Poster

Phase I characterization of the novel cathepsin C inhibitor BI 1291583

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Phase I characterization of the novel cathepsin C inhibitor BI 1291583

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INTRODUCTION

- Many chronic inflammatory respiratory diseases involve an imbalance between neutrophil-derived serine proteases (NSPs) and their inhibitors.[1,2]
- Currently there is no approved treatment for respiratory diseases driven by neutrophilic inflammation, such as bronchiectasis (high unmet need).
- Cathepsin C (CatC; also known as dipeptidyl peptidase 1) activates the NSPs neutrophil elastase (NE), proteinase 3 and cathepsin G, which, in part, mediate airway inflammation in chronic inflammatory lung disease.[3-5]
- BI 1291583 is a reversible, potent and selective CatC inhibitor that may ameliorate neutrophilic inflammation in the lungs.[6]
- BI 1291583 has completed five Phase I trials on healthy subjects.
- An ongoing Phase II trial for BI 1291583 in patients with bronchiectasis aims to evaluate the efficacy, safety and tolerability of BI 1291583 in preventing pulmonary exacerbations and to provide dose-ranging data. This trial is currently recruiting patients.
  - The primary endpoint is the time to first pulmonary exacerbation up to Week 48 after first drug administration.[7]

AIM

- To present Phase I characterization of BI 1291583, a novel CatC inhibitor currently undergoing a Phase II clinical trial

METHODS

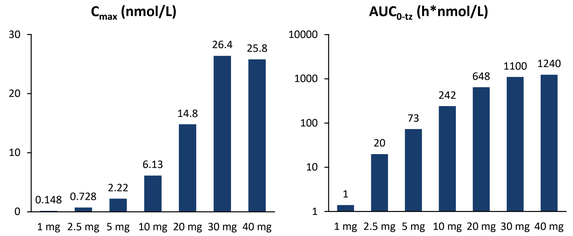
- We conducted five Phase I trials of BI 1291583 in healthy subjects:
  1) 1–40 mg single-rising-dose (SRD; NCT03414008)
  2) relative bioavailability, safety and tolerability of 2 x 7.5 mg doses with and without food (NCT03837964)
  3) drug–drug interaction of 2.5 mg doses with and without itraconazole, a strong cytochrome 3A and P-gp enzyme inhibitor (NCT03890887)
  4) multiple-rising-dose (MRD) with 1 mg and 2.5 mg (NCT03868540)
  5) a second MRD with 5 mg and 10 mg (NCT04866160)

CONCLUSIONS

- **BI 1291583 was safe and well tolerated; no clinically relevant food effect was observed on systemic exposure.**
- **Maximum 2-fold increase in exposure when BI 1291583 co-administered with a combined strong Cytochrome 3A and P-gp enzyme inhibitor (itraconazole).**
- **BI 1291583 demonstrated positive PD and PK outcomes.**

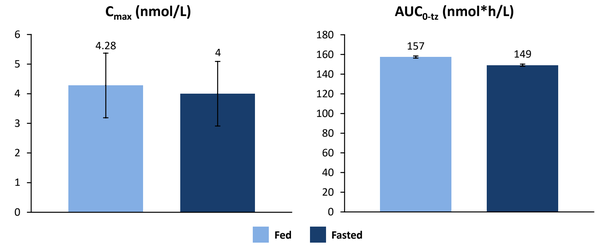
RESULTS

1) SRD PK data: 1–40 mg (oral solution)



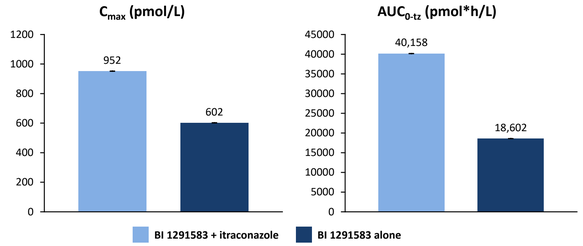
- 54 healthy male volunteers (n=5 or 6 per dose group, 14 patients received placebo)
- BI 1291583 readily absorbed at 1–40 mg
- Apparent $t_{1/2}$ was long, ranging from 33.6 to 60.2 hours
- PK supra-proportional over the dose range investigated

2) Food effect: 7.5 mg



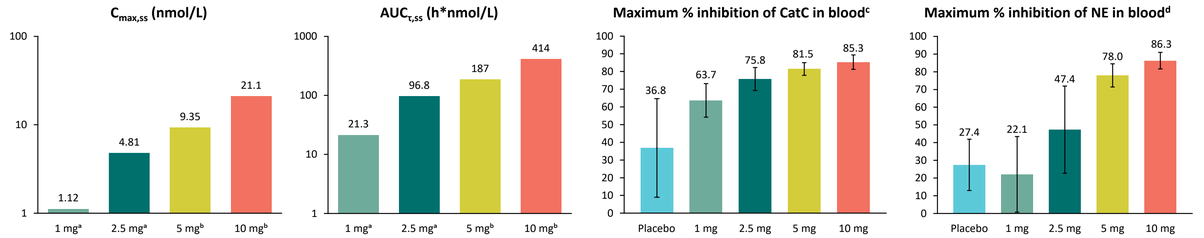
- 12 healthy male volunteers (n=11 included in each assessment)
- Single oral dose (7.5 mg)
- Under both fed and fasted conditions, BI 1291583 PK parameters were generally similar

3) Drug–drug interaction: 2.5 mg (tablet) with 200 mg itraconazole



- 14 healthy male volunteers (n=14 for all groups)
- Maximum 2-fold increase in exposure when BI 1291583 co-administered with a combined strong Cytochrome 3A and P-gp enzyme inhibitor (itraconazole [200 mg in solution])

4 & 5) MRD PK and PD data: 1–10 mg (tablets)



- 48 healthy volunteers (20 male and 4 female, 6 patients received placebo[a]; 24 males, 6 received placebo[b])
- Steady state reached after 14 days
- Multiple oral administrations of BI 1291583 resulted in accumulation as expected; consistent with the long half life

- Mean CatC inhibition: 1 mg = 64%; 2.5 mg = 76%; 5 mg = 81%
- CatC inhibition 6 hours post-dose (dose dependent)
- Inhibition reached plateau around 5 mg

- Mean NE inhibition: 1 mg = 22%; 2.5 mg = 47%; 5 mg = 78%
- NE activity recovers following drug cessation
- NE inhibition delayed versus CatC inhibition

[a]NCT03868450. [b]NCT04866160. [c]Mean and SD, normalized to white blood cell count. [d]Mean and SD, normalized to neutrophil count.

1–5) Safety

- On-treatment adverse events (AEs) were similar between groups (67% BI 1291583 and 83% placebo in the MRD trials).
- Most AEs were of mild-to-moderate intensity. There were only two severe TEAEs; both were considered unrelated to trial medication:
  - Event 1: gastrointestinal infection (BI 1291583 1 mg; trial 1; SRD)
  - Event 2: a case of joint injury under fed condition (BI 1291583 7.5 mg; trial 2; food effect study).
- Trial discontinuation due to AE: In trial 4 (MRD 1 mg and 2.5 mg), one subject (1 mg dose group) discontinued trial medication due to "C-reactive protein increased" and "thrombophlebitis"; both events were assessed as not drug-related.
- No deaths, serious AEs, or AEs of special interest occurred.
- No trends or patterns noted in safety lab, vital signs and electrocardiogram observations.
- Treatment-related skin exfoliation was comparable between BI 1291583 and placebo (in the MRD trials).
- Treatment with BI 1291583 was considered safe and well tolerated.

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ABBREVIATIONS

AE, adverse event; AUC, area under the curve; CatC, cathepsin C; C_{max}, maximum measured concentration of the analyte in plasma; $C_{max,ss}$, C_{max} at steady state; MRD, multiple-rising-dose; NE, neutrophil elastase; NSP, neutrophil serine protease; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation; SRD, single-rising-dose; TEAE, treatment-emergent adverse event; t_{max}, time to maximum concentration; $t_{1/2}$, terminal half-life; τ_{ss}, from time 0 to time τ at steady state.

DISCLOSURES

P Badorrek and F Seitz have nothing to disclose. C Diefenbach, H Kögler, A Eleftheraki, D Sarubbi and R Sennewald are employees of Boehringer Ingelheim. JM Hohlfeld reports grant support paid to his institution from AltamiraPharma GmbH, Astellas Pharma GmbH, AstraZeneca AB, Bayer AG, Beiersdorf AG, Boehringer Ingelheim Pharma GmbH & Co. KG, CSL Behring GmbH, Desitin Arzneimittel GmbH, F. Hoffmann-La Roche AG, Genentech, Inc., GlaxoSmithKline GmbH & Co. KG, Janssen Pharmaceutical NV, M&P Pharma AG, Novartis AG, Sanofi-Aventis Deutschland GmbH and UCB Pharma GmbH, personal fees from Roche, personal fees for consultancy from Boehringer Ingelheim Pharma GmbH & Co. KG and Merck & Co, Inc., personal fees for lectures from HAL Allergy Group and Novartis AG, and personal fees for board service from CSL Behring GmbH and Nocion.

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