inventiva

Developing breakthrough therapies in NASH, systemic sclerosis and mucopolysaccharidosis (MPS)

Wainwright 2018 Healthcare Conference

September 2018

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A clinical stage biopharma with a focus on fibrosis

State of the art R&D capabilities	▶ Fournier/Solvay and Abbott spin-off in 2012 ▶ State of the art owned 12,000 m² R&D facility and a library of ~240,000 compounds ▶ Solid portfolio of patents: 11 families approved
Leading technology in gene-modulation	▶ Expert in gene-modulation (nuclear receptors, transcription factors, epigenetic targets) ▶ Large fibrosis expertise ▶ Promising and innovative preclinical pipeline in oncology
Three innovative clinical programs	▶ **Lanifibranor NASH:** phase IIb enrolling since February 2017. Results expected second-half 2019 • NASH market potential: $35-40bn(1) ▶ **Lanifibranor Diffuse Cutaneous Systemic Sclerosis:** phase IIb enrollment completed in October 2017. Results expected early-2019. • SSc market potential: > €1.8bn(2) ▶ **Odiparcil MPS VI:** biomarker study finalized and Phase IIa study initiated. Results expected first semester 2019.
Two royalty bearing collaborations	▶ **AbbVie:** Multi-year collaboration on RORγ. Inventiva eligible to research funding, milestone payments and royalties ▶ **BI:** collaboration in Idiopathic Pulmonary Fibrosis (IPF). Inventiva eligible to research funding, and up to 170M€ in milestones plus royalties on sales

Source: (1) Deutsche Bank Markets Research 2014; (2) Venture Valuation 2015.

Strong cash position and shareholder base

Key financials

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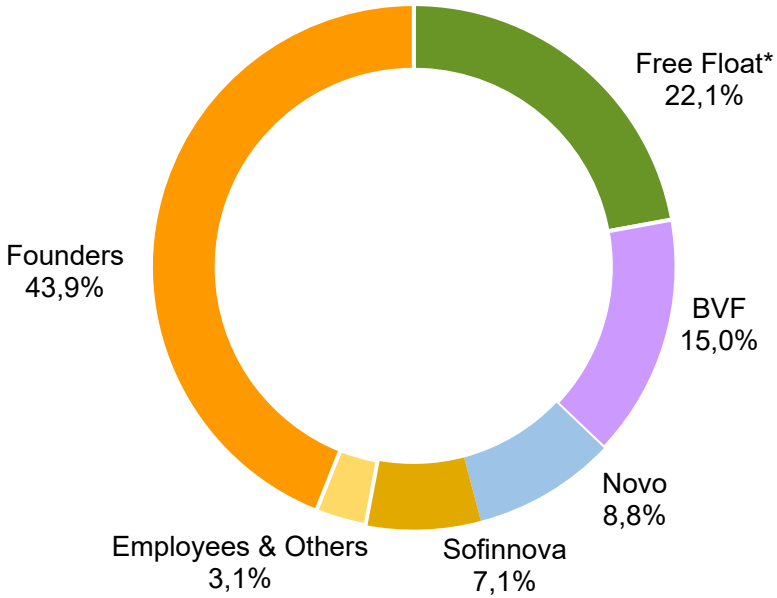
ELIGIBLE PEA PME

ISIN code	FR0013233012
Market	Euronext Paris
Shares outstanding	22,257,277
Market cap (August 27 2018)	€197m
Cash position (June 30 2018)	€75,9m compared to €59,0m in December 2017. Successful €48.5m Euronext IPO (February 2017) and €35,5m private placement (April 2018)
Revenues in 2017 (31 December 2017)	€6.5m (including €2.5m from Boehringer Ingelheim) compared to €9.4m in 2016
R&D expenditures in 2017 (31 December 2017)	€26.7m compared to €22.1m in 2016

Shareholder base



Including Perceptive Advisors

Analyst Coverage

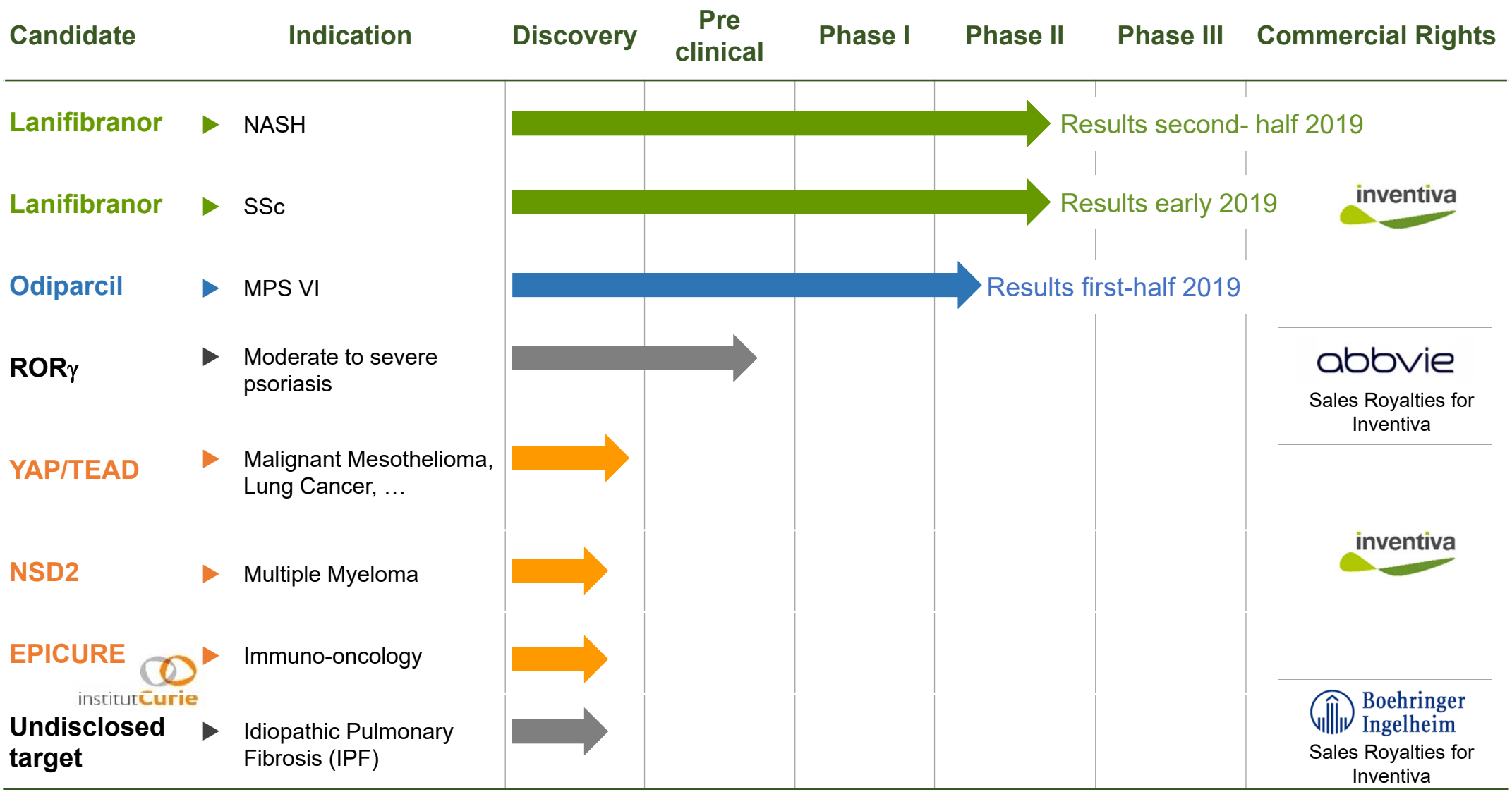
SOCIETE GENERALE Corporate & Investment Banking

GILBERT DUPONT

KBC

LIFESCI CAPITAL

Large pipeline reaching major inflection points

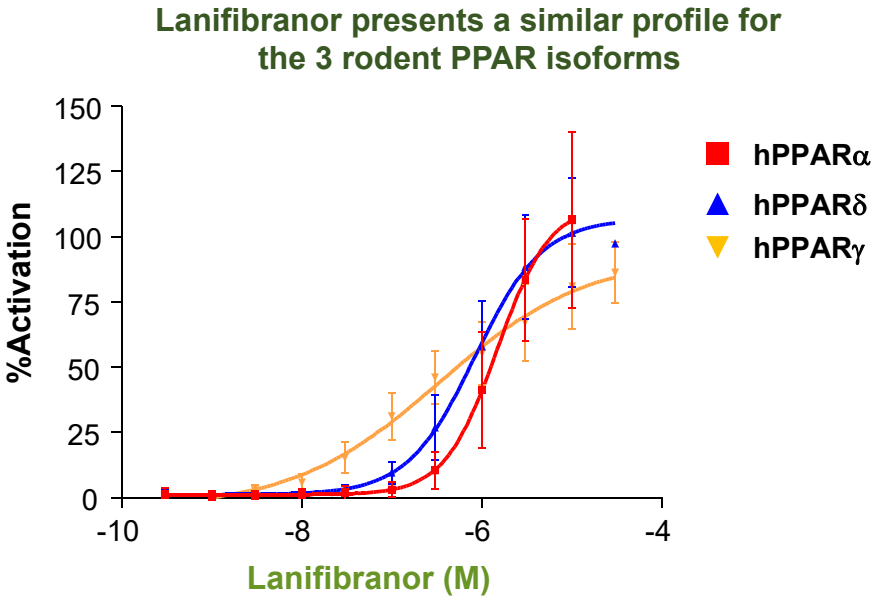


Lanifibranor NASH and SSc

A new generation pan-PPAR agonist for a safe and efficacious treatment of fibrotic conditions

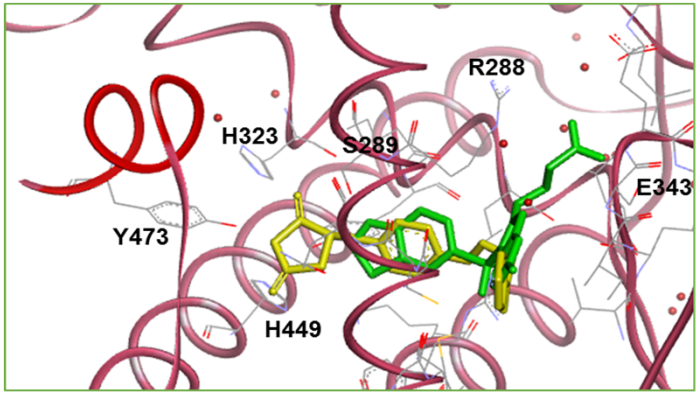
Lanifibranor: a next generation panPPAR with moderate and well balanced activity on the 3 PPAR isoforms

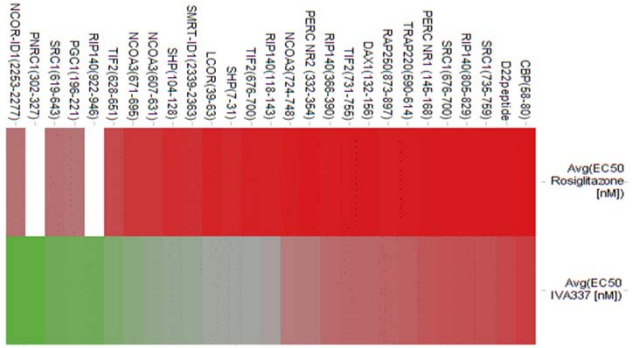
Lanifibranor (formerly IVA337) dose response curves and EC50s for hPPARs (nM)



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

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





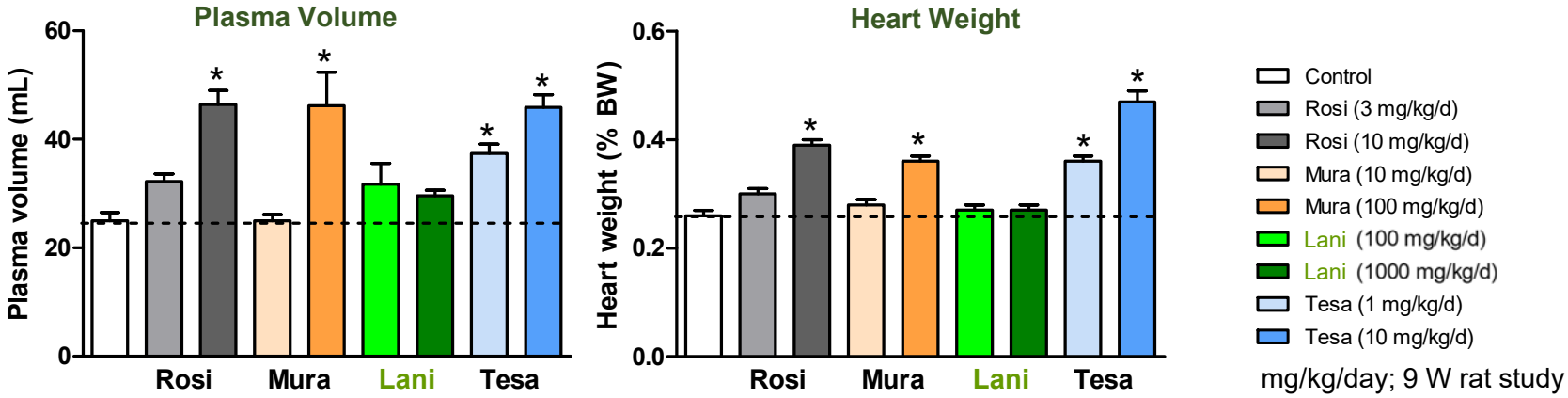
Potency scale: red 10 nM; grey: 500 nM; green 5 000 nM

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

A favorable safety profile differing from previously developed PPARs

Organ	Molecule	Reported PPAR liabilities	Lanifibranor effects	No Observed Adverse Effect Level (NOAEL)
Heart	▶ Glitazone	▶ Fluid retention ▶ Cardiac hypertrophy	Not observed	1000 mg/kg in rodents and primates 26w study
Skeletal muscle	▶ Fibrate	▶ Myofiber degeneration	Not observed	
Kidney	▶ Fibrate	▶ > 50% increases in creatinine, Degenerative changes in renal tubules	Not observed	625 mg/kg in primates 52w study
Urinary bladder	▶ Glitazone	▶ Proliferative changes in bladder epithelium	Not observed	

Contrasting with other PPARγ agonists , lanifibranor does not produce plasma volume expansion



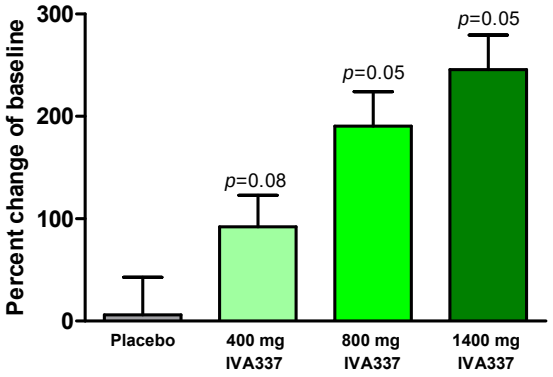
Source: Company data.

Phase I and Phase IIa clinical studies confirmed lanifibranor safety and efficacy on key metabolic markers

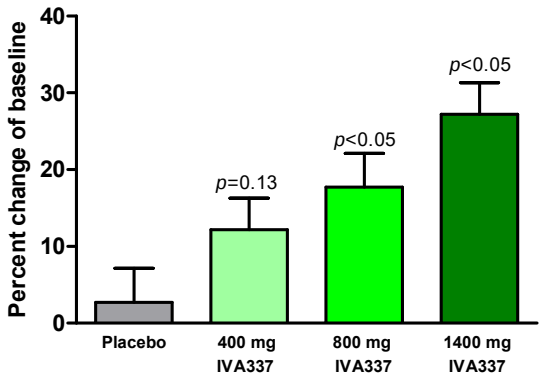
Lanifibranor (IVA337) significantly improves metabolic markers in type II diabetic patients

- Insulin resistance (HOMA-IR, adiponectin)
- Dyslipidemia (increase in HDL-C, reduction of TG)

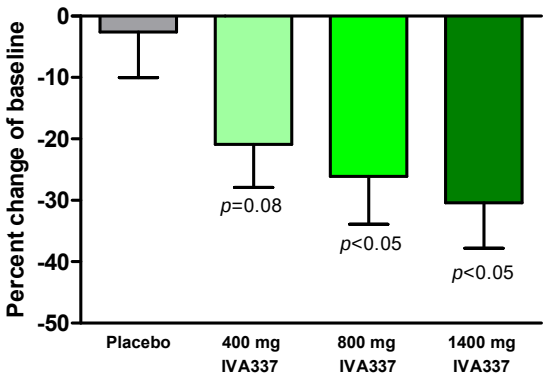
Adiponectin (PPARγ)



HDL Cholesterol (PPARα/δ)



Triglycerides (PPARα/δ)



Clinical findings underline the favorable tolerability of lanifibranor

- 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 hemodilution
- No clinically relevant weight gain

*Source: Company data and * Ohashi, Endocr Metab Immune Disord Drug Targets. 2015.*

Lanifibranor: a mechanism of action addressing all the key features of NASH

PPARα,γ

Metabolism

- Insulin sensitivity
- HDLc
- TG

PPARα,γ

Steatosis

- FA uptake
- FA catabolism
- Lipogenesis

Lanifibranor

Moderate and balanced panPPAR agonist activity regulating genes in:

- PPARα: hepatocytes
- PPARδ: kuppfer cells
- PPARγ: hepatic stellate cells

PPARα,δ,γ

Necroinflammation

- NFkB-dependent gene activation
- Inflammasome
- Ballooning

PPARγ

Fibrosis

- Stellate cell proliferation and activation
- Collagen and fibronectin production

NATIVE Phase IIb in NASH

Trial design

Principal investigator

- Pr Francque (Universitair Ziekenhuis, Antwerpen, Belgium)

Status

- Trial enrolling
- Results expected second half 2019

Randomisation

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

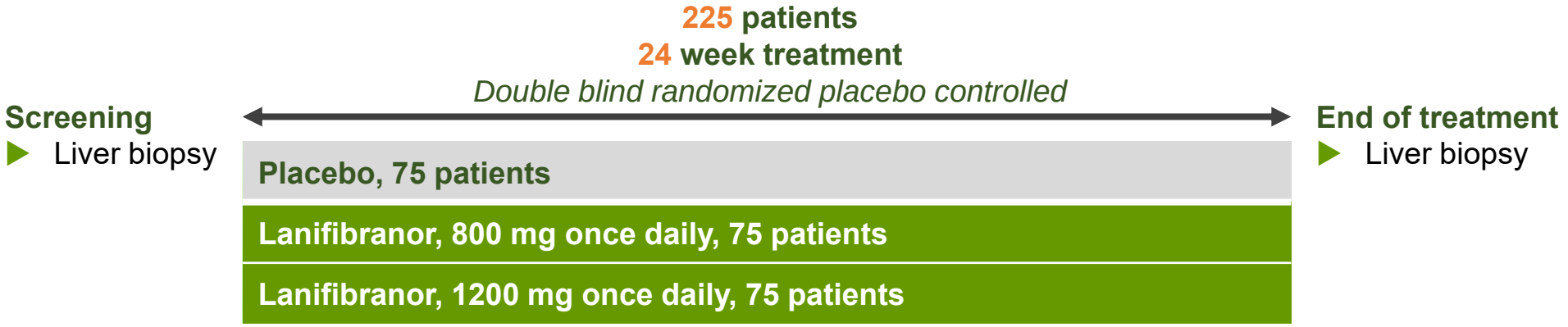
Inclusion criteria

- Liver biopsy
- Moderate to severe patients with a inflammation and ballooning score of 3 or 4
- Steatosis score ≥ 1 and fibrosis score < 4 (no cirrhosis)

Primary endpoint

- Decrease from baseline ≥ 2 points of the inflammation and ballooning score without worsening of fibrosis
- Central reading for pre- (before randomization) and post treatment biopsy

Clinicaltrials.gov identifier: NCT03008070



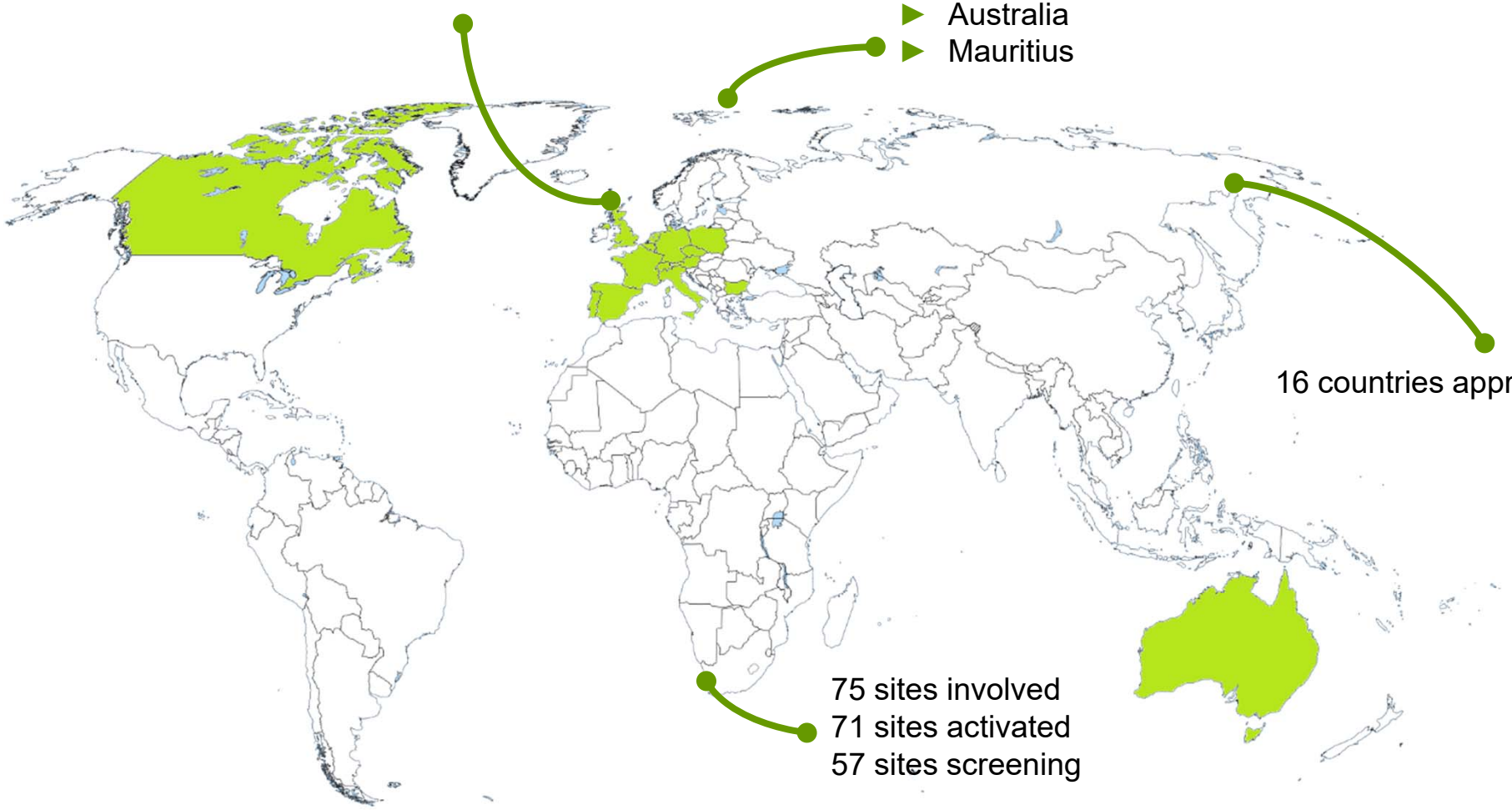
More information on: http://www.native-trial.com/

NATIVE: Phase IIb in NASH

NATIVE
NASH TRIAL TO VALIDATE IVA337 EFFICACY

Principal investigator: Pr Sven Francque, Belgium

16 countries worldwide
- 13 in EU
- Canada
- Australia
- Mauritius



16 countries approved

75 sites involved
71 sites activated
57 sites screening

Results expected second-half 2019

US investigator initiated Phase II trial in T2DM patients with NAFLD(1)

Trial design

Principal investigator

- Pr. Kenneth Cusi (University of Florida)

Status

- IND approved
- FPFV August 2018
- HR expected early 2020

Randomisation

- Randomized (1:1), double-blind, placebo-controlled
- Non-obese subject control group for the metabolic and imaging procedures
- N= 64 calculated assuming a 35% relative reduction of IHGT(2)

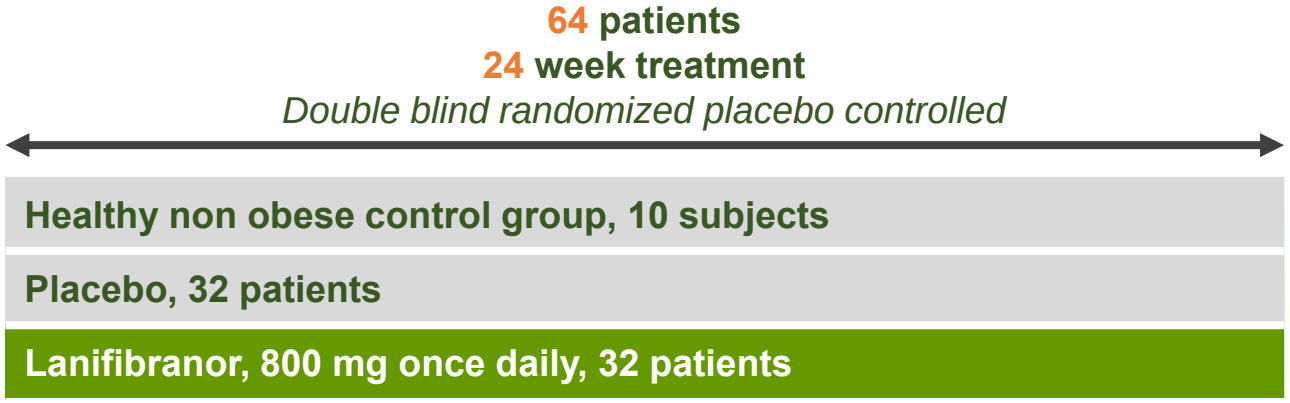
Primary endpoint

- Change from baseline to week 24 in IHTG

Key secondary endpoints

- Proportion of responders (IHTG, NAFLD resolution)
- Change in hepatic fibrosis (MRE(3), biomarkers)
- Change in metabolic outcomes (insulin sensitivity, DNL(4), glycemic control, lipids)
- Safety

Clinicaltrials.gov identifier: NCT03459079



(1) NAFLD: Nonalcoholic fatty liver disease (2) Intrahepatic triglycerides (3) Magnetic resonance elastography (4) De-novo lipogenesis

Systemic sclerosis overview

A severe disease with no approved treatment (1)

- Systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular damage and progressive fibrosis of the skin and visceral organs
- There are two subtypes:
  - Limited cutaneous (lcSSc; ~60% of patients): restricted skin involvement, but with major internal organ involvement
  - Diffuse cutaneous (dcSSc; ~ 40% of patients): extensive skin and organ involvement
- Current treatments include: immunosuppressant agents, corticosteroids as low-dose, or specific therapies targeting the symptoms (endothelin-receptor antagonists to treat digital ulcers, ACE inhibitors to treat renal crisis, …)
- High burden cost to society and of drugs approved in symptomatic indications
- Modified Rodnan Skin Score (MRSS) accepted by FDA and EMA as an end-point for marketing approval
- Potential for conditional approval

Patients: more than 170,000 patients diagnosed and a total market potential > €1.8bn (2) by 2030

USA	Europe Top 5	Japan
~102,000 patients (2)	~67,000 patients (2)	~4,800 patients (2)

Mortality rate is greater than in any other rheumatic disease(3)

Source: (1) Eular SSc Trials and Research Group, EUSTAR, SSc Research Foundation, Canadian SSc research group ; (2) Venture Valuation 2015. (3) ACR 2017 SSc Disease education

Lanifibranor could addresses all the relevant clinical features of systemic sclerosis

Lanifibranor reduces vasculopathy and inflammatory driven lung fibrosis

Lanifibranor restores lung functional capacity

Lanifibranor inhibits pulmonary arteries remodeling with positive impact on pulmonary artery pressure

Lanifibranor reduces established skin fibrosis

Lanifibranor reduces right ventricular systolic pressure and right ventricular hypertrophy

Lanifibranor reduces kidney fibrosis

Orphan status designation obtained in the US and Europe for lanifibranor in SSc

Source: Ruzehaji N, et al. Ann Rheum Dis 2016;75:2175–2183. doi:10.1136/annrheumdis-2015-208029 2175

FASST Phase IIb in SSc

Trial design

Principal investigator

- Principal investigators: Pr Allanore (Hôpital Cochin, Paris) and Pr Denton (University College of London)
- Other: Pr Matucci (Florence University, Italy), Pr Distler (University of Erlangen, Germany), Pr Distler (Universitaet Zurich, Switzerland)
- US scientific advisors: Pr John Varga (Northwestern University), Pr Dinesh Khanna (Michigan University)

Status

- Last patient recruited in October 2017
- Results expected early 2019

Inclusion criteria

- MRSS (Modified Rodnan Skin Score) between 10 and 25
- SSc diagnosed from less than 3 years

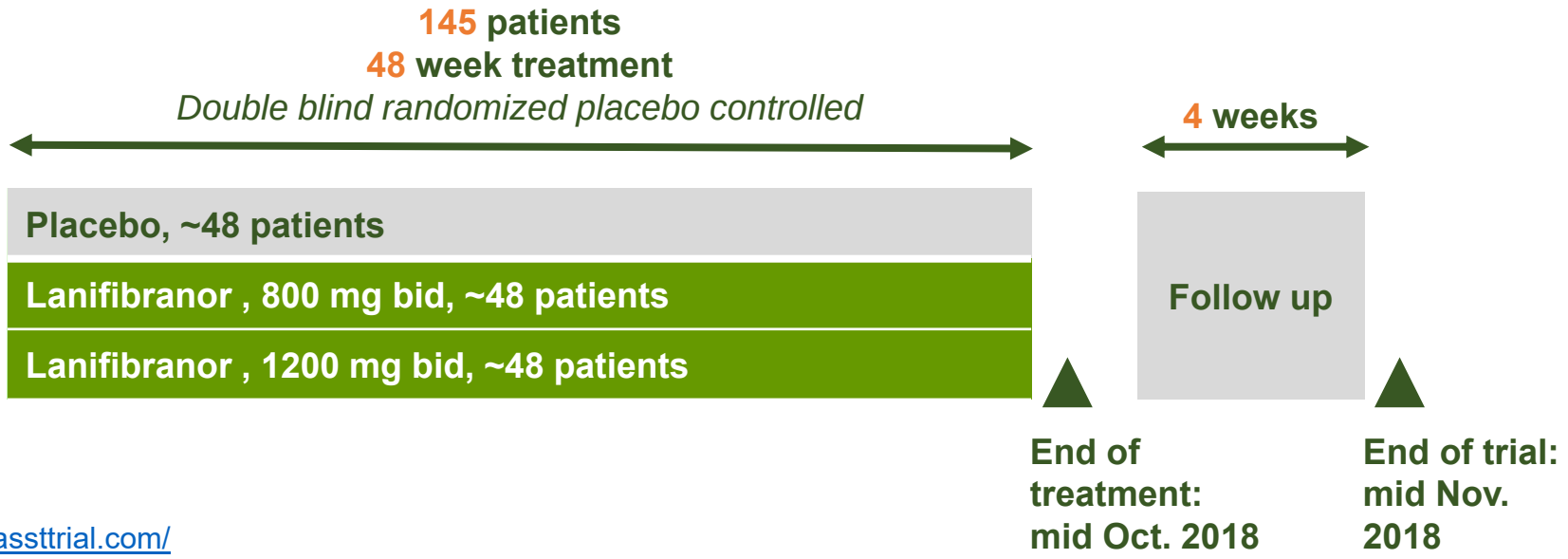
Primary endpoint

- Mean change of the MRSS from baseline to 48 weeks

Key sencondary endpoints

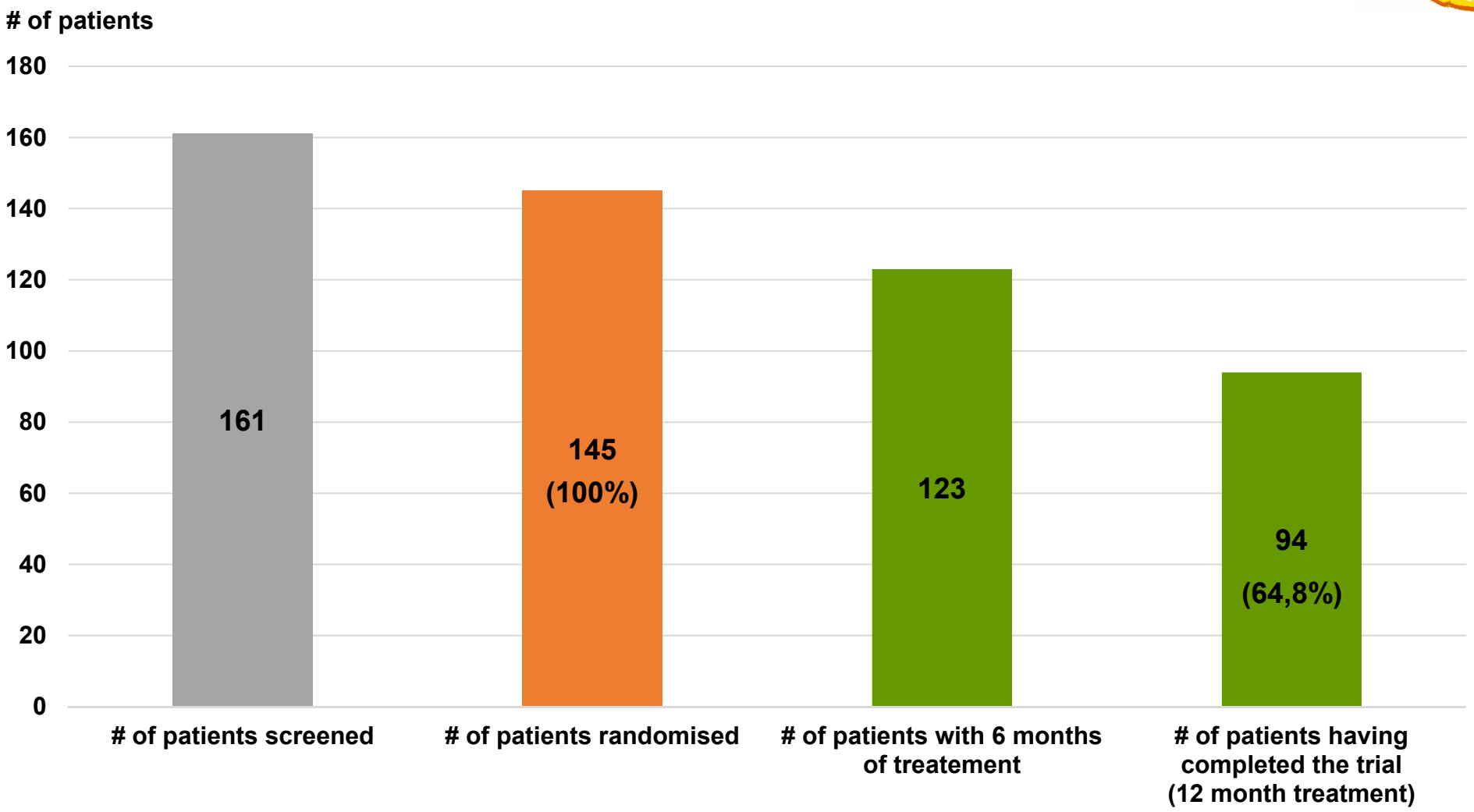
- MRSS responder rate, change from baseline in FVC%, digital ulcers, severe organs involvement, safety

Clinicaltrials.gov identifier: NCT02503644



More information on: http://www.fassttrial.com/

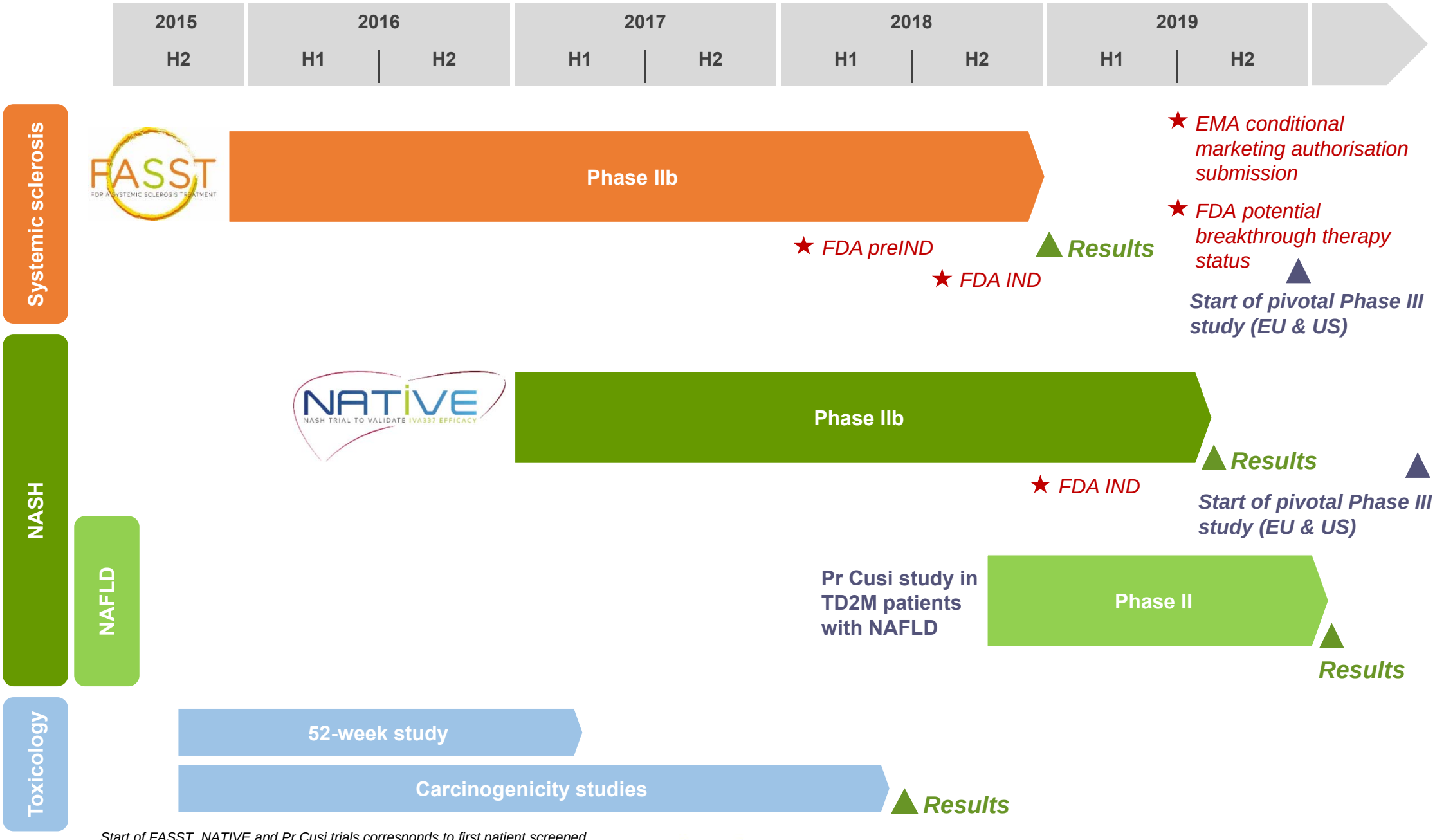
FASST: 100% of patients randomized and close to 65% of patients have already completed the trial(1)



The last of the three planned DSMB was held early July 2018: all of them recommended to continue the study unchanged
Results expected early 2019

(1) Situation at June 28th 2018

Lanifibranor: a phase III ready program in both SSc and NASH by 2019



Start of FASST ,NATIVE and Pr Cusi trials corresponds to first patient screened

Odiparcil

The first oral therapy to treat five forms of mucopolysaccharidosis (MPS): MPS I, II, IV, VI and VII

MPS are devastating diseases with high unmet medical needs

MPS diseases are inherited lysosomal storage diseases

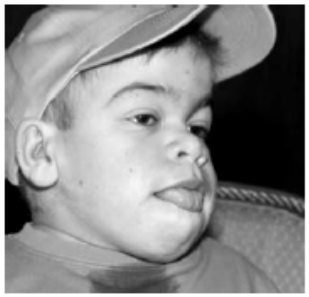
Autosomal recessive disorder characterized by accumulation of glycosaminoglycan(s) (GAG) due to lack of an enzyme

Seven distinct clinical types based on the enzyme affected

Odiparcil could be the first substrate reduction therapy for five forms of MPS:

- **MPS I**: ~3,000 / 4,000 patients(1)
- **MPS II**: ~2,000 patients(1)
- **MPS IV** type A: ~2,000 patients(1)
- **MPS VI**: ~1,100 patients(1), increased frequency in Turkish and Portuguese subpopulations(2)
- **MPS VII**: very rare

Kathleen (MPS I)



Scotty (MPS II)

Karima (MPS VI)

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

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

(1) Retinal degeneration with no corneal clouding

Source: (1) MPS society; (2) Valayannopoulos V, Nicely H, Harmatz P, Turbeville S; Mucopolysaccharidosis VI. Orphanet J Rare Dis. 2010 Apr 12;5:5.

Enzyme replacement therapy (ERT) are commercially successful, but with limited therapeutic efficacy

Enzyme Replacement Therapies

Recombinant human enzymes, administered once a week as an intravenous infusion over 4 hours
Approximately 50% of patients experience infusion reactions initially, some can be life threatening

Product	Company	MPS	Est. yearly cost	2017 sales
Aldurazyme (laronidase)	genzyme	MPS I	$ 217K	$ 207M
elaprase (idursulfase)	Shire	MPS II	$ 522K	$ 616M
Vimizim (elosulfase alfa)	BIOMARIN	MPS IVA	$ 578K	$ 413M
Naglazyme (GALSULFASE - rch)	BIOMARIN	MPS VI	$ 476K	$ 332M
Mepsevii (vestronidase alfa-vjbk) injection, for intravenous use	ultragenyx pharmaceutical	MPS VII	$ 550K	n/a, approved Nov 2017

Source: Sales - Company annual reports 2017; WAC without discounts for a 25-kg patient - BioCentury "Making of MEPSEVII" Dec 11, 2017

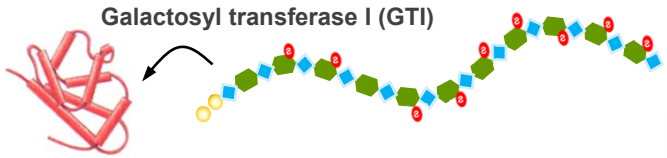
ERT have not been able to resolve the symptoms occurring in certain regions of the ophthalmology system, joints, cartilages, cardiac valves, … due to poor penetration of the enzyme(1)

Source: (1) H. Noh, J. I. Lee; Current and potential therapeutic strategies for muvopolysaccharidoses; Journal of Clinical Pharmacy

Odiparcil original mechanism of action could provide additive benefit to enzyme replacement therapies (ERT)

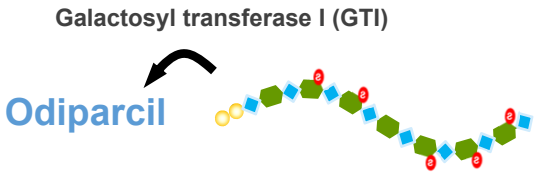
Odiparcil diverts endogenous protein-bound GAG synthesis to soluble Odiparcil-bound chondroitin sulfate (CS) and dermatan sulfate (DS) synthesis

Synthesis of proteoglycans (HS, CS, DS)



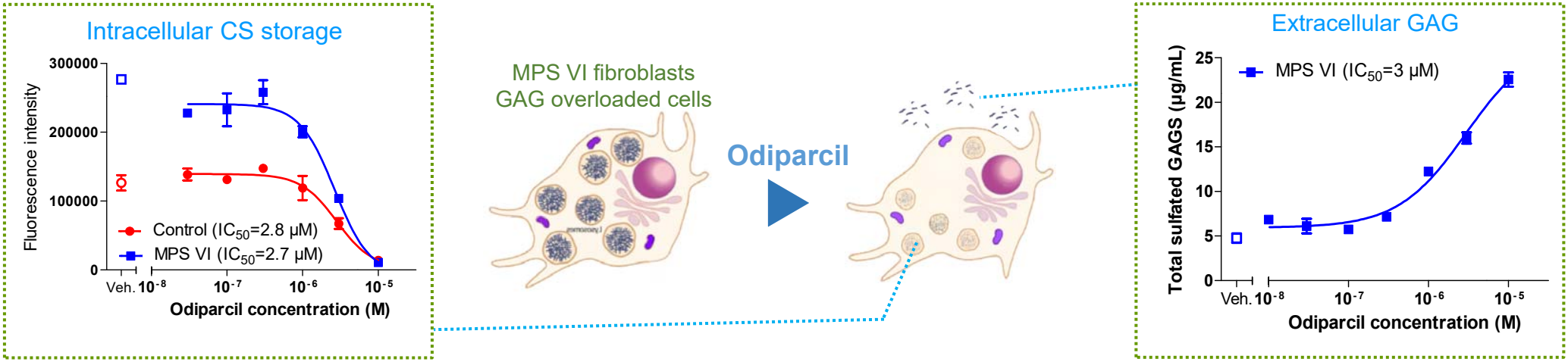
GTI activity

Substrate	Vm/Km
D-xylose	0.8
Odiparcil	1857



Synthesis of soluble DS and CS

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



Odiparcil by decreasing GAG accumulation in tissues and cells should reduce GAG storage in MPS VI patients and improve their disease state

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

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

Type (Incidence)[1]	Name	Severity	Targeted MPS	Dermatan Accumulation	Chondroitin Accumulation	Heparan Accumulation	Keratan Accumulation	Other
MPS I-H (1/100 000)	Hurler syndrome	Most severe form	✓	☑		☑		
MPS I-S (1/100 000)	Scheie syndrome	Mildest	✓	☑				
MPS-IH/S (1/100 000)	Hurler-Scheie syndrome	More severe than MPS I-S, but less severe than MPS I-H	✓	☑		In some cases		
MPS II Types A & B 1/100 000 to 1/170 000	Hunter syndrome Only MPS inherited as an X-linked trait	Type A more severe than B	✓	☑		☑		
MPS III Types A to D 1/70 000	Sanfilippo syndrome	Severe				☑		
MPS IV Type A 1/200 000 to 300 000[2]	Morquio syndrome	Quite severe 95% of Morquio patients	✓		☑		☑	
MPS IV Type B 1/200 000 to 300 000[2]	Morquio syndrome	Quite severe Type A more severe than B					☑	
MPS VI 1/250 000 to 600 000	Maroteaux-Lamy syndrome	Mild to severe	✓	☑	☑			
MPS VII (1/250 000)	Sly syndrome	Mild to severe	✓	☑	☑	☑		
MPS IX (rare)	Natowicz syndrome	Severe						Hyaluronic acid

MPS VI selected as first indication to demonstrate odiparcil efficacy

Source: raredisease.org ; (1) MPS society ; (2) for both type A and B

Odiparcil has the potential to positively differentiate versus current enzyme replacement therapies

	Odiparcil	Aldurazyme, Elaprase, Naglazyme, Vimizim, Mepsevii	HSCT (Hematopoietic stem cell transplantation)
Effect on mobility	✓	✓	✓
Eye, cartilage, bones, heart valves, spinal cord compression	✓	✗	✗
Safety	✓	✓	✗
Dose regimen	✓	✗	✗

Patent granted in the US and the EU with limit of exclusivity in 2039 and orphan status granted in Europe and the US

Source: Company evaluation

Odiparcil iMProveS phase IIa study in MPS VI patients

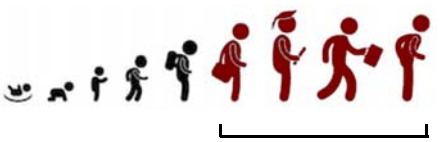
iMProveS
IMPROVE MPS TREATMENT

Phase IIa

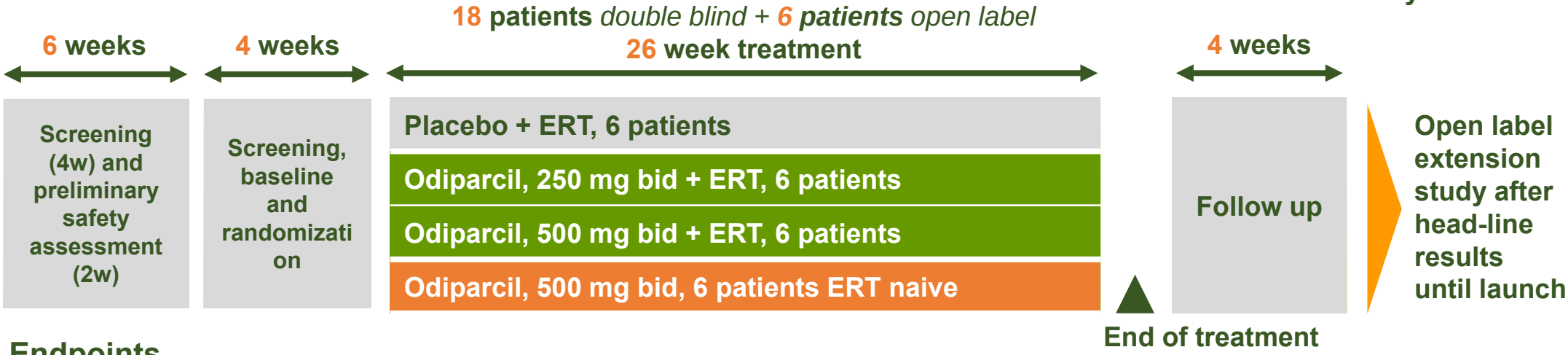
- Phase 3 enabling study with evidence for dose selection and PK / PD response characterization
- **Clinicaltrials.gov identifier:** NCT03370653

Population

- Receiving ERT (N=18)
- Not receiving ERT (N=6)



≥ 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 minutes walk test, upper limb function, shoulder mobility range)
- Cardiac, vascular and respiratory functions
- Eye impairment, hearing capacity, pain assessment, quality of life questionnaires

Status

- Design discussed with EMA (2016)
- Recruiting
- EU, multicenter: UK, Germany, France, Portugal
- HLR: end of first semester 2019

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

Current odiparcil SAFE-KIDDS(1) phase Ib study design in MPS VI children

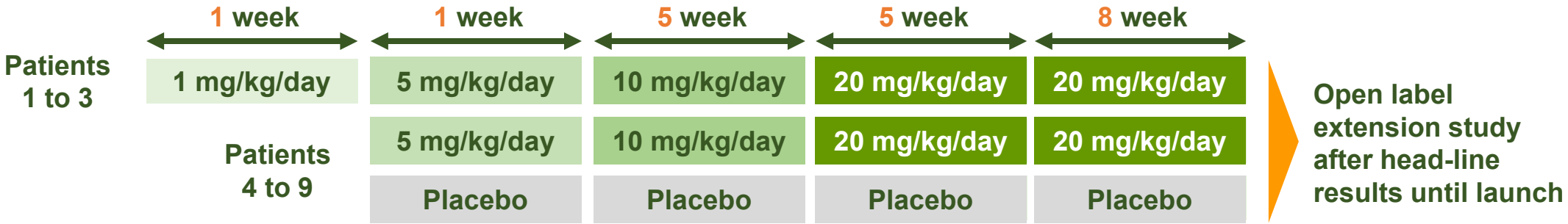
Phase Ib

- Phase 3 enabling study with PK / PD of escalating doses, assessment of palatability and efficacy
- Dose escalating, sequential inclusion (patient 1, then patients 2 and 3 and then patients 4 to 9), prospective study
  - First 3 patients: open label
  - Next 6 patients: two-arm, randomized, placebo-controlled

Population

- Receiving ERT (N=9)

5 - 15yo



Endpoints

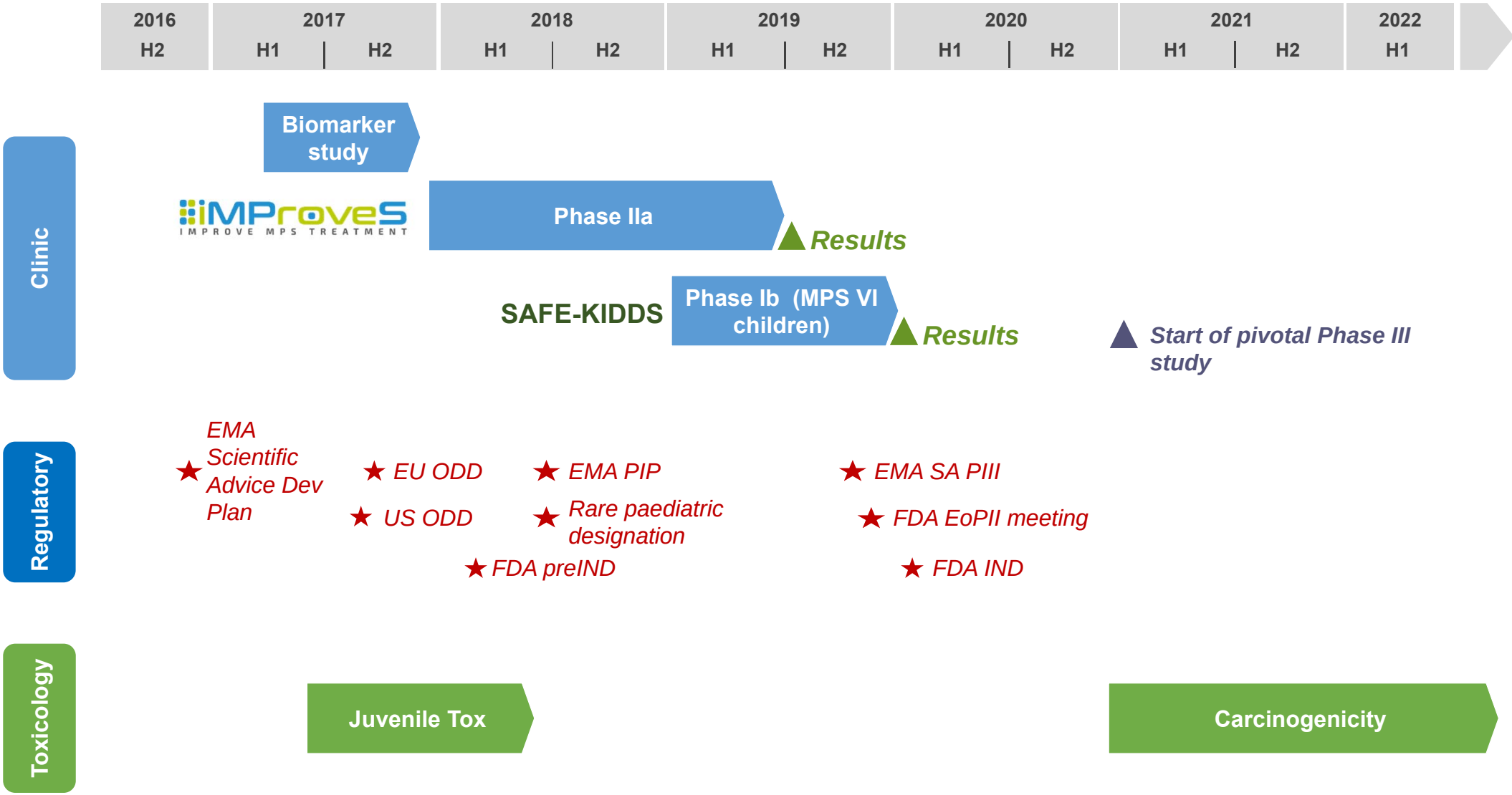
- Safety
- Efficacy
  - Endurance and motor proficiency (walking test, respiratory), mobility, ophthalmology, hearing, cardiovascular test, Quality of life questionnaires (including pain)
- Pharmacokinetics
- Palatability

Status

- Design discussed with FDA (2018)
- EU, multicenter: UK & France
- HLR: early 2020

*(1) A Phase Ib **SAFE**ty, pharmaco**KI**netics and pharmaco**D**ynamics, **D**ose escalating **S**tudy of odiparcil in pediatric population with MPS type VI*

Odiparcil overall development plan in MPS VI



Start of iMProves trial corresponds to corresponds to first patient screened

Yap-Tead program and R&D collaborations

Yap-Tead: a newly discovered oncogenic signaling pathway where Inventiva could be the first to start a clinical trial

The Hippo pathway: a newly discovered oncogenic signaling pathway, where Inventiva has established a leading position

- The program addresses both rare cancers (malignant mesothelioma, uveal melanoma, …) as well as large cancers (NSCLC, TNBC, hepatoblastoma, hepatocellular carcinoma,…)
- Two patents filed covering one chemical family
- Chemistry work ongoing on a second chemical family
- Significant evidence, in cellular setup, that Inventiva compounds are YAP-TEAD interaction inhibitors
- *in vivo* activity demonstrated in xenograft model
- Program currently in lead-optimization

The program is expected to enter into Phase I/II-enabling preclinical development in 2019

Two successful collaborations in place with AbbVie and Boehringer Ingelheim

RORγ collaboration

- RORγ program addresses large markets currently dominated by biologics
- RORγ could prove to be superior to biologics
- Inventiva and AbbVie identified clinical and preclinical compounds
- Inventiva eligible to multiple milestones payments and sales royalties on a product with block-buster potential

ABBV-157 expected to enter phase I in 2018

Fibrosis collaboration

- Multi-year R&D collaboration and licensing partnership
- Joint team until pre-CC stage. BI to take full responsibility of clinical development and commercialization
- Following the validation of this new target supporting its therapeutic potential in fibrotic conditions, Boehringer Ingelheim exercised the option to jointly develop this target triggering a milestone payment of 2,5 M€
- Inventiva eligible to up to 170 M€ in milestones plus royalties

LO milestone expected in 2019

Near-term catalysts

Recent achievements and upcoming milestones

	2017	2018	2019
Lanifibranor	☑ 12 month monkey study finalized ☑ Lanifibranor INN name from WHO ☑ Last patient phase IIb SSc	☑ 2 year carcinogenicity study results ☑ US fibrosis indication patent ☑ US IND ☑ First patient in NAFLD phase II ▶ Last patient phase IIb NASH	▶ **Results Phase IIb SSc** ▶ **Results Phase IIb NASH**
Odiparcil	☑ MPS patent granted in US ☑ US orphan status designation ☑ EU orphan status designation ☑ First patient Phase IIa in MPS VI	☑ MPS VI biomarker study results ☑ Juvenile tox results ▶ Rare pediatric disease designation MPS VI ▶ Start Phase Ib in children	▶ **Results Phase IIa MPS VI** ▶ **Results Phase Ib in children**
Collab.	☑ 2,5M€ milestone from Boehringer Ingelheim (option exercise) ☑ ABBV-157 preclinical nomination ☑ AbbVie RORγ collaboration renewal	▶ Start Phase I with ABBV-157	
Discovery	☑ Yap-Tead: in vivo activity obtained ☑ Epicure: target validated	☑ Yap-Tead: Vivo POC ▶ Epicure: HTL	▶ **Yap-Tead: start of Phase I/II enabling preclinical development**
Finance	☑ IPO on Euronext	☑ Capital increase	