A randomized, placebo-controlled, double blind Phase IIa clinical trial to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of 12 weeks of treatment of an autotaxin inhibitor (GLPG1690) in individuals with Idiopathic Pulmonary Fibrosis (FLORA trial)

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THE LANCET
Respiratory Medicine

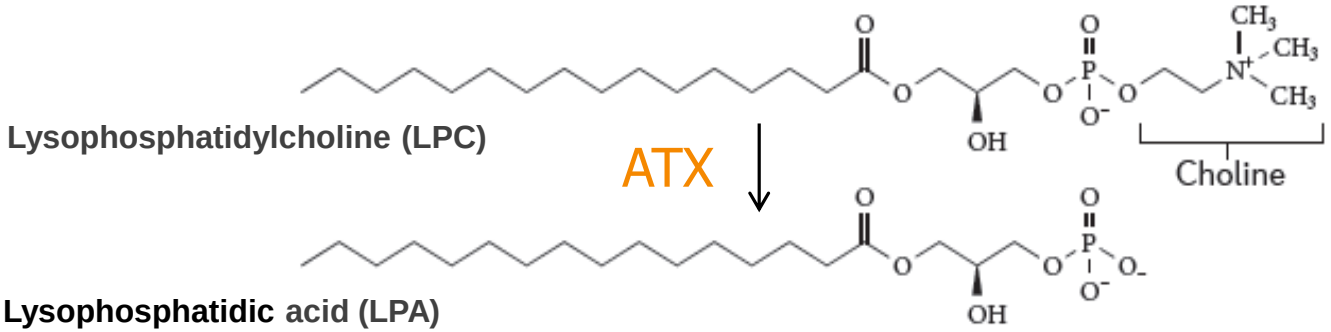
Articles

Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial

Toby M Maher, Ellen M van der Aar, Olivier Van de Steen, Lisa Allamassey, Julie Desrivot, Sonia Dupont, Liesbeth Fagard, Paul Ford, Ann Fieuw, Wim Wuyts

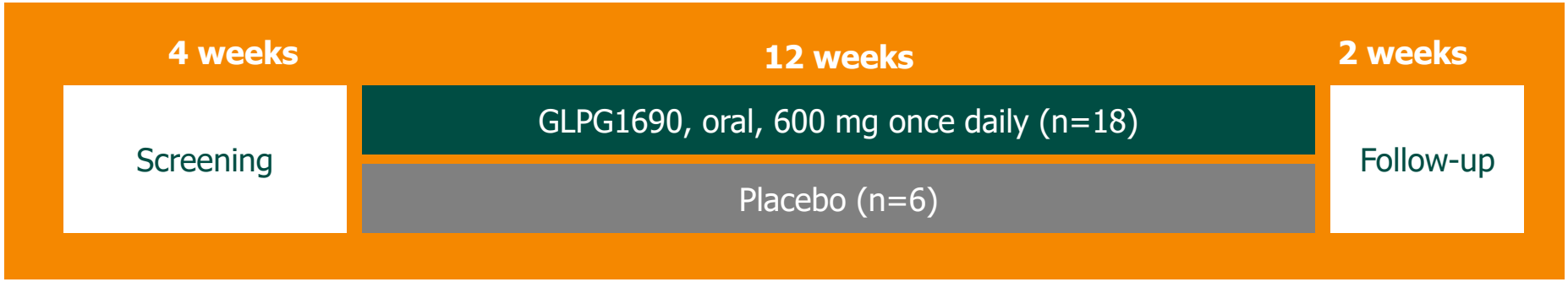
GLPG1690: Autotaxin inhibitor

- Autotaxin (ATX) is an enzyme that converts lysophosphatidylcholine to the bioactive lipid lysophosphatidic acid (LPA)



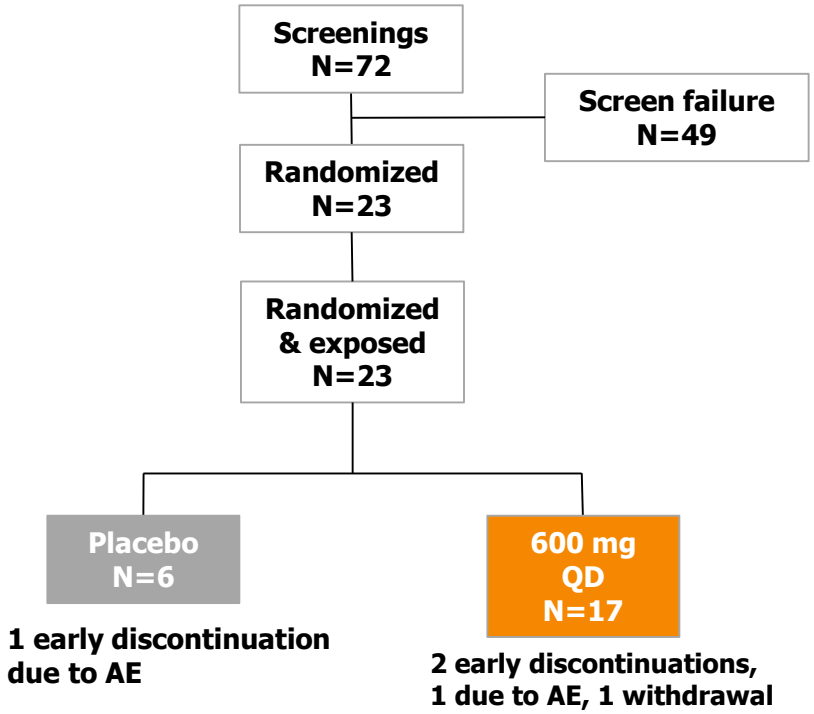
- LPA, which is involved in inflammatory and fibrotic processes, has been linked to the pathophysiology of IPF
- Increased LPA and ATX levels found in bronchoalveolar lavage fluid and lung tissue of IPF patients, respectively

FLORA Study Design



- Main inclusion/exclusion criteria
  - IPF patients diagnosed by HRCT/biopsy, centrally confirmed
  - FVC≥50% predicted of normal, DLCO ≥30% predicted of normal, FEV1/FVC ≥0.7
  - No pirfenidone/nintedanib 4 weeks prior to screening
  - No exacerbations of IPF 6 weeks before screening and during screening period
- Primary endpoints: safety, tolerability, PK/PD
- Secondary endpoints: spirometry, QoL, Functional Respiratory Imaging, biomarkers

Patient disposition and reason for early termination



Treatment	Number of days in the study	Termination	Reason for early termination
Placebo	77	Discontinued	AE: transient AV block II degree type II
600 mg	56	Discontinued	Withdrawal by subject
600 mg	7	Discontinued	AE: metastatic cholangiocarcinoma

Patient demographics and disease characteristics

	Placebo (n=6)	‘1690 (n=17)	Total (n=23)
Males n (%)	5 (83)	10 (59)	15 (65)
Age (mean, yrs)	62.5	66.6	65.6
BMI (mean, kg/m^2)	32.4	29.4	30.2
Smokers, n (%) former never	 3 (50) 3 (50)	 6 (35) 11 (65)	 9 (39) 14 (61)
Duration of IPF (mean, yrs)	1.0	1.9	1.7
DLCO (mean, % predicted of normal)	40.6	37.8	38.6
Baseline FVC (mean, L)	2.7	2.8	2.8
Baseline FVC (mean, % predicted of normal)	69.7	75.3	73.8

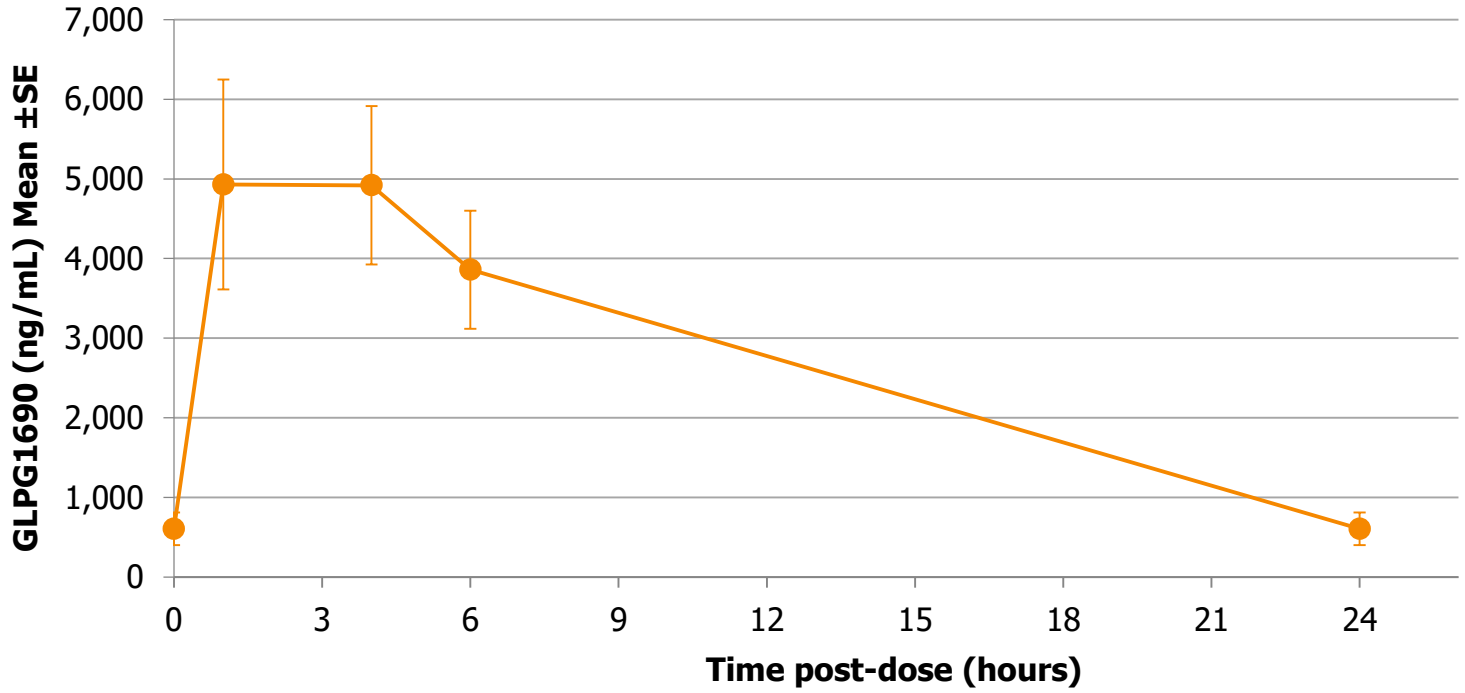
Safety and tolerability

Treatment emergent AEs

Overview TEAEs	Placebo (N=6)	‘1690 (N=17)
AE	67% (4)	65% (11)
Serious AE	33% (2)	6% (1)
Mild AE	0% (0)	24% (4)
Moderate AE	50% (3)	35% (6)
Severe AE	17% (1)	6% (1)
Related* AE	0% (0)	12% (2)
Temporarily stopped treatment	0% (0)	12% (2)
Permanently stopped treatment	17% (1)	6% (1)

* As judged by investigator during the trial

Mean GLPG1690 plasma profile and PK parameters at Week 4

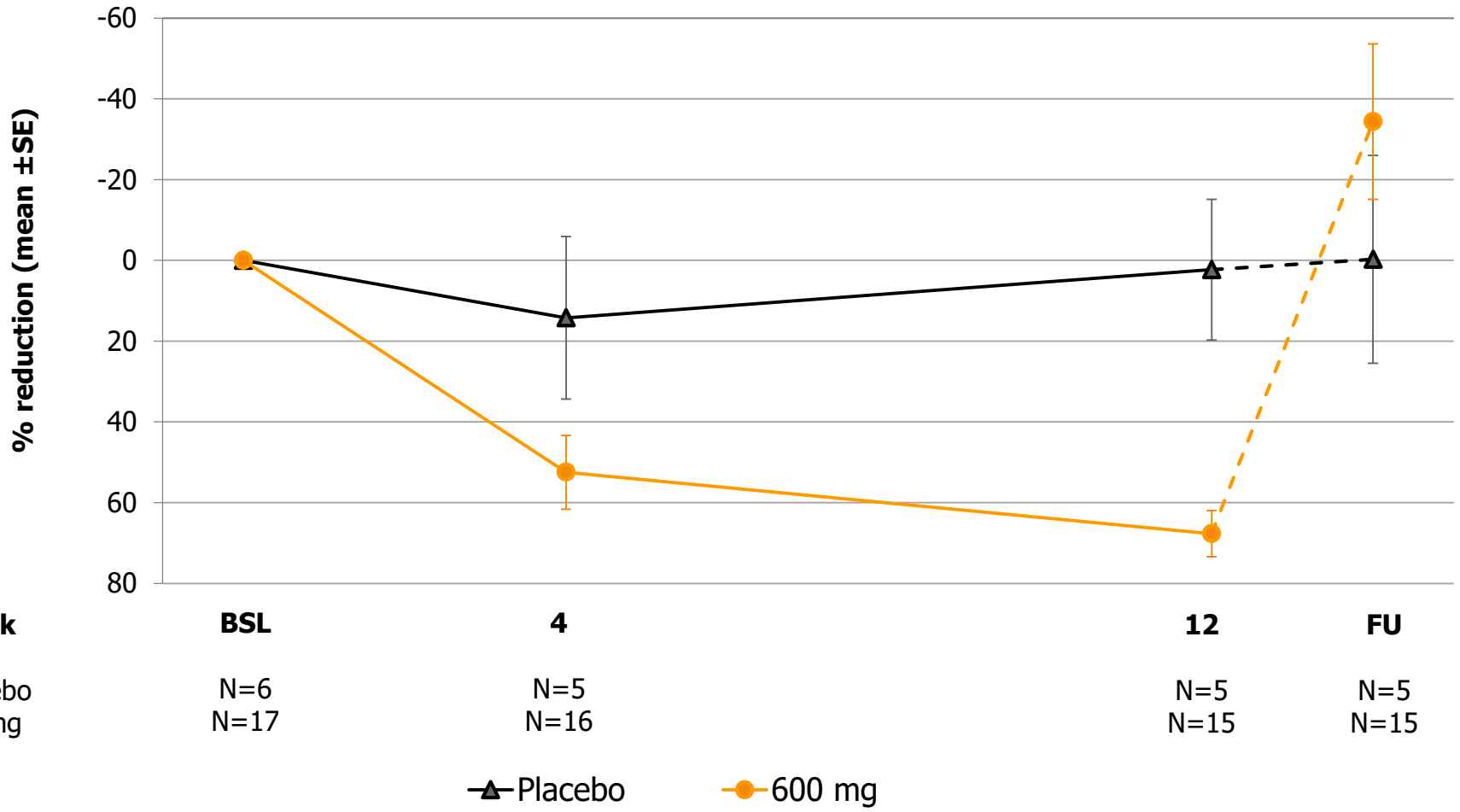


PK parameters at Week 4	C_{max} (µg/mL)	t_{max} (h)[1]	AUC_{0-T} (µg.h/mL)
Mean (CV%)	6.06 (81.2)	4 (1.5-6)	55.6 (83.9)

[1] Median (range) for t_{max}

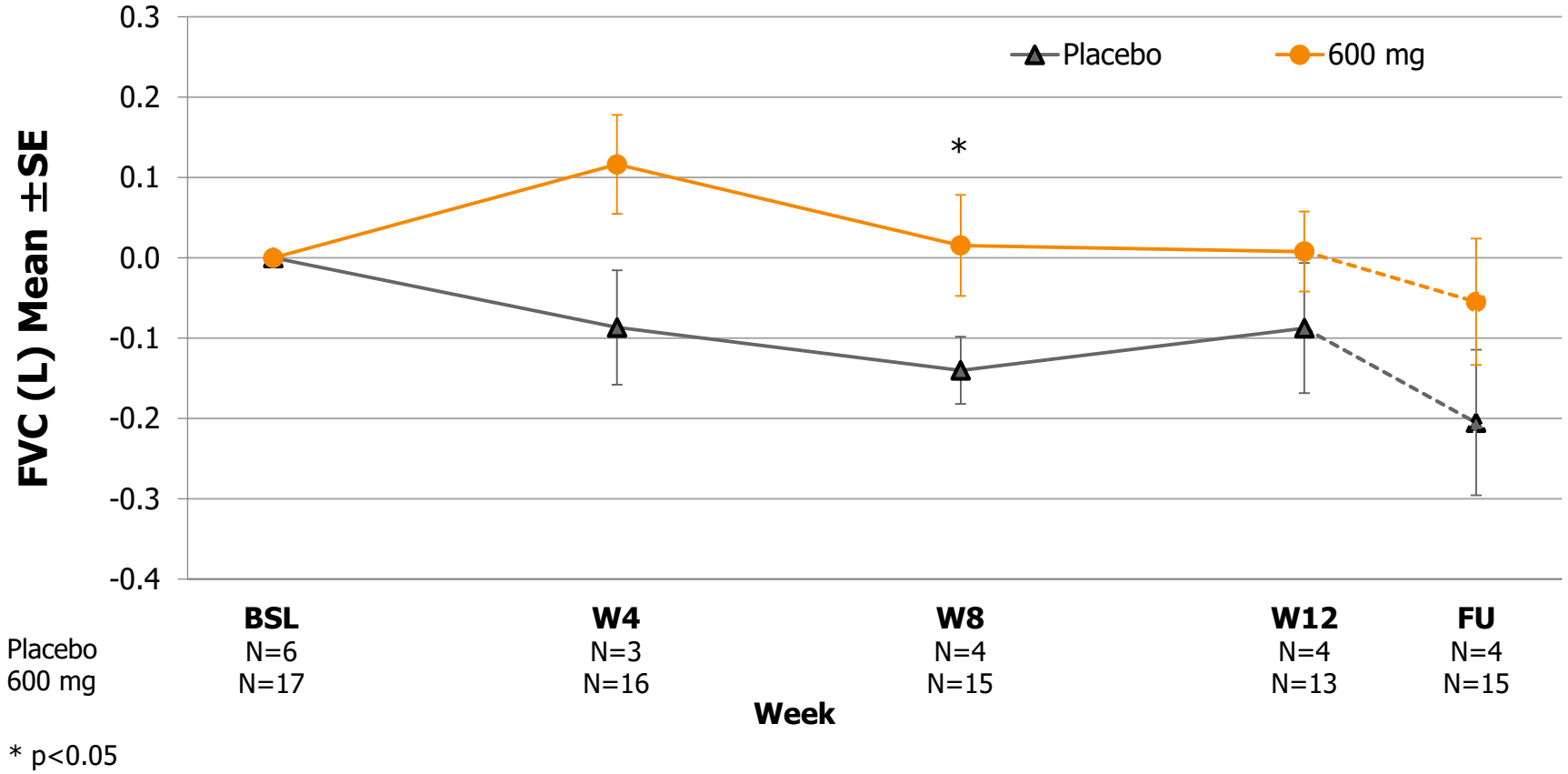
24h data point = predose assuming steady state

Plasma LPA 18:2, % reduction over time



BSL = baseline
FU = follow up
Dotted line = off treatment

FVC (L) at site, change from baseline

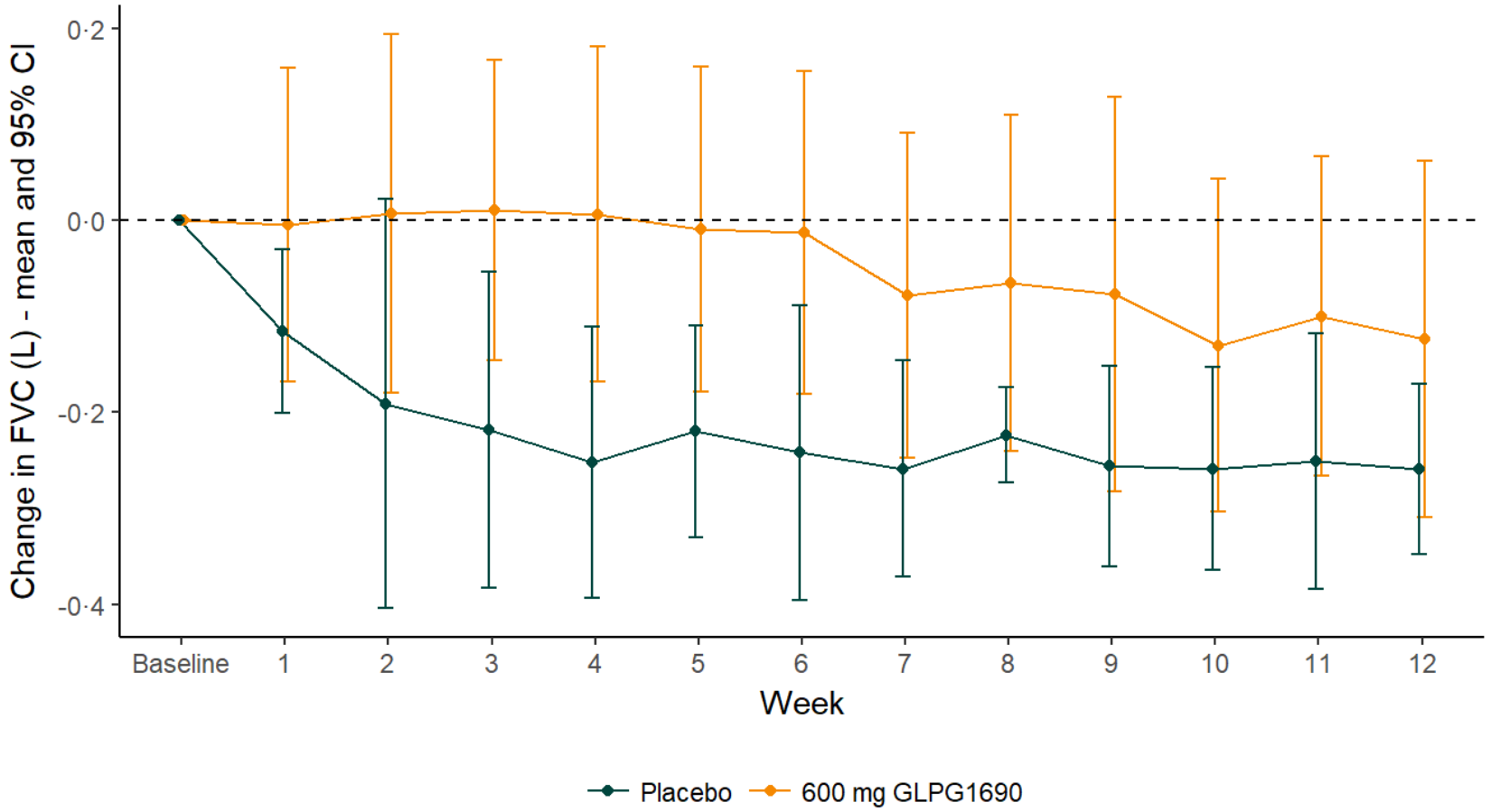


* p<0.05

	Wk4		Wk8		Wk12		Follow-up	
	Placebo	'1690	Placebo	'1690	Placebo	'1690	Placebo	'1690
FVC (Δ baseline, mL)	-87	+116	-140	+15	**-87**	**+8**	-205	-55

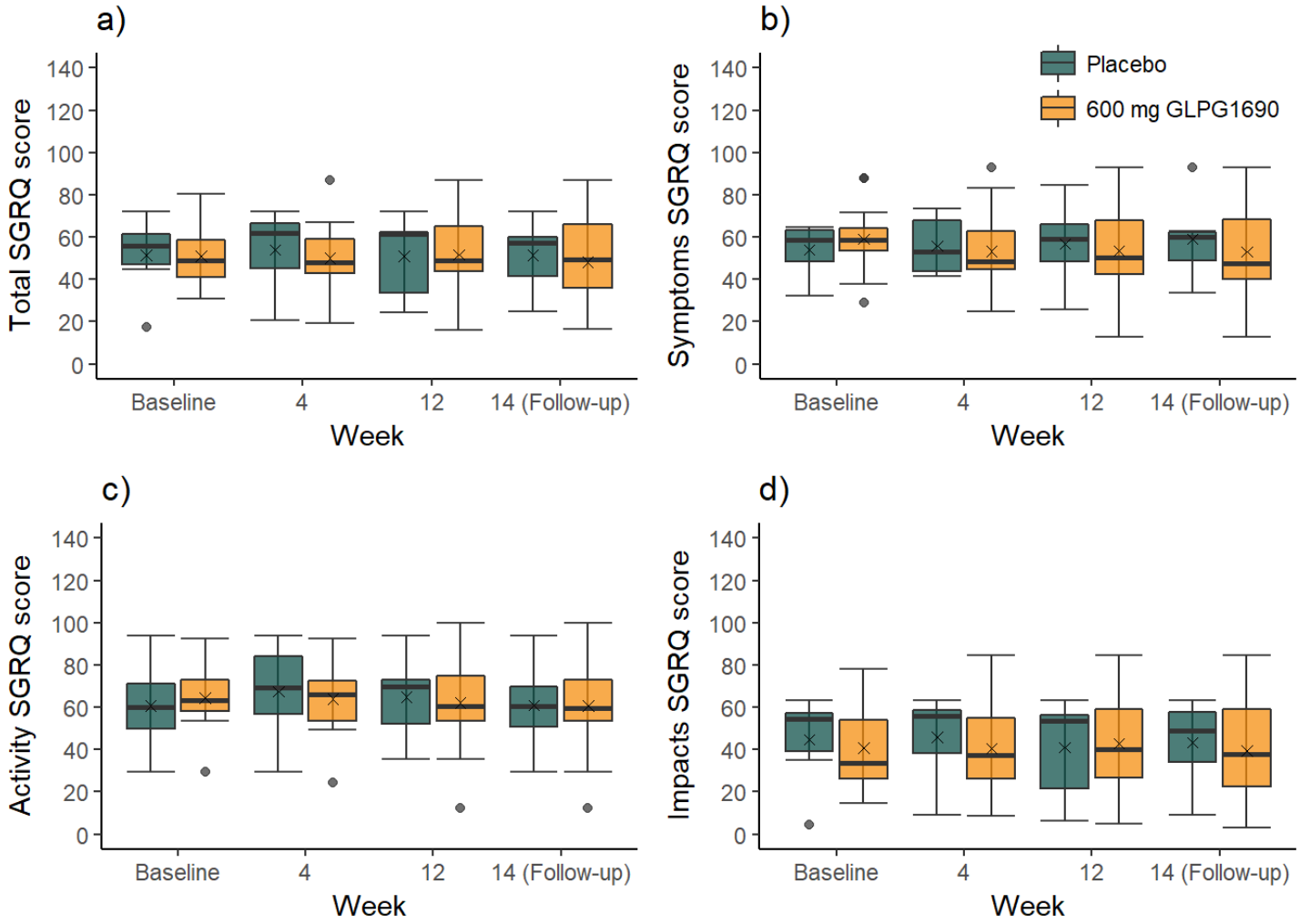
FVC = Forced vital capacity BSL = baseline FU = follow up
Dotted line = off treatment

FVC (L) by home spirometry
(weekly averages)



n = 16 for GLPG1690 600 mg
n = 6 for placebo
FVC = Forced Vital Capacity

SGRQ, actual values



SGRQ = St. George's Respiratory QOL Questionnaire
x = mean, ── = median

Functional Respiratory Imaging

- Presented at Mini Symposium ATS on Tuesday May 22nd, 2018 2:15 PM – 4:15 PM

FLORA results: Conclusion
Safety, PK, PD and efficacy

- No important safety or tolerability issues identified
- Pharmacokinetics and pharmacodynamics similar to data in healthy volunteers
  - Target engagement demonstrated through plasma LPA 18:2 reduction
- FVC stabilized at week 12 in GLPG1690 arm
- GLPG1690 Phase 3 program in IPF starting fall 2018

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