Galápagos

CLINICAL STUDY REPORT

Project Number:	GLPG1690		
Study Number:	GLPG1690-CL-304		
Study Title:	A Phase 3, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of GLPG1690 in addition to local standard of care for minimum 52 weeks in subjects with idiopathic pulmonary fibrosis		
Development Phase:	3		
Indication:	Idiopathic Pulmonary Fibrosis		
Test Product:	Ziritaxestat (GLPG1690)		
EudraCT Number:	2018-001406-29	IND Number:	130687
ClinicalTrials.gov Identifier:	NCT03733444		
Sponsor:	Galapagos NV		
Medical Leader:	5.1.2.e , 5.1.2.e		
Coordinating Investigator:	5.1.2.e , Erasmus Medisch Centrum Rotterdam, Dr. Molewaterplein 40, Researchbueau Longziekten, 3015 GD Rotterdam, The Netherlands		
Study Initiation:	5-Nov-2018	Early Study Termination:	10-Feb-2021
		Study Completion:	30-Mar-2021
Report Type:	Abbreviated Report		
Status:	Final		
Date of Report:	18-Oct-2021	Version:	1.0

This clinical study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

2. SYNOPSIS

Name of company: Galapagos NV Public and Scientific contact: Galapagos Medical Information, Galapagos NV, [redacted]@glpg.com	
Name of finished product: Not applicable.	**Name of active ingredient:** G451990 (which is the compound code for ziritaxestat or GLPG1690) Note: throughout this clinical study report (CSR), ziritaxestat is used while GLPG1690 was used in the Clinical Study Protocol.
Phase of development of clinical study: Phase 3	
Title of study: A Phase 3, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of GLPG1690 in addition to local standard of care for minimum 52 weeks in subjects with idiopathic pulmonary fibrosis Study Number: GLPG1690-CL-304; EudraCT Number: 2018-001406-29; ClinicalTrials.gov identifier: NCT03733444; IND Number: 130687	
Coordinating investigator name, number of clinical study sites that enrolled subjects, and countries: [redacted], 121 sites enrolled subjects in 15 countries	
Publication (reference): Maher, T. M., Kreuter, M., Lederer, D. J., Brown, K. K., Wuyts, W., Verbruggen, N., Stutvoet, S., Fieuw, A., Ford, P., Abi-Saab, W., & Wijsenbeek, M. (2019). Rationale, design and objectives of two phase III, randomised, placebo-controlled studies of GLPG1690, a novel autotaxin inhibitor, in idiopathic pulmonary fibrosis (ISABELA 1 and 2). BMJ Open Respiratory Research, 6(1), e000422. https://doi.org/10.1136/bmjresp-2019-000422	
Study period: Study Initiation: 05-Nov-2018 Early Study Termination: 10-Feb-2021 Study Completion: 30-Mar-2021 The study was prematurely terminated based on recommendations of the Independent Data Monitoring Committee.	**Reporting period:** The reporting period was the same as the study period.

Objectives and endpoints:

A complete list of objectives and endpoints and of analyses that were modified or not performed due to early termination of the study are provided in the CSR body.

Objectives	**Endpoints**
Primary	
To evaluate the efficacy of 2 doses of ziritaxestat in addition to local standard of care (SoC) compared to placebo in subjects with idiopathic pulmonary fibrosis (IPF) as evaluated by the rate of decline of FVC over a period of 52 weeks	Rate of decline of FVC (in mL) over a period of 52 weeks
Secondary	
Key Secondary Objectives	Key Secondary Endpoints
To evaluate the impact of 2 doses of ziritaxestat in addition to local SoC compared to placebo in subjects with IPF on: • disease progression defined as deterioration of FVC or all-cause mortality at 52 weeks • respiratory-related hospitalization until the end of the study • changes in quality of life (measured by St. George's Respiratory Questionnaire [SGRQ] total score) at 52 weeks	Disease progression defined as the composite endpoint of first occurrence of ≥10% absolute decline in percent predicted forced vital capacity (%FVC) or all-cause mortality at 52 weeks Time to first respiratory-related hospitalization until the end of the study Change from baseline in the SGRQ total score at 52 weeks

Study design:

This clinical Phase 3 study was a randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the efficacy and safety of 2 doses (200 mg once daily [q.d.] and 600 mg q.d.) of orally administered ziritaxestat in addition to local SoC for at least 52 weeks in adult subjects with a centrally confirmed diagnosis of idiopathic pulmonary fibrosis (IPF). Local SoC for IPF was defined as receiving either pirfenidone or nintedanib at a stable dose for at least 2 months before screening, and during screening; or neither pirfenidone or nintedanib (for any reason). A schematic diagram of the clinical study design is provided below.

Number of subjects:

The planned number of subjects was 750, with 250 per treatment group. The study randomized 781 subjects, 260 in the 600 mg ziritaxestat treatment group, 262 in the 200 mg ziritaxestat treatment group and 259 in the placebo treatment group.

Countries (number of sites): Japan (19), Korea (6), New Zeeland (4), South Africa (6), France (4), Germany (7), Hungary (3), Italy (6), The Netherlands (6), Poland (6), Israel (6), Argentina (5), Mexico (4), Canada (7), United States of America (32).

Diagnosis and key eligibility criterion:

Male or female subjects aged 40 years or older with a diagnosis of IPF within 5 years prior to the screening visit, as per applicable American Thoracic Society / European Respiratory Society (ERS) / Japanese Respiratory Society (JRS) / Latin American Thoracic Association (ALAT) guidelines at the time of diagnosis.

Treatment(s) and treatment schedule:

Subjects were randomized in a 1:1:1 ratio to receive ziritaxestat 600 mg q.d., ziritaxestat 200 mg q.d., or matching placebo for at least 52 weeks.

Investigational product, dosage, mode of administration, batch number(s):

Ziritaxestat 600 mg was taken orally as 3 ziritaxestat 200-mg tablets with food.
Ziritaxestat 200 mg was taken orally as 1 ziritaxestat 200-mg tablet and 2 placebo tablets, matching the ziritaxestat 200-mg tablet.
Placebo was taken orally as 3 placebo tablets, matching the ziritaxestat 200-mg tablet.

Batch numbers are provided in the CSR body.

Statistical methods:

Efficacy Endpoints

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Safety Endpoints

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Summary of results and conclusions

Subject information:

The study randomized 781 subjects and 777 were included in the full analysis set (FAS).

Since the study was terminated prematurely, no subjects completed treatment as per protocol. For 79.3% of subjects, the reason for study discontinuation was study termination by the sponsor. At Week 52 of the study (i.e. Day 407 as defined by the time windows for the primary endpoint), 284 of the 777 subjects (36.6%) were still on treatment.

The demographics and baseline disease characteristics were as expected for subjects with IPF, and were balanced across the 3 treatment groups.

Efficacy results:

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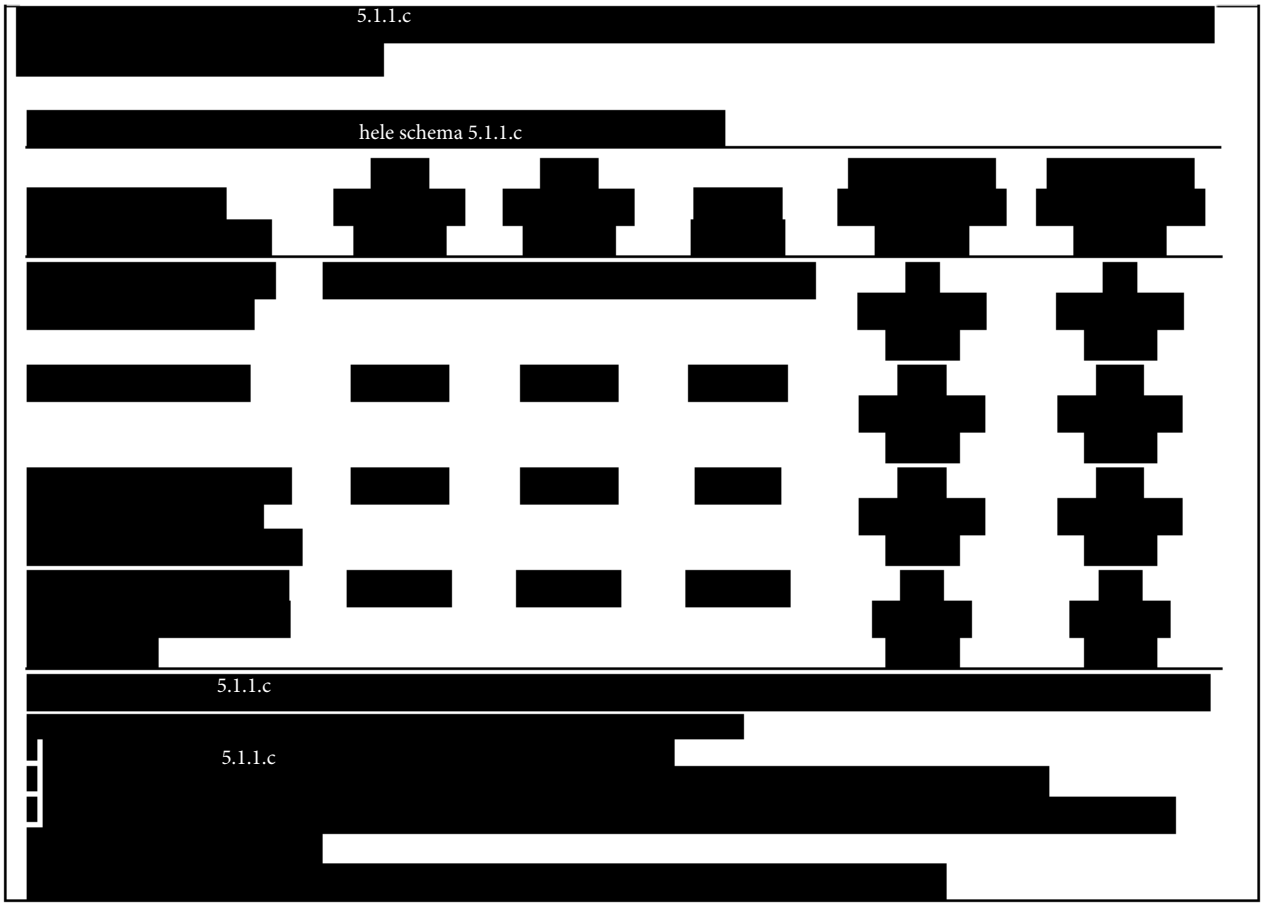
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Safety results:

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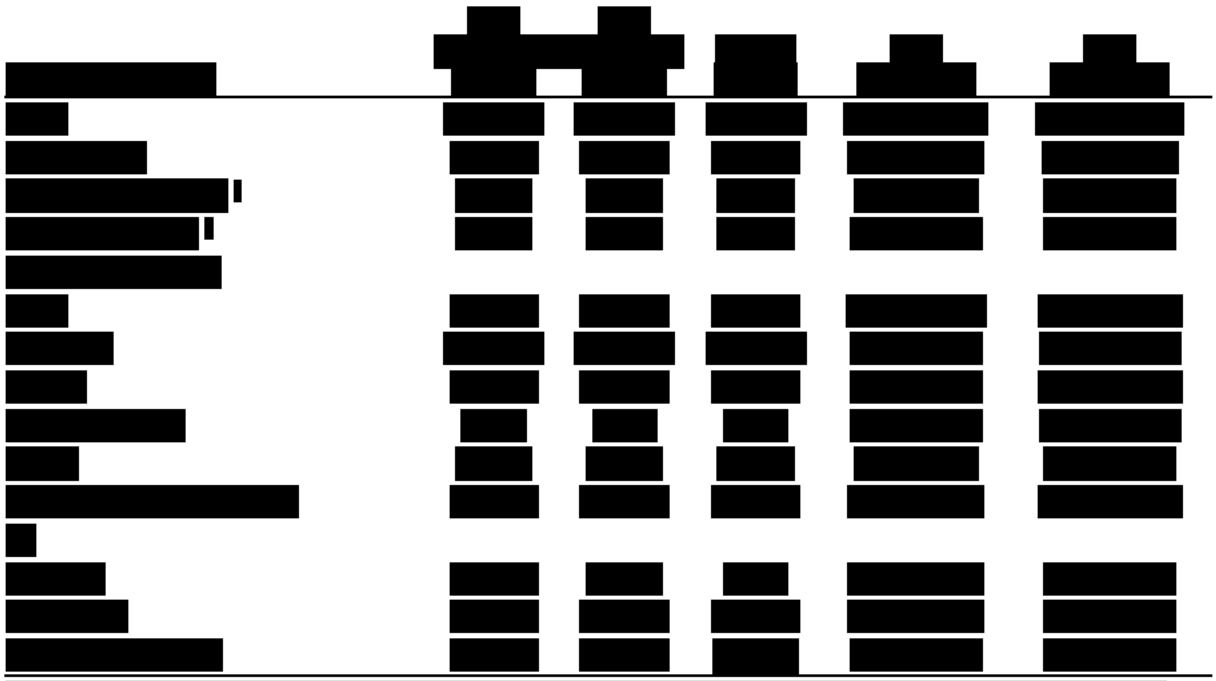

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Study limitations:

The study was prematurely terminated based on the outcome of the IDMC assessment.

Conclusions:

- This was 1 of 2 identically designed Phase 3 studies to evaluate the efficacy and safety of ziritaxestat as a treatment for IPF. This study was terminated early based on the safety concern of increased mortality with 600 mg ziritaxestat, and lack of efficacy signal with 600 mg and 200 mg ziritaxestat based on the pooled data of both Phase 3 studies.
- There was no difference in the primary endpoint of rate of decline of FVC over time between both ziritaxestat groups and the placebo group. There were also no relevant differences in efficacy between either of the 2 ziritaxestat doses and placebo for the key secondary endpoints of time to disease progression and change from baseline in SGRQ. There was an approximately 2-fold greater risk ratio in the ziritaxestat groups compared to placebo in the time to first respiratory-related hospitalization.
- There was a higher percentage of subjects with TEAEs with fatal outcome in the ziritaxestat 600 mg group and 200 mg groups (8.5% and 7.7%, respectively) compared to the placebo group (3.9%). There was also a higher percentage of subjects with SAEs in the ziritaxestat 600 mg group and 200 mg groups (24.7% and 24.2%, respectively) compared to placebo (16.3%).

Date and version of this report:

Abbreviated CSR, Regulatory Review Version 1.0, 18 October 2021