Phase I characterization of the novel cathepsin C inhibitor BI 1291583
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Phase 1 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 active proteinases (NSPs) and their inhibitors.1
• Currently there is no approved treatment for respiratory diseases driven by neutrophilic inflammation, such as bronchiectasis.2
• Cathepsin C (CatC; also known as disintegrilysin or CTSL) activates the NSPs neutrophil elastase (NE) and proteinase 3 (PR3) and is thus, in part, mediates airway inflammation in chronic inflammatory lung disease.2
• BI 1291583 is a reversible, potent and selective CatC inhibitor that may ameliorate neutrophilic inflammation in the lungs.2
• BI 1291583 has completed five Phase I trials in healthy subjects.
• As an ongoing Phase I trial of 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 currently recruits patients.
• The primary endpoint is the time to first pulmonary exacerbation up to week 68 after first drug administration.7

AIM

• To present Phase 1 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 volunteers:3,7
  1) 40 mg single oral dose (SO) (NCT03837964)
  2) Relative bioavailability, safety and tolerability of 0.75 to 7.5 mg doses with and without food (NCT07710987) (dose dependent)
  3) Drug-drug interaction of 2.5 mg doses with and without itraconazole, a strong Cytochrome 3A and P-glycoprotein (P-gp) inhibitor (NCT19809287)
  4) Multiple single dose (MSD) PK with 5 mg and 7.5 mg (NCT04866160)
  5) A second MSD PK with 5 mg and 10 mg (NCT04866160).
• 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-administrated with a combination of itraconazole 2.5 mg and P-gp inhibitor (itraconazole).
• BI 1291583 demonstrated positive PD and PK outcomes.

RESULTS

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

• 54 healthy male volunteers (n=6 in each dose group, 14 at each dose level (70 participants))
• Apparent t\(_{1/2}\) was long, ranging from 33.6 to 60.2 hours
• PK were proportional over the dose range investigated.

2) Food effect: 7.5 mg

• 17 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 (tablets) with 200 mg itraconazole

• 14 healthy male volunteers (n=11 for all groups)
• Maximum 3-fold increase in exposure when BI 1291583 co-administrated with a combined strong Cytochrome 3A and P-gp inhibitor (itraconazole 200 mg in solution)

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

• 40 healthy volunteers (20 male and 20 female, 6 received placebo: 20 males, 6 received placebo)
• Steady-state reached after 14 days
• Multiple oral administrations of BI 1291583 resulted in accumulation as expected, consistent with the long t\(_{1/2}\)

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• Mean NE inhibition: 1 mg = 12%; 2.5 mg = 47%; 5 mg = 76%; NE activity recovery following drug cessation: NE inhibition delayed versus CatC inhibition

CONCLUSIONS

• On-treatment adverse events [AEs]: were similar between groups (37% BI 1291583 and 85% placebo in the MSD trials)
• Most AEs were of mild to moderate intensity; there were only two severe TEAs; 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 1 mg; trial 1; SRD)
• Trial discontinuation due to AE: trial 1 (4 mg; 2.5 mg and 2 mg), one subject (3 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 in laboratory data, vital signs and electrocardiogram observations.
• Treatment-related skin edema was comparable between BI 1291583 and placebo (in the MSD trials).
• Treatment with BI 1291583 was considered safe and well tolerated.

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