# Development of a novel powder formulation for treatment of idiopathic pulmonary fibrosis

**Wayne Morley[1], Irene Parisini[1], Martina Larini[1], Arnaud Fillius[1], Paola Zarantonello[1] Lise Gravelle[2] & Anders Pedersen[2]**

[1]Aptuit S.r.l, Via Alexander Fleming 4, Verona, 37135, Italy

[2]Galecto Biotech AB, Cobis Science Park, Ole Maaloes Vej 3, Copenhagen, DK-2200, Denmark

## Summary

Idiopathic Pulmonary Fibrosis is a fatal disease that leads to a reduction in lung capacity. A novel inhalation formulation of TD139, a small molecule Galectin-3 inhibitor, was developed and a fast approach from formulation development to Phase I Clinical Supply was established under cGMP (current Good Manufacturing Practice) environment. Four dose strengths were developed including two containing only API (Active Pharmaceutical Ingredient) without excipients (100% API) and two formulations containing 3% API, blended with Lactose using a high shear blender. Over a 3 month period the formulations demonstrated a stable FPD (Fine Particle Dose, as a percentage of label claim) at standard and stressed conditions (25°C/60%RH and 40°C/75%RH, respectively), indicating good stability and robustness of the formulations. The project showed market potential for the TD139 product, and an effective approach to manufacturing, with the first patient dosed within six months of starting the project.

## Introduction

Lung diseases such as asthma and COPD (chronic obstructive pulmonary disease) are common worldwide and many inhalers (dry powder inhalers - DPIs, pressurised metered dose inhalers – pMDIs, and nebulizers) have been prescribed. Other diseases include lung cancer, emphysema and cystic fibrosis, for which therapies have been investigated [1]. However, other lung diseases have been discovered and medical needs for these are still unmet. One of these is IPF (Idiopathic Pulmonary Fibrosis). IPF is a progressive, irreversible, ultimately fatal lung disease characterized by a reduction in lung capacity and rapid decline in lung function, due to scarring of the lung tissue, which causes patients to have a limited quality of life. IPF is an orphan indication that affects between 200,000 and 300,000 in the Western world [2]. Currently, only limited treatment options are available. Ofev® (Nintedanib) and Esbriet® (pirfenidone) have been recently approved by the FDA as oral administration to treat IPF [3]. Both are anti-fibrotic drugs and Nintedanib is a tyrosine-kinase receptor [3].

To the authors' knowledge, there are no approved drugs for inhaled administration for the treatment of IPF. Galecto Biotech AB along with Lund University, Sweden, and Edinburgh University, have developed a novel drug to treat fibrotic conditions: TD139. This molecule acts as a potent inhibitor of the galactoside binding pockets of galectins (*i.e*. Galectin 3) to reduce fibrosis in animal models. The aim of the study was to develop a formulation containing TD139 as API alone and/or in combination with coarse carrier particles (lactose monohydrate). The formulations were developed as for fit for purpose to start a Phase I clinical study within 6 months from API delivery.

## Results and discussion

*Formulation development*

High shear blending (Diosna P1-6, Dierks & Söhne GmbH) was used to pre-blend two types of lactose (Respitose SV003 and Lactohale 230 both from DFE pharma, Veghel, Netherlands). Four doses were manufactured of either neat API (5 mg and 50 mg) or API in combination with pre-blended lactose Respitose SV003 and Lactohale 230 (3% blends: 0.15 mg dose strength and 1.5 mg dose strength) controlling the environmental conditions within 15-25ºC and 40-60% RH (relative humidity). Size 3 HPMC capsules (Qualicaps Europe, Madrid, Spain) were filled accurately by Xcelodose 600S (Capsugel, Cambridge UK).

*Aerosol particle size distribution assessment*

Aerosol particle size distribution (APSD) assessment was carried out using the Next Generation Impactor (NGI) method, in accordance with the European Pharmacopoeia, using an RS01 Plastiape Monohaler®. One HPMC capsule was actuated per replicate of APSD (three replicates in total per dose strength). NGI and model HCP5 vacuum pump were purchased from Copley Scientific Ltd. (Nottingham, UK). The NGI plates were coated with 5% (v/v) Tween 20 (Sigma-Aldrich, Italy) in methanol (Sigma-Aldrich, Italy). The mobile phase was a 75:25 (v/v) mixture of aqueous:acetonitrile. The stationary phase was a Chromolith Performance RP18e column (100 mm x 4.6 mm) (Phenomenex, UK) with UV detection at 254 nm. Statistical analysis was performed in Minitab using one-way ANOVA and post-hoc Tukey's test (multiple comparisons) or Student's two-tailed t-test for pair-wise comparisons, both at 95 % confidence intervals.

*Shelf life stability*

Shelf life stability was assessed in order to start the clinical study. The shelf life was assessed for all four dose strengths at time: initial, 1 month and 3 months; at 25°C/60%RH and 40°C/75%RH; performing APSD, delivered dose by DUSA, impurity and assay, content uniformity, water content and activity. Only the APSD data are reported in this abstract. An ICH (International Conference on Harmonisation) stability study was also performed on the clinical batches. That study is not included in this abstract.

**Results and discussion**

APSD was performed on four dose strengths and TD139 stage deposition (as a percentage of label claim) is shown in Figure 1. Greater deposition in the capsules can be seen for the 0.15 mg dose (one of the 3% blends) compared to the other formulations. This led to lower impactor stage deposition than the 1.5, 5 and 50 mg dose strengths ($p<0.05$, Figure 1).

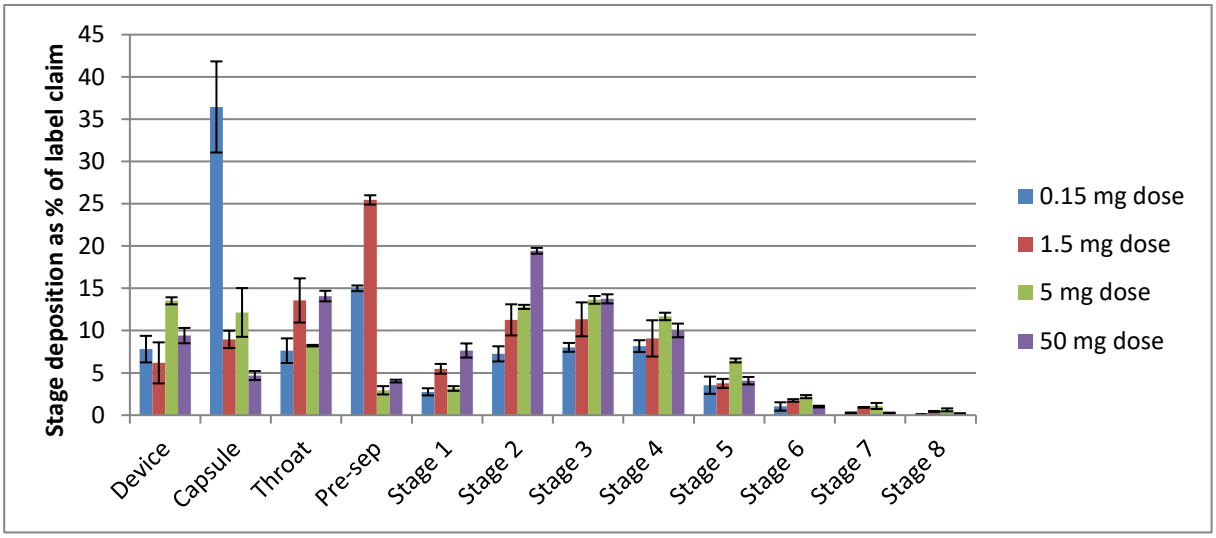


**Figure 1. Stage deposition as % of label claim for four dose strengths of TD139: 0.15 mg (blue), 1.5 mg (red), 5 mg (green) and 50 mg (purple).**

As for other inhalation drugs the presence of carrier has a tendency to lower the emitted fine respirable fraction[4,5] (Table 1).

**Table 1. Fine particle dose below 5 µm ($FPD_{5µm}$), fine particle fraction% delivered dose below 5 µm ($FPF\%_{5µm}$), mass median aerodynamic diameter ($MMAD_{stages\ 1\text{-}8}$) and geometric standard deviation (GSD)) of four dose strengths containing TD139 (mean ± SD, n=3).**

| 3% Blend (dose strength) | $FPD_{5µm}$ (µg/dose) | $FPD_{5µm}$ (% label claim) | $FPF\%_{5µm}$ (% Delivered dose) | MMAD (µm) | GSD (µm) |
|---|---|---|---|---|---|
| 0.15 mg | 38.6 ± 3.1 | 25.7 ± 2.1 | 48.0 ± 1.4 | 2.6 ± 0.3 | 1.9 ± 0.1 |
| 1.5 mg | 515.9 ± 83.2 | 34.4 ± 5.5 | 41.3 ± 4.7 | 2.9 ± 0.0 | 2.0 ± 0.0 |
| **Neat API (dose strength)** | **$FPD_{5µm}$ (µg/dose)** | **$FPD_{5µm}$ (% label claim)** | **$FPF\%_{5µm}$ (% Delivered dose)** | **MMAD (µm)** | **GSD (µm)** |
| 5 mg | 2.2 ± 0.0 | 44.0 ± 0.2 | 70.8 ± 1.0 | 2.6 ± 0.0 | 1.8 ± 0.0 |
| 50 mg | 20.8 ± 1.1 | 41.6 ± 2.2 | 55.8 ± 1.8 | 3.5 ± 0.1 | 1.8 ± 0.0 |

The 3% formulations showed slightly different $FPD_{5µm}$ (% label claim) and $FPF_{5µm}$ (% delivered dose) values between each other ($p<0.05$, Table 1). On the other hand, neat API formulations showed a significant increase in both $FPD_{5µm}$ and $FPF_{5µm}$ than the 3% formulations due to the absence of a carrier fraction ($p<0.05$). Carriers are usually used as bulk powder agents to improve flowability of micronized cohesive powder. However, drug-only formulations usually present higher delivery [6] (Figure 1). Interestingly, the highest dose strength blend (1.5 mg) showed a similar $FPD_{5µm}$ % label claim to the 5 mg neat API, but had a lower $FPF_{5µm}$ (% delivered dose). The greater quantity of micronized API would lead to a greater cohesiveness between particles - and larger agglomerates might not be able to be deagglomerate during aerosolization [6]. This led to a higher MMAD for the 50 mg dose than the 5 mg dose of TD139.

Stability assessment at 25°C/60%RH and 40°C/75%RH over 3 months (Figure 2) showed promising FPD as a percentage of label claim data: no significant variability in FPD was detected ($p>0.05$). The formulations were stable

also at stressed condition (*e.g.* 40°C/75%RH). A stable FPD ensures that the quantity of drug delivered locally to the patient remains consistent throughout the clinical study.

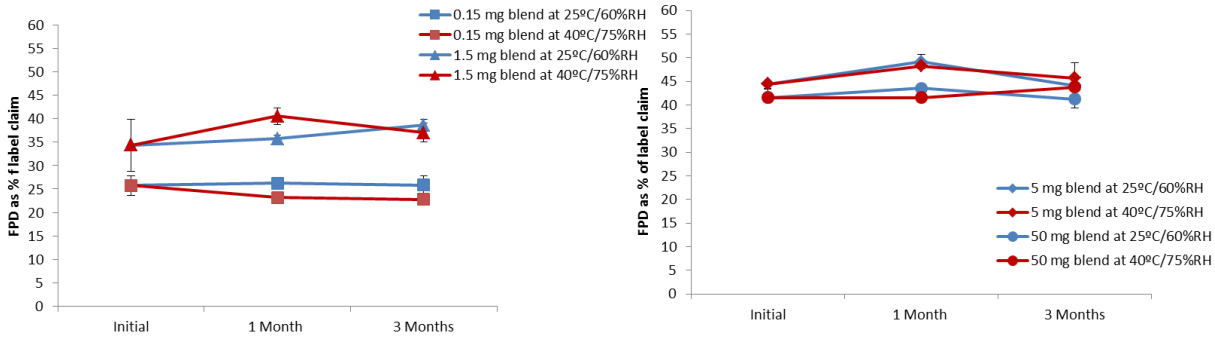


**Figure 2. Distribution of fine particle dose (FPD) as % of label claim for 3% blends (A: 0.15 and 1.5 mg, square and triangle respectively) and neat API (B: 5 and 50 mg, diamond and circle, respectively) up to 3 months at 25°C/60%RH (blue) and 40°C/75%RH (red)**

*Timelines from formulation development to clinical supply*

This approach shows the strategy and specific timelines for each of the phases of development for the delivery of supplies to the clinic within 6 months of starting development of the formulation. To achieve a fast track approach the development and validation of the analytical methods and the formulation development was performed concurrently. In Figure 3 a Gantt chart illustrates the Phase I development project plan.

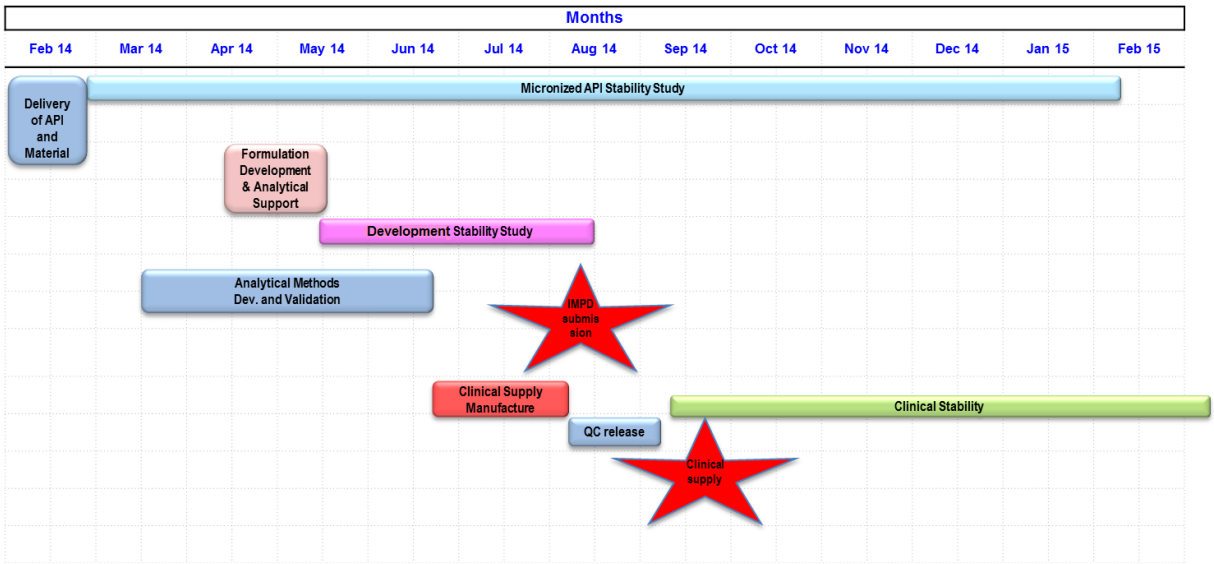


**Figure 3 Phase I development Gantt chart.**

The formulation work supported commencement of a Phase I study to assess safety of increasing drug levels of TD139.

## Conclusions

The study showed the capability to perform a fast formulation development and clinical study of a novel drug for inhaled delivery. Both neat API and 3% blend formulation showed successful fine particle dose and fine particle fraction data over the other formulations with the neat being better. Moreover, the stability study showed that the FPD remained constant at long-term and accelerated ICH conditions. The safety of TD139 in carrier-free and in carrier-based formulations was confirmed during the clinical study in healthy volunteers.

## Acknowledgments

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