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GLPG1837 in Subjects with Cystic Fibrosis (CF) and the G551D Mutation: results from a Phase II study (SAPHIRA1)

ECFS, Sevilla, Spain
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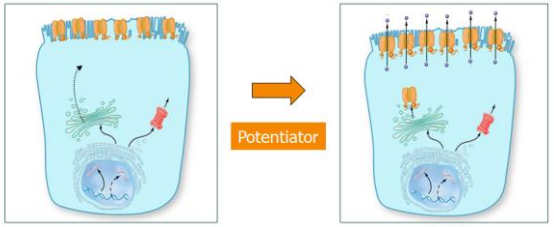
Jane Davies on behalf of the SAPHIRA1 Study Team

Disclosures

- Jane Davies:
  - Imperial College London has received fees for the following activities:
    - Galapagos: clinical trial leadership
    - Abbvie: Advisory Boards
    - Vertex, Proteostasis, Bayer: Advisory Boards & clinical trials roles

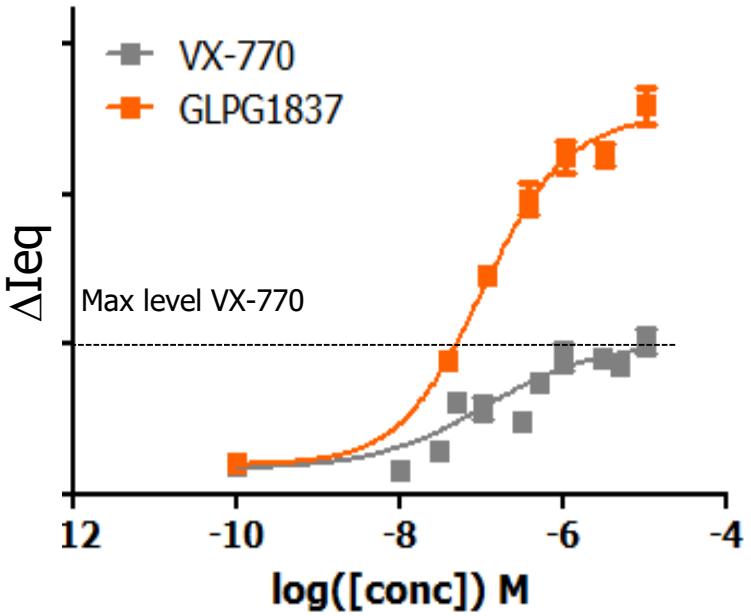
Introduction & Background



GLPG1837

- Investigational CFTR potentiator molecule
- Highly efficacious in opening G551D CFTR in *in vitro* models
- Generally well tolerated in Phase I clinical studies
- Evaluated in S1251N CFTR patients, generally well tolerated (SAPHIRA2, De Boeck *et al*. NACFC 2016)

G551D/ F508del HBE



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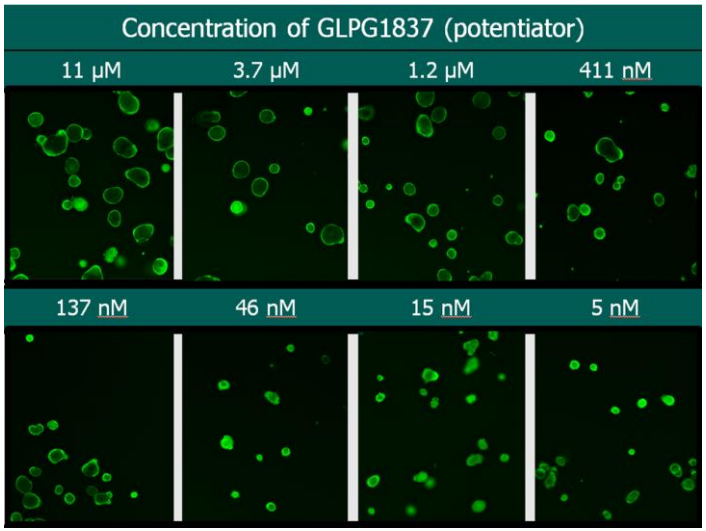
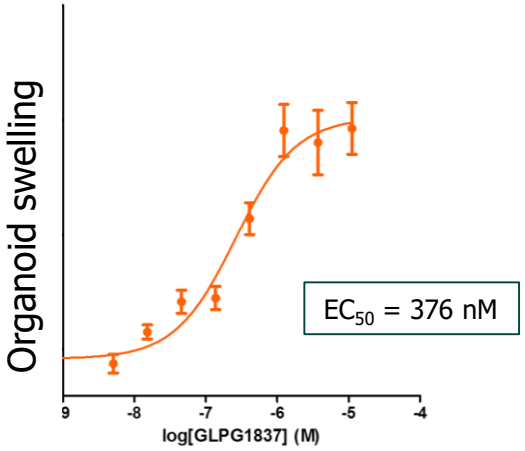
GLPG1837

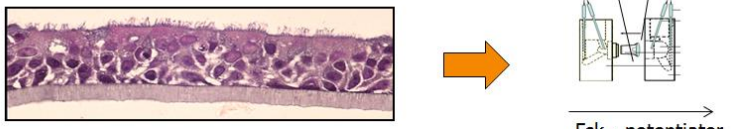
Pre-clinical data

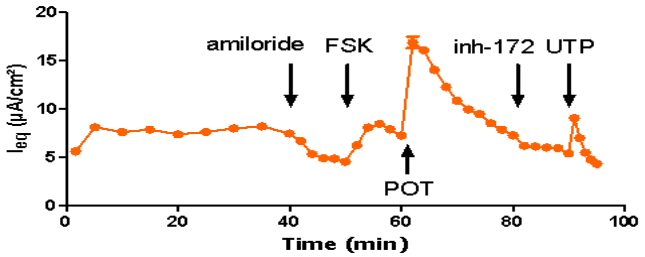
Swelling of patient-derived intestinal organoids

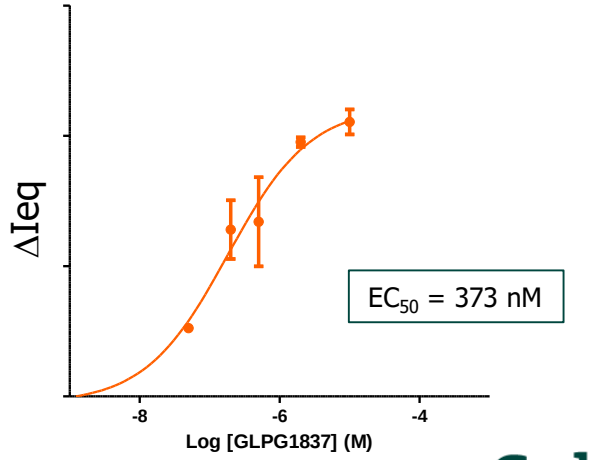




Electrophysiology (TECC) on primary lung cells







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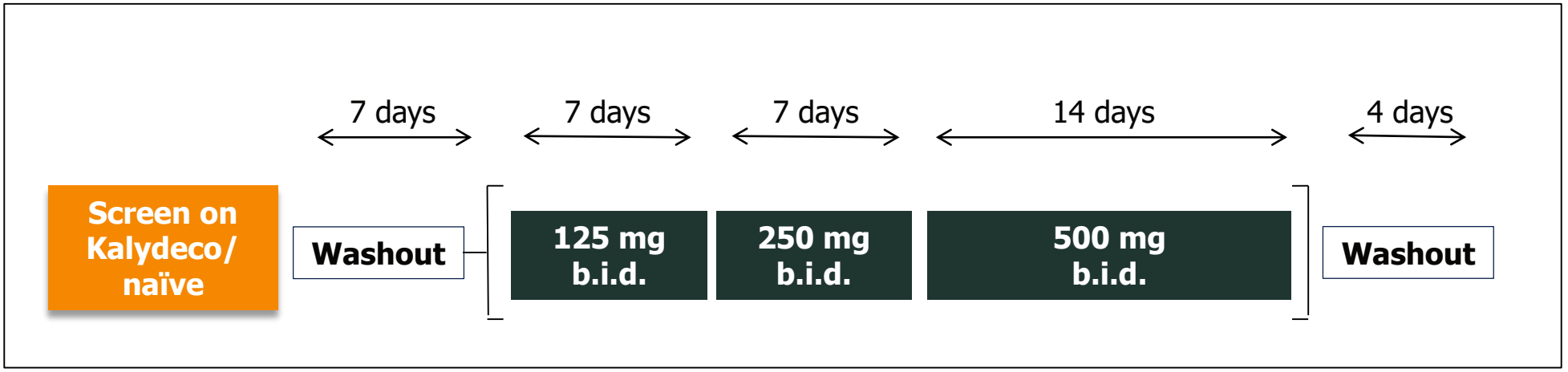
Study Design & Objectives



- Key Eligibility Criteria
  - Adult patient with G551D CFTR
  - Ivacaftor pre-treatment allowed (7 days-washout prior to dosing)
  - Screening ppFEV1 ≥ 40%
- Study Objectives
  - Primary: safety and tolerability
  - Secondary: Sweat Chloride, pharmacokinetics (PK), Spirometry

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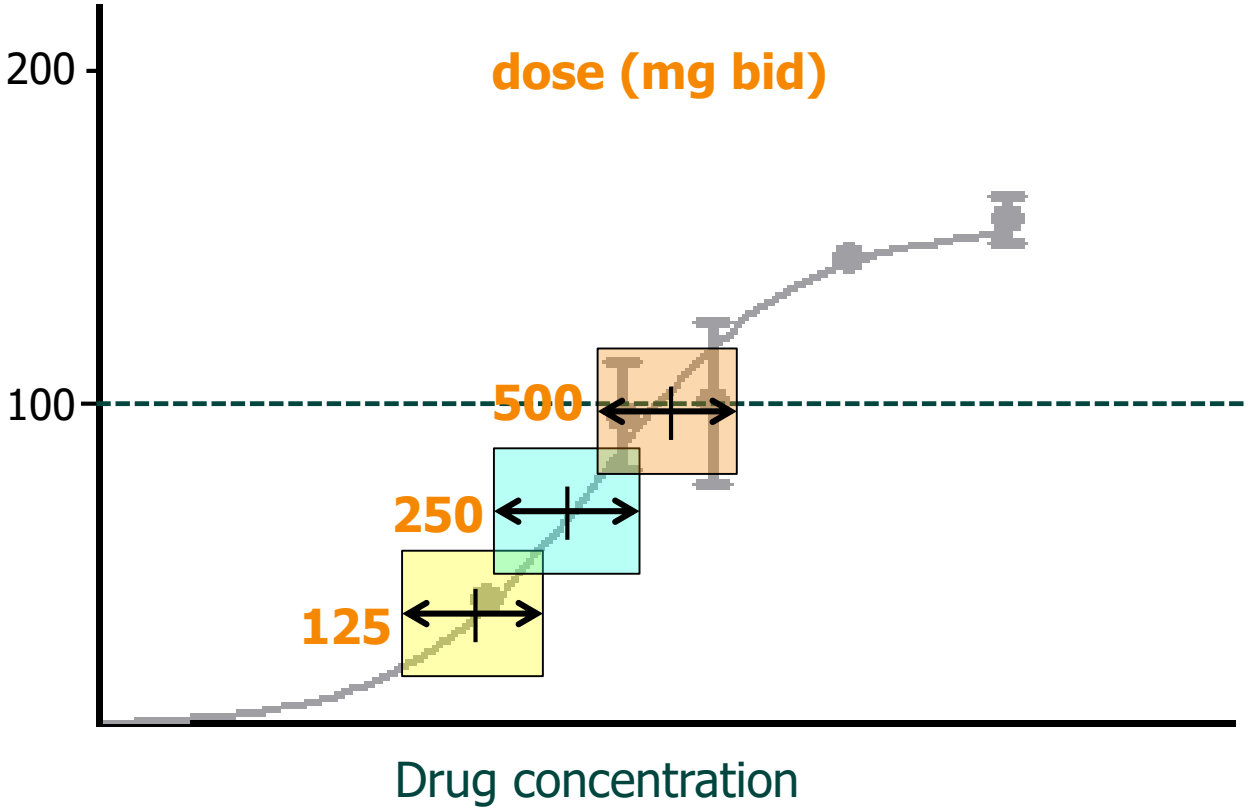
Dose Selection vs Efficacy

% efficacy *vs.* kalydeco



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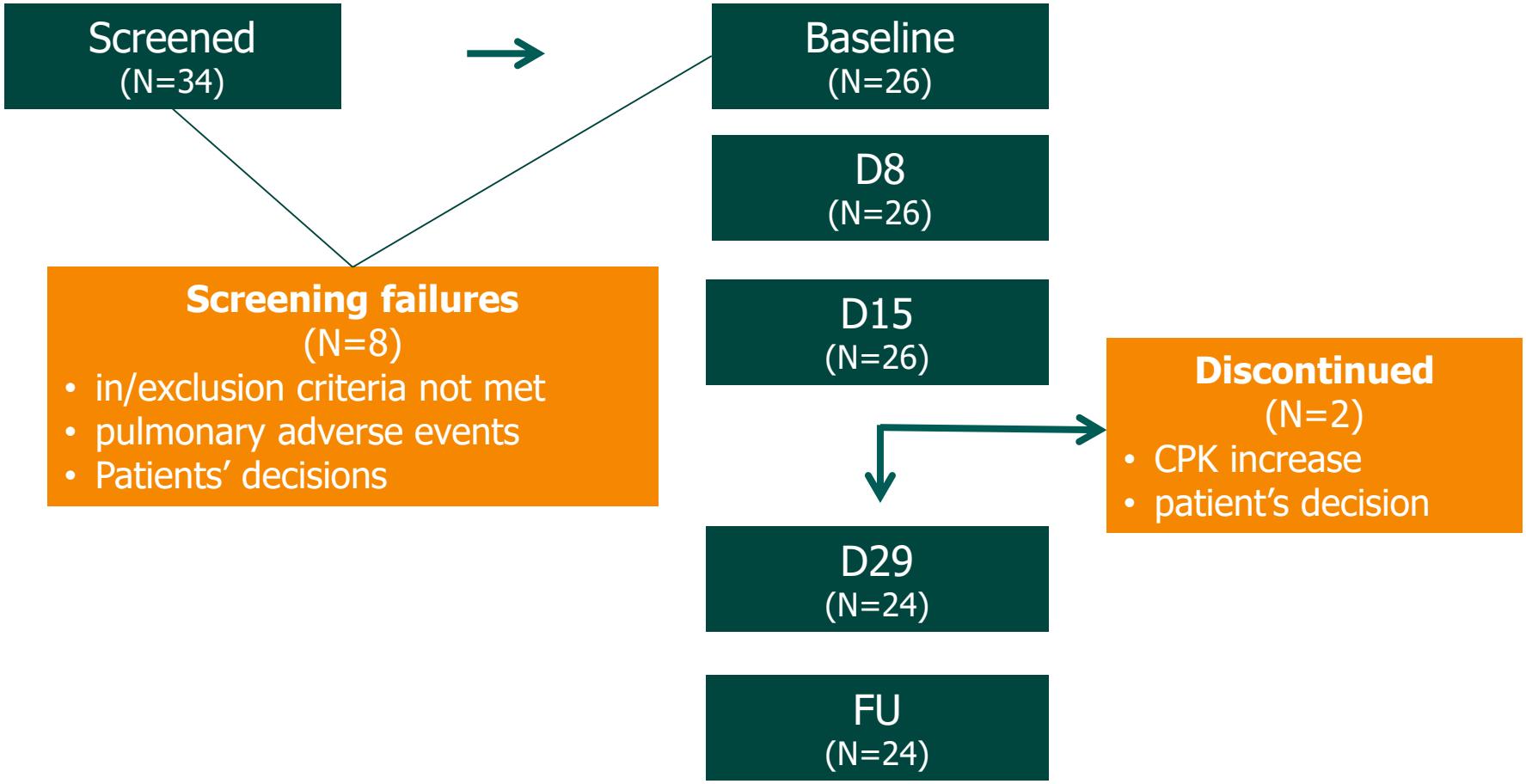
Countries & Study Conduct

- Study Initiation: February 23rd 2016
- Study Completion: October 6th 2016
- 26 patients enrolled

Patient disposition



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Baseline characteristics

Baseline Characteristic	ITT Population (N=26)
Age, years, mean Range	30.3 19 - 51
Weight, kg, mean	67.6
Male, n (%)	12 (46.2%)
[Sw Cl]@Baseline, mmol/L, mean Range	97.7 63 - 116
Percent predicted FEV1, mean (range) < 40%, n (%) 40% – 60%, n (%) 60% – 80%, n (%) > 80%, n (%)	69.2 (30 – 104) 2 (8%) 7 (28%) 8 (32%) 8 (32%)
F508del CFTR 2nd Allele (%)	18 (69.2%)
Ivacaftor use, n (%) Mean duration, weeks (range)	25 (96.2%) 169.9 (44 – 337)

Safety and Tolerability

Adverse Events reported by ≥ 5% of patients

MedDRA preferred Term N (%)	GLPG1837 125 mg b.i.d. (7 days)	GLPG1837 250 mg b.i.d. (7 days)	GLPG1837 500 mg b.i.d. (14 days)
Any Adverse Event	14 (53.8%)	14 (53.8%)	20 (76.9%)
Headache	4 (15.4%)	6 (23.1%)	6 (23.1%)
Sputum Increased	6 (23.1%)	-	-
Cough	2 (7.7%)	1 (3.8%)	2 (7.7%)
Haemoptysis	2 (7.7%)	-	-
Chest Discomfort	2 (7.7%)	1 (3.8%)	2 (7.7%)
Fatigue	4 (15.4%)	5 (19.2%)	-
Chest Pain	-	-	2 (7.7%)
Nausea	1 (3.8%)	1 (3.8%)	2 (7.7%)
Abdominal Pain Upper	2 (7.7%)	1 (3.8%)	2 (7.7%)
Abdominal Pain	-	1 (3.8%)	2 (7.7%)
GGT Increase	1 (3.8%)	-	2 (7.7%)

- Adverse Events: predominantly mild or moderate
- Two Serious Adverse Events in 2 patients: non-cardiac CPK increase (premature withdrawal) - Pulmonary Exacerbation (D28) resulting in hospitalization

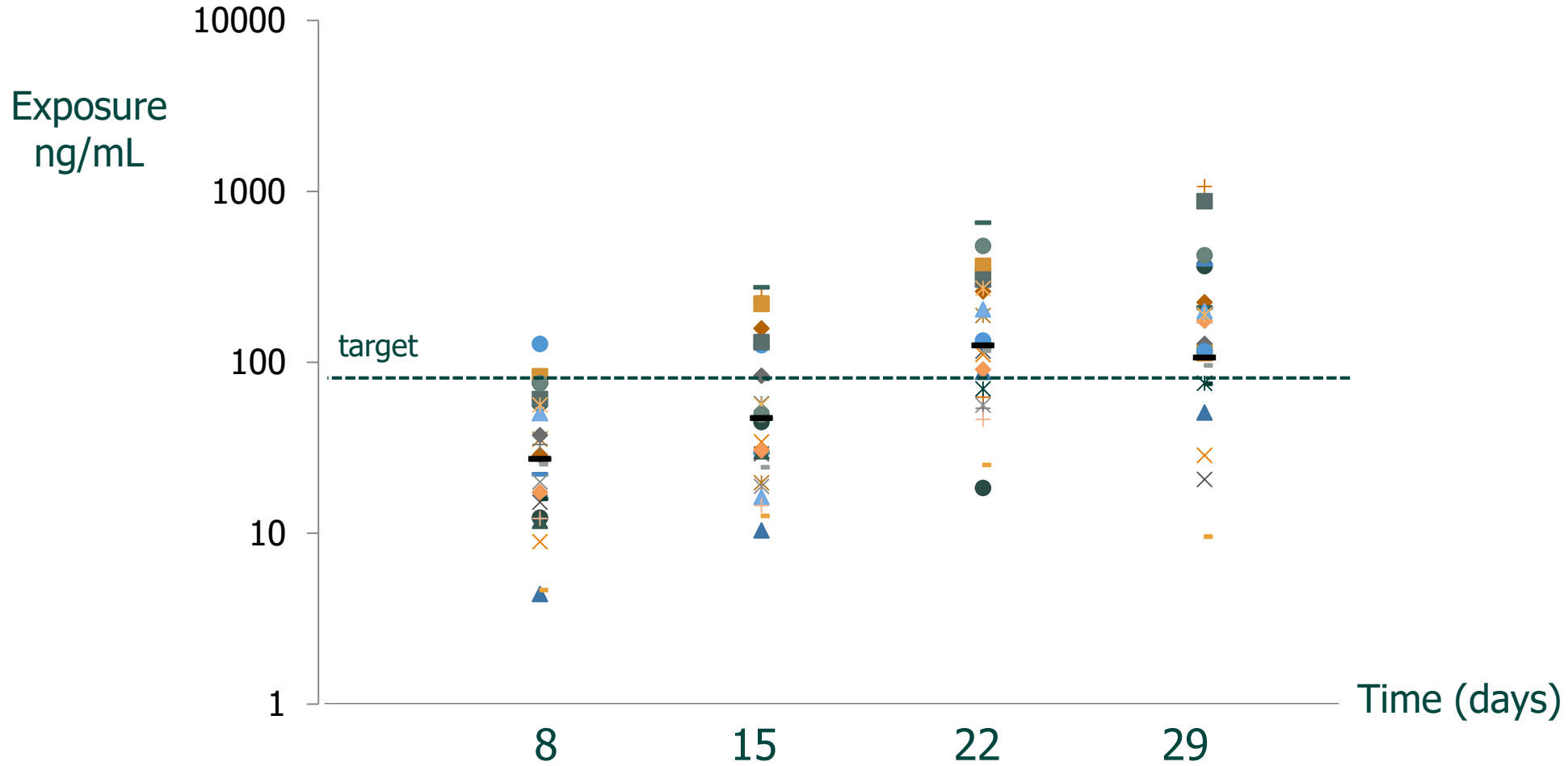
Safety and Tolerability
Lab results (liver biochemical & function test)

Liver Parameter	Normal Range	Baseline Mean (min, max)	D8 Mean (min, max)	D15 Mean (min, max)	D22 Mean (min, max)	D29 Mean (min, max)
AST	5-34 IU/L	20.8 (12, 36)	19.3 (9, 33)	21.8 (11, 56)	21.2 (12, 32)	21.8 (14, 38)
ALT	0-55 IU/L	22.0 (11, 66)	20.7 (9, 42)	23.5 (11, 54)	23.5 (10, 46)	28.2 (12, 73)
Alkaline Phosphatase	40-150 IU/L	98.5 (44, 306)	105.7 (45, 214)	112.7 (52, 215)	115.1 (51, 195)	120.7 (59, 245)
Bilirubin	0-21 µmol/L	9.6 (3, 19)	4.8 (3, 7)	5.0 (3, 8)	5.8 (4, 8)	5.7 (3, 8)
GGT	12-64 IU/L	21.2 (7, 145)	28.1 (10, 122)	41.7 (15, 152)	49.3 (17, 147)	61.7 (18, 240)

Increase in GGT
without associated changes other liver biochemical and function tests

Pharmacokinetics

Predose C_{trough} on days 8, 15, 22, 29



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Mean Absolute Sweat Chloride Change ITT Population (overall)

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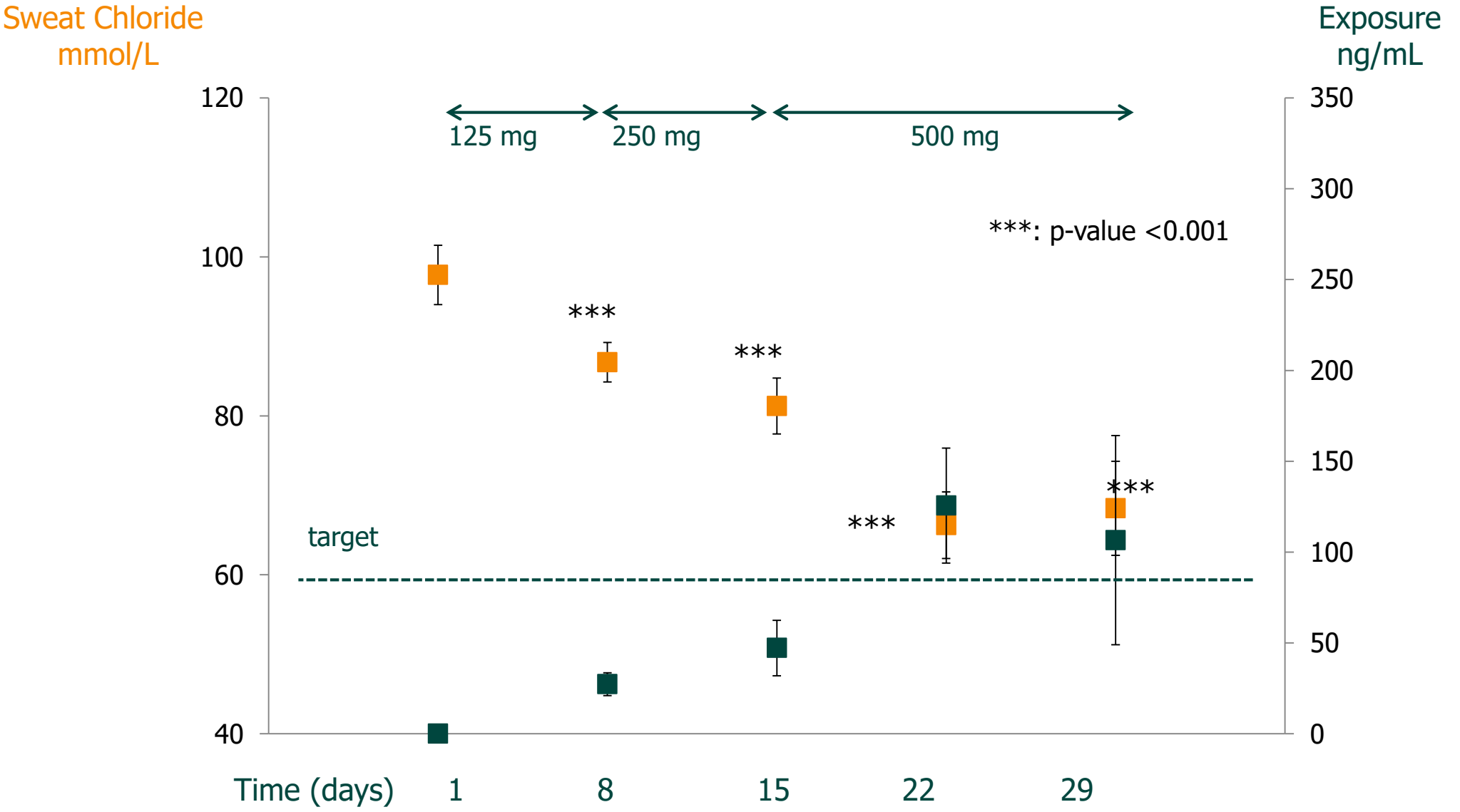
Sweat Chloride Change vs Exposure



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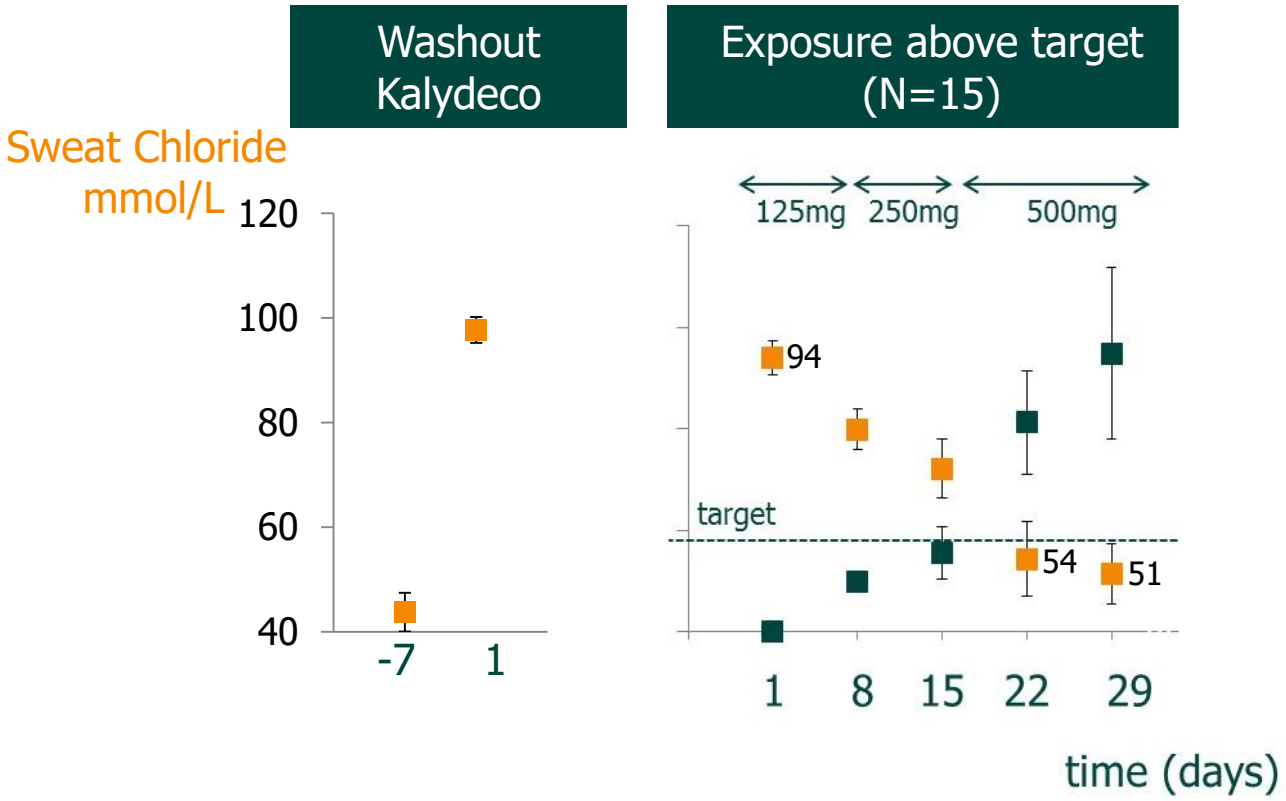
Sweat Chloride Change vs Exposure

Post-hoc exploratory sub-group Analysis



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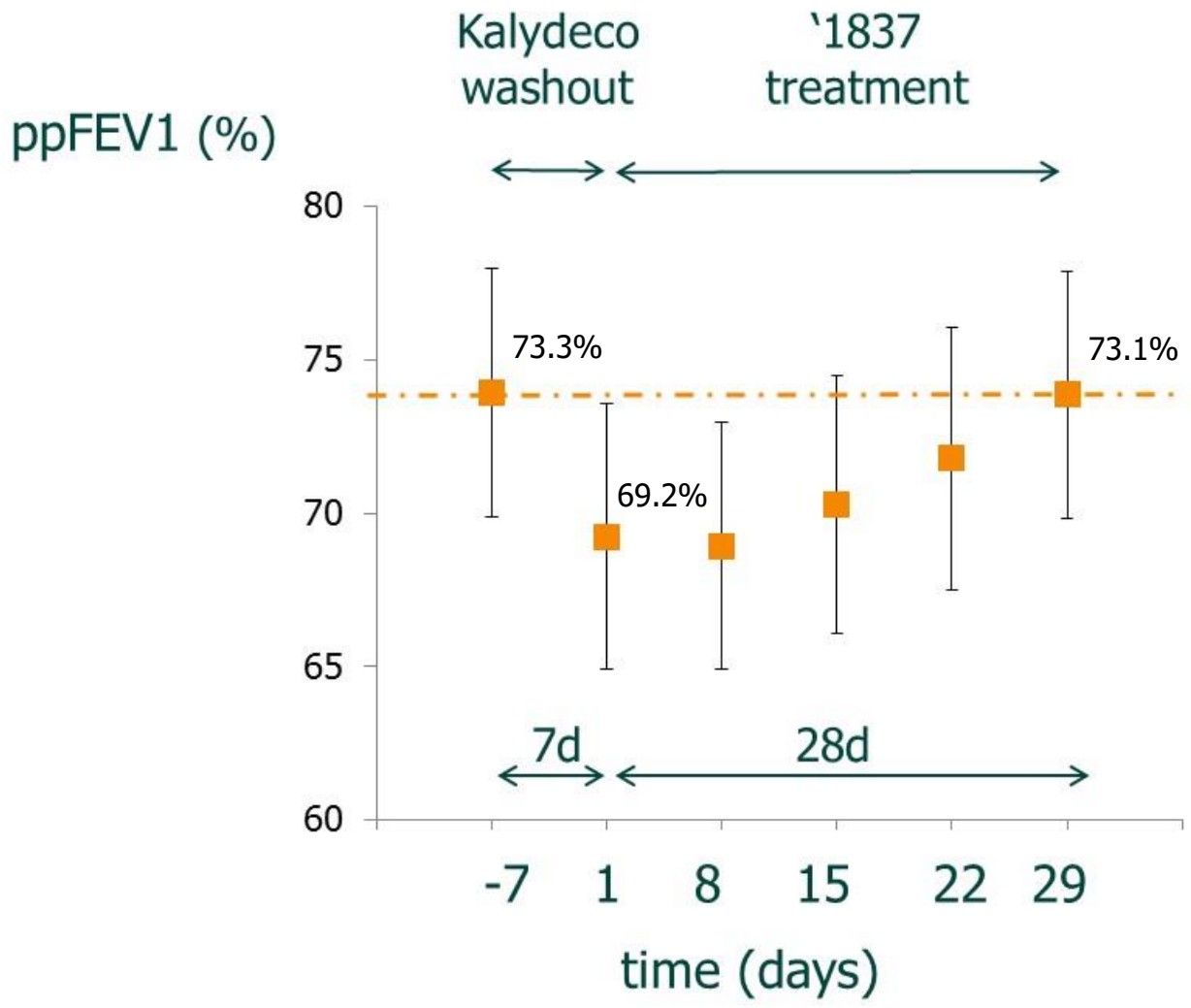
Mean Absolute Change ppFEV1

Sub-group Analysis: Ivacaftor Pre-treated



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Summary & Conclusions

- GLPG1837 appears generally well tolerated over dose range tested
  - Most common adverse events were headache and respiratory related
  - Isolated GGT elevations observed
- Significant reductions in sweat chloride observed
  - Larger reductions in sub-group exceeding predicted target plasma concentration
  - Effect similar to Kalydeco on G551D
- Full recovery of ppFEV1 decline resulting from Kalydeco washout
- Predictive value of current *in vitro* models demonstrated
- First clinical trial with investigational CFTR potentiator molecule showing promising results in an era of efficacious standard of care

Acknowledgements

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Patients for participating in the trial