Lanifibranor: a next generation pan-PPAR agonist for the treatment of NASH

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Inventiva: a clinical stage biopharma with a focus on fibrosis

Three late stage clinical programs

Two royalty bearing collaborations with AbbVie and Boehringer Ingelheim

Pre-clinical pipeline in oncology and fibrosis

Listed on Euronext Paris: 59M€ of cash financing the company until mid-19

Strong shareholder base: BVF (US), Novo Ventures (DK), Perceptive (US), Sphera (IL)
Coordinated activation of PPARs for NASH and fibrosis resolution


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panPPAR clinical rationale in NASH

- **PPARγ** activation by pioglitazone significantly improves steatosis, ballooning and inflammation as well as metabolic markers in NASH patients after 6 or 18 months of treatment:

<table>
<thead>
<tr>
<th></th>
<th>6 mo (Belfort et al, 2006)</th>
<th>18 mo (Cusi et al, 2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis (% patients improved)</td>
<td>65% vs 38%, p &lt; 0.001</td>
<td>71% vs 26%, p &lt; 0.001</td>
</tr>
<tr>
<td>Inflammation (% patients improved)</td>
<td>65% vs 29%, p &lt; 0.001</td>
<td>49% vs 22%, p &lt; 0.001</td>
</tr>
<tr>
<td>Ballooning (% patients improved)</td>
<td>54% vs 24%, p &lt; 0.001</td>
<td>51% vs 24%, p &lt; 0.001</td>
</tr>
<tr>
<td>NASH resolution (% patients)</td>
<td>NA</td>
<td>51% vs 19%, p &lt; 0.001</td>
</tr>
</tbody>
</table>

- **Pioglitazone**: improvement of advanced fibrosis (stage F3-F4) in patients with biopsy-proven NASH, defined as the number of NASH patients whose fibrosis stage changed from F3-F4 to F0-F2 at the End Of T

  Musso G et al, Hepatology 2017

- **PPARα/δ** activation by elafibranor leads to significant improvement of ballooning and inflammation as well as metabolic markers in NASH patients after 12 months of treatment (Ratziu et al, Gastroenterology, 2016)
Lanifibranor: a next generation panPPAR with moderate and well balanced activity on the 3 PPAR isoforms

Lanifibranor presents a similar profile for the 3 rodent PPAR isoforms

Lanifibranor dose response curves

<table>
<thead>
<tr>
<th>Compound</th>
<th>PPARα</th>
<th>PPARδ</th>
<th>PPARγ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanifibranor</td>
<td>1630</td>
<td>850</td>
<td>230</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>2400</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>-</td>
<td>-</td>
<td>263</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>-</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Elafibranor(1)</td>
<td>10</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Seladelpar(2)</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>


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

J Med Chem. 2018 Feb 15. doi: 10.1021/acs.jmedchem.7b01285

Potency scale: red 10 nM; grey: 500 nM; green 5 000 nM
Lanifibranor has a good safety profile differing from previously developed PPAR agonists

Results from 6 and 12 months tox studies in primates and rodents show a good safety profile

<table>
<thead>
<tr>
<th>Organ</th>
<th>PPAR Subtype</th>
<th>Reported liabilities</th>
<th>Lanifibranor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>γ</td>
<td>Fluid retention, Cardiac hypertrophy</td>
<td>Not observed</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>α or δ</td>
<td>Myofiber degeneration</td>
<td>Not observed</td>
</tr>
<tr>
<td>Kidney</td>
<td>α</td>
<td>&gt; 50% increases in creatinine, Degenerative changes in renal tubules</td>
<td>Not observed</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>γ</td>
<td>Proliferative changes in bladder epithelium</td>
<td>Not observed</td>
</tr>
</tbody>
</table>

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

![Graph showing plasma volume and heart weight comparison](image)
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

PPARα,δ,γ
- Necroinflammation
  - NFκB-dependent gene activation
  - Inflammasome
  - Ballooning

PPARγ
- Fibrosis
  - Stellate cell proliferation and activation
  - Collagen and fibronectin production

**Lanifibranor**
Moderate and balanced panPPAR agonist activity regulating genes in:
- PPARα: hepatocytes
- PPARδ: kupffer cells
- PPARγ: hepatic stellate cells
Lanifibranor suppresses proliferation and activation of human hepatic stellate cells

Effect of different PPAR agonists in PDGF induced proliferation assay

Stiffness-induced activation

Lanifibranor inhibits proliferation and activation of HSC with a better efficacy than selective PPAR agonists.
Phase I and Phase IIa clinical studies confirmed lanifibranor safety and efficacy on key metabolic markers

- Improves insulin sensitivity (HOMA-IR, adiponectin)
- Improves dyslipidemia (increase in HDL-C, reduction of TG)

> Clinical findings underline the excellent 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 weight gain
- 800 and 1200 mg doses investigated in Phase 2b trials
NATIVE Phase IIb in NASH

Trial design

Status
▶ Trial enrolling

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

Clinicaltrials.gov identifier:
▶ NCT03008070

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

225 patients
24 week treatment
Double blind randomized placebo controlled

Screening
▶ Liver biopsy

End of treatment
▶ Liver biopsy

Placebo, 75 patients
Lanifibranor, 800 mg once daily, 75 patients
Lanifibranor, 1200 mg once daily, 75 patients

More information on: http://www.native-trial.com/
NATIVE: Phase IIb in NASH

Principal investigator: Pr Sven Francque, Belgium

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

14 countries approved

76 sites involved
45 sites activated
42 sites screening

Results expected second-half 2019
Lanifibranor a phase III ready program in NASH and SSc by 2019

2015
H2

2016
H1 | H2

2017
H1 | H2

2018
H1 | H2

2019
H1 | H2

- **EMA conditional marketing authorisation submission**
- **FDA potential breakthrough therapy status**
- **FDA preIND**
- **FDA IND**
- **Results**
- **Start of pivotal Phase III study (EU & US)**

**NASH**

**Tocilizumab**

**Phase IIb**

**Results**

**FDp IND**

**52-week study**

**Carcinogenicity studies**

**Results**

**Start of FASST and NATIVE trials corresponds to first patient screened**

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