Inventiva rewarded for its innovative approach with IVA337 at the 4th Systemic Sclerosis World Congress

- Presentation on IVA337’s anti-fibrotic properties receives award and picked out from over 400 submissions
- Oral presentation by Professor Yannick Allanore, Professor of Rheumatology at Hôpital Cochin, on the preventive and curative properties of IVA337 in a systemic sclerosis model
- Confirmation of IVA337’s potential in the treatment of systemic sclerosis (phase IIb trial ongoing)

Daix (France), February 25th 2016 - Inventiva, a biopharmaceutical company specialised in nuclear receptors, transcription factors and epigenetics for the development of innovative therapies for fibrosis, oncology and orphan diseases, announces that the organising committee of the 4th Systemic Sclerosis World Congress awarded Inventiva with a prize for the innovative approach it has taken with its lead product, IVA337, currently in a Phase IIb trial for the treatment of systemic sclerosis.

The research presented shows that IVA337 can treat the fibrosis of organs affected by systemic sclerosis via a unique mechanism of action. More than 400 submissions were presented at this congress of reference held by the World Scleroderma Foundation which brings together for three days the world experts of the disease and representatives from patient associations.

In its poster entitled “Pan PPAR agonist IVA337 has an anti-fibrotic effect in multiple in vitro and in vivo fibrosis models”, Inventiva demonstrated in several in vitro and in vivo fibrosis models (lungs, liver, kidneys, etc.) the anti-fibrotic action of its lead product IVA337, a next-generation Pan PPAR agonist. This provides further evidence of the major role played by PPARs in fibrogenesis.

Additional data concerning the effects of IVA337 on skin fibrosis were also presented during the Congress by Professor Yannick Allanore, Professor of Rheumatology at Hôpital Cochin in Paris, in his presentation entitled: “Pan PPAR agonist IVA337 is effective in prevention and treatment of experimental skin fibrosis”.

“We are very proud to have been selected from over 400 high-level research submissions presented at this Congress, which is the most important scientific global event in the field of systemic sclerosis,” commented Pierre Broqua, Chief Scientific Officer and co-Founder of Inventiva. “This recognition reflects IVA337’s promising therapeutic potential, not only in systemic sclerosis, but also in other indications involving fibrosis, such as NASH, for which no effective treatments exist yet.”

Alongside the ongoing phase IIb trial in the treatment of systemic sclerosis, in which it plans to enrol a total of 135 patients in 8 European countries, Inventiva also shortly intends to launch a phase IIb clinical trial for the treatment of NASH. NASH is a severe fibrotic disease of the liver that may cause cirrhosis or cancer and that affects several million people worldwide.
About the Systemic Sclerosis World Congress:

The Systemic Sclerosis World Congress is held by the World Scleroderma Foundation, an organisation dedicated to initiating and supporting research into systemic sclerosis. This globally renowned conference aims to bring together and facilitate the sharing of expertise by all those involved in the field of systemic sclerosis through presentations, workshops and a programme specifically dedicated to patients.

About systemic sclerosis:

Systemic sclerosis is a rare and complex disease affecting the auto-immune system, the microvascular system and conjunctive tissues. This fibrotic disease mainly affects the skin, but also the lungs, the heart, the gastrointestinal tract and the kidneys. Due to the progressive failure of different organs, systemic sclerosis is a severe disease with a high mortality rate. Once patients are diagnosed with systemic sclerosis, generally between the ages of 40 and 50, the median survival period is of 11 years. Close to 170,000 people suffer from systemic sclerosis, with women outnumbering men by a ratio of more than five to one.²

The disease owes its original name of scleroderma, which derives from the Greek words skleros (hard) and derma (skin), to the skin condition it provokes. The disease causes severe physical and psycho-social consequences that may be deadly for patients whose vital organs are affected. The extension of this skin fibrosis has led to the classification of two sub-categories, respectively called limited systemic sclerosis and diffuse systemic sclerosis. The latter is more serious and is targeted in the FASST trial.

To date, only symptomatic drugs with limited therapeutic effects are available in order to attenuate the consequences of fibrosis progression. However, they do not prevent, delay nor reverse the disease’s devastating process.

About Inventiva: [www.inventivapharma.com](http://www.inventivapharma.com)

Inventiva is a biopharmaceutical company specialized in the development of drugs interacting with nuclear receptors, transcription factors and epigenetic modulation. Inventiva opens up novel breakthrough therapies against fibrotic diseases, cancers and orphan diseases with substantial unmet medical needs.

IVA337, its lead product, is an anti-fibrotic treatment with a unique mechanism of action via the activation of all three alpha, gamma and delta PPARs (peroxisome proliferator-activated receptors), which play key roles in controlling the fibrotic process. Its anti-fibrotic action targets two indications with substantial unmet medical needs: NASH, a severe and increasingly prevalent liver disease already affecting over 30 million people in the United States, and systemic sclerosis, a disease with a very high mortality rate and for which there is no approved treatment to date.

Inventiva is also developing IVA336, a clinical program for the treatment of three different forms of mucopolysaccharidosis (MPS I or Hurler-Sheie syndrome, MPS II or Sly syndrome and MPS VI also known as Maroteaux-Lamy syndrome). In addition, Inventiva also has a preclinical stage oncology portfolio and benefits from partnerships with world-leading research entities such as the Institut Curie. A strategic partnership has also been put in place with AbbVie, providing Inventiva with eligibility to preclinical, clinical, regulatory and commercial milestone payments and royalties on the products resulting from the partnership.

Inventiva employs over 100 highly qualified scientists and owns state-of-the-art R&D facilities near Dijon, acquired from the international pharmaceutical group Abbott. Inventiva also has access to its proprietary library of over 240,000 molecules as well as biology, chemistry and pharmacology platforms.

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¹ Journal of Rheumatology, 2013
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The pan-PPAR agonist IVA337 has anti-fibrotic effects in multiple in vitro and in vivo fibrosis models.

1 INTRODUCTION

Background: Numerous evidences point to a fundamental role of peroxisome proliferator-activated receptors (PPARs) in the control of fibrogenesis. Anti-fibrotic effects have been observed following treatment with PPARα, PPARα or PPARδ agonists in several fibrosis models affecting specific aspects of fibrogenesis in different organs. This suggests that a pan-PPAR agonist might represent an attractive anti-fibrotic therapeutic approach.

Objective: To investigate the anti-fibrotic effects in vitro and in vivo of IVA337, a well-balanced pan-PPAR agonist (EC50: PPARα 0.2 µM, PPARα 0.9 µM, PPARδ 0.5 µM).

Methods: The effects of IVA337 were investigated in primary human lung fibroblasts and pulmonary artery smooth muscle cells in vitro and in lung, liver and kidney fibrosis models in vivo.

2 IVA337 PHARMACOLOGY PROFILE AND TARGET ENGAGEMENT

IVA337 has a well-balanced and moderate potency on the 3 PPAR isoforms (in vitro transactivation assay).

Target engagement in the lung study

Plasma Adiponectin

Plasma Triglycerides

Target engagement in the liver study

Serum Adiponectin

Serum Triglycerides

Target engagement in the kidney study

Fibronectin

Osteopontin

IVA337 is a moderate and well-balanced pan-PPAR agonist. In vitro, activation of PPARα and PPARδ by IVA337 is demonstrated by a dose-dependent increase of circulating adiponectin and a decrease of circulating triglycerides, respectively.

3 IVA337 IN VITRO ACTIVITY IN HUMAN FIBROBLASTS

- FMT assay
- TGFβ dose response
- Proliferation assay
- PDGF dose response

TGFβ-induced FMT (SMA expression) in primary human lung fibroblasts

PDGF-induced proliferation in primary human lung fibroblasts

IVA337 decreases SMA and ECM genes mRNA expression in primary human lung fibroblasts

IVA337 inhibits collagen I secretion from MRC5 lung fibroblasts

IVA337 inhibits TGFβ-induced fibroblast to myofibroblast transition (FMT) and PDGF-induced proliferation in primary human lung fibroblasts. In addition, IVA337 decreases SMA and extracellular matrix (ECM) genes expression and inhibits collagen secretion. Similar data on FMT and proliferation were obtained in primary human skin fibroblasts (not shown).

4 IVA337 IN VITRO ACTIVITY IN SMOOTH MUSCLE CELLS

PDGF-induced proliferation in PASMCs

IVAS37 inhibits PDGF-induced proliferation in primary human artery smooth muscle cells (PASMC). In addition, IVA337 inhibits contractility in 3D collagen gel contraction assay. Thus, IVA337 could inhibit aspects of vascular remodelling during fibrogenesis.

5 IVA337 ACTIVITY IN BLEOMYCIN LUNG FIBROSIS MODEL

Concentrated Bleomycin and compound treatment

Mice were sacrificed. Collagen and lungs were harvested

Collagen deposition (PSD)

Fibrotic areas in the lung

IVA337 blocks fibrogenesis in a prophylactic Bleomycin lung fibrosis model. 14 days treatment inhibits collagen accumulation as well as the expression of a set of fibrotic and inflammatory genes and proteins.

6 IVA337 ASSESSMENT IN CCL4 LIVER FIBROSIS MODEL

CTB64 mice received CCL4 or CCL4 dissolved in sunflower oil daily for 2 weeks.

Mice were sacrificed. Blood and liver were harvested

Collected samples

Collagen deposition (PSD)

Fibronectin

TGFβ-1

TGFβ-2

TGFβ-3

IVA337 inhibits fibrogenesis and reverses established fibrosis induced by CCL4 in the liver, as demonstrated by decreased collagen accumulation and inhibition of expression of fibrotic and inflammatory markers.

7 IVA337 ACTIVITY IN KIDNEY FIBROSIS / INJURY MODELS

Unilateral ureteral obstruction (UUO) model

CTB64 mice were immunized with sheep IgG or CFA

Mice were sacrificed. Blood, urine and kidneys were harvested

Collagen deposition (PSD)

APAAP

Apolipoprotein B (ApoB) model

CTB64 mice were immunized with sheep IgG or CFA

Mice were sacrificed. Blood, urine and kidneys were harvested

IVA337 prevents kidney inflammation and fibrosis in the UUO and ApoB glomerulonephritis models as demonstrated by decreased collagen accumulation and inflammatory markers.

8 CONCLUSIONS

Our findings confirm that PPARs play an important role in fibrogenesis and demonstrate that simultaneous activation of all PPAR isoforms by IVA337 exerts potent anti-fibrotic, anti-vascular remodelling and anti-inflammatory effects. These findings support the potential therapeutic effect of IVA337 for the treatment of SSc and other fibrotic conditions including IPF, NASH and DN. IVA337 is currently under investigation in cssSc patients (FASST clinical trial).

Additional data on skin fibrosis will be presented on 19 Feb, Session 5 at 17:40 by Prof. Yannick Alaman

PPARs AGONIST IVA337 IS EFFECTIVE IN PREVENTION AND TREATMENT OF EXPERIMENTAL SKIN FIBROSIS