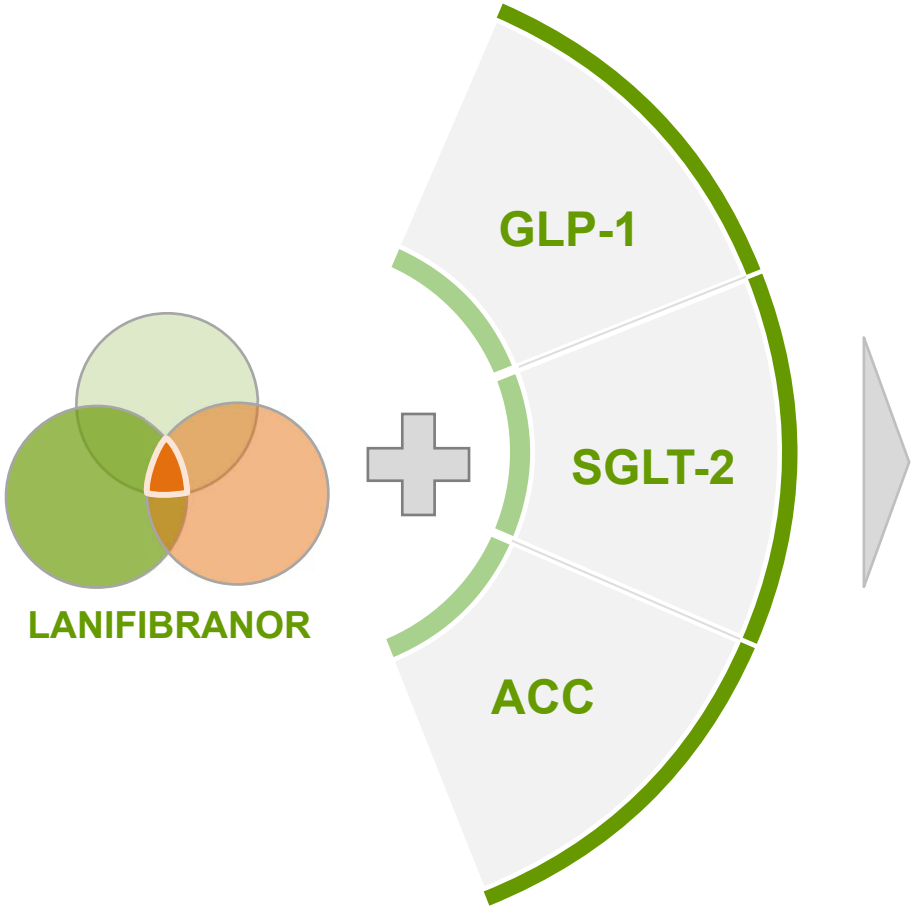
Lanifibranor, 800 mg once daily, ~15 patients

Trial could provide additional supporting clinical data regarding lanifibranor's potential for the treatment of NASH

(1) Intrahepatic triglycerides (2) De-novo lipogenesis (3) Proton Magnetic Resonance Spectroscopy (4) Magnetic resonance elastography

Lanifibranor can be evaluated in combination with other therapies to further strengthen its value proposition

Examples and potential benefits of combination therapies

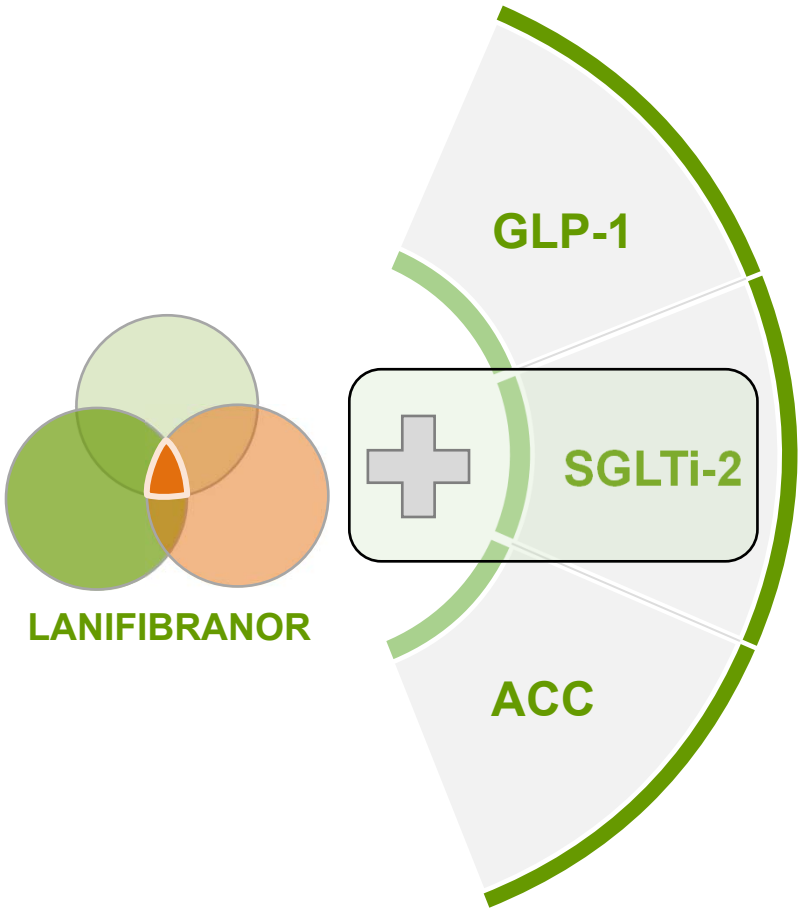


- **Potential complementary effects** on the multistep disease biology of NASH (disturbances of lipid and carbohydrate metabolism, insulin resistance, inflammation, fibrosis)
- Eventually **potentiate therapeutic efficacy** on histological endpoints: NASH resolution and fibrosis
- Ideally could manage metabolically ‘healthy’ **weight increase** in combination with lanifibranor

Combination of SGLT2i with pioglitazone has shown additional metabolic health benefits and favorable weight management

OUTLOOK | SGLT2 combination study

Lanifibranor and SGLT2 inhibitor rationale



- **Four randomized trials**
  - Pioglitazone alone vs pioglitazone + sGLT2i
  - N = 1411 T2D patients
    - Centers were in US, Canada, South America, China, Japan, India, Europe
    - Patients were on a stable dose of pioglitazone (monotherapy or with metformin)
  - Duration 24-72 weeks
- **Efficts of combination vs monotherapy with pioglitazone**
  - Efficacy:
    - Larger decrease of HbA1c; more patients reaching HbA1C < 7%
    - Larger reduction of fasting blood glucose level
    - Weight reduction
    - Blood pressure reduction
  - Safety
    - No difference in death, heart failure, hypoglycemia, urinary tract infection
    - More frequent genital infections

LEGEND Study Design

Lanifibranor in Combination with the SGLT2 Inhibitor empagliflozin in patients with NASH and Type 2 Diabetes

LEGEND Study

Principal investigator

- Prof. M. Lai, gastroenterologist-hepatologist, associate professor of medicine; Beth Israel Deaconess Medical Center (USA)
- Prof. O. Holleboom, academic medical specialist (diabetes and metabolism) at the Amsterdam University Medical Center (NL)
- ClinicalTrials.gov Identifier: NCT05232071

Status

- Study to be conducted in ~40 sites in Belgium, France, Holland, UK and the US.
- IND accepted by FDA
- **First site activated:** H1 2022
- **Topline results**: H2 2023

Inclusion criteria

- Adult patients with diabetes and NASH

Primary outcome measures

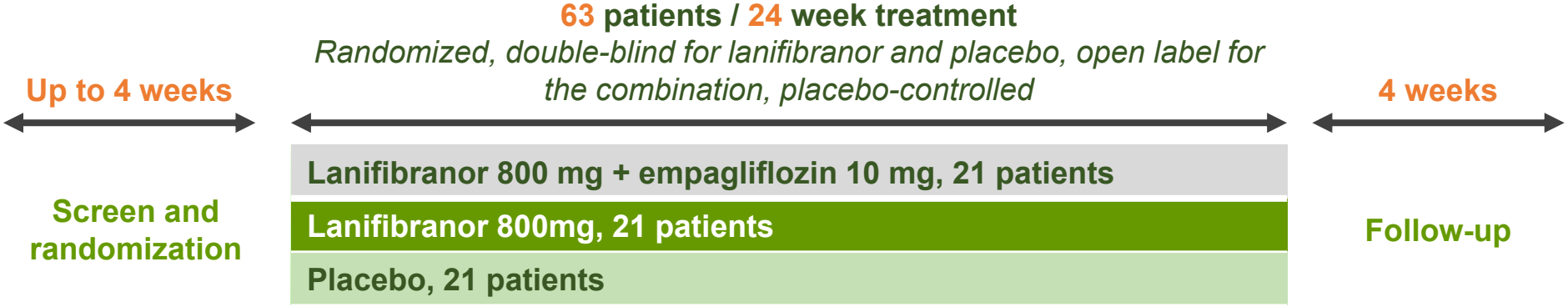
- HbA1c change

Secondary outcome measures

- MRI-based imaging to collect non-invasive data on hepatic fat, inflammation and fibrosis
- Glycaemic/lipid parameters, inflammatory markers
- Changes in body fat composition

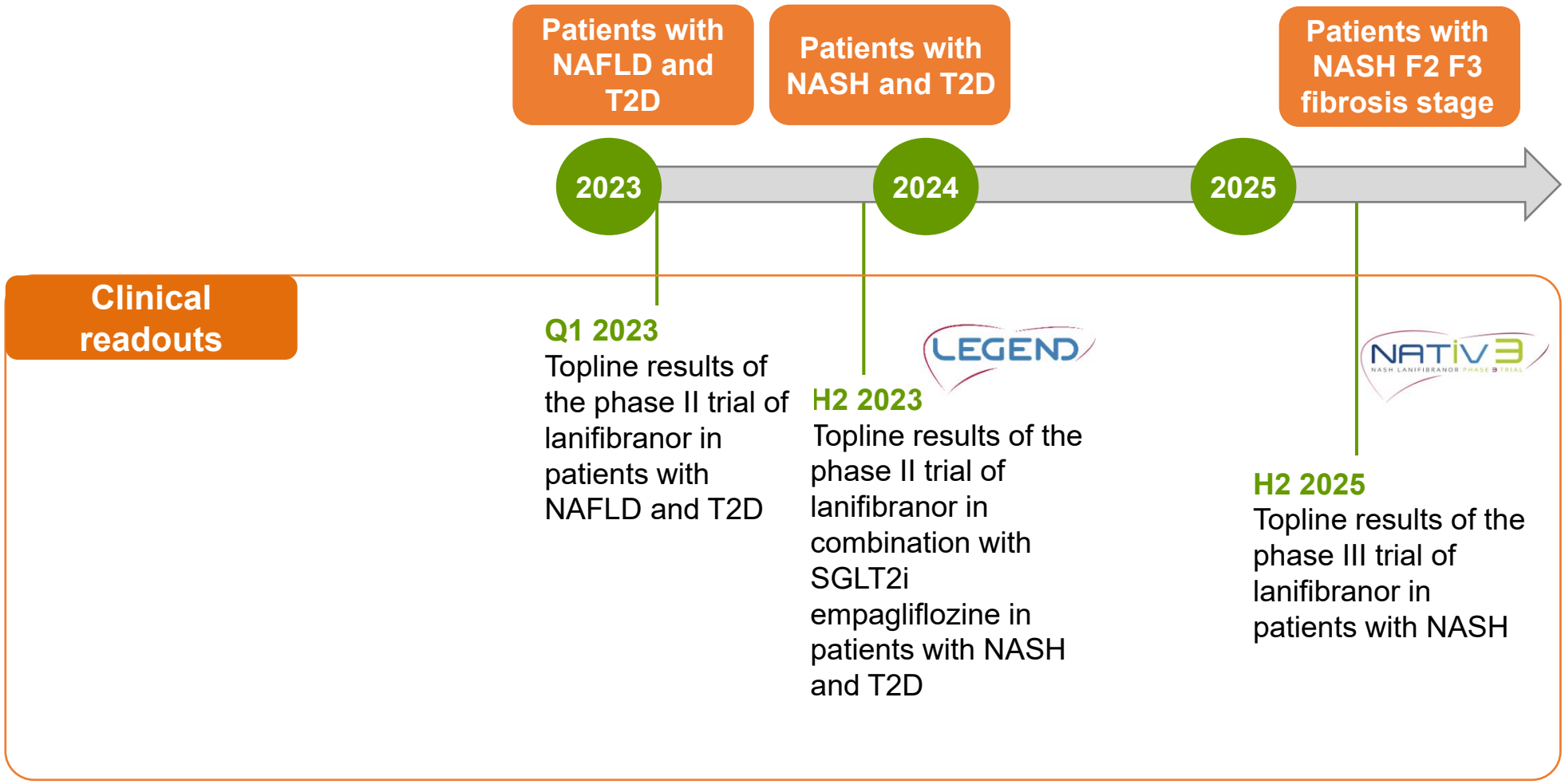
Other outcome measures (safety/exploratory)

- AEs, body weight, PK, IHTG, cT1, biomarkers



Lanifibranor anticipated upcoming clinical readouts

CLINICAL READOUTS



Odiparcil in mucopolysaccharidosis (MPS)

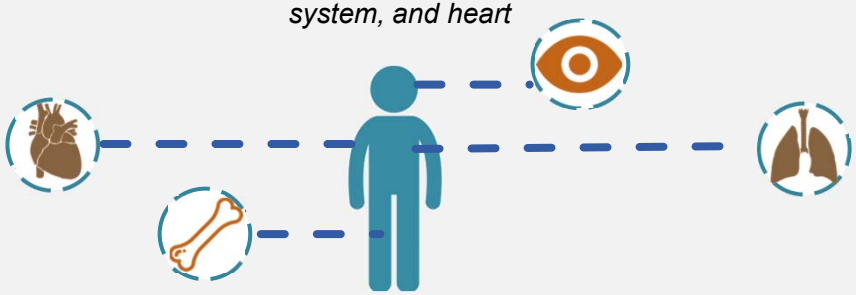
MPS VI is a devastating rare lysosomal storage disorder

Rare, Hereditary Lysosomal Storage Disorder

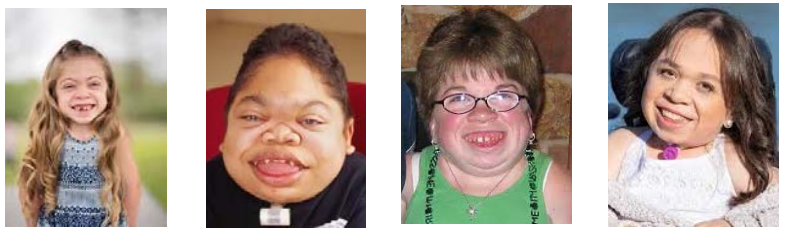
- Mucopolysaccharidoses (MPS) is an inherited disorder characterized by the absence of lysosomal enzymes required for the breakdown of glycosaminoglycans (GAGs)
- MPS VI pathogenesis is caused by mutations in the ARSB gene encoding the enzyme arylsulfatase B leading to dermatan sulfate (DS) and chondroitin sulfate (CS) accumulation
- MPS VI is a devastating disease leading to reduced life expectancy up to only the teens or early 20s in more rapidly advancing cases and 40 to 50s in slower progressing cases

Wide-Spread Systemic Condition

Impaired degradation of GAGs and its subsequent accumulation impairs multiple vital tissues and organs, including the eyes, bones, respiratory system, and heart



Currently Treated Population	Potential for Market Expansion
There are ~**1,000** patients treated with Naglazyme[1] globally	Oral therapy would **significantly expand** the number of eligible patients that cannot receive ERTs



Global Birth Incidence:
1 in 250,000 – 600,000

MPS VI Symptoms	
• Coarse facies	• Poor vision (corneal clouding)
• Short stature	• Spinal cord compression
• Odontoid hypoplasia	• Kyphoscoliosis (lung restriction)
• Joint stiffness	• Cardiac/respiratory disease
• Organomegaly	• Dysostosis multiplex
• Hearing loss	• Genu valgum (knock knees)

Source: Giugliani, P (2007); Notes: [1]Only approved MPS VI treatment

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**
- **Limited penetration into protected or poorly vascularized tissues** such as cornea or cartilage, where MPS symptoms often manifest

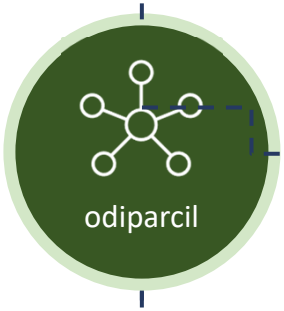
Product	Company	MPS	Est. yearly cost	2021 sales
Aldurazyme (laronidase)	genzyme	MPS I	$ 217K	€ 243M
elaprase (idursulfase)	Takeda	MPS II	$ 522K	$ 538M(1)
Vimizim (elosulfase alfa)	BIOMARIN	MPS IVA	$ 578K	$ 623M
Naglazyme (GALSULFASE - rch)	BIOMARIN	MPS VI	$ 476K	$ 380M
Mepsevii (vestronidase alfa-vjbk) injection, for Intravenous use	ultragenyx pharmaceutical	MPS VII	$ 550K	$ 16M

Source: Sales - Full year 2021 press-release; WAC without discounts for a 25-kg patient - BioCentury "Making of MEPSEVII" Dec 11, 2017; (1) Takeda Annual Securities Report from April 1, 2021 to March 31, 2022; 1 yen = 0,0074$; elaprase FY sales 73,119 JPY

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 GAG reduction therapy designed to potentially treat several forms of MPS



- Odiparcil reduces GAG accumulation in multiple organs in both developing and established disease MPS VI models
- Penetrates and clears GAGs from difficult-to-reach tissues, including valve, tracheal, and knee cartilage and cornea, in preclinical models
- Odiparcil found to be well-tolerated in MPS VI patients and in 1000s of patients previously tested(1)
- Functional improvements to mobility and respiratory function in MPS VI patients
- Clinical efficacy signals in both ERT treated patients and ERT-naïve MPS VI patients
- Orphan Drug Designation granted in the U.S. and EU. Rare Pediatric Disease Designation in MPS VI granted in the U.S. FAST Track designation granted by FDA
- Method of use patent granted in the United States and in Europe with LOE(2) 2039, including 5-year extension

If approved, we believe odiparcil has the potential to become a valuable treatment option for MPS VI patients :

- Oral delivery
- Capable of penetrating key tissues that ERTs are unable to target
- Could potentially ameliorate established disease
- Could potentially improve quality of life

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

Odiparcil key highlights

We believe odiparcil has the potential to be a differentiated treatment addressing unmet needs for a life-threatening condition

- Potential game changer as the first product candidate with the ability to broadly address a wide range of clinical manifestations in MPS VI patients
- Naglazyme 2021 global sales: $380M[(1)]
- Believed to be the only late-stage product candidate in development for the treatment for MPS VI with the potential to target other MPS subtypes
- Favourable safety profile shown in multiple clinical trials

Demonstrated Key Functional Improvements to MPS VI Patients in Phase 2a

7-10+

Years of Market Exclusivity in US & EU

Oral Route of Administration

Est. ~3 Years to Market if Phase 2/3 Trial Positive

Ready to start pivotal trial

Orphan Drug Designation – US & EU
Fast-Track Designation – US

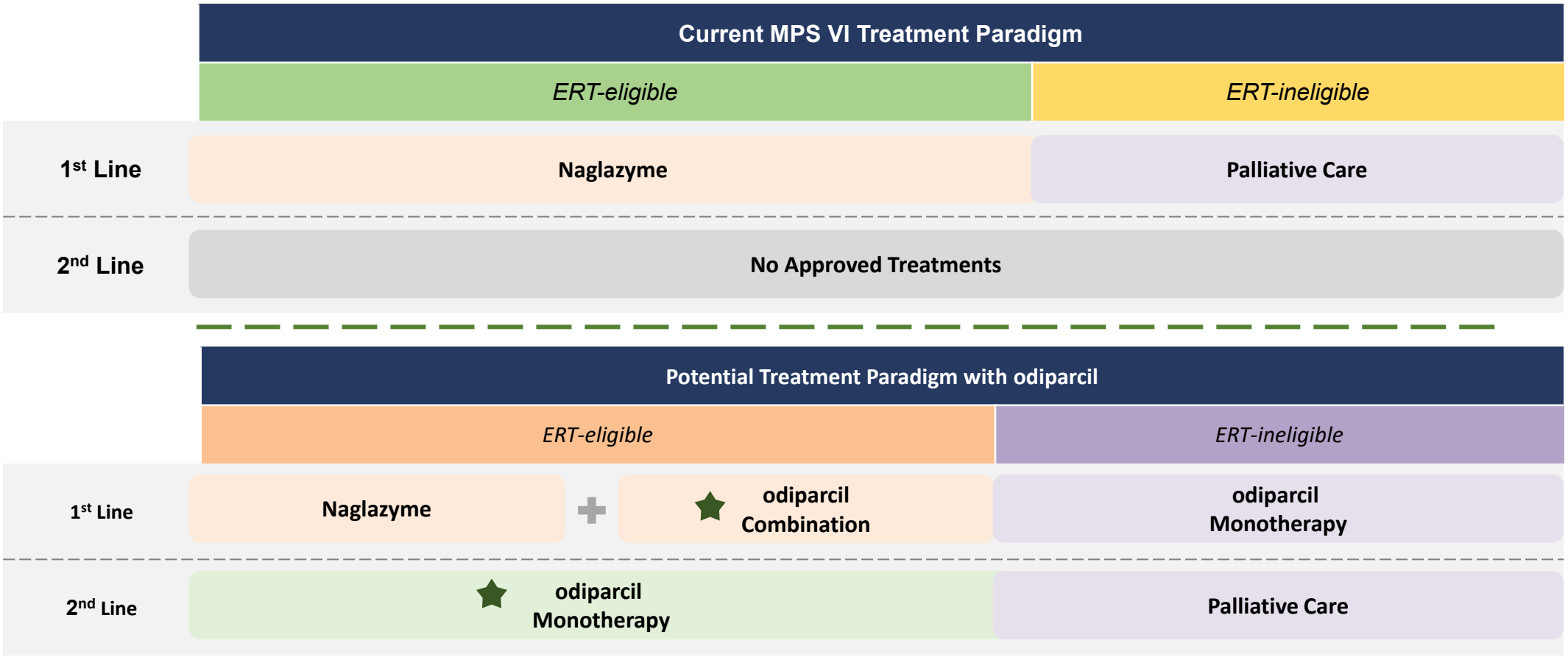
Activity in Developed & Established Disease MPS VI Models

If approved eligible to Receive US Rare Pediatric Voucher

(1) Biomarin Full year 2021 press-release

MPS VI treatment paradigm

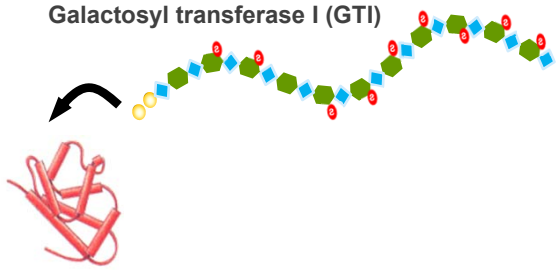
Odiparcil aims at improving the treatment options for both ERT eligible and ineligible patients



Differentiated mechanism of action potentially synergistic with ERT

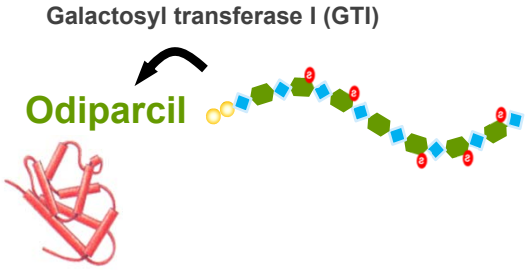
Odiparcil acts to divert endogenous protein-bound GAG synthesis to soluble odiparcil-bound chondroitin sulfate (CS) and dermatan sulfate (DS) synthesis

Synthesis of proteoglycans (HS, CS, DS)



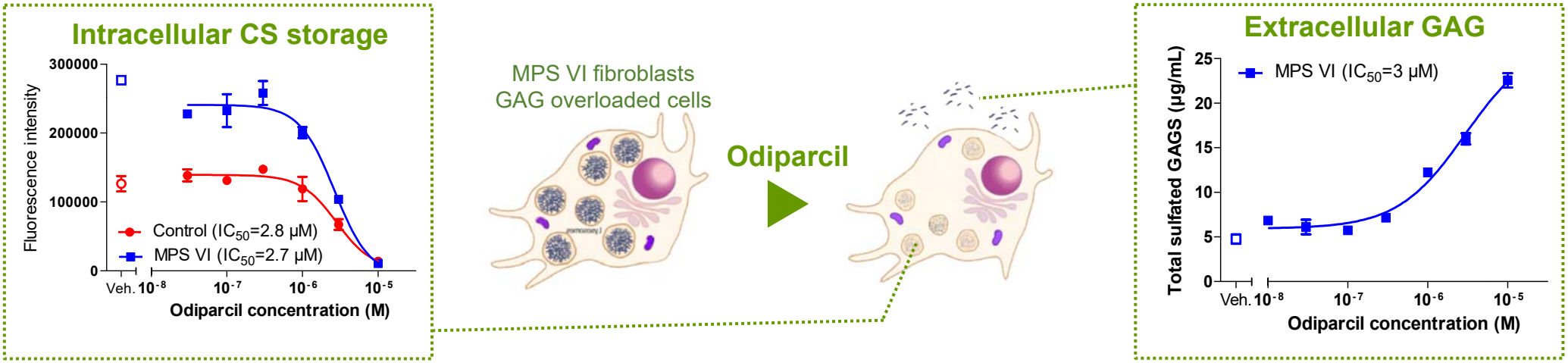
GTI activity

Substrate	Vm/Km
D-xylose	0.8
Odiparcil	1857



Synthesis of soluble DS and CS

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



Odiparcil associated with reduced 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

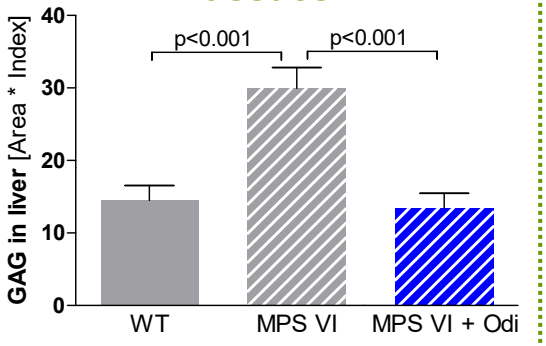
Odiparcil mechanism of action potentially relevant to MPS subtypes with excess DS and CS

MPS Type	Frequency	DS	CS	HS(1)	KS(2)
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	✓	✓	✓	

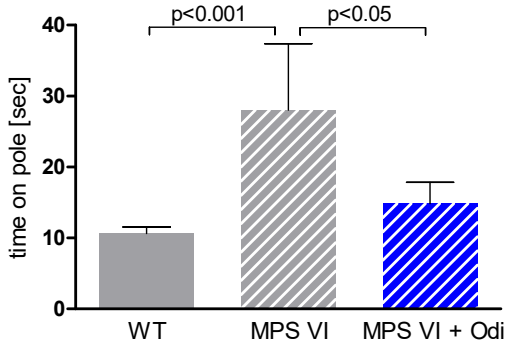
Source:Rheumatology 2011 Therapy for mucopolysaccharodises; Vassili Valayannopoulos and Frits A. Wijburg; (1) Heparan Sulfate; (2) Keratan Sulfate

Odiparcil GAG clearance mechanism of action observed in MPS VI mice

Odiparcil and GAG accumulation in livers tissues

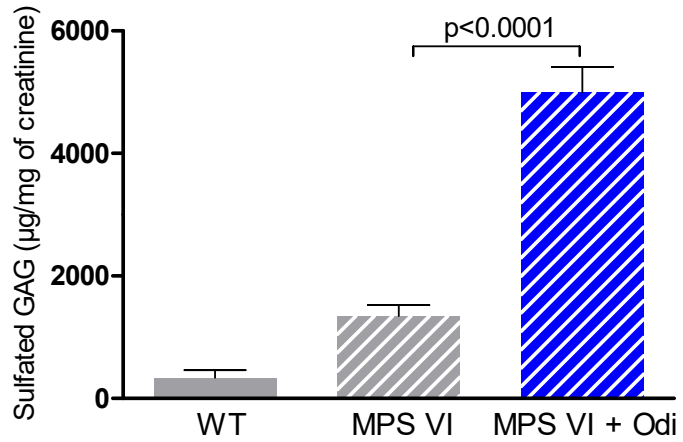


Odiparcil and animal mobility



Wild-type and MPS VI mice

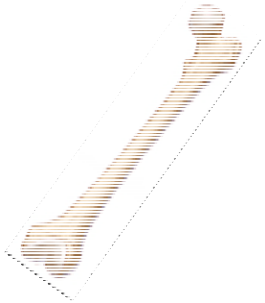
Soluble GAGs produced from odiparcil are excreted in urine

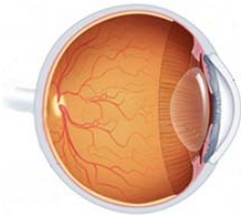


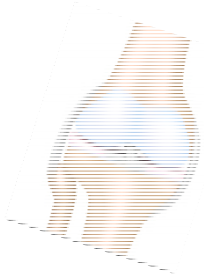
Source: Company data

Odiparcil penetrates tissues where ERT has limited efficacy

Odiparcil observed to be well distributed in tissues and organs poorly penetrated by recombinant enzymes







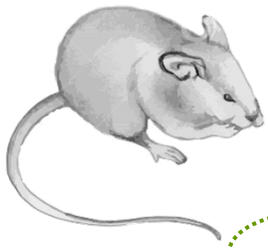
	Heart	Bone	Cornea	Cartilage
Odiparcil[(1)]	✓	✓	✓	✓
rhASB[(2)]	✓	Not tested	Not detected	Not detected

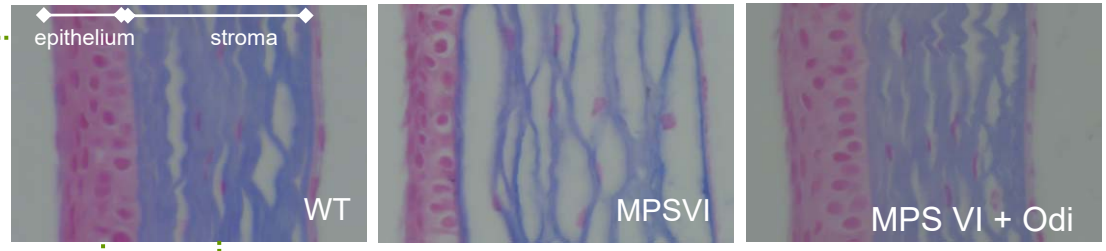
Meaningful concentrations of odiparcil observed in tissues that are poorly vascularized or protected by a barrier: bone, corneal tissue and cartilage

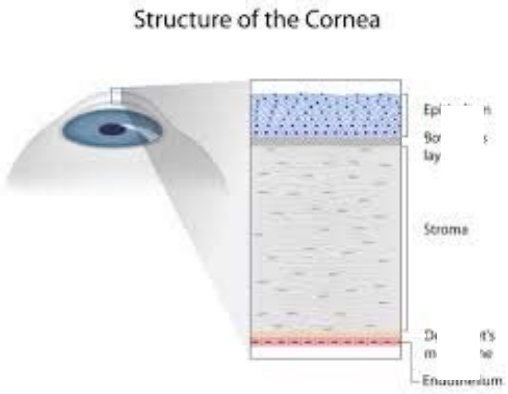
Source: (1) Odiparcil: tissue distribution following 25mg/kg oral administration , TID for 5 days; (2) Recombinant human ARB: Expressed as ratio of ARSB enzyme activity in the liver in MPS VI cats after repeat infusion (conditions: preliminary trial, Trial A and Trial B from Auclair et al. 2003)

Odiparcil reverses corneal impairment in MPS VI mice

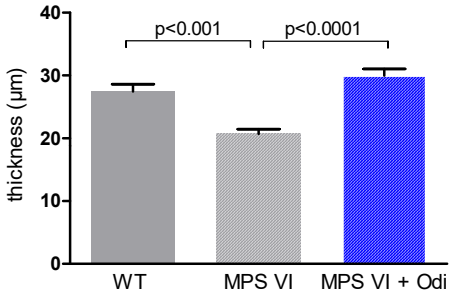
Odiparcil administration observed to affect corneal structure and corneal GAG storage





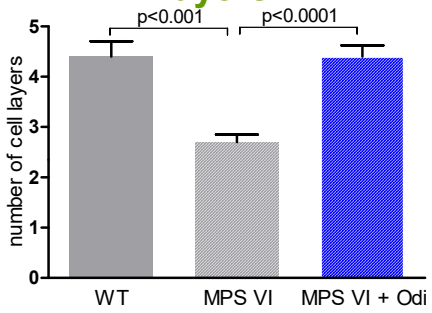


Odiparcil effect on corneal epithelium thickness



N=10 for all groups

Odiparcil effect on number of corneal epithelium cell layers



Odiparcil effect on 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 2a STUDY DESIGN

iMProveS
IMPROVE MPS TREATMENT

iMProves Phase 2a Study

- IMProveS Phase 2a in MPS VI patients was designed and executed in collaboration with leading MPS VI experts and patient organizations
- Trial enrolled both ERT-eligible and ERT-naïve patients with established disease to best represent the current MPS VI patient population.
- Primary endpoint was assessment of odiparcil safety in MPS VI patients, but the trial demonstrated compelling signals of functional improvements in patients

iMProveS Endpoints and Patient Population

Safety and efficacy of two doses of odiparcil

Secondary Endpoint:

- **Characterize dose response, pharmacokinetics, and pharmacodynamics**

Phase 2a Patient Population

>16 years old
Established Disease
MPS VI patients

Preliminary Safety Assessment 1+1 week

2 MPS VI Patients

ERT
+
Odiparcil
Week 1: 250mg bid
Week 2: 500mg bid

Randomization and/or treatment start

15 MPS VI patients double blind + 5 MPS VI patients open label 26-week treatment duration

Placebo + ERT	15 Patients (5 per arm)
Odiparcil, 250 mg bid + ERT	
Odiparcil, 500 mg bid + ERT	
Odiparcil, 500 mg bid monotherapy	5 Patients

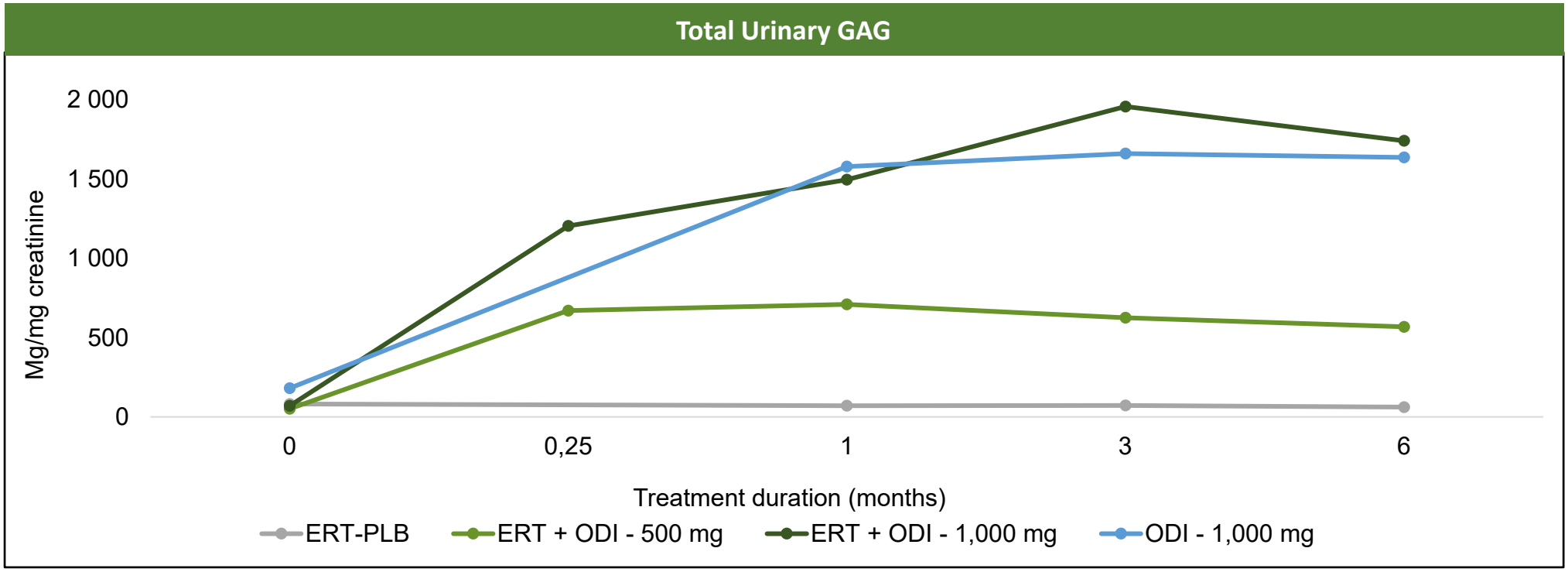
Treatment end

4 weeks

Follow-up

Clinical Proof of Concept: GAG clearance

Daily oral odiparcil regimen in the IMProveS trial resulted in significant clearance of urinary GAGs



Odiparcil demonstrates a consistent dose-proportional clearance of urinary GAGs over 6 months in MPS VI patients

Efficacy endpoints assessed in the iMProveS trial

iMProveS
IMPROVE MPS TREATMENT

Efficacy endpoints assessed span beyond functional parameters addressed by ERTs

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

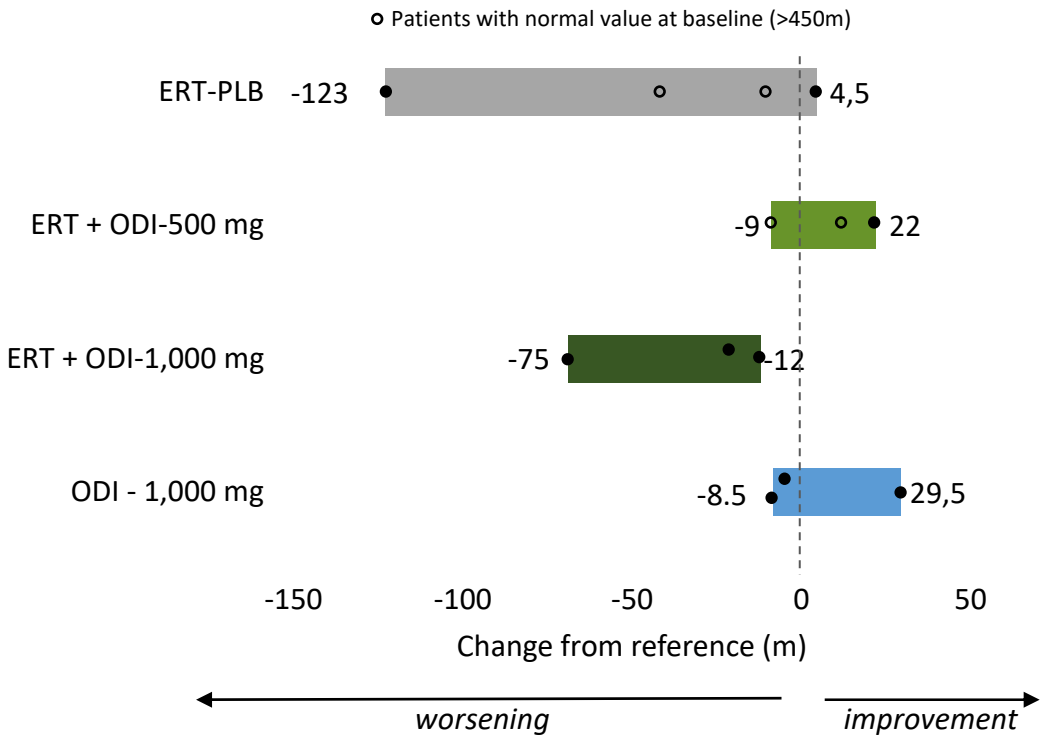
Audiology

- Pure tone audiometry (PTA)

Clinical Proof of Concept: functional parameters

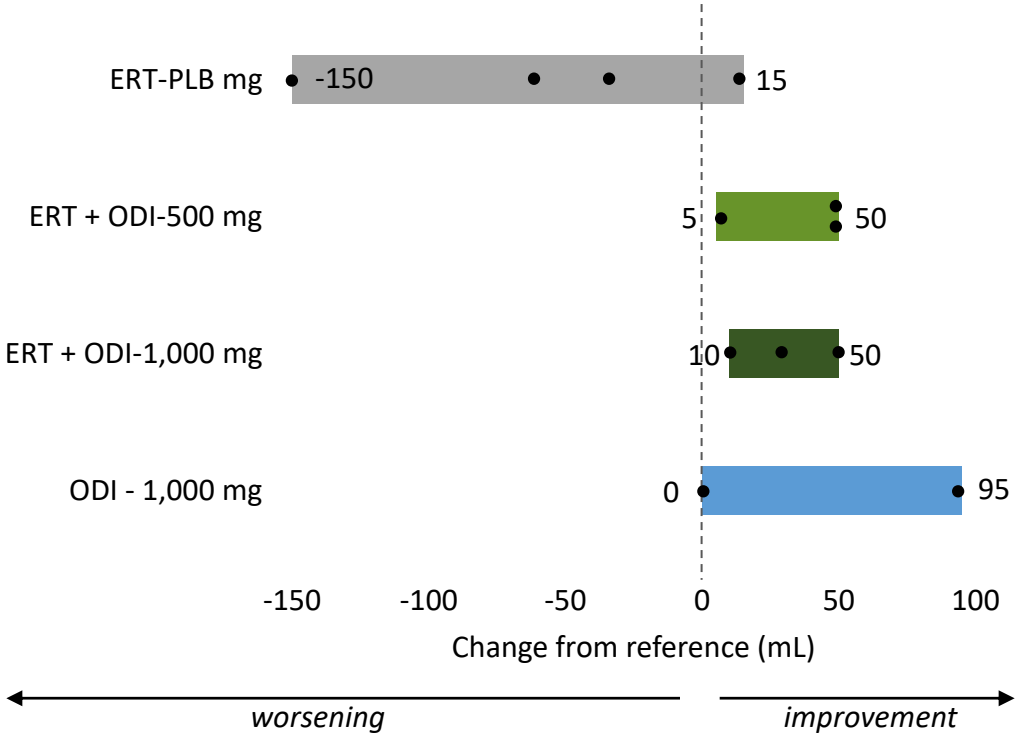
Improvement on 6MWT and respiratory function (FVC) in adult patients with established disease

6 Minute Walking Test (6MWT)



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

Forced Vital Capacity (FVC)



Improvement in all odiparcil treated groups compared to ERT-placebo

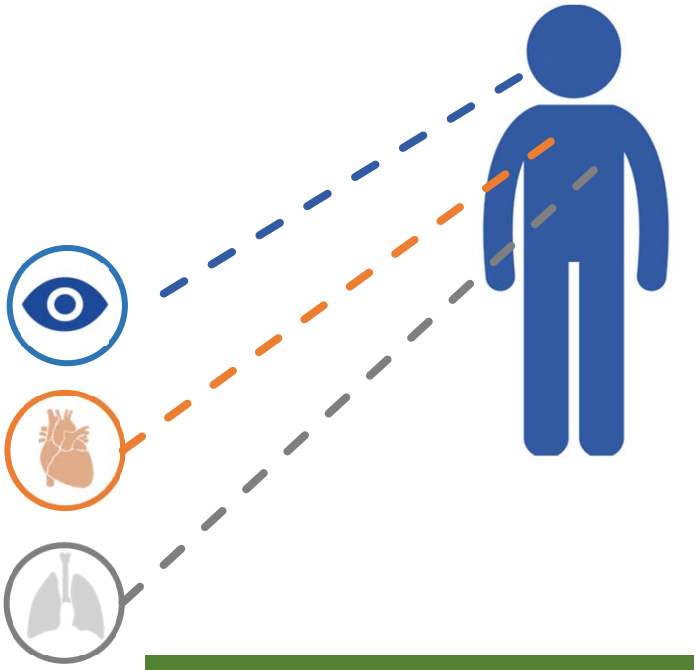
Patients treated with odiparcil showed improvement on forced vital capacity for respiratory function and a positive trend in the six-minute walking test

BID: Twice-daily

Functional evaluation of individual evaluable patients

Odiparcil improves key organ function in difficult-to-reach tissues that ERT does not address

Improvements in the ERT Combination cohort (N=10)			
Outcomes	**Improvement threshold**	**Number of improved patients**	
		ERT-Placebo (n=4)	ERT-odiparcil (n=6)
Ophthalmology	Corneal opacity measure*	1	2
Cardiology	Echocardiogram	1	3
Respiratory[R]	Functional Vital Capacity: Slight improvement: +3-8% Improvement: +>8%**	0	3



No Improvement
SI: Slight improvement
I: Improvement

*Assessed by Expert Opinion
** Improvement threshold based on NICE guideline
[R] Based on relative change

Odiparcil addresses several clinical manifestations that are not addressed with standard ERT treatment

Trends observed using the descriptive statistical analyses based on treatment groups are confirmed by the evaluation of individual data

Patient improvements with odiparcil / ERT combination

iMProveS
IMPROVE MPS TREATMENT

5 out of 6 patients in the odiparcil + ERT group improved on parameters not addressed by ERT

Patient A

- **Slightly improved** on respiratory function (FVC: +9%)
- **Improved** on COM (+13 on non-transplanted eye)
- **Slightly improved** on cardio (decrease severity mitral regurgitation)

Patient B

- **Slightly improved** on respiratory function (FVC: +5%)
- **Slightly improved** on cardio (decrease in Left Ventricular Mass Index LVMI)

Patient C

- **Improved** on COM (+11, +14)
- **Slightly improved** on cardio (no longer mitral regurgitation)

Patient D

- **Slightly improved** on respiratory function (FVC: +4%)

Patient E

- **Improved** on cardio (decrease LVMI, decrease severity aortic regurgitation) + vascular (decrease of CIMT both carotids)

Patient F

- **No improvement**

Improved on Several Parameters | *Improved on One Parameter* | *Did not Show Improvement*

Odiparcil showed high potential for efficacy as nearly all patients improved on at least one parameter not addressed by ERTs, and half of the patients improved on several of these parameters

CIMT: carotid intima media thickness; COM: Corneal clouding measurement; FVC: Forced vital capacity; LVMI: left ventricle mass index.

Safety and tollerability

Odiparcil has robust safety data from extensive studies

Safety Summary
Odiparcil has been tested for safety in over 1,900 patients through trials done by GSK[1] at doses up to 1500 mg
The iMProveS study confirmed the safety profile from previous Phase I and Phase II clinical studies and no new safety findings were observed
The primary safety objective was met in the iMProveS study
There was only one serious adverse event assessed as treatment related, a skin reaction

Adverse Events in MPS Trial

Number of clinical SAEs	Placebo N = 5	odiparcil N = 15
Bronchopneumopathy*	1	
Calculus Bladder	1	
Rash**		1
Acute Respiratory Failure		1
Urinary Tract Infection		1
Device Breakage***		1
Venous Occlusion***		1

* Leading to death; ** Assessed treatment-related by the investigators; *** Same patient

1. Trial performed in a different indication, development stopped due to strategic reasons; SEAs: Serious stands for hospitalization or considered Important medical event by the investigator.

Overview of odiparcil regulatory status

	EUROPE	USA
Overview of Discussions	• EMA Scientific Advice Meeting – Jul 2020 • ANSM Scientific Advice Meeting – Apr 2019 • MHRA Scientific Advice Meeting – Mar 2019 • EMA Scientific Advice Meeting – Oct 2016	• Type C Meeting – August 2022 • Type C Meeting – Nov 2020 • P-IND Meeting – Mar 2018
Key Feedback	• Guidance on dose-finding study • Direction on potential label-expansion in MPS VI patients less than 5-years-old • Elements of phase 2/3 trial to support future NDA for odiparcil	• **Feedback that odiparcil could be dosed in pediatric MPS VI patients 5 years of age and above** • **Guidance on path to approval** • **Direction on endpoints choice**
Designations Received	✓ MPS VI Orphan Drug Designation	✓ MPS VI Orphan Drug Designation ✓ Fast Track Designation in MPS VI ✓ Rare Pediatric Designation in MPS VI

Odiparcil potential path to regulatory submission

The proposed clinical trial design contemplates to enroll 50 pediatric patients for 12 months, potentially leading to filing for odiparcil's approval as ERT combination therapy in patients 5 y/o to adults

iMProveS Study (Ph IIa)
(≥16yo)
- Combination with ERT (n = 15)
- Monotherapy (n = 5)

Ph II / III PRODIGY
(5 – 15yo)
- Combination with ERT

Part 1

- Two arms:
(1) ERT/placebo arm
(2) ERT/odiparcil arm
- 12-month treatment duration; 50 patients

Potential FDA Approval

Adjunct with ERT in Patients 5yo to Adult

Part 2 (continues as filing takes place)

- 12-month safety extension
- All patients (50) rolled over into the ERT/odiparcil arm

Multidomain Approach for Endpoint Measurement

Primary Endpoints
- 6MWT measured at regular intervals up until week 52 with heart and oxygen monitoring before and after test

Secondary and Exploratory Endpoints
- 3MSC and pain assessment via FPS-R and NPRS
- MDRI (incl. 6MWT FPS-R or NPRS, 3MSC, COM)

Stratification by pubertal status and 6MWT

Key
- Trial Designed
- Trial Completed
- FDA Feedback Received
- File for Approval

ERT = Enzyme replacement therapy; 6MWT = 6-minute walking test; 3MSC = 3-minute stair climb; MDRI = Multi-Domain Responder Index; FPS-R = Faces Pain Scale-Revised; NPRS = Numeric Pain Rating Scale; COM = Corneal opacification measure

Inventiva continues to review potential options to further develop odiparcil for the treatment of MPS VI, which may include pursuing a partnership

YAP-TEAD and TGF-β programs

YAP-TEAD and TGF-β programs

YAP-TEAD program

- Hippo signalling pathway is potentially implicated in the **process of cell differentiation and proliferation**, tissue growth and organ size
- Inventiva compounds observed to **disrupt interaction between YAP and TEAD** along the pathway
- Potentially **relevant in multiple cancer indications** including malignant mesothelioma, lung cancer and triple negative breast cancer
- *In vitro* evidence for **synergies with standard of care** and suppression of tumor resistance
- ***In vivo* tumor repression observed** in pre-clinical models (alone and in combination with standard of care)
- Proprietary chemistry
- Lead and back-up compounds available
- Pre-clinical candidate screening and **clinical candidate selection** ongoing
- **Pre-clinical development start planned in 2023**

TGF-β program

- TGF-b is a cytokine that is a key driver of fibrosis and acts by activating fibroblasts into myofibroblasts, driving the production of fibrotic tissues
- Target validated
- **Program progressing into lead generation**

Recent and upcoming catalysts

Recent and anticipated key milestones

Lanifibranor

- ☑ Activation of first clinical sites and start of patient screening in NATiV3 phase III trial in NASH
- ☑ Activation of first clinical sites and start of patient screening in LEGEND phase IIa trial in NASH
- ☑ Signature of licensing and collaboration agreement for the development of lanifibranor in Greater China
- ▶ Topline results of Phase II trial in T2D patients with NAFLD **– anticipated by middle of Q2 2023**
- ▶ Topline results of Phase II of lanifibranor in combination with empagliflozin in patients with NASH and T2D **– anticipated H2 2023**

Odiparcil

- ☑ FDA feedback that a single phase II/III trial could potentially support a future odiparcil marketing application

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