Developing innovative therapies in NASH

Corporate Presentation

October 2022

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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 and estimates with respect to Inventiva’s pre-clinical programs and clinical trials, including recruitment, screening and enrolment for those trials, including the LEGEND trial for the treatment of NAFLD, the NATiV3 Phase III clinical trial with lanifibranor in NASH, the investigator-initiated Phase II trial of lanifibranor in patients with NAFLD and T2D, and the expected Phase IIb clinical trial of cedirogant led by AbbVie, potential development of odiparcil including potential trial design and regulatory pathway, clinical trial data releases and publications, the information, insights and impacts that may be gathered from clinical trials, the potential therapeutic benefits of lanifibranor generally and in combination with empagliflozin, the potential therapeutic benefits of odiparcil, the design of trials and any potential amendments to trial design and the anticipated benefits related thereto, the Company’s agreement with Sino Biopharm, including expectations with respect to enrollment of patients in Greater China in the NATiV3 trial, pipeline and preclinical and clinical development plans, milestone payments, royalties and product sales, potential proceeds under the Company’s financing arrangements, future activities, expectations, plans, growth, business prospects, competitive advantages and opportunities, including pipeline product development of Inventiva and the sufficiency of Inventiva’s cash resources and cash runway. 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, 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 may encounter substantial delays in its clinical trials or Inventiva may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities, enrolment 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, enrolment and completion of Inventiva’s clinical trials on anticipated timelines, and macroeconomic conditions, including global inflation and uncertain financial markets. 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, 2021 filed with the Autorité des Marchés Financiers on March 11, 2022, the Annual Report on Form 20-F for the year ended December 31, 2021 filed with the Securities and Exchange Commission on March 11, 2022 and the financial report for the first half of 2022 filed Securities and Exchange Commission for additional information in relation to such factors, risks and uncertainties.

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. The information with respect to Sino Biopharm included in this presentation is based on [disclosures made by Sino Biopharm] and is not the responsibility of Inventiva.

Key take-aways

A Phase III First-in Class & Best-in-Class NASH Drug

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

Positive Phase IIb topline data with statistical significance on 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 Q1 2023 and H2 2023

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

A Phase IIb Clinical Stage Collaboration with AbbVie

Cedirogant/ABBV-157 Small molecule RORγT Inverse Agonist

Potential to more effectively inhibit IL-17 production than antagonist approaches

Promising activity in Phase I study in psoriasis patients

Phase IIb dose-ranging study initiated Q4 2021 and expected to end Q1 2023

Inventiva eligible to receive milestone payments and sales royalties

Strong 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 €25m second tranche of the bullet loan facility secured with the European Investment Bank

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 and 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

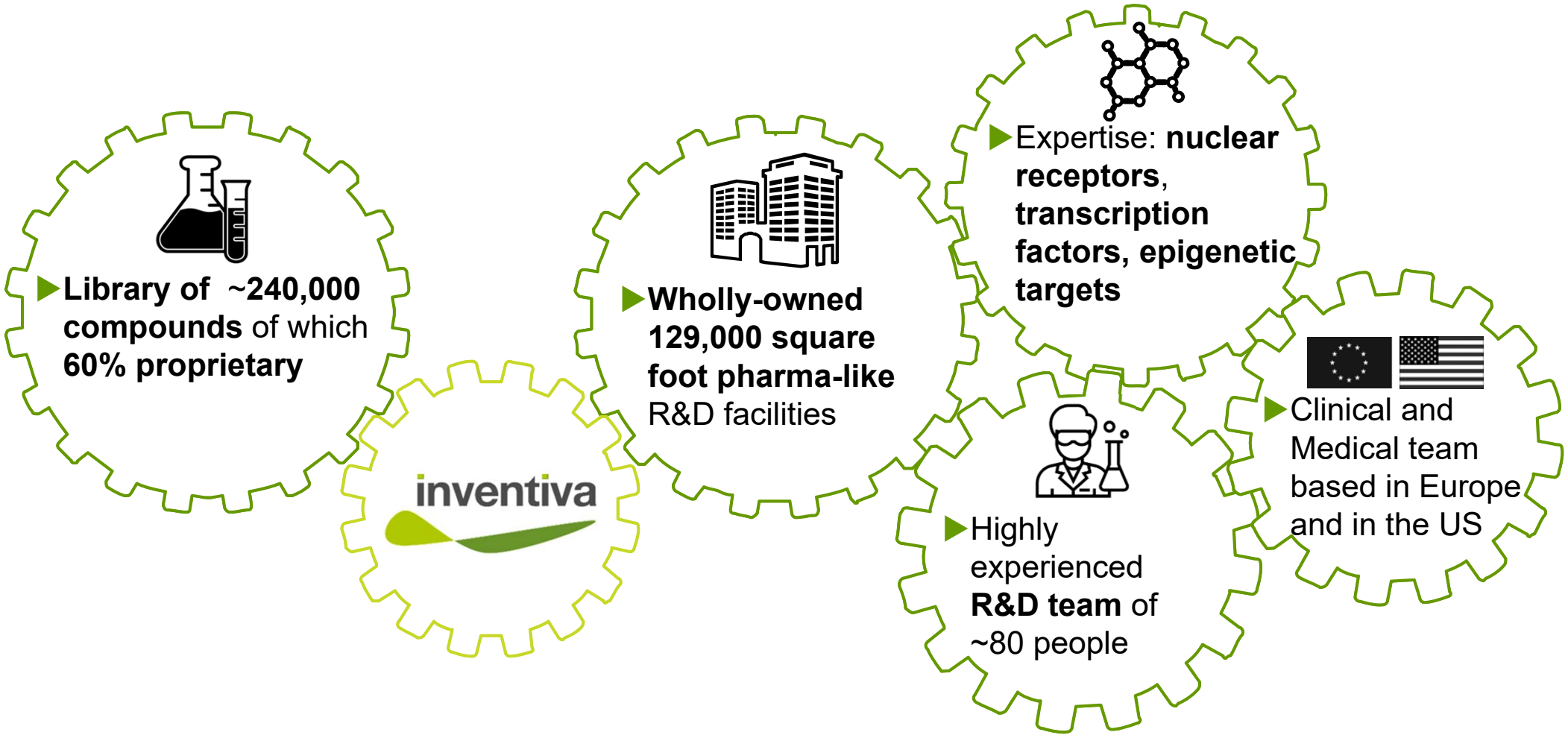
Alice Roudot-Ketelers, PharmD, VP Clinical Operations and Pharmaceutical Development

- 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

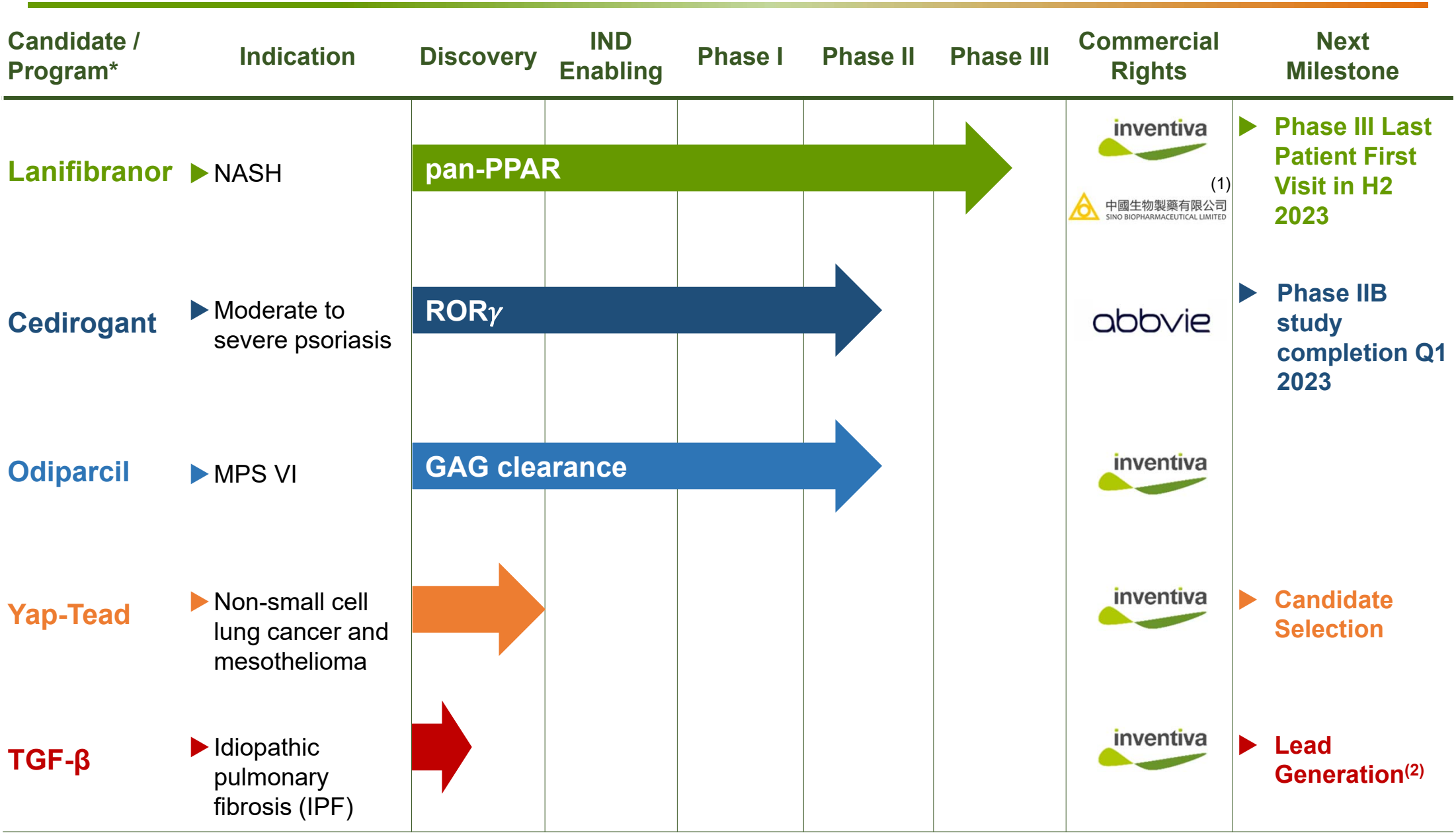
- Former buyside portfolio manager and analyst for +15 years in public equities and VC
- U.S. based

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



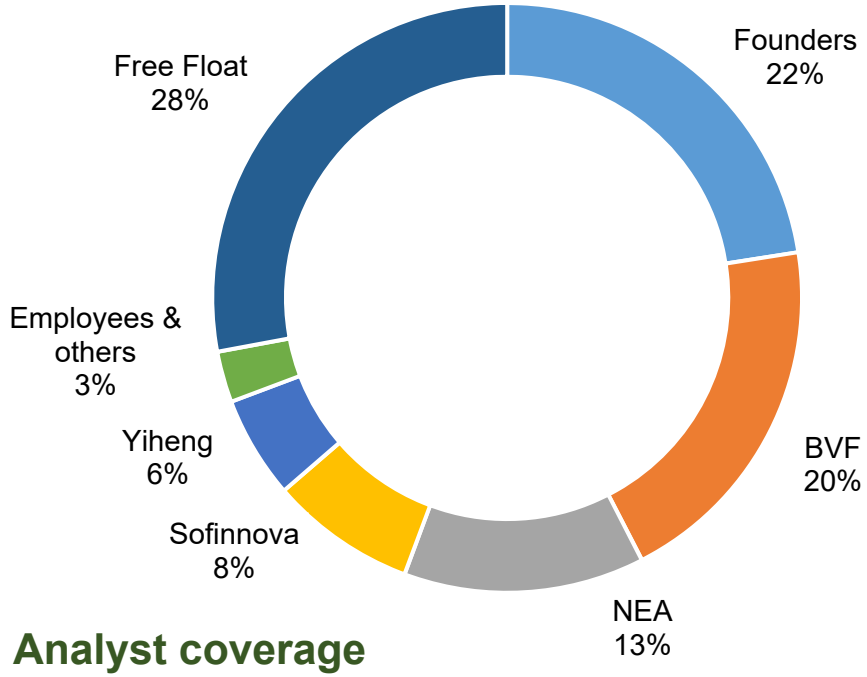
(1) Licensing agreement covering China, Hong-Kong, Macao and Taiwan (2) Lead generation means identifying molecules in anticipation of selecting candidates

Key financials and shareholder base

Key financials

ISIN code	FR0013233012 / US46124U1079
Market	Euronext Paris / Nasdaq GM
Shares outstanding	42,134,169
Market cap (October 2, 2022)	Euronext Paris: €153m Nasdaq Global Market: $163m
Cash position (as of June 30,2022)	€87.2m (vs €95.4m as of December 31, 2021)(1) Current expected cash runway through Q4 2023(2)
Revenues (H1 2022)	€0.1m compared to €0.1m in H1 2021
R&D expenditures (H1 2022)	€29.9m compared to €19.1m in H1 2021

Shareholder base



Analyst coverage

Jefferies	L. Codrington / M. J. Yee
Guggenheim	S. Fernandez
HC Wainwright	E. Arce
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 in the category "other current assets" in the IFRS consolidated statement of financial position for €10.7 million as of June 30, 2022 and for €8.8 million as of December 31, 2021, considered by the Company as liquid and easily available*

(2) *Taking into consideration Sino Biopharm licensing deal and first tranche of EIB*

Lanifibranor in Nonalcoholic Steatohepatitis (NASH)

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

- **Moderate and balanced pan-PPAR agonist activity** (PPARα, PPARγ and PPARδ) with differentiated chemical structure
- **Once daily oral administration**
- **Effects observed** on insulin-sensitivity, dyslipidemia, steatosis, ballooning, inflammation, hepatic fibrosis and cirrhosis in pre-clinical models
- **Phase IIa(1) trial demonstrated pan-PPAR agonist activity,** supporting dose selection for NASH Phase IIb clinical trial
- **Positive Phase IIb trial topline results announced in June 2020** and published by the New England Journal of Medicine
- **Favorable tolerability profile** observed in:
  - 24-months rodent and 12-month monkey studies leading to **PPAR class clinical hold lifted** by FDA
  - **Non-clinical toxicology package considered by FDA as complete and acceptable to support NDA filing** for the treatment of NASH and improvement of liver fibrosis
  - Phase I trials with more than **200** healthy volunteers(2) and Phase IIa trial with **47** T2D patients
  - Over **250** patients treated for 24 or 48 weeks in Phase IIb clinical trials in NASH and other indications
  - In connection with these trials, lanifibranor underwent a total of **7 DSMB reviews without changes recommended to the different trial protocols**
  - **Thorough QT/QTc study completed** demonstrating no impact on QT intervals
- Composition of matter patent delivered in 55 countries and method of use patent granted in the U.S., China and in the EU: **limit of exclusivity in the U.S. is 2035**
- **FAST Track** (including in NASH patients with compensated cirrhosis) **and Breakthrough Therapy** designations granted by FDA

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

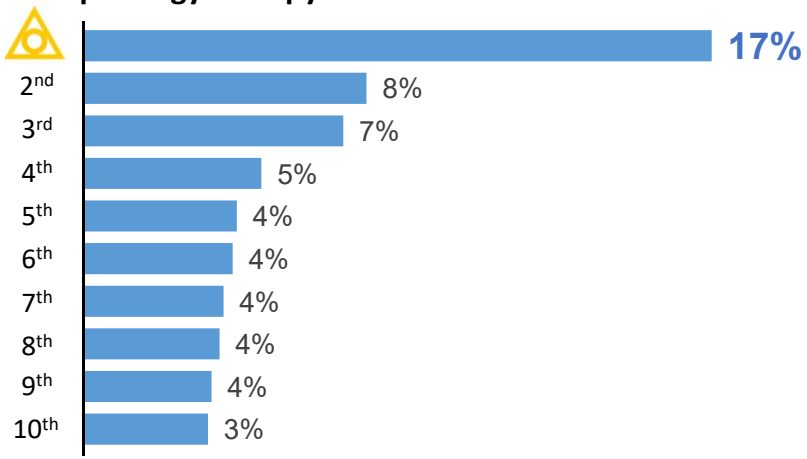
Licensing and commercialization agreement in Greater China

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
  - Top tier sales organisation with 13,900+ reps, covering 32 provinces and more than 90% of hospitals, using both traditional sales and emerging online channels

The largest market share in China

Hepatology therapy market share of China in 2021 (4)



Licensing key terms

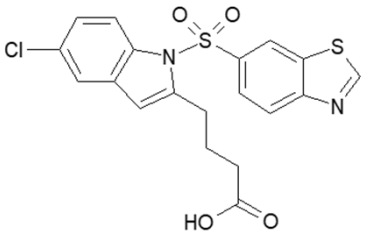
- Licensing and commercialization covering China, Hong-Kong, Macao and Taiwan
- Inventiva expected to receive a $12 million upfront payment following the recent signature
- Additional $5 million expected in the short-term if certain clinical milestones are met
- Potential to receive a total of $290 million of clinical, regulatory and commercial milestone payments.
- Subject to regulatory approval, Inventiva will 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 will 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

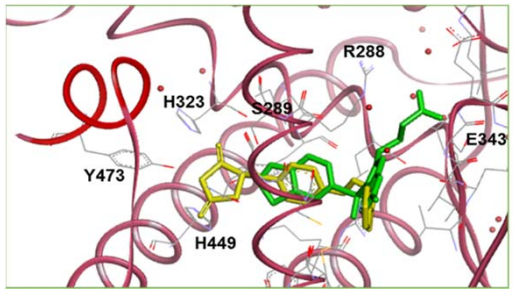
LANIFIBRANOR

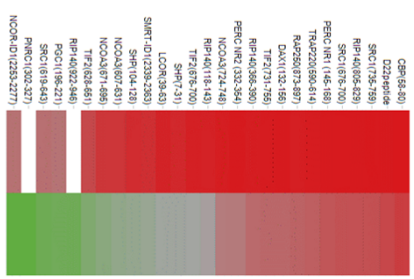
Differentiated oral small molecule …



- 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)

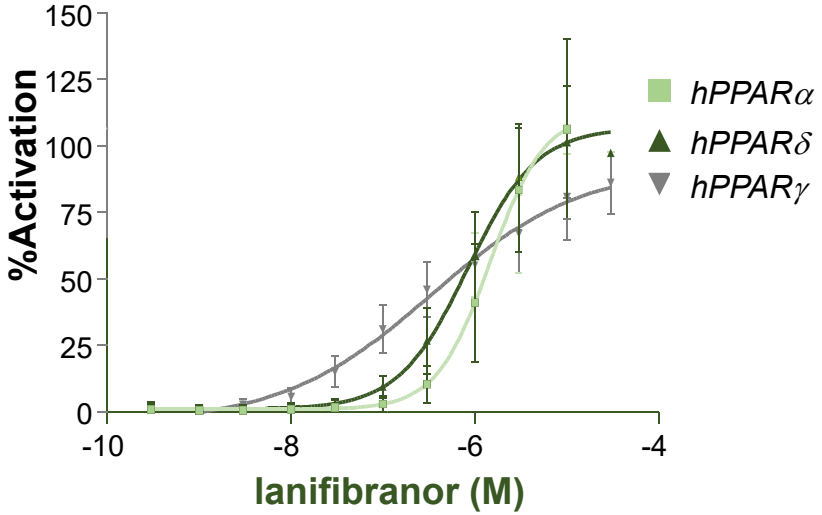
… that binds differently than glitazone to PPARγ





- Induces different coactivator recruitment^^

Moderate and balanced pan-PPAR agonist activity



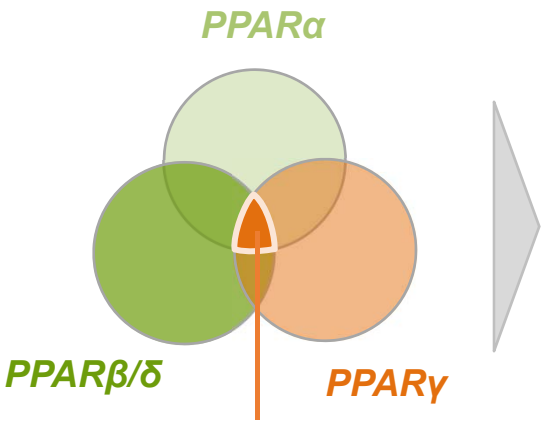
Compound	PPARα EC50 (nM)	PPARδ EC50 (nM)	PPARγ EC50 (nM)
Lanifibranor*	**1630**	**850**	**230**
Fenofibrate	*2400*	*-*	*-*
Pioglitazone	*-*	*-*	*263*
Rosiglitazone	*-*	*-*	*13*
*Elafibranor***	*10*	*100*	*-*
*Seladelpar^*	*-*	*2*	*-*

*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 are not observed in lanifibranor

SAFETY

Organ	Isoforms activated	Reported PPAR side effects	lanifibranor effects
HEART	*PPARγ*	▶ Fluid retention ▶ Cardiac hypertrophy	NOT OBSERVED
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

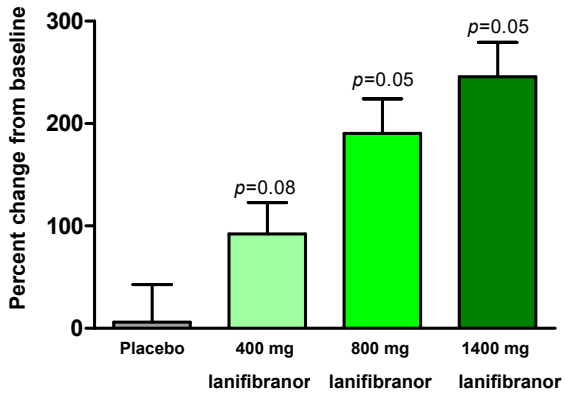
Source: Company data

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

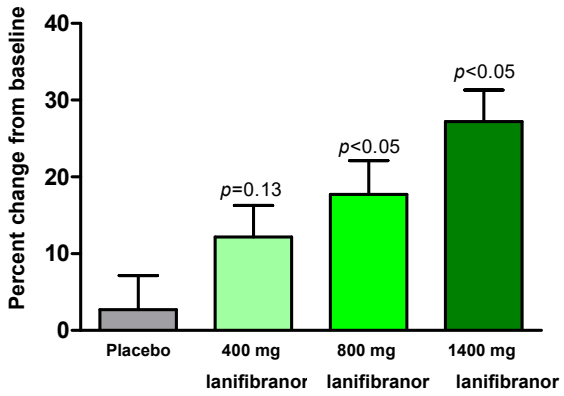
PHASE I AND IIa

Lanifibranor metabolic markers in type II diabetic patients

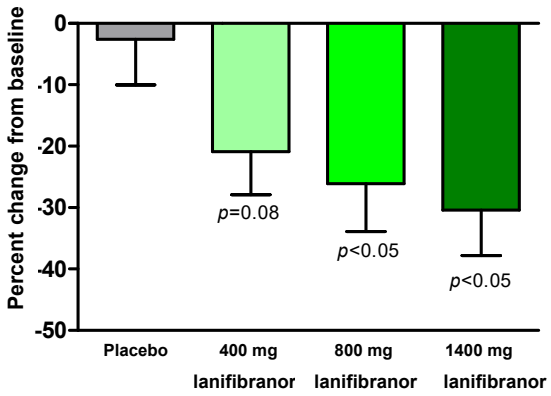
Adiponectin (PPARγ)**



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 tolerance 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

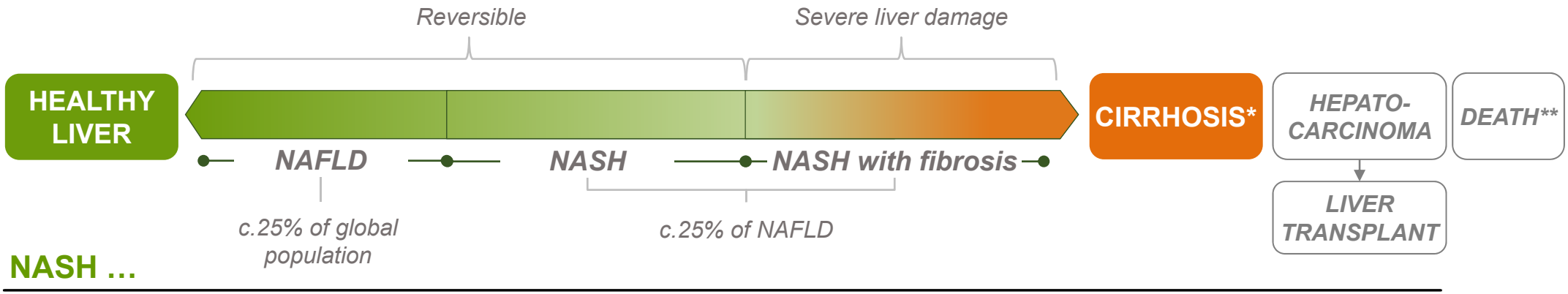
- Improvement of fibrosis
- Inhibition of stellate cell activation

- 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

The Phase IIb NATIVE trial studied 800 mg and 1200 mg once-daily lanifibranor across 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)]:

The NEW ENGLAND JOURNAL of MEDICINE

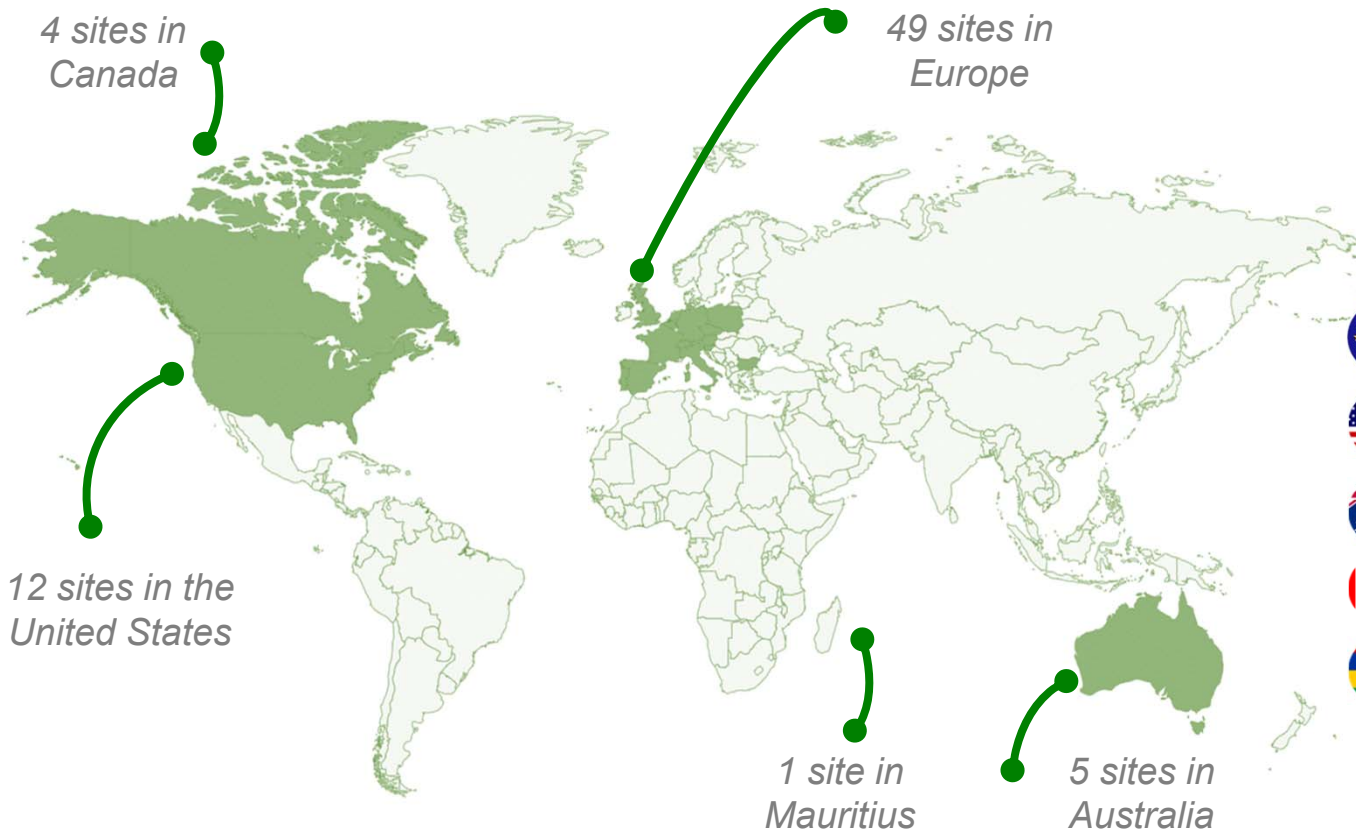
ESTABLISHED IN 1812 OCTOBER 21, 2021 VOL. 385 NO. 17

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

(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 at baseline

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%)

A number of liver enzyme, plasma lipid level and glucose metabolism parameters were recorded at baseline

PHASE IIb | DESIGN | BASELINE

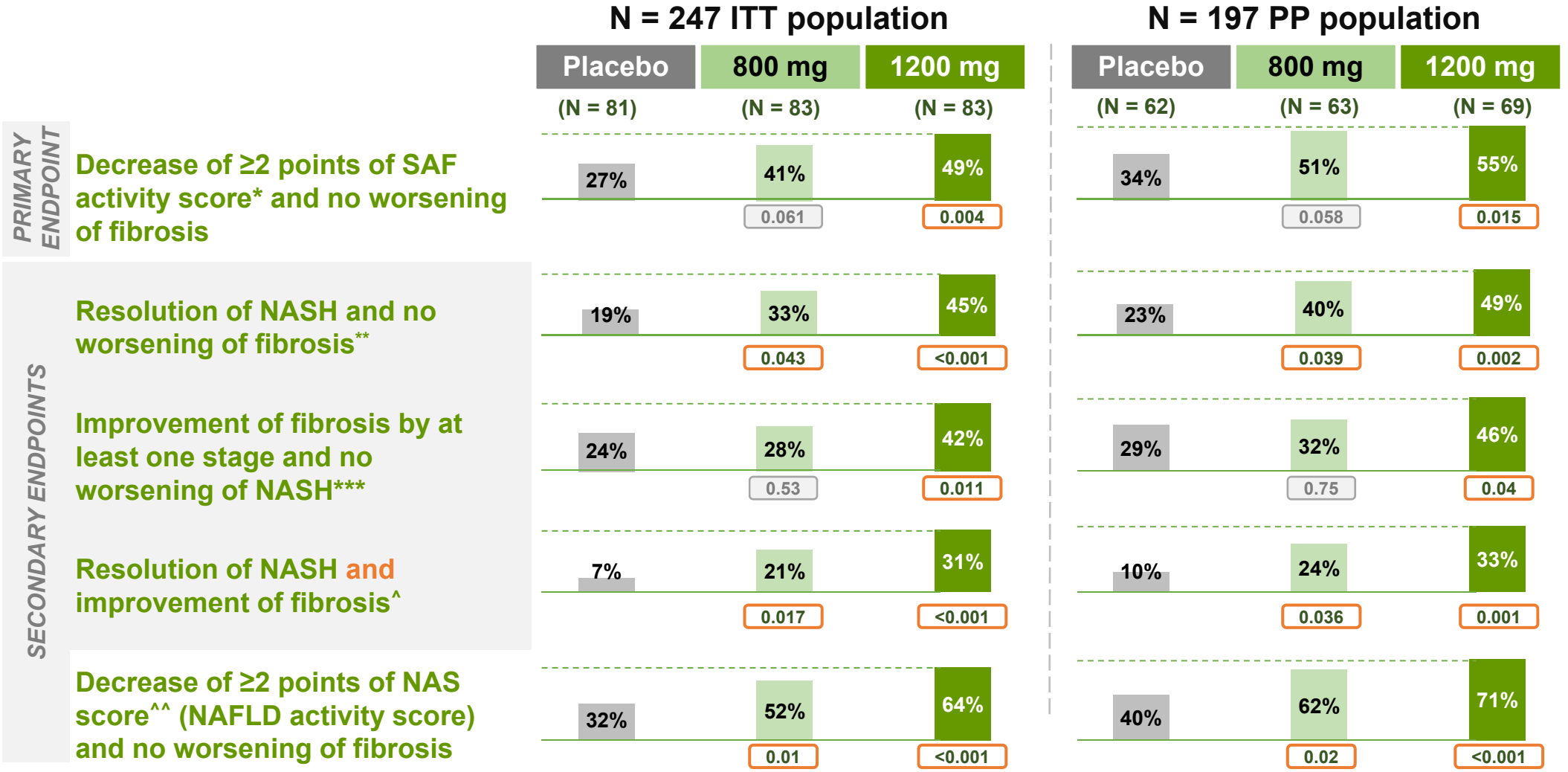
Parameters (unit) mean ± SD	Placebo - N = 81	lanifibranor 800 mg/day N = 83	lanifibranor 1200 mg/day N = 83
Liver enzymes			
Alanine aminotransferase, ALT (UI/L)	56.9 ± 31.6	64.1 ± 41.4	63.6 ± 43.4
Aspartate aminotransferase, AST (UI/L)	43.3 ± 24.1	53.9 ± 43.4	43.9 ± 24.8
Gamma glutamyl transferase, 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 diabetic patients (n= 103)			
Fasting Glucose (mmol/L)	6.9 ± 2.0	7.3 ± 2.2	6.6 ±1.2
HbA1c (%)	6.5 ± 0.7	6.7 ± 0.8	6.6 ± 0.7
Insulin (pmol/L)	222.7 ± 186.5	246.3 ± 213.4	278.5 ± 233.5

Lanifibranor is the first candidate to achieve statistically significant results on the two Phase III FDA and EMA primary endpoints

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.*

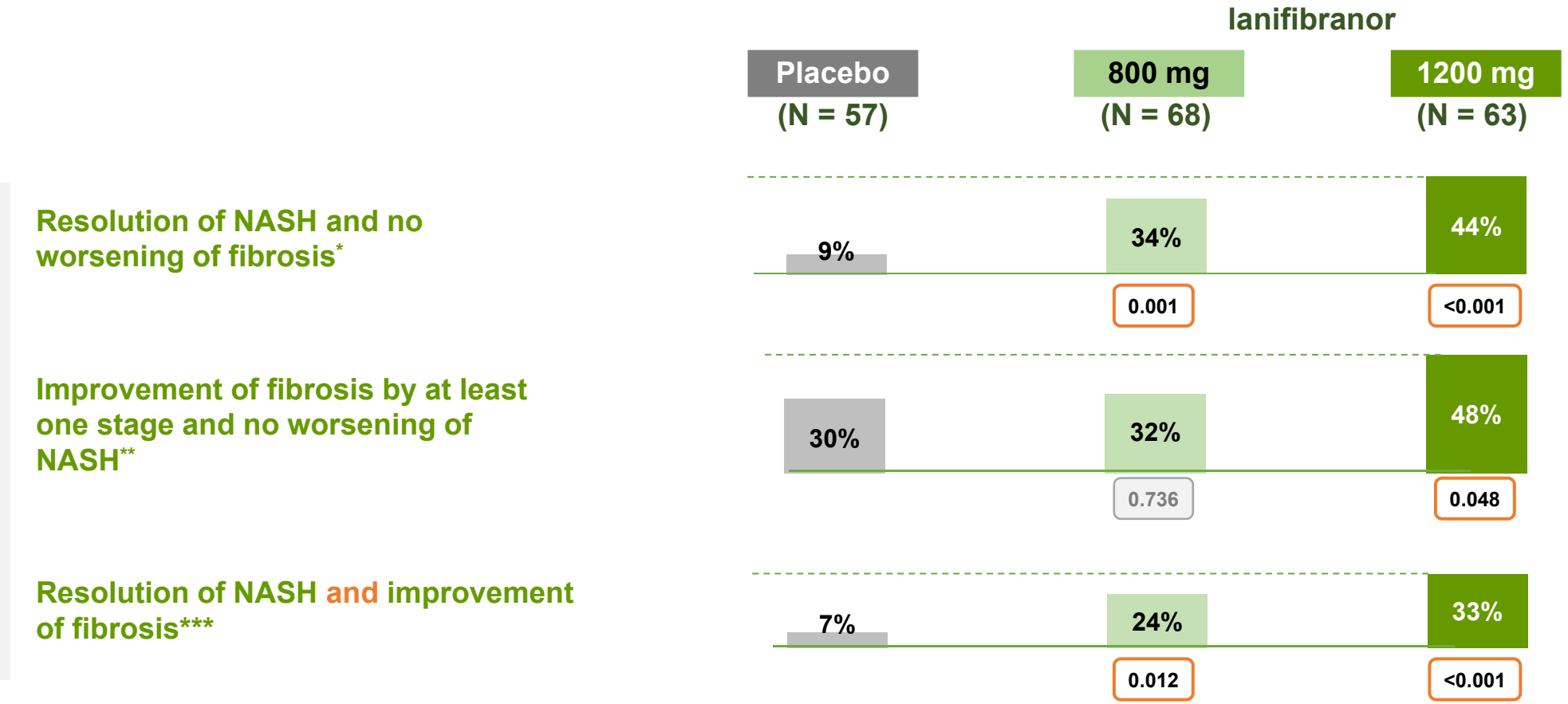
In F2-F3 patients, statistical significance was demonstrated for the main key histological secondary endpoints

PHASE IIb | EFFICACY | F2-F3 POPULATION

xx Statistically significant xx Non-statistically significant

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

SECONDARY ENDPOINTS

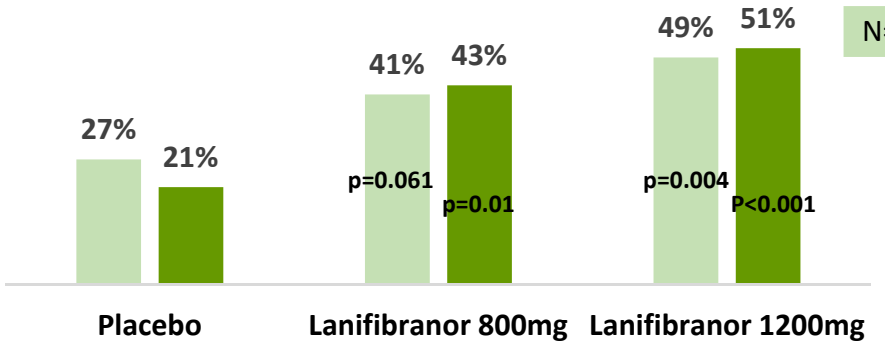


- Similar results in the PP population
- Consistent response in diabetic and non-diabetic patients

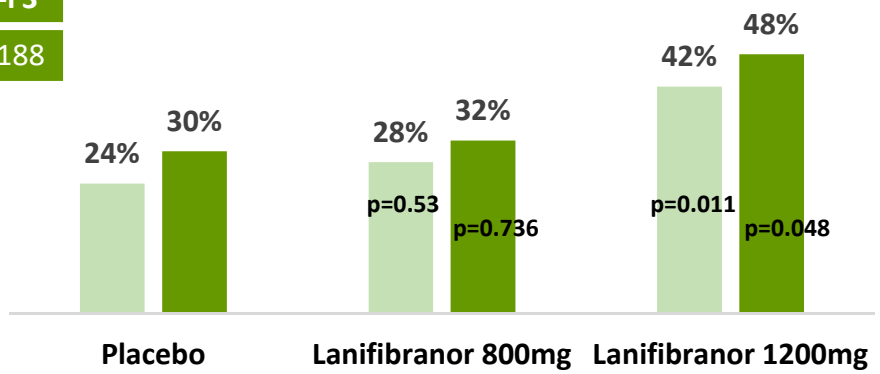
** Resolution of NASH and no worsening of fibrosis at week 24: NAS-I = 0 or 1 (NAS-Inflammation), NAS-B = 0 (NAS-Ballooning) and no worsening of NAS-F from baseline; ** Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH at week 24; *** Resolution of NASH and improvement of fibrosis at week 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 of F2-F3

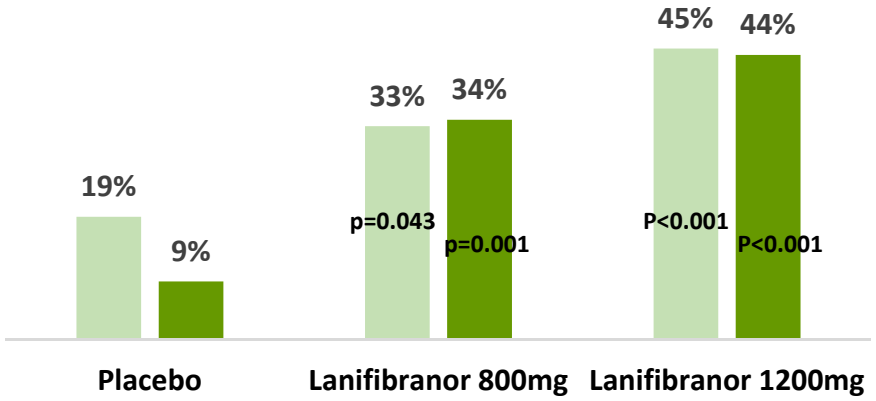
Reduction of 2 points of SAF Activity Score and no worsening of fibrosis



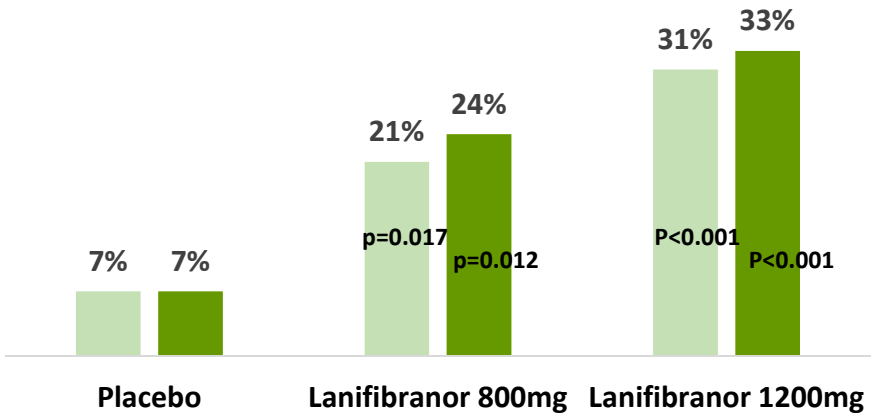
Fibrosis improvement w/o worsening of NASH



NASH resolution w/o worsening of fibrosis



NASH resolution AND Improvement of fibrosis



Effect is higher in the F2-F3 subpopulation

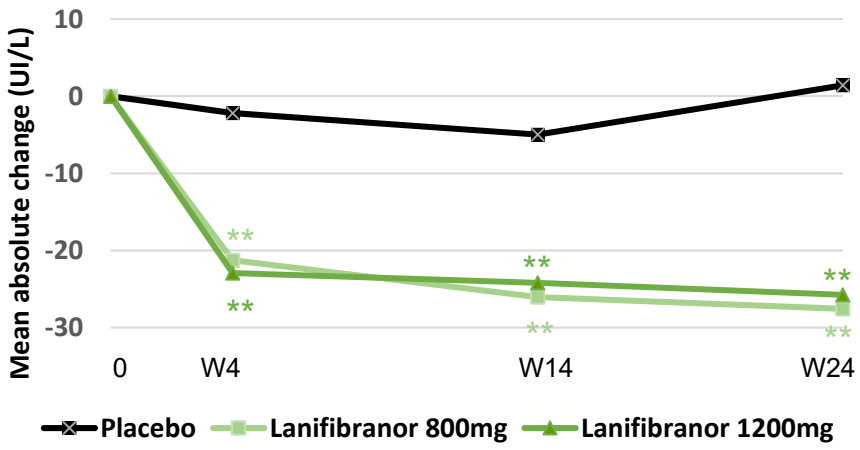
A statistically significant decrease in liver enzymes was observed

PHASE IIb | EFFICACY | OTHER

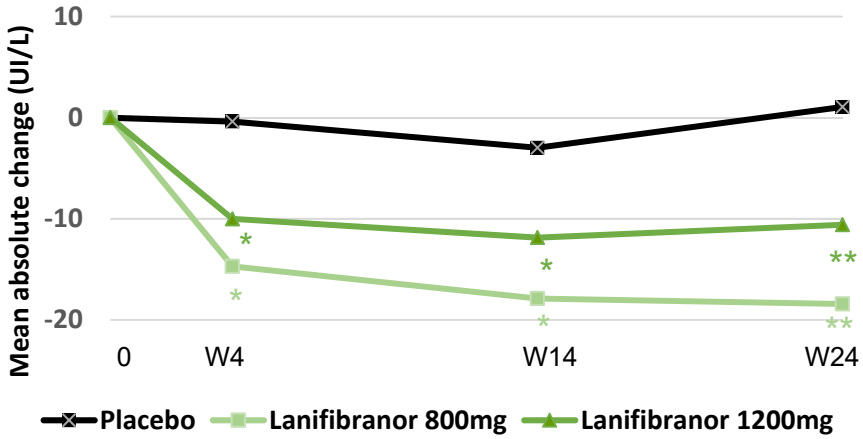
SECONDARY ENDPOINTS

Other secondary endpoints in ITT (N = 247)

Absolute change from baseline in ALT

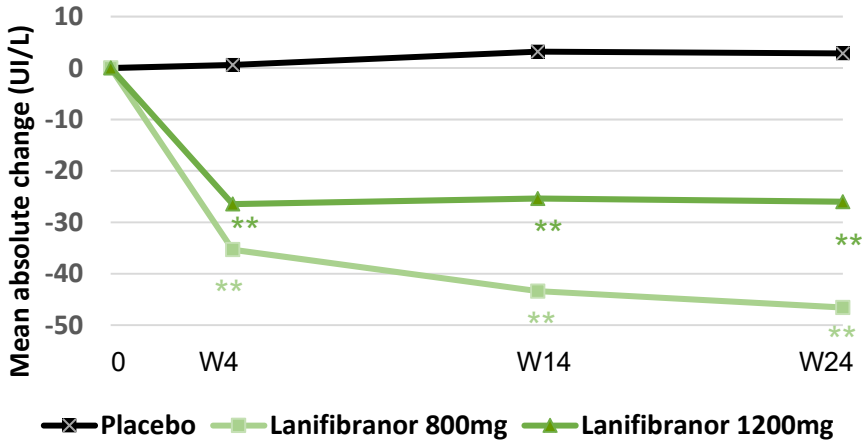


Absolute change from baseline in AST



* p<0.01 **p<0.001

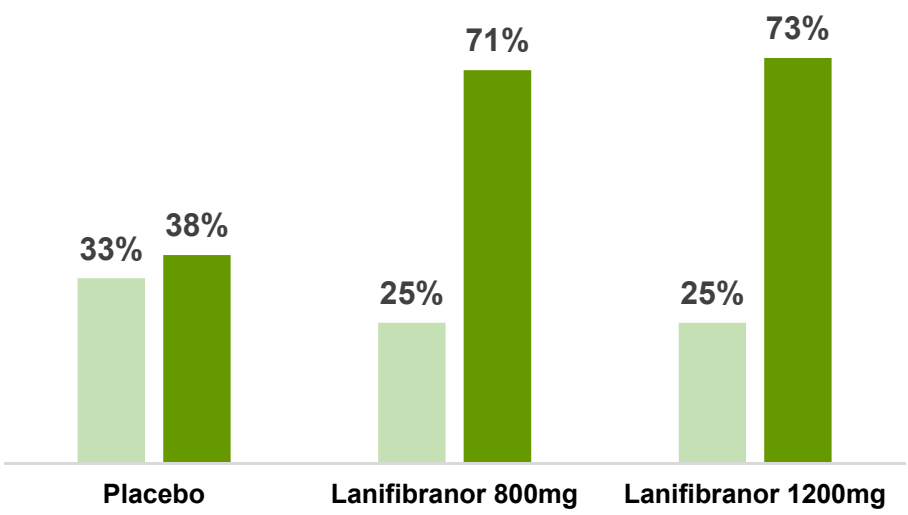
Absolute change from baseline in GGT



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

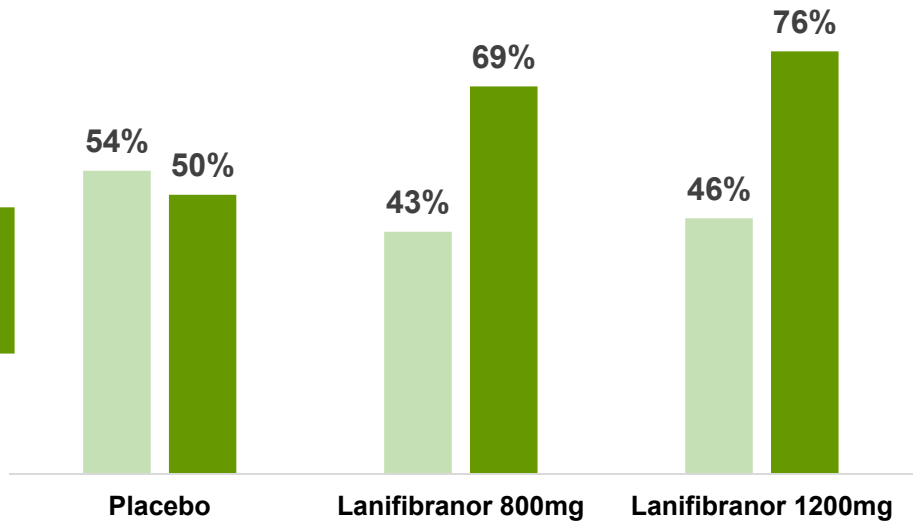


Lower Limit of Normal (LLN)= 0 U/L, Upper Limit of Normal (ULN)= 41 U/L for males, 33 U/L for females

Baseline

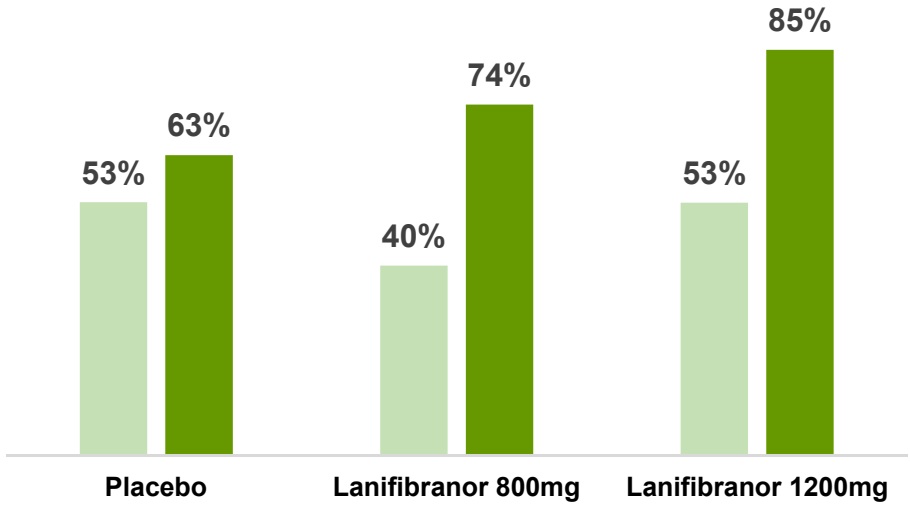
End of treatment (Week 24)

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

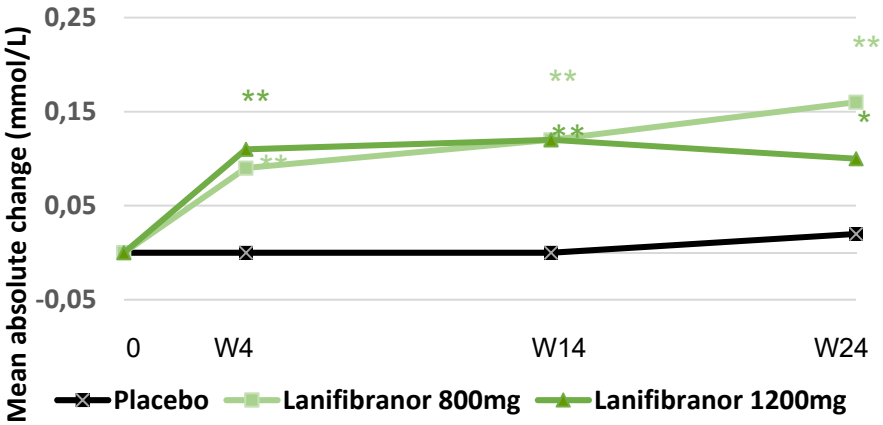
PHASE IIb | EFFICACY | OTHER

SECONDARY ENDPOINTS

Other secondary endpoints in ITT (N = 247)

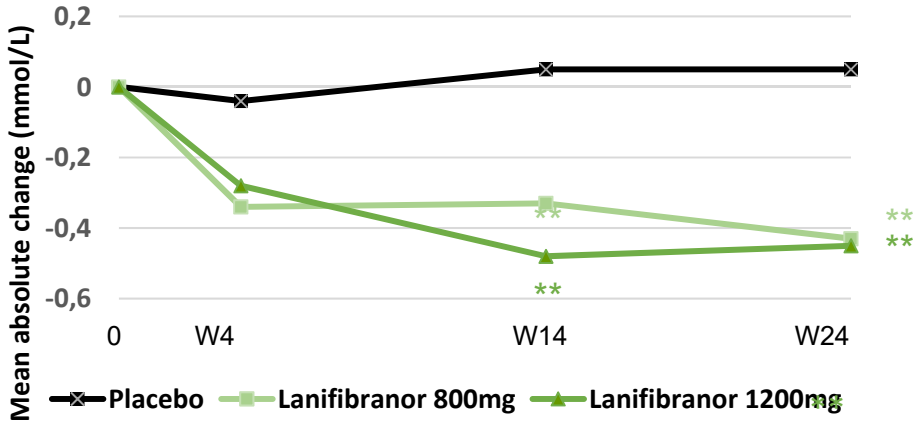
* p<0.01 **p<0.001

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

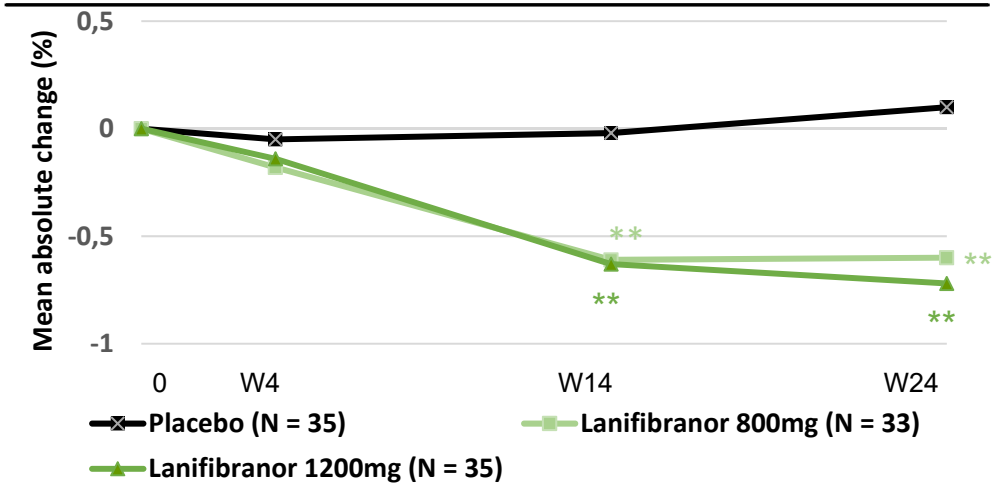
In patients with NASH and T2D, statistically significant reductions of fasting glucose and insulin, HbA1c were observed

PHASE IIb | EFFICACY | OTHER

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

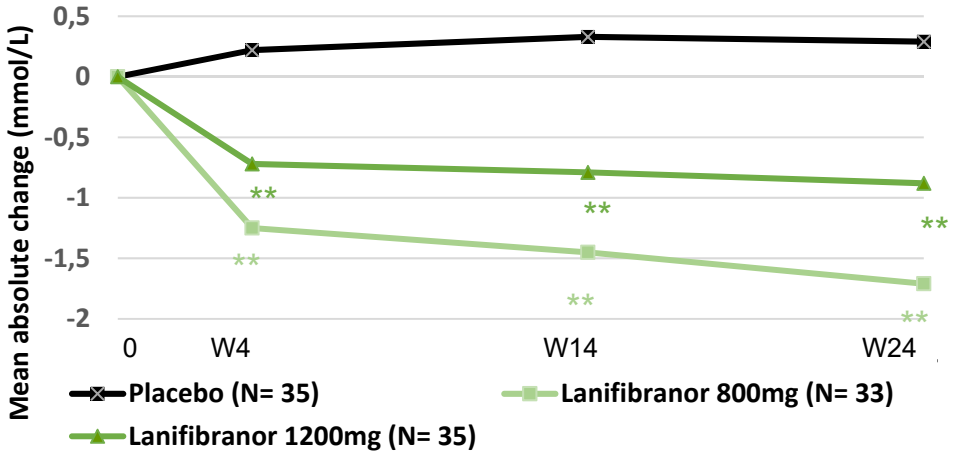
SECONDARY ENDPOINTS

Absolute change from baseline in HbA1c

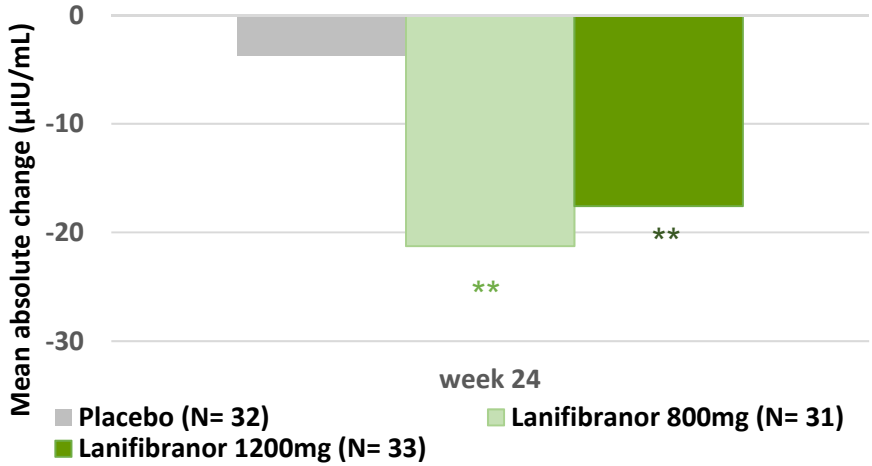


**p<0.001

Absolute change from baseline in fasting glucose



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 analysis on NATIVE phase 2b results have enlarged lanifibranor spectrum of efficacy

EFICACY: Sub-analysis

AASLD November 13-16, 2020 The Liver Meeting®

- Presentation during the plenary session of **NATIVE phase 2b trial**

EASL 2021 The International Liver Congress™ 23-26 June 2021

- Lanifibranor **effect on histology endpoints is higher in the F2-F3 patients**
- Lanifibranor **has beneficial effects on cardiovascular risk** biomarkers
- Preclinical data showing the **combination of lanifibranor and firsocostat**, an ACC inhibitor from Gilead, reached greater efficacy than monotherapy

AASLD Nov. 12-15, 2021 The Liver Meeting®

- Lanifibranor improves **markers of glucose metabolism in prediabetic patients**
- Analysis showing a **decrease in lanifibranor treated patients of steatosis measured by CAP/Fibroscan**(1)
- Following treatment with lanifibranor **NASH resolution responders were significantly more likely to also be fibrosis improvers**
- Lanifibranor showed **reduction in LSEC**(2) **capillarization**
- **Lanifibranor improves NASH, fibrosis and diastolic dysfunction** in a hamster model of diet-induced NASH and diastolic dysfunction

- **Beneficial effects of lanifibranor on markers of cardiometabolic health** in patients with NASH showing that they are independent of weight change
- **Beneficial effect of lanifibranor treatment on the FibroScan-aspartate aminotransferase (Fast™)** score, a promising non-invasive test (NIT) for active NASH with significant fibrosis
- **Identification of biomarkers** of histological response in patients with non-cirrhotic NASH treated with lanifibranor

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

Lanifibranor has continued to show 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)	-	-

Focus of next slide

(1) One patient with moderate diarrhea

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

(3) 2 SUSARs: one patient with mild cardiac failure; one patient with moderate urticaria

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

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

* One AE of severe intensity

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%)

Peripheral edemas were not flagged as a concern by study investigators

PHASE IIb | **SAFETY** | **PERIPHERAL OEDEMA**

#	Treatment group	Verbatim of AE edema peripheral	Intensity	Action taken or Corrective treatment	Relationship to treatment
1	**Placebo**	edema in the lower leg and knees	Moderate	IMP interrupted + Meloxicam	Unlikely
2		bilateral lower extremity edema	Mild	No actions taken	Unlikely
3	**800 mg**	*bilateral lower extremity edema*	Mild	No actions taken	*Unrelated*
4		*edema in bilateral feet*			*Unlikely*
5		peripheral edema bilateral			Possible
6		right and left ankle swelling			Possible
7		*foot edema bilateral*	*Moderate*	*Bioflavonoids*	*Unrelated*
8	**1200 mg**	*leg edema - both legs*	*Mild*	*Torasemid*	*Unrelated*
9		*edema in the 2 ankles*		*No actions taken*	*Unrelated*
10		*edema lower leg, both sides*			*Unrelated*
11		*peripheral edema , both ankles*			*Unrelated*
12		bilateral edema leg			Probable
13		*bilateral postural extremities edema*	*Moderate*	*IMP stopped*	*Unrelated*
14		legs edema	Severe	IMP interrupted	Possible

Peripheral edemas were not flagged as a concern by study investigators and were:

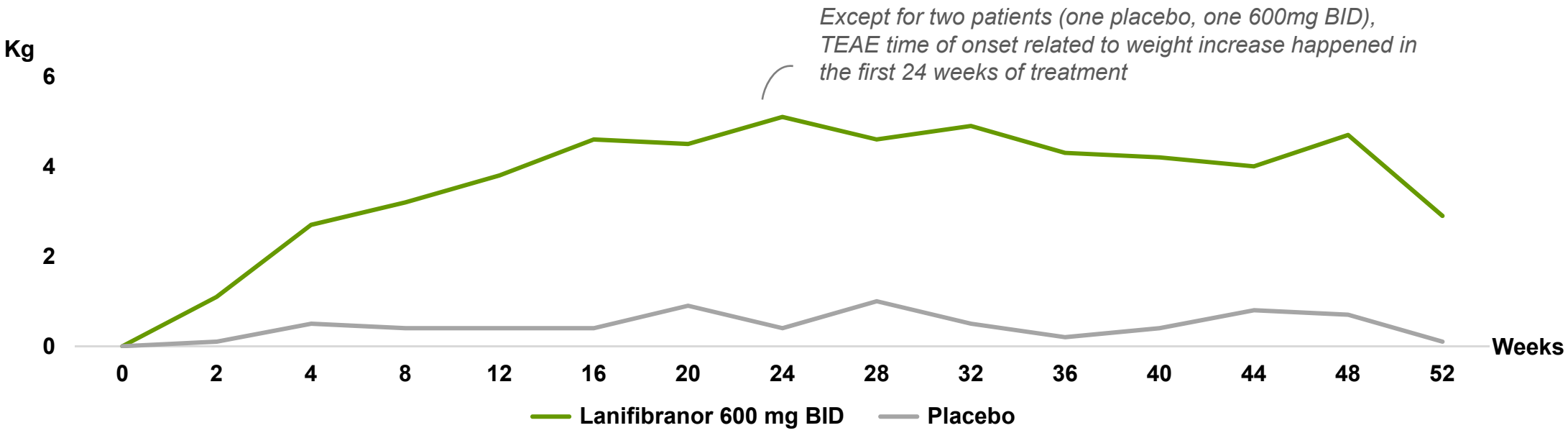
- Limited
- Transient
- Mostly mild
- Majority unrelated and not requiring treatment

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)

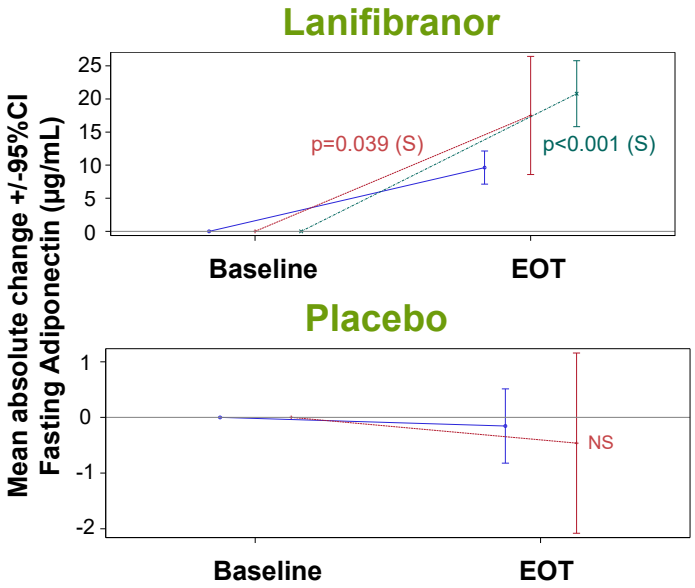
PHASE IIb | SAFETY | WEIGHT GAIN

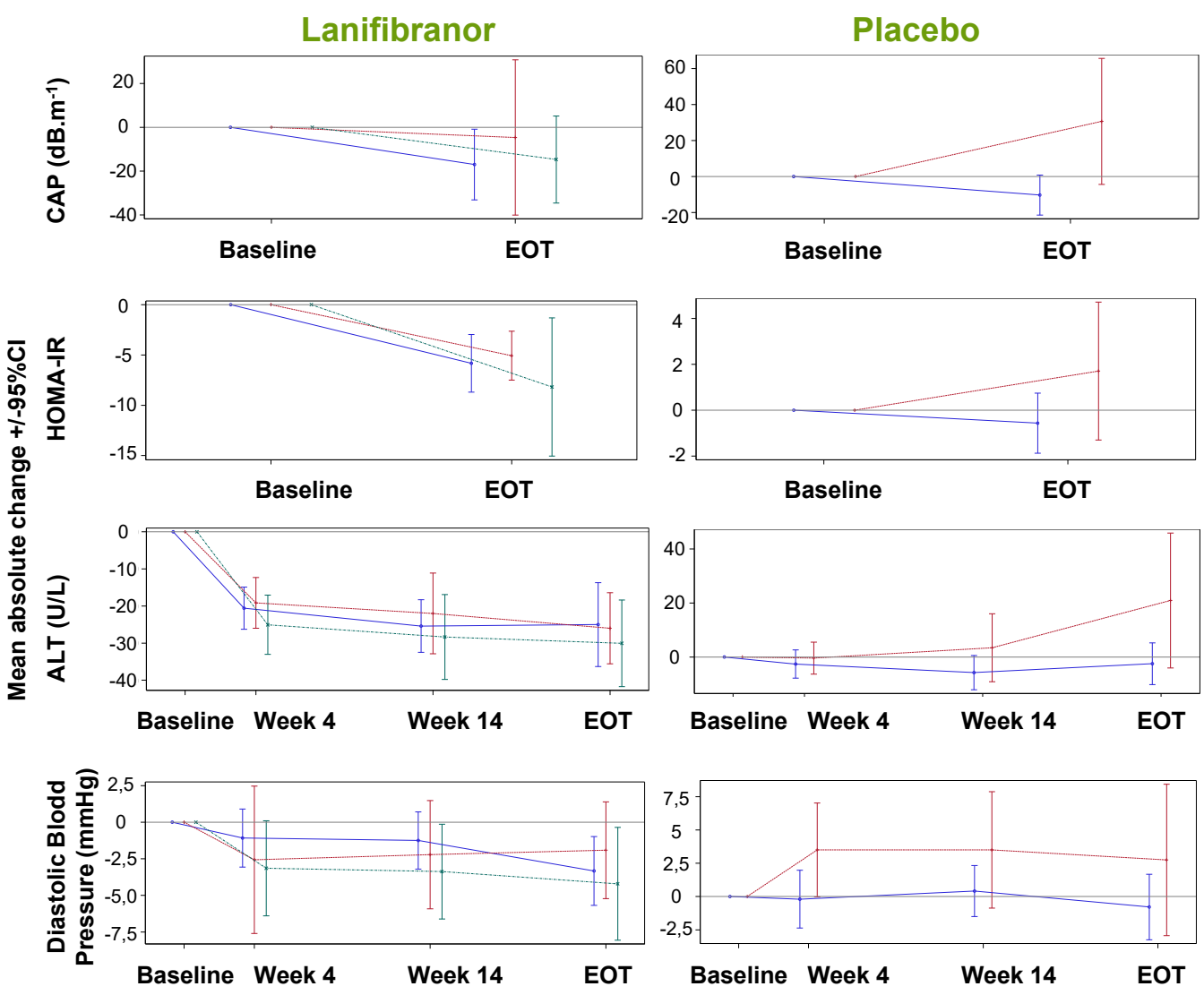
- NATIVE enrolled 247 patients with SAF activity score 3-4 and fibrosis stage F0-F3 in 3 arms: lanifibranor 800, 1200 mg/d and placebo for 24 weeks
- 217 (lanifibranor: 144, placebo: 73) patients who completed the trial with weight data at baseline and end of treatment (EOT) were included in the analyses
- 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

Compared to key competitors, lanifibranor is the only asset that addresses all key features of NASH

EFFICACY

Oral ← → *Injectables*

	Lanifibranor *(PPAR)*	Ocaliva *(FXR)*	Resmetirom *(THR-β)*	Aramchol *(Other)*	Efruxifermin *(FGF)*	Semaglutide *(GLP-1)*
	inventiva	Intercept	Madrigal Pharmaceuticals	Galmed Pharmaceuticals	akero	novo nordisk
STATUS	Phase III	CRL	Phase III	Phase III	Phase II	Phase III
ROUTE OF ADMINISTRATION	Oral	Oral	Oral	Oral	Injectable	Injectable
INSULIN-RESISTANCE	✓	✗	✗	✗	✓	✓
STEATOSIS	✓	✗	✓	✓	✓	✓
NECRO-INFLAMMATION	✓	✗	✓	Unclear	✓	✓
FIBROSIS	✓	✓	Unclear	✗	✓	✗

Source: Newsome et al., 2020; Company websites

NASH Competitive landscape

Lanifibranor, only oral drug achieving statistical significance on both endpoints

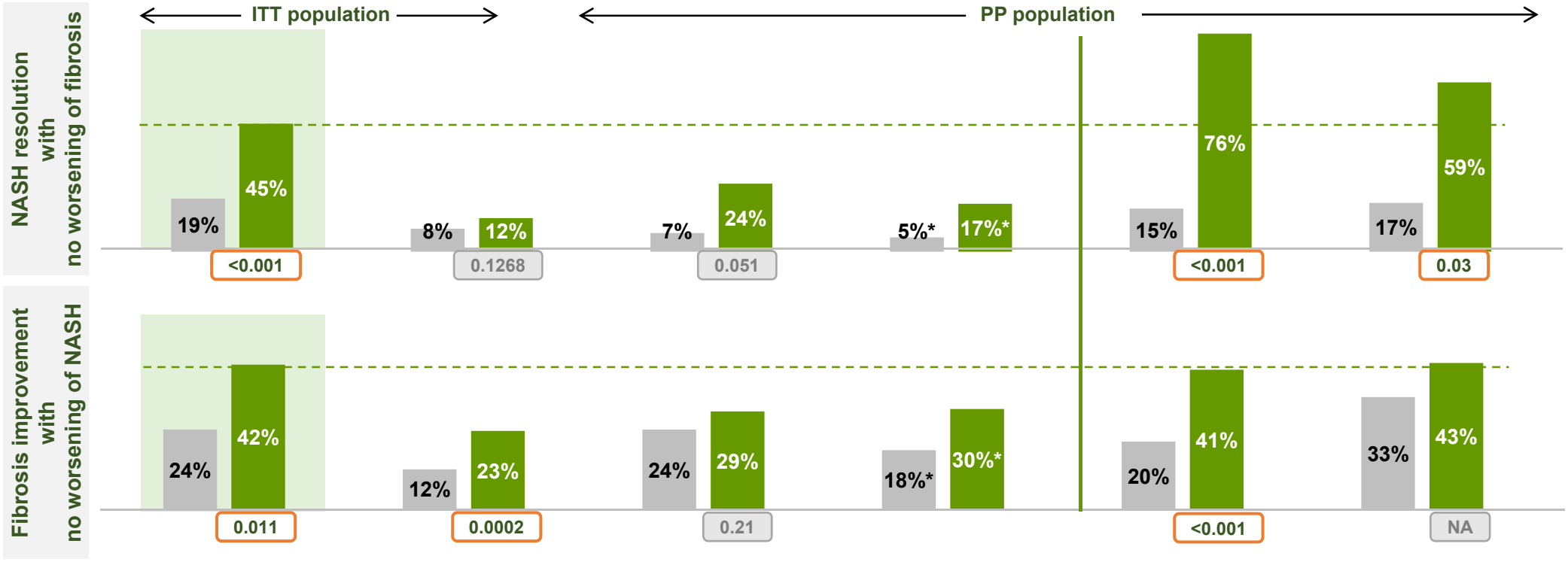
EFFICACY

Active | Placebo | xx Statistically significant | xx Non-statistically significant

Only oral drug achieving statistical significance on both endpoints

Oral ⟷ *Injectables*

	Lanifibranor	Ocaliva	Resmetirom	Aramchol	Efruxifermin	Semaglutide
Time point of data collection	**Phase II 6 months**	Phase III 18 months	Phase II 9 months	Phase II 12 months	Phase IIb 6 months	Phase II 18 months
# of patients	**247**	931	125	247	113	320
	ITT population		**PP population**			



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.
**** Efruxifermin 50mg results only. Source: Akero Phase 2b HARMONY Readout Presentation – September 13, 2022***

Source: lanifibranor native results 1200 mg/day, ITT population; ocaliva 25mg : REGENERATE Phase II trial: company press release February 19, 2019; Newsome et al., 2020: Ratziu et al, Gastorenterology 2016; 150:1147-1159 ; resmetirom 80mg ± 20mg: Harrison et al, Lancet 2019 ; S0140-6736(19) 32517-6; Aramchol 600mg :AASLD 2018 presentation

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

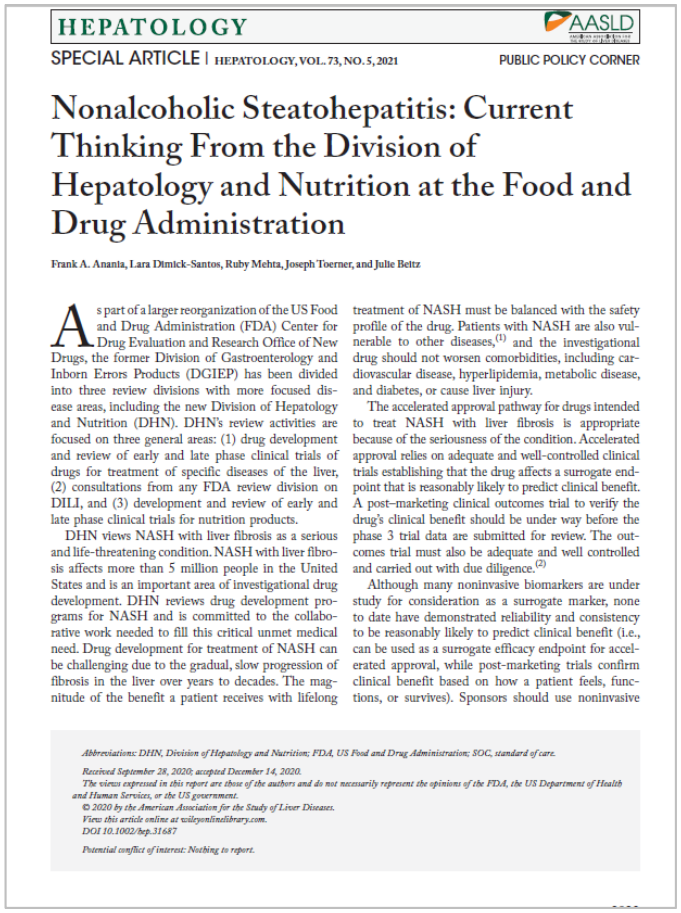
- Physicians express **less concerned about oedema** noting the majority are mild

"… 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 current thinking on NASH (May 2021)



HEPATOLOGY

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

Frank A. Anania, 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

Abbreviations: DHN, Division of Hepatology and Nutrition; FDA, US Food and Drug Administration; SOC, standard of care.

Received September 28, 2020; accepted December 14, 2020.

The views expressed in this report are those of the authors and do not necessarily represent the opinions of the FDA, the US Department of Health and Human Services, or the US government.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.31687

Potential conflict of interest: Nothing to report.

"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"

"We encourage use and evaluation of noninvasive biomarkers … to be considered for use as a surrogate efficacy endpoint reasonably likely to predict clinical benefit"

Source: Anania FA, Dimick-Santos L, Mehta R, Toerner J, Beitz J. Nonalcoholic Steatohepatitis: Current Thinking From the Division of Hepatology and Nutrition at the Food and Drug Administration. Hepatology. 2021 May;73(5):2023-2027. doi: 10.1002/hep.31687. PMID: 33340111.

Lanifibranor: comprehensive efficacy on the histology and biology of NASH

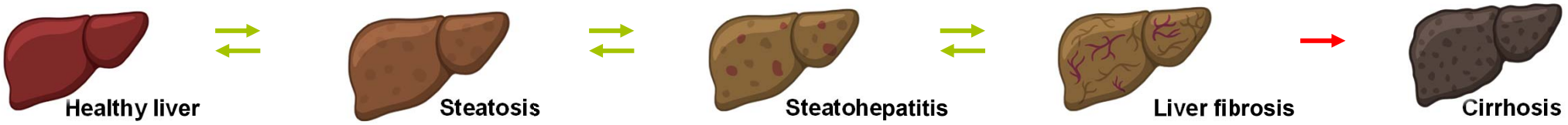
HISTOLOGY AND MARKERS

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 fibrosis: 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
- fasting HOMA index

Improves markers of glucose metabolism in patients with prediabetes

CARDIOVASCULAR RISK MARKERS

Improves cardiovascular risk

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

Improves lipids metabolism

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

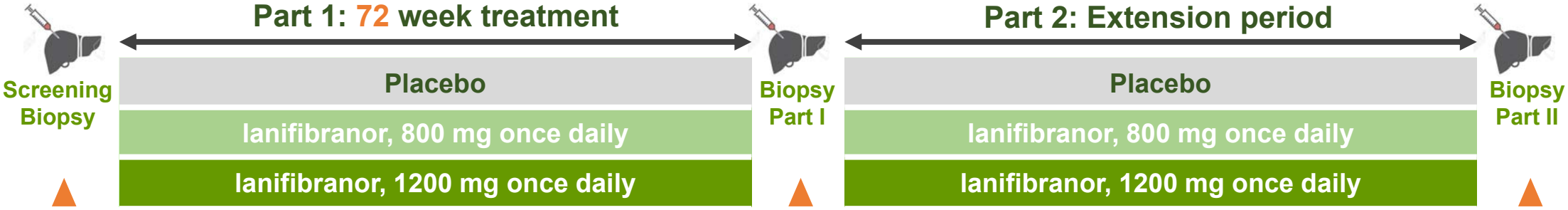
- DBP

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

Phase III NATiV3 clinical trial: design overview

PHASE III **OVERVIEW**

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



PRINCIPAL INVESTIGATORS: Pr. Sven Francque and Pr. Arun Sanyal

MAIN INCLUSION CRITERIA aligned to Phase IIb trial:

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

RANDOMISATION AND STRATIFICATION

- Randomisation 1:1:1
- Stratification on T2DM and F2/F3 patients
- At least 30% of patients from the U.S.

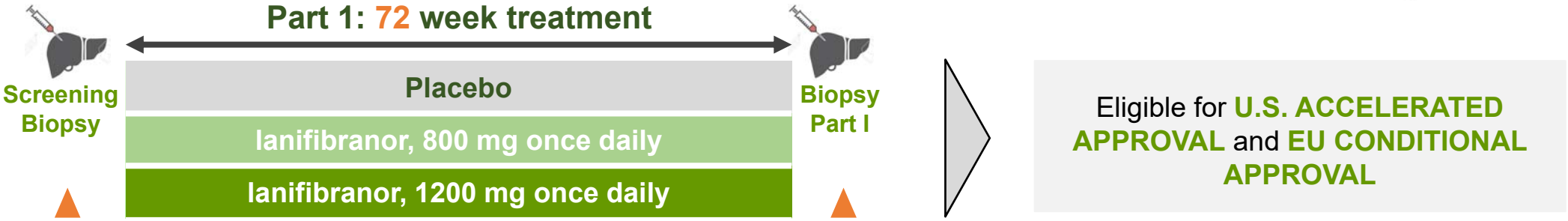
STATISTICAL POWERING: 90% considered for sample size calculations

CENTRAL BIOPSY consensus scoring review done by three pathologists

Phase III NATiV3 Part 1 interim histology analysis will enable to seek U.S. accelerated approval and E.U. conditional approval

PHASE III | OVERVIEW

Part 1 F2-F3 Phase III



PRIMARY ENDPOINT at week 72 on c.900 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

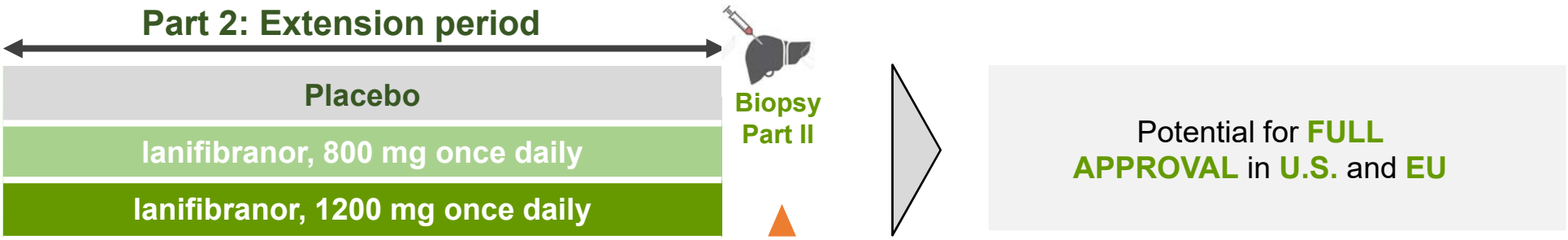
OTHER SECONDARY ENDPOINTS AND HIGH-LEVEL KEY EXPLORATORY ENDPOINTS *(non-exhaustive)*

- Glycaemic parameters at week 12 and week 24 in patients with T2DM not well controlled: proportion of patients with HbA1c back to normal
- Composite endpoint of diabetic patients having both NASH resolution and fibrosis improvement
- Improvement in renal function
- Reduction of cardiovascular risk (including major adverse cardiovascular events 'MACE'; non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, hospitalisation for unstable angina)
- Quality of life (NASH-CLDQ) and PRO (PROMIS)

Phase III NATiV3 Part 2 extension study will allow for a broader "full approval"

PHASE III OVERVIEW

Part 2 F2-F3 Phase III



KEY ENDPOINTS IN PART 2 *(non-exhaustive)*

- Based on time to first clinical event on c.2,000 patients
  - histological progression to cirrhosis
  - all cause mortality
  - hepatic decompensation events
    - hepatic encephalopathy
    - variceal bleeding
    - new onset ascites requiring treatment
    - spontaneous bacterial peritonitis
  - MELD score ≥15
  - liver transplant

TRIAL END DATE

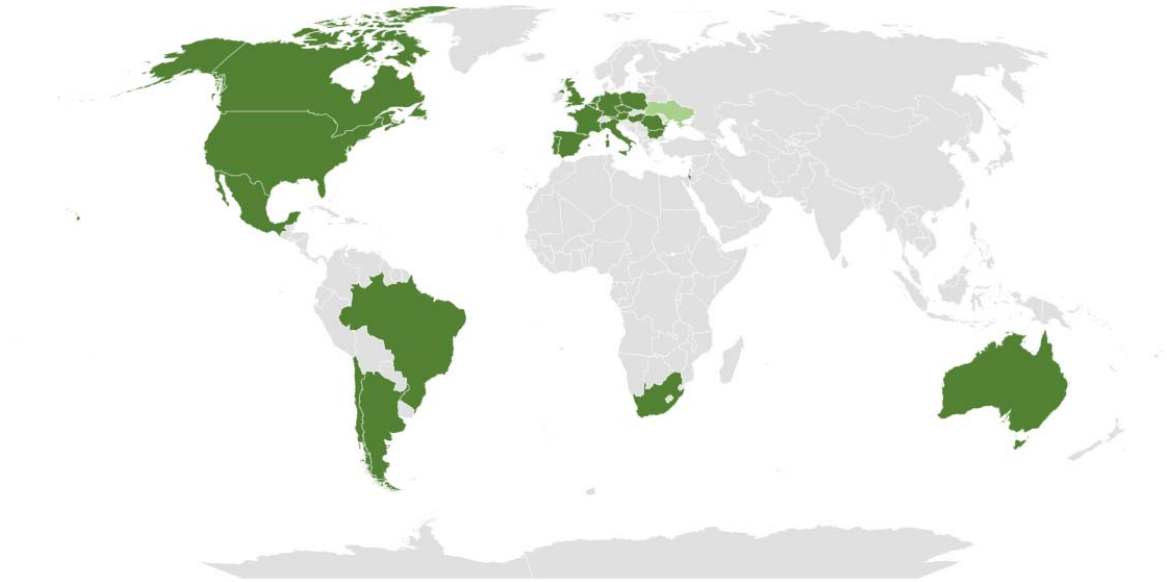
- Defined by first occurrence of following events (whichever comes first):
  - pre-defined number of clinical events registered

TIMING OF FINAL BIOPSY

- On per-patient basis, defined by:
  - Suggested progression to cirrhosis based on non-invasive testing, or
  - trial has ended

Status update of the NATiV3, Phase III clinical trial evaluating lanifibranor in patients with NASH

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



NATiV3 country on hold

NATiV3 participating countries

- 24 countries included of which 23 countries with full regulatory approval
- Activities paused in Ukraine where 10 sites were qualified including 3 sites already screening patients
- Discontinue sites located in Russia (12 sites)
- 463 sites qualified, 297 sites activated in 23 countries (status at end of August 2022)

The primary composite endpoint combining NASH resolution and fibrosis improvement will help differentiate from key competitors

PHASE III **EFFICACY**

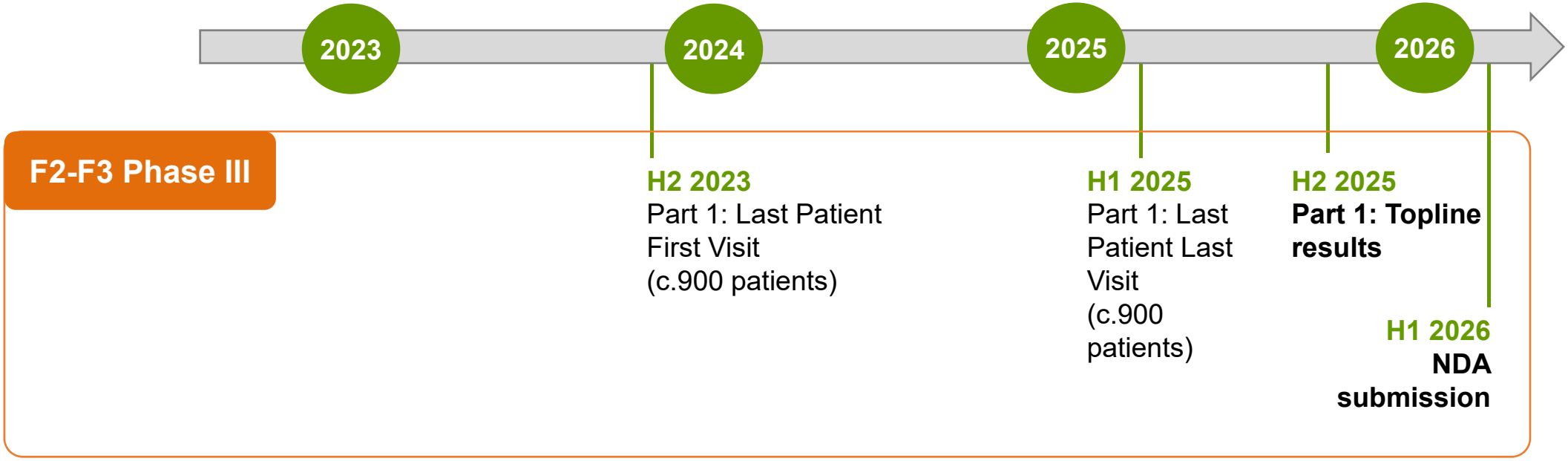
- The primary endpoint “resolution of NASH and improvement of fibrosis” addresses the major pathways of the disease: achieving both of these histological outcomes reflects a stronger impact on disease modification compared with improvement in either steatohepatitis or fibrosis alone
- If met, **a label for the treatment of NASH and the improvement in liver fibrosis** in adult non-cirrhotic NASH patients will be requested

Phase III study	lanifibranor (800 - 1200mg) At W72	Obeticholic acid (10 - 25mg) At W72	Resmetirom (80 - 100mg) At W52	Semaglutide - At W72
Resolution of NASH and improvement of fibrosis	**Primary**	Secondary (not met)	/	Secondary
Fibrosis improvement and no worsening of NASH	**Key secondary**	**Primary** (met)	**Primary**	**Primary**
NASH resolution and no worsening of fibrosis	**Key secondary**	**Primary** (not met)	**Primary** *(with reduction of at least 2 pts of NAS)*	**Primary**
NASH resolution and fibrosis improvement in patients with diabetes	**Secondary**	/	/	

Note: / : information not available*

Key milestones of the Phase III study in NASH (Part 1)

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

- 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

- **Results expected for Q1 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

34 patients; 24 week treatment

Double blind randomized placebo controlled

Healthy non-obese control group, 10 subjects

Placebo, 17 patients

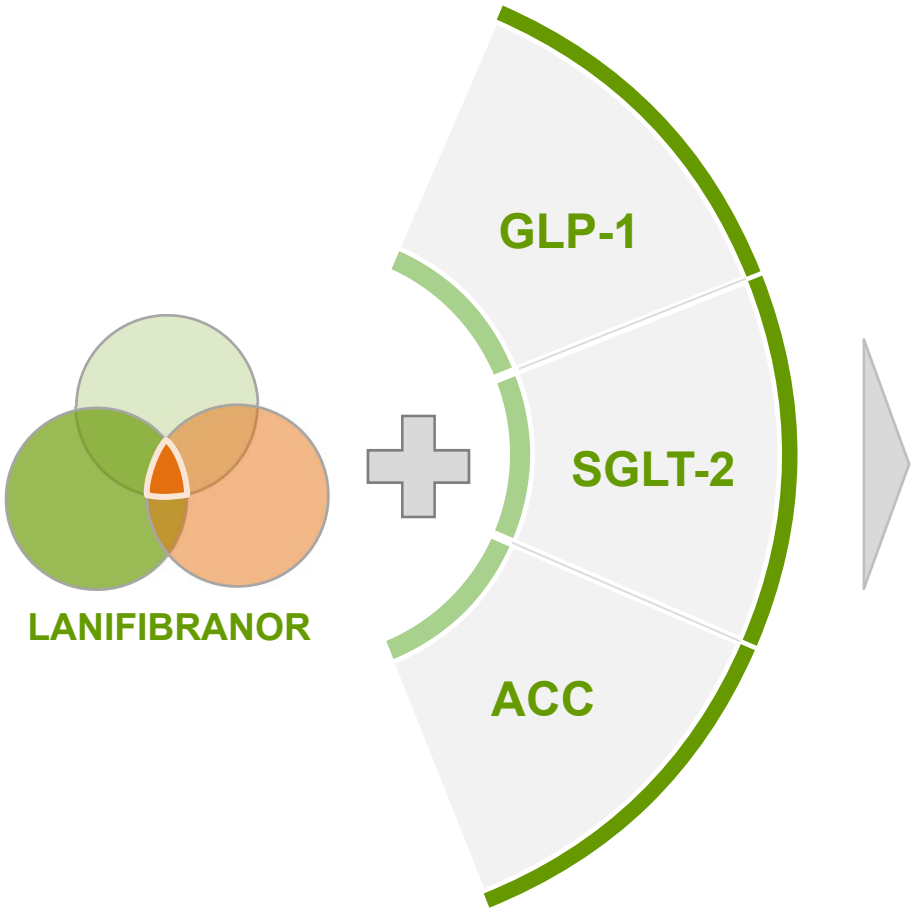
Lanifibranor, 800 mg once daily, 17 patients

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 used in association with other therapies to further strengthen its value proposition

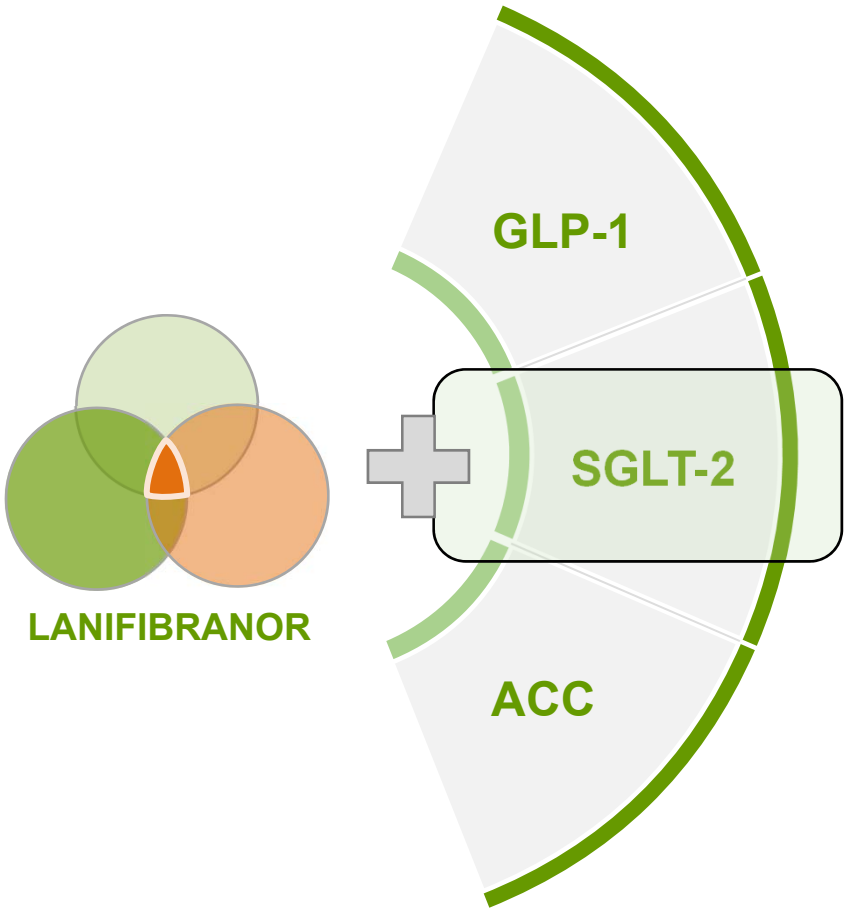
Examples and potential benefits of combination therapies



- **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 association with lanifibranor

Combination of SGLT2 with pioglitazone has shown additional metabolic health benefits and favorable weight management

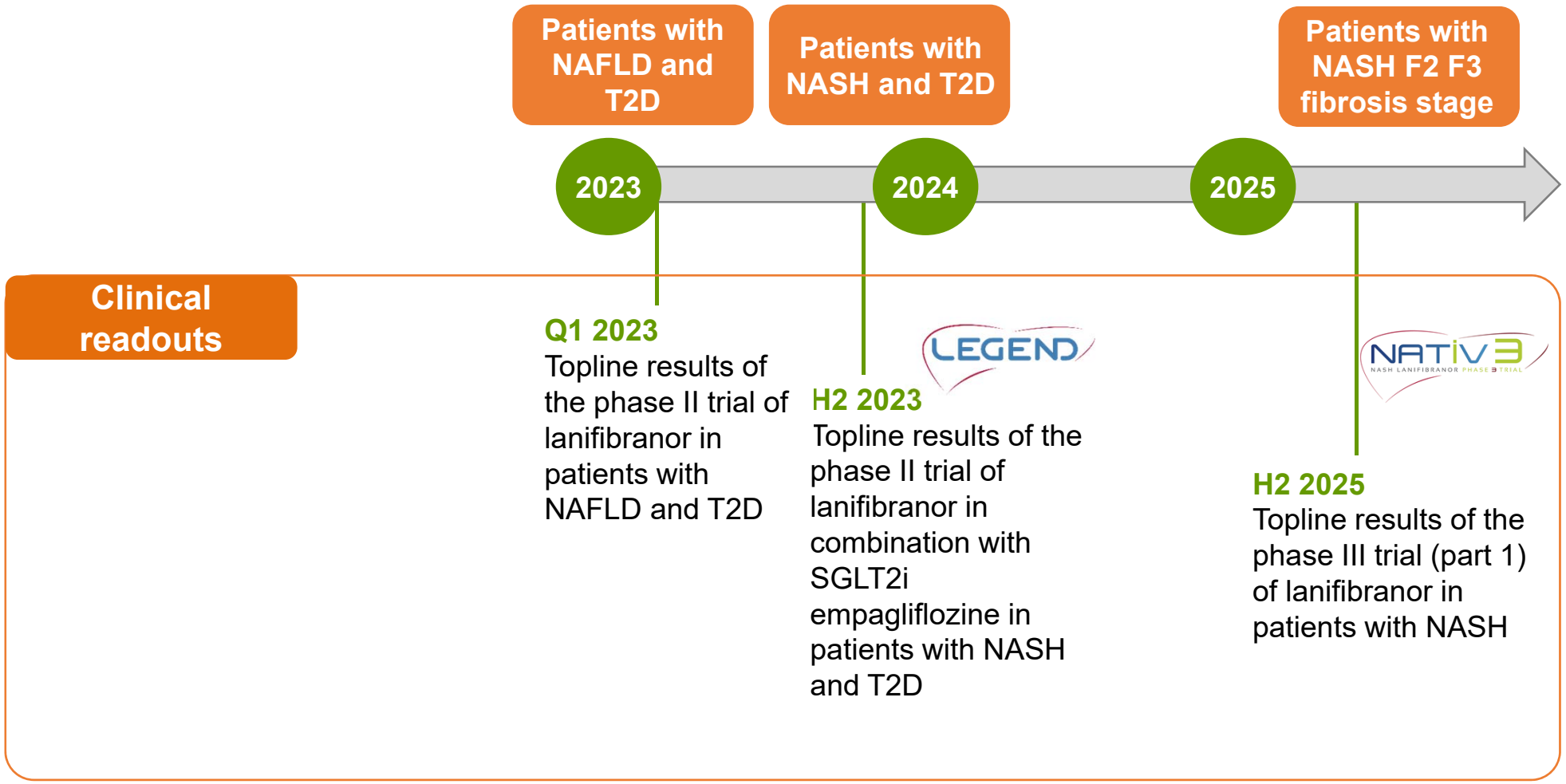
Lanifibranor and SGLT2 rationale



- **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

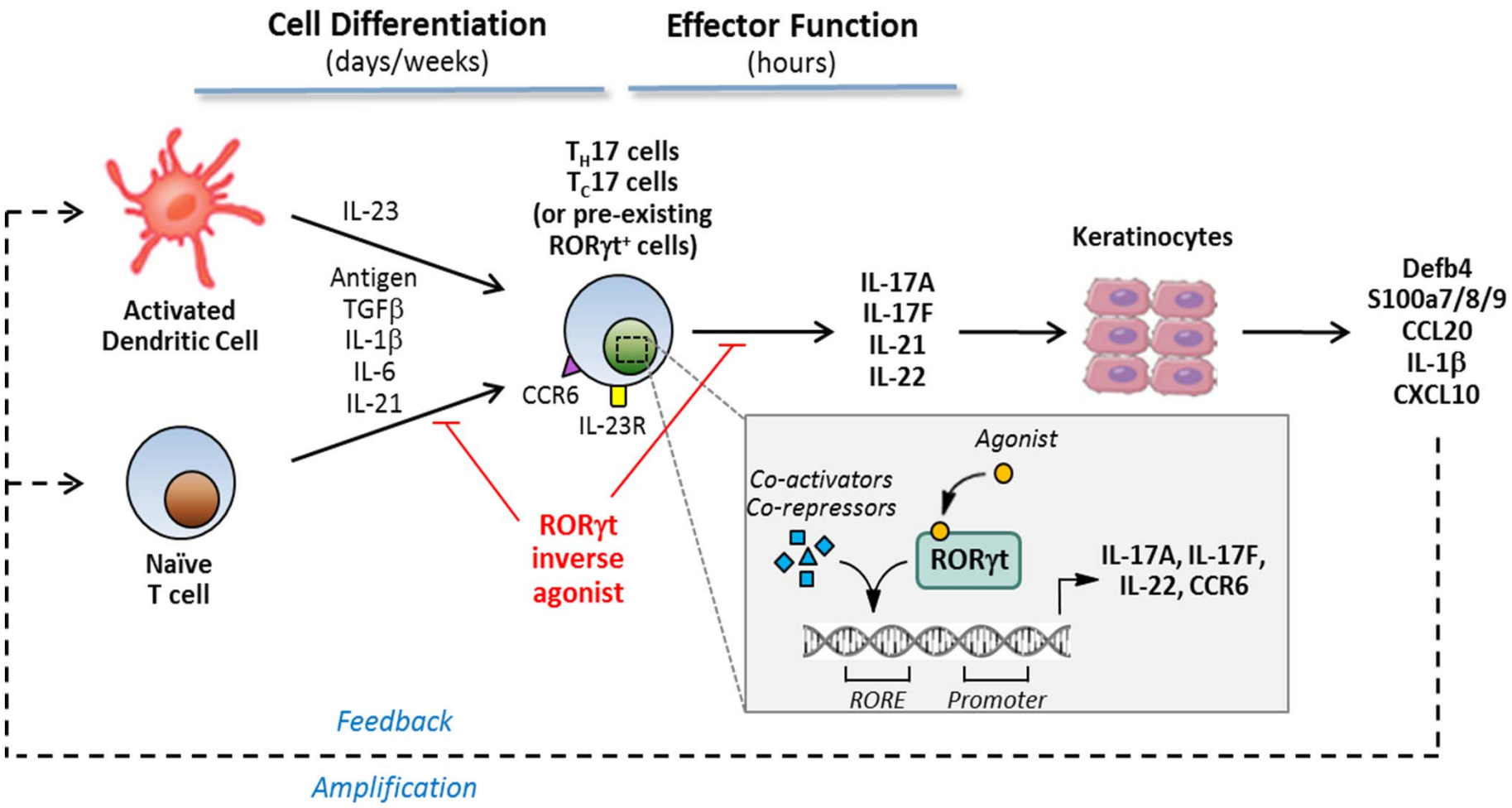
Lanifibranor upcoming clinical readouts

CLINICAL READOUTS



Cedirogant

RORγ controls Th17 cell differentiation and effector function



- The success of anti-IL17 or anti-IL23 biologics in the treatment of psoriasis validates the IL23-IL17 pathway as an important target for therapy

Source: Jetten et al. Nature 2010

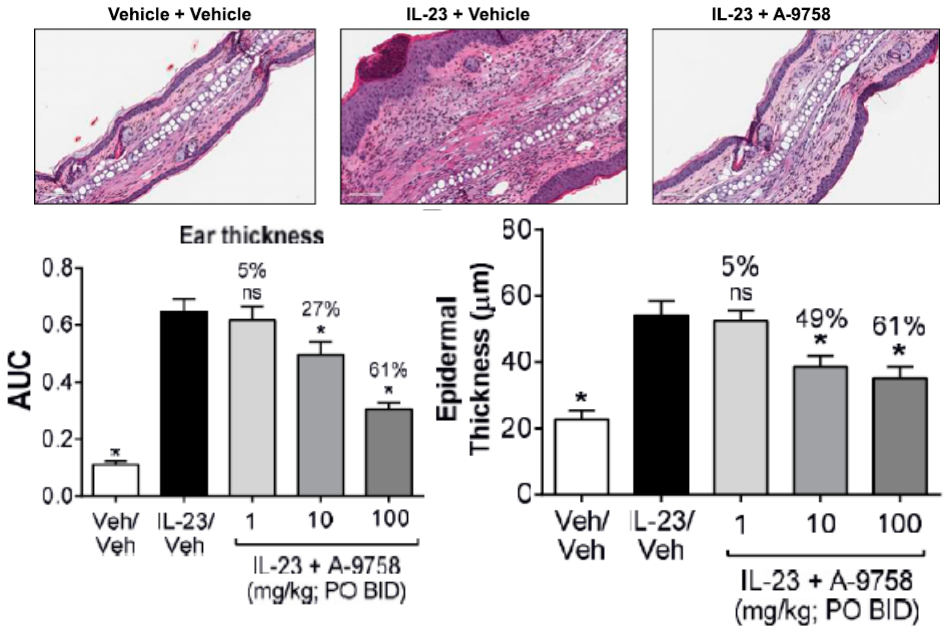
Cedirogant: a clinical stage RORγ inverse agonist with potential in several auto-immune diseases

RORγ is believed to be a master regulator of Th17 differentiation and IL-17 expression, an approach validated by several successful biologics

- Pharmacological inhibition of RORγ by small molecules has been observed **to suppress Th17 production, block cutaneous inflammation in animal models of psoriasis and inhibit TH17 signature gene expression** by cells isolated from psoriatic patient samples
- Potential to more effectively inhibit IL-17 production than antagonist approaches
- RORγ: a **validated drug target** for the treatment of psoriasis and other auto-immune diseases

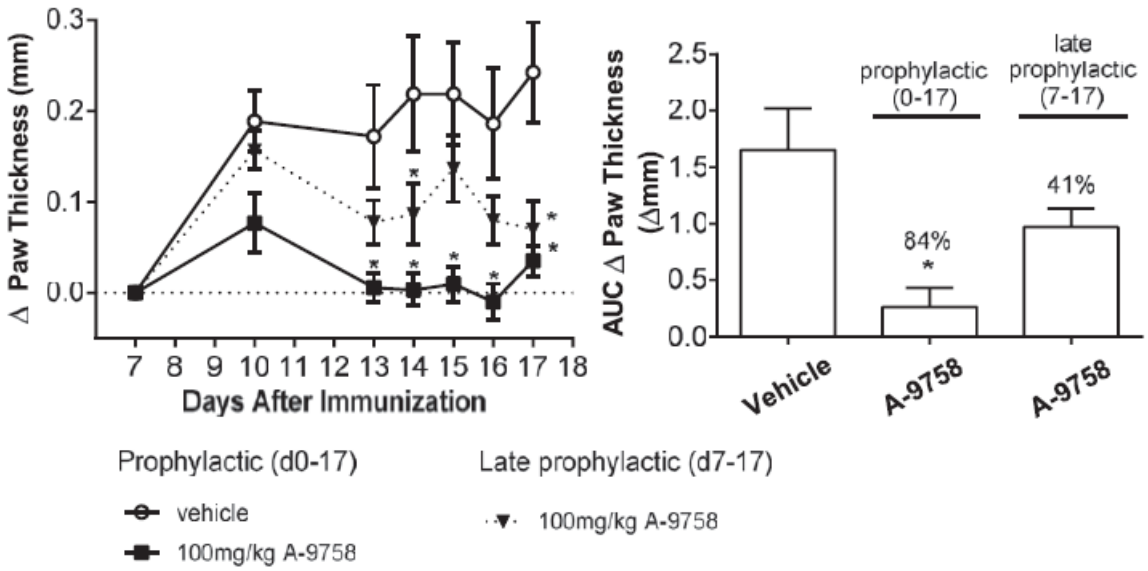
A-9758(1) attenuates IL-23 mediated skin inflammation

Effect of RORγ inhibition on IL-23 mediated psoriasiform dermatitis



A-9758(1) blocks GPI-mediated arthritis

Effect of RORγ inhibition on paw swelling both on prophylactic and late prophylactic treatment



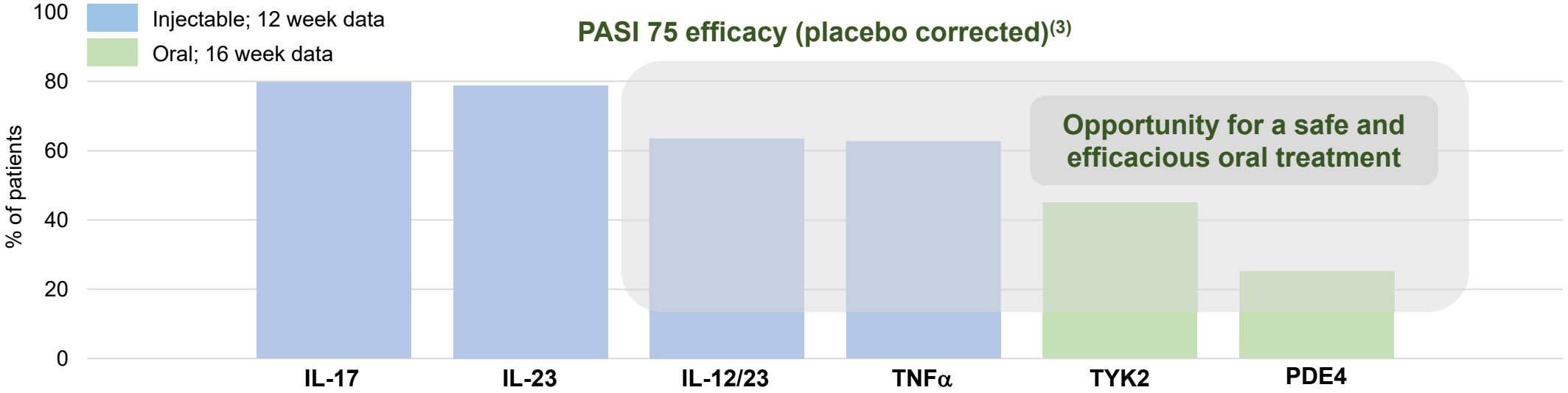
(1) A-9758 is first generation compound developed within the collaboration with AbbVie previously to identifying cedirogant

Source: Inhibition of interleukin-32 mediated inflammation with a novel small molecule inverse agonosit RORγt; The Journal of Pharmacology and Experimental Therapeutics 371:208-218, October 2019

Psoriasis: a $20b global market dominated by injectables

- Psoriasis is a common skin condition that affects 2-4% of the population in western countries with global sales in 2020 of approx. $20b(1)
- The market is dominated by IL-12/23, IL-17 and TNFα which, despite being injectables, account for more than 80% of the market(1)
- Despite an inferior efficacy and safety profile to approved injectables, Otezla (PDE4, oral) generated $2,2b(2) of sales and was acquired by Amgen for $13,4b in 2019

There is space for more efficacious oral drugs in psoriasis

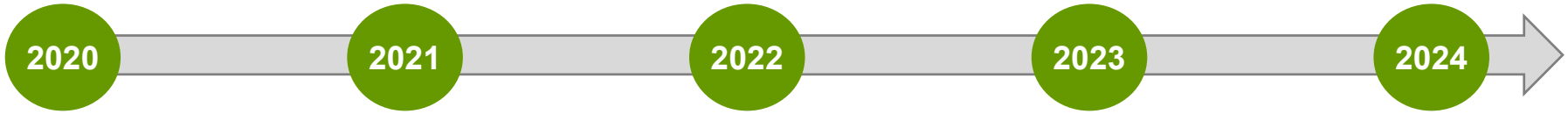


	IL-17	IL-23	IL-12/23	TNFα	TYK2	PDE4
+	• Efficacy • Safety	• Efficacy • Safety • Infrequent dosing	• Safety • Infrequent dosing	• Safety	• Oral • Efficacy vs PDE4	• Oral
−	• Injectable • Frequent dosing	• Injectable	• Injectable	• Injectable • Frequent dosing	• Efficacy • Potential JAK labeling	• Efficacy • GI toxicity

(1) Evaluate Pharma ; (2) 2021 company annual report; (3) Efficacy represents average of PASI-75 in 2 Phase III trials; IL17 trials : FIXTURE and UNDERCOVER 2; IL23 trials ULtIMMa-1 & ULtIMMa-2; TNFα: REVEAL and CHAMPION; IL-12/23 trials: PHOENIX 1 and PHOENIX 2; TYK2 trials: POETYK PSO 1 and POETYK PSO 2; PDE4 trials: ESTEEM 1 and ESTEEM 2

Cedirogant (ABBV-157) is currently evaluated in a Phase IIb trial in adults with moderate to severe psoriasis

- Single ascending dose and multiple ascending dose trials in healthy volunteers completed
- Phase Ib: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of ABBV-157 in Healthy Volunteers and in Subjects With Chronic Plaque Psoriasis
  - 4 week, 65 participants (patients and healthy volunteers)
  - in patients with chronic plaque psoriasis, cedirogant showed promising activity as an oral psoriasis agent
- Phase IIb initiated in November 2021



December 2019
- 3.5 M€ milestone for the inclusion of the first patient with psoriasis in a Phase Ib trial

April 2021
- Phase Ib trial completion date(1)

November 2021
- Launch of phase IIb trial in psoriasis(2)

January 2022
- 4.0 M€ milestone payment for first patient randomized

March 2023
- Trial completion date of phase IIb trial in psoriasis(2)

"In our Phase Ib study, 157 showed promising activity as an oral psoriasis agent and we plan to move the asset forward to a larger Phase IIb dose-ranging study in the second half of this year … with respect to oral psoriasis agents, we would want to come in from an efficacy perspective with something that clearly exceeded the threshold that existed in the past with Otezla ... we'd be looking for that Humira-like efficacy or greater as something that we would like to use to enter the space within oral, obviously, coupled with a strong safety profile."

Dr. Michael Severino AbbVie Vice Chairman and President(3)

ABBV-157 is Cedirogant AbbVie code; (1) Source clinicaltrials.gov NCT03922607; (2) Source clinicaltrials.gov NCT05044234; (3) AbbVie Q1 2021 earnings call April 30 2021 9 AM ET; Transcript from FactSet

Cedirogant Phase IIb in adults with moderate to severe psoriasis

A Phase IIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of Cedirogant (ABBV-157) in Adult Subjects With Moderate to Severe Psoriasis

Status

- Sponsor: **AbbVie**
- ClinicalTrials.gov Identifier: NCT05044234
- Approx. 200 adult participants with moderate to severe plaque psoriasis will be enrolled at approx. 55 sites
- Estimated study start date: **November, 2021**
- Estimated study completion date: **March, 2023**

Inclusion criteria

- Participants with stable moderate to severe plaque psoriasis of at least 6 months duration and who are candidates for systemic therapy or phototherapy

Primary outcome measures

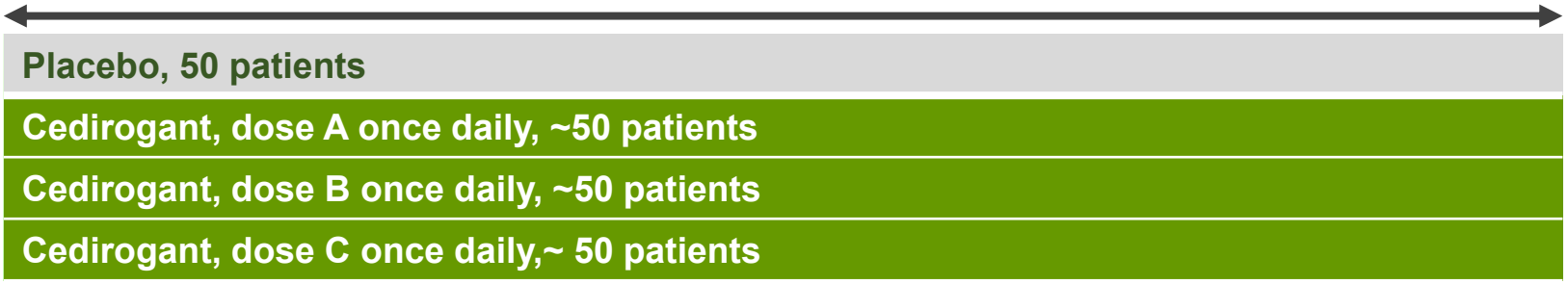
- Percentage of participants achieving >=75% reduction from baseline in Psoriasis Area Severity Index(1) (PASI) score (PASI 75)

Secondary outcome measures

- Percentage of participants achieving a Static Physician Global Assessment(2) (sPGA) score of clear or almost clear
- Percentage of participants achieving >=50% / >=90% / 100% reduction from baseline in PASI Score (PASI 50; PASI 90; PASI 100)
- Percentage of participants achieving Psoriasis Symptoms Scale(3) (PSS) total score of 0 for participants with PSS >0 at baseline
- Percentage of participants achieving an Itch Numerical Rating Scale(4) (NRS) >=4 point improvement from baseline for participants with Itch NRS >=4 at baseline

200 patients / 16 week treatment / ~45 sites

Double blind randomized placebo controlled



(1) The PASI is a tool that provides a numeric scoring for participants' overall psoriasis disease state, ranging from 0 to 72, with a higher score indicating more severe disease; (2) The sPGA is a 5-point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. A lower score indicates less body coverage, with 0 being clear and 1 being almost clear; (3) The PSS is a 4-item patient-reported outcome instrument that assesses the severity of psoriasis symptoms in patients with moderate to severe psoriasis. Current symptom severity is assessed using a 5-point Likert-type scale ranging from 0 (none) to 4 (very severe); (4) The Itch NRS is an 11-point scale that participants complete daily to describe the intensity of their itch using a 24-hour recall period. Scores vary between 0, representing "no itching" and 10, representing "worst itch imaginable

Source: clinicaltrials.gov

RORγ competitive landscape

Product name	Company	Development Phase	Comments
Cedirogant	abbvie	**Phase 2**	**Oral once daily**
Bevurogant	Boehringer Ingelheim	Phase 2	Program not mentioned anymore in BI annual report
AUR-101	AURIGENE Accelerating Discovery	Phase 2	Twice daily
JTE-451	JTI JAPAN TOBACCO INTERNATIONAL	Phase 2	Results posted on clinicaltrials.gov do not meet target product profile
IMU-935	Immunic THERAPEUTICS	Phase 1	Once daily and twice daily in MAD phase I Early

Source: Companies web sites; clinicaltrials.gov

Cedirogant royalties have the potential to be an important source of revenues

- Cedirogant potential profile: **Humira (TNFα) in a pill + better safety**
- Inventiva eligible to receive development, regulatory, commercial milestones and **tiered royalties from the mid-single to low-double digits**
- **Composition of matter patent** filed in June 2016 and approved in October 2018
- Cedirogant is targeting indications where competitors have reached block-buster status

Brand	Company	Target	Posology	2021 sales[1]
HUMIRA adalimumab	AbbVie	Anti-TNFα	Injectable	$20,7b
Stelara (ustekinumab)	J&J	IL-12/23	Injectable	$9,1b
Cosentyx (secukinumab)	Novartis	IL-17A	Injectable	$4,7b
Skyrizi (risankizumab) injection	AbbVie / BI	IL-23	Injectable	$2,9b
Otezla (apremilast) tablets	Celgene / Amgen	PDE4	Oral	$2,2b
taltz (ixekizumab) injection	Eli Lilly	IL-17A	Injectable	$2,2b

(1) Company Q1 2022 and full year 2021 press releases; Note : sales include other indications such as psoriatic arthritis, ankylosing spondylitis, rheumatic arthritis,…

Odiparcil – MPS

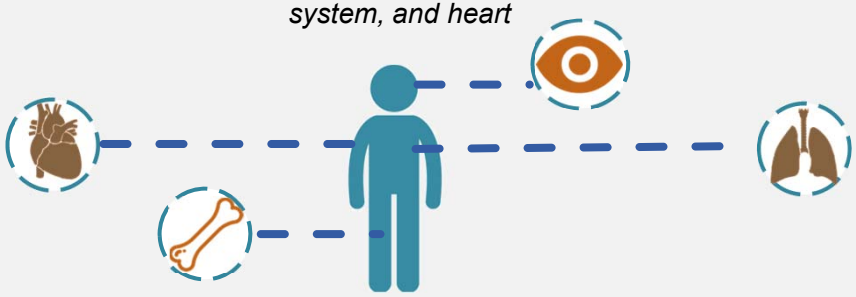
MPS VI is a devastating rare lysosomal storage disorder

Rare, Hereditary Lysosomal Storage Disorder

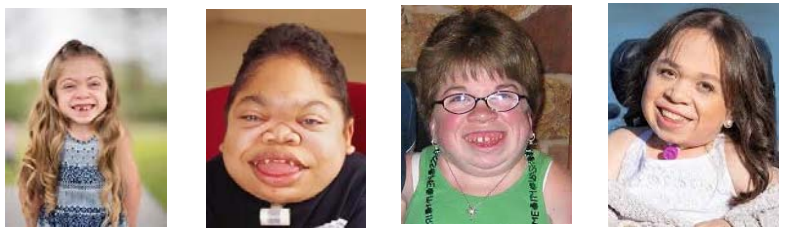
- Mucopolysaccharidoses (MPS) is an inherited disorder characterized by the absence of lysosomal enzymes required for the breakdown of glycosaminoglycans (GAGs)
- MPS VI pathogenesis is caused by mutations in the ARSB gene encoding the enzyme arylsulfatase B leading to dermatan sulfate (DS) and chondroitin 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

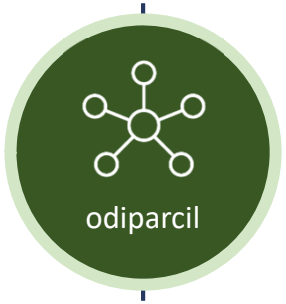
Source: H. Noh, J. I. Lee; Current and potential therapeutic strategies for mucopolysaccharidoses; Journal of Clinical Pharmacy

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

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

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

Summary of key data generated to date



- 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 well-tolerated in MPS VI patients and in 1000s of patients previously tested
- 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

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
- Ameliorate established disease
- Could potentially improve quality of life

Odiparcil is supported by a robust preclinical and clinical data package

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 therapy 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 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

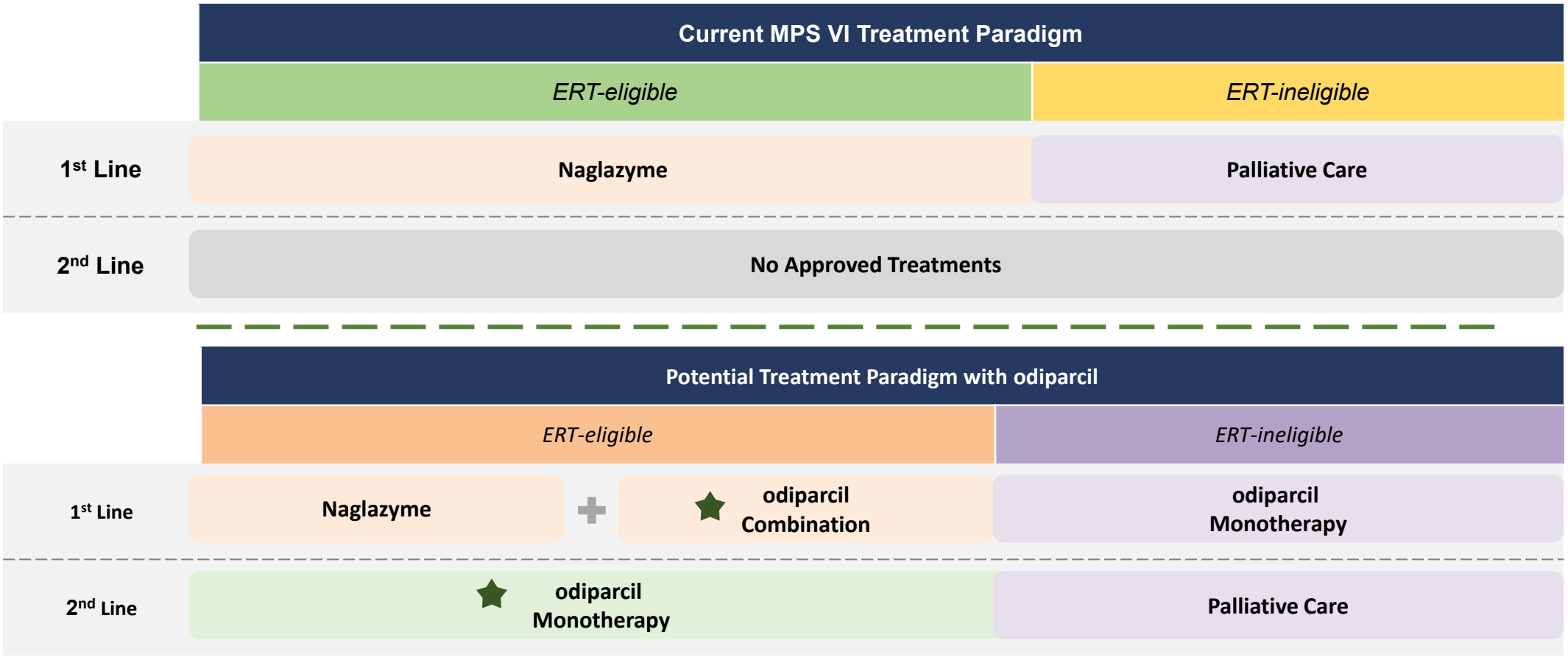
Activity in Developed & Established Disease MPS VI Models

If approved eligible to Receive US Rare Pediatric Voucher

(1) Biomarin Full year 2021 press-release

MPS VI treatment paradigm

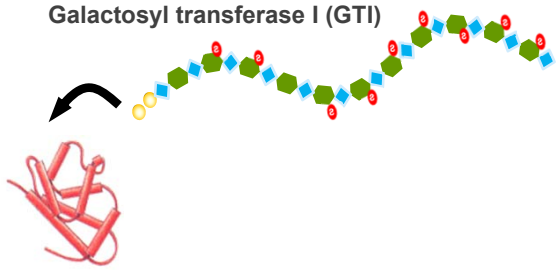
Odiparcil aims at improving the treatment options for both ERT eligible and ineligible patients



Differentiated mechanism of action potentially synergistic with ERT

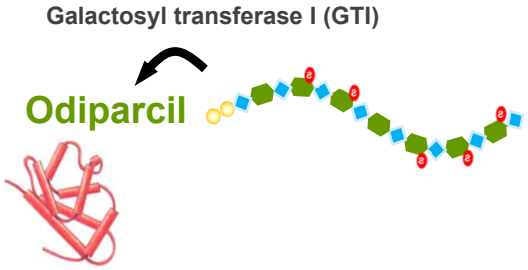
Odiparcil acts to divert endogenous protein-bound GAG synthesis to soluble odiparcil-bound chondroitin sulfate (CS) and dermatan sulfate (DS) synthesis

Synthesis of proteoglycans (HS, CS, DS)



GTI activity

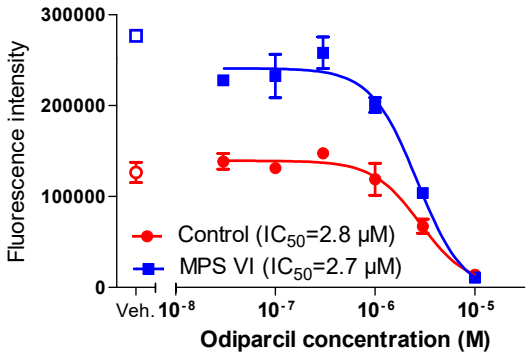
Substrate	Vm/Km
D-xylose	0.8
Odiparcil	1857

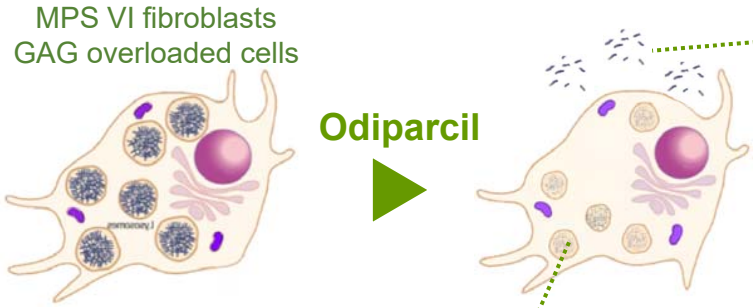


Synthesis of soluble DS and CS

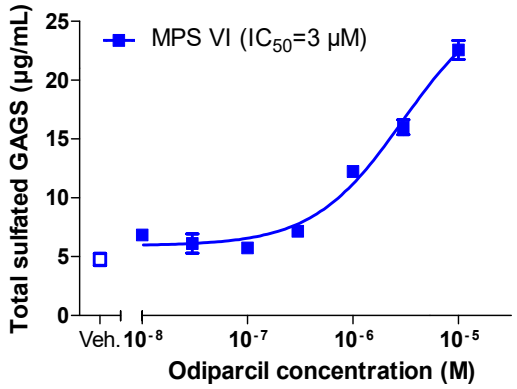
Odiparcil and intracellular GAG accumulation *in vitro* in MPS VI patient cells

Intracellular CS storage





Extracellular GAG



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

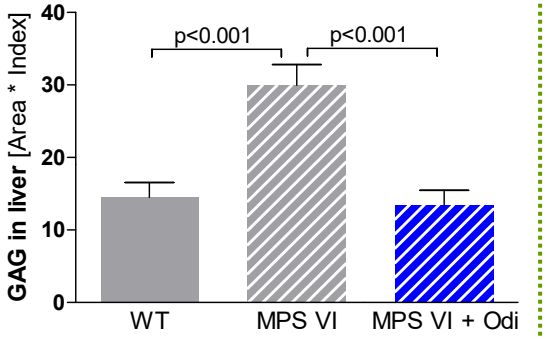
Odiparcil mechanism of action potentially relevant to MPS subtypes with excess DS and CS

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	✓	✓	✓	

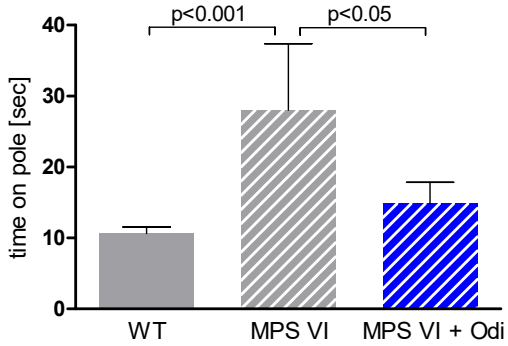
Source:Rheumatology 2011 Therapy for mucopolysaccharodises; Vassili Valayannopoulos and Frits A. Wijburg; (1) Heparan Sulfate; (2) Keratan Sulfate

Odiparcil GAG clearance mechanism of action observed in MPS VI mice

Odiparcil and GAG accumulation in livers tissues

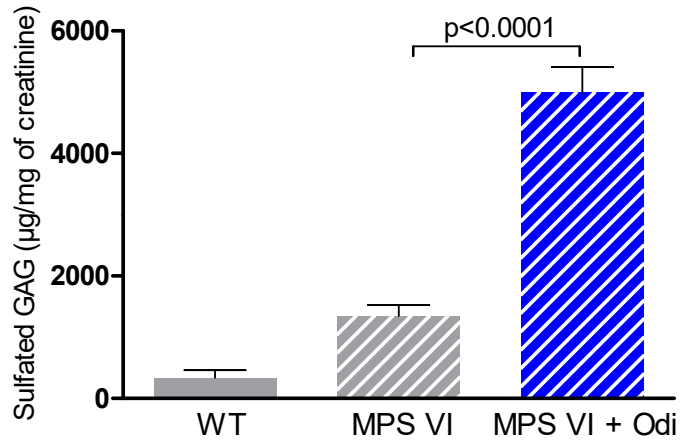


Odiparcil and animal mobility



Wild-type and MPS VI mice

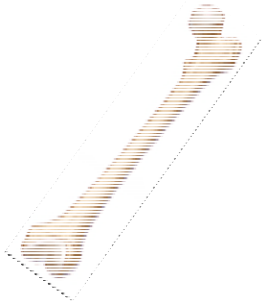
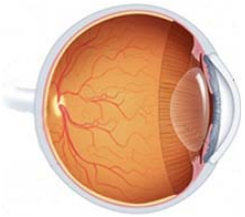
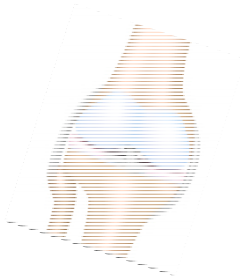
Soluble GAGs produced from odiparcil are excreted in urine



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

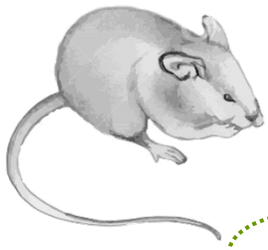
	Heart	Bone	Cornea	Cartilage
				
Odiparcil[1]	✓	✓	✓	✓
rhASB[2]	✓	**Not tested**	**Not detected**	**Not detected**

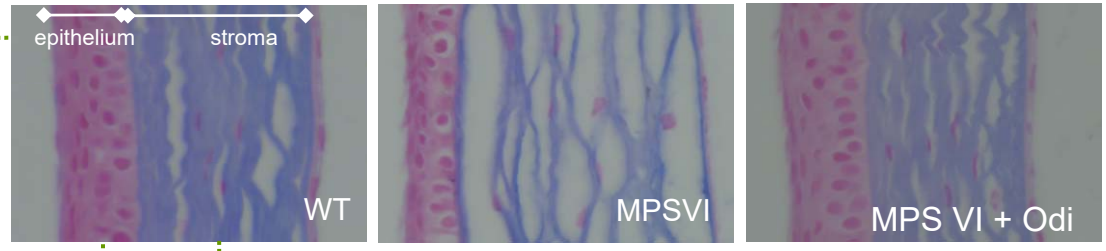
Meaningful concentrations of odiparcil observed in tissues that are poorly vascularized or protected by a barrier: bone, corneal tissue and cartilage

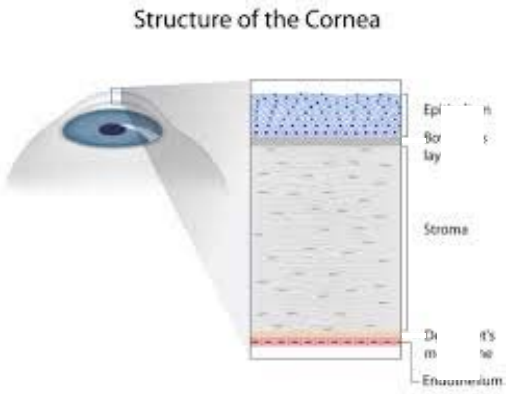
Source: (1) Odiparcil: tissue distribution following 25mg/kg oral administration , TID for 5 days; (2) Recombinant human ARB: Expressed as ratio of ARSB enzyme activity in the liver in MPS VI cats after repeat infusion (conditions: preliminary trial, Trial A and Trial B from Auclair et al. 2003)

Odiparcil reverses corneal impairment in MPS VI mice

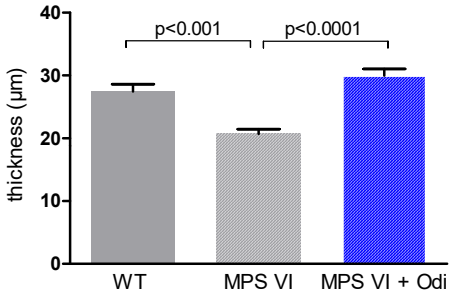
Odiparcil administration observed to affect corneal structure and corneal GAG storage





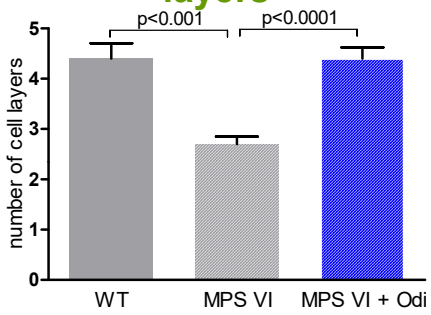


Odiparcil effect on corneal epithelium thickness



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

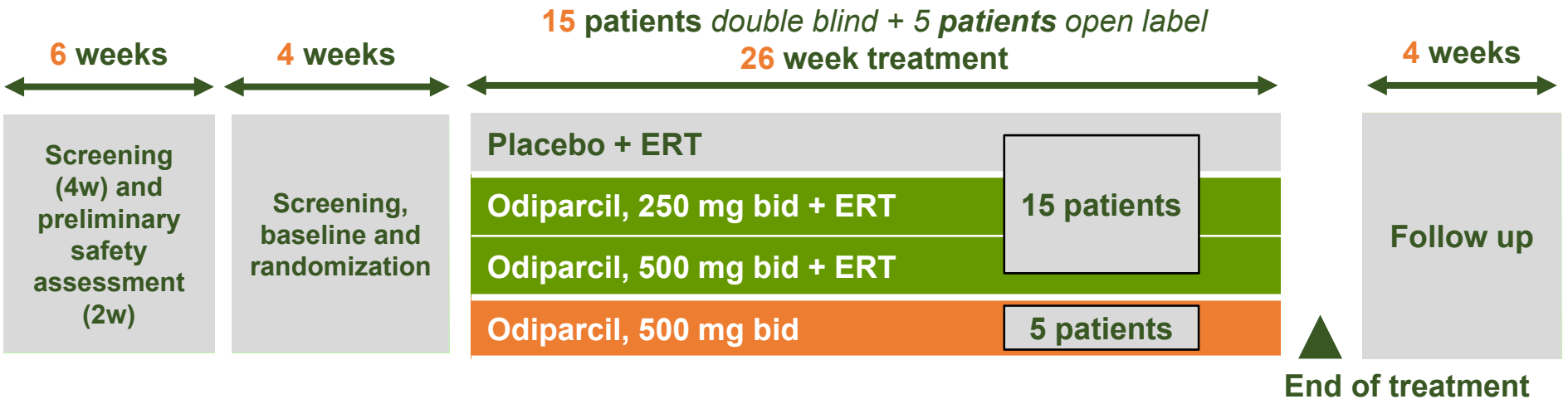
iMProveS Phase IIa trial of odiparcil in MPS VI

Phase IIa

- Safety and efficacy trial with evidence for dose selection and PK / PD response characterization
- **Clinicaltrials.gov identifier:** NCT03370653

Population

≥ 16yo



Endpoints

Safety

- Clinical and biological assessments (standard tests)

Pharmacokinetics

- Odiparcil plasma levels

Efficacy

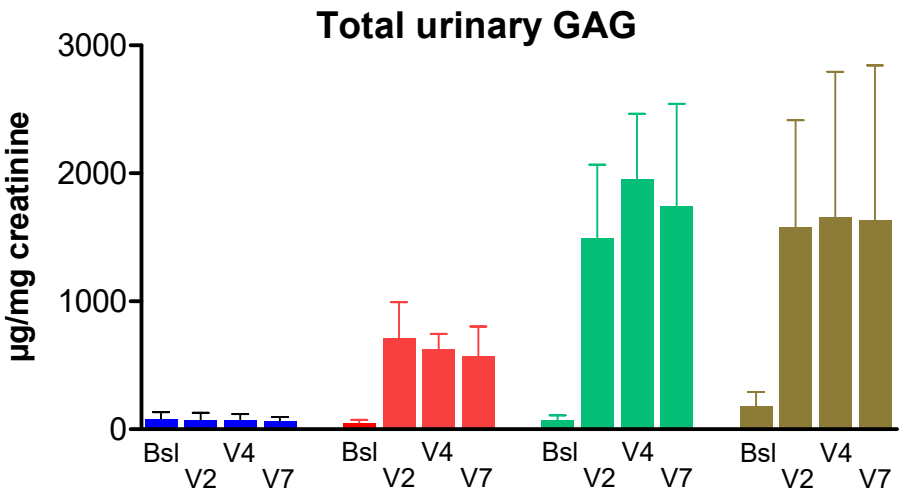
- Leukocyte, skin and urinary GAG content
- Activity and mobility tests (6 minute walk test, upper limb function, shoulder mobility range)
- Cardiac, vascular and respiratory functions
- Eye impairment, hearing capacity, pain assessment, quality of life questionnaires

Safety data

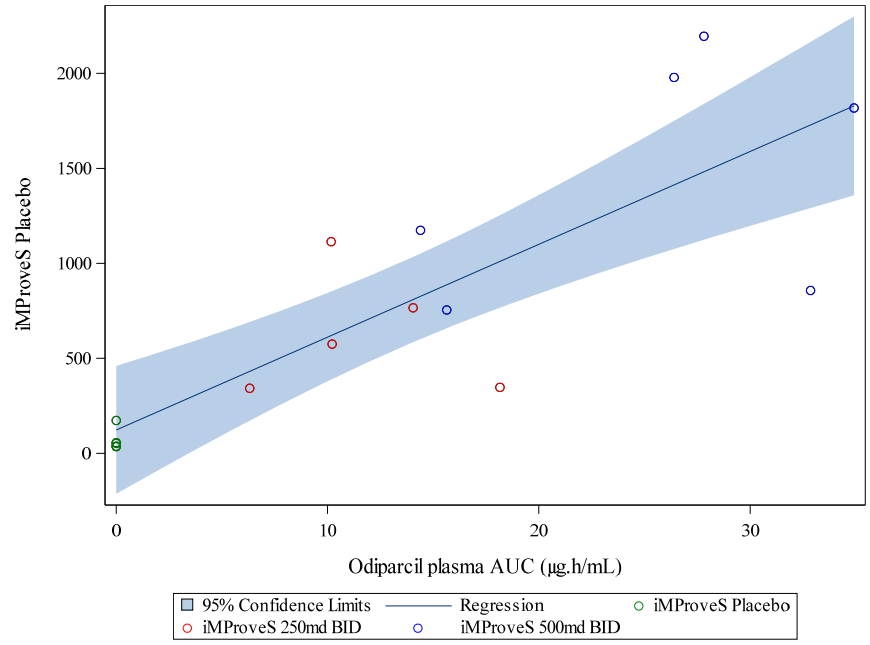
- The **clinical trial met its safety primary endpoint with a favourable tolerability profile consistent with that** observed in previous Phase I and Phase II clinical trials
- The majority of adverse events were **mild or moderate**
- One death occurred in the placebo group
- Three serious adverse events (SAEs) were assessed as treatment-related in patients in the odiparcil groups.
  - Two SAEs were biological findings qualified as laboratory false-positive
  - One SAE was a skin reaction, which is frequently observed in MPS patients treated with ERT
- Compared to previous Phase I and II clinical trials conducted with odiparcil in another indication, **no new safety conclusions were drawn**

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

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



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



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

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

- The PK profile in MPS VI patients treated with odiparcil is not observed to be impacted by ERT and is consistent with profiles previously observed in other Phase I and Phase II trials in another indication

Efficacy endpoints

iMProveS
IMPROVE MPS TREATMENT

Partially addressed by ERT

Endurance and mobility

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

Respiratory function

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

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

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

Cardiac and vascular system

- ECG, Echocardiogram
- Carotid intima media thickness (CIMT)

Ophthalmology

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

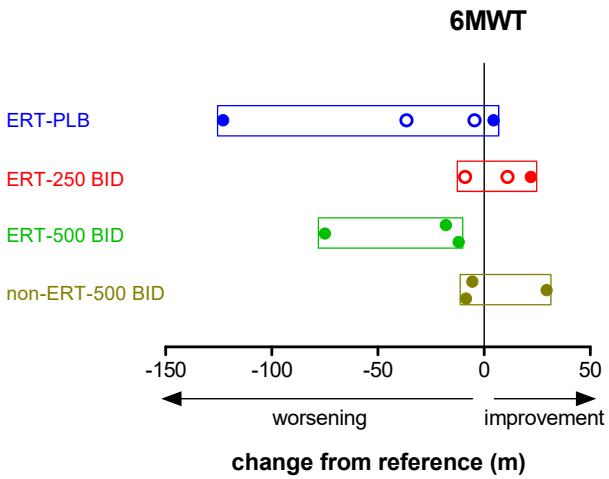
Pain assessment

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

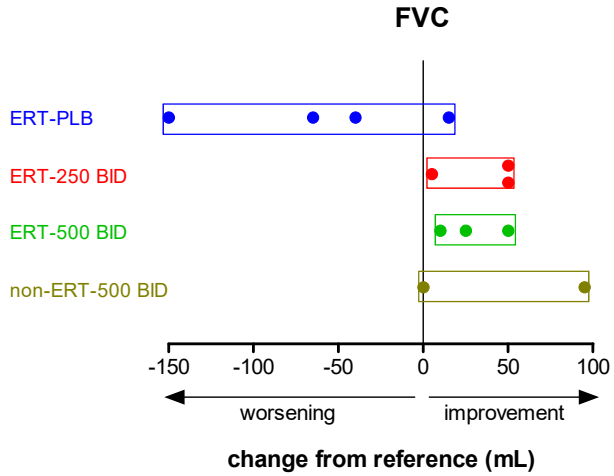
Audiology

- Pure tone audiometry (PTA)

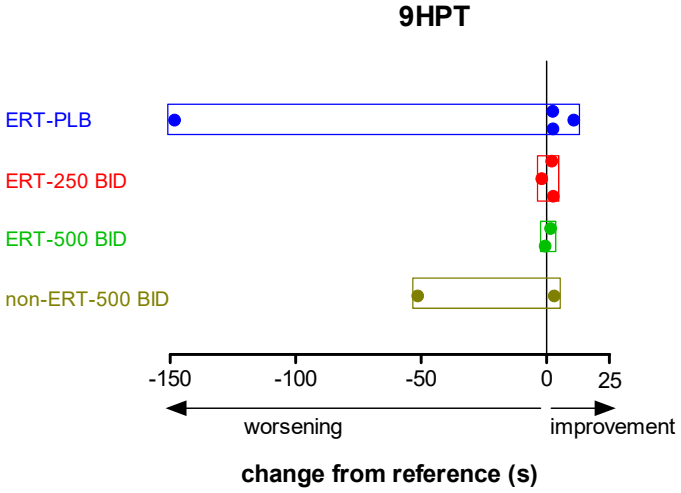
Efficacy data: trends of improvement on 6MWT and FVC

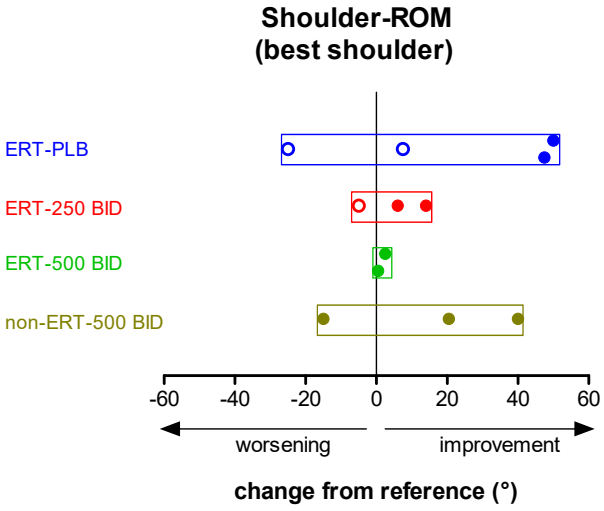


Trends of improvement in ERT-250 BID and non-ERT-500 BID compared to ERT-placebo



Improvement in all odiparcil treated groups compared to ERT-placebo





No significant differences between groups observed

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

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

(1) Patient presenting a CIMT reduction in both carotids
(2) Corneal transplant of the other eye
LVMI: left ventricular mass index (echocardiogram); CIMT: carotida intima media thickness

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

Odiparcil 500mg Bid (N=3)	Respiratory (FVC)	Ophthalmology	Cardiology	Range of Motion	Other
Patient H	Improved FVC by +18%	NA	Stable	Improved range of motion on both shoulders (+17.8%/+21.0%)	Pain improved
Patient I	Stable	Stable	Slightly Worsened	Improved range of motion on both shoulders (+8.1%/+8.5%)	Pain improved
Patient J • Severe patient hospitalized • Poor compliance	NA	Stable	Worsening	Worsening	Pain improved

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 Awarded	✓ 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 odiparcil 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 development of 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 Q1 2023**
- ▶ Topline results of Phase II of lanifibranor in combination with empagliflozine 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

Cedirogant

abbvie

- ☑ Clinical POC trial (Phase IB) in psoriasis
- ☑ Launch of phase IIB trial in psoriasis and milestone from AbbVie
- ▶ Results of Phase IIb – **anticipated H1 2023**

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