Final pooled data from Phase II studies (AIRLEAF®, CLAIRLEAF®) of the dipeptidyl peptidase 1 (or Cathepsin C) inhibitor verducatib in bronchiectasis

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Objectives

To provide additional supporting data on the long-term efficacy and safety of the DPP1 nhibitor verducatib in bronchiectasis.

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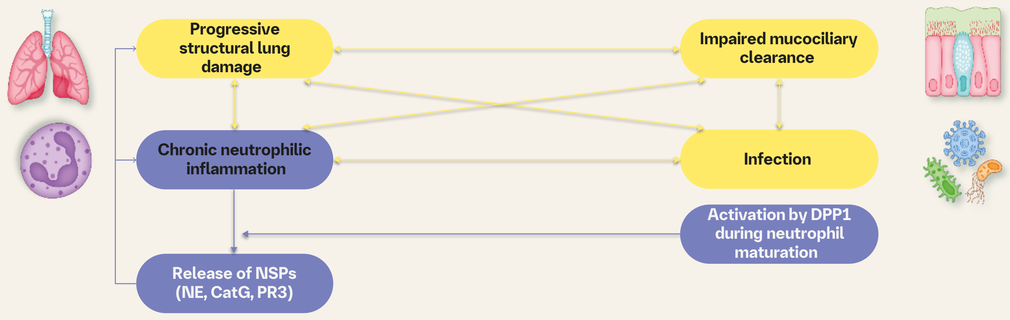
Introduction

- One of the key drivers of the chronic lung disease, BE, is neutrophilic inflammation, which is caused by an imbalance between NSPs and their natural inhibitors.[1–4]
- NSPs are activated by DPP1 (also known as CatC), making DPP1 inhibition an attractive target to reduce NSP activity in BE.[3,5,6]



- Long-term data on efficacy and safety are needed for DPP1 inhibitors in BE.
- The Phase II AIRLEAF® study (NCT05238675) evaluated the efficacy, safety, and optimal dosing of verducatib (BI 1291583),[3] a reversible, highly potent and selective inhibitor of DPP1, in people with BE.[3,7] Verducatib reduced the risk of experiencing PExs in AIRLEAF®.[3]
- CLAIRLEAF® (NCT05846230)[8] is a rollover study evaluating the long-term safety and efficacy of verducatib in people with BE who completed verducatib treatment in AIRLEAF® (NCFBE) and CLAIRAFLY® (CFBE; NCT05865886).[9]
- Verducatib 2.5 mg is being investigated in people with BE, irrespective of etiology, in the Phase III AIRTIVITY® study (NCT06872892).[10]
- Here, we present the final pooled analysis from all participants with NCFBE who received verducatib in the AIRLEAF® and CLAIRLEAF® studies. This is based on final data from these studies. Data from participants with CFBE from CLAIRAFLY® and CLAIRLEAF® were not included in this analysis.

Methods

- AIRLEAF® was a multinational, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study that enrolled 322 adults with CT-confirmed BE. Participants had a broad range of underlying etiologies,including COPD and asthma, as well as idiopathic BE.
- Key inclusion criteria for AIRLEAF®:
  - Aged 18–85 years with CT-confirmed BE (scans not older than 5 years)
  - History of PExs requiring antibiotic treatment prior to screening (either ≥2 in the past year, or 1 in the past year with an SGRQ Symptoms score >40)
  - Current sputum producers with a history of chronic expectoration
- Participants who completed treatment in AIRLEAF® were eligible to enter CLAIRLEAF®, a randomized, double-blind,parallel-group, rollover study. Upon entering CLAIRLEAF®, those on active therapy in AIRLEAF® remained on the same blind verducatib dose. Those in the placebo group in AIRLEAF® were blindly randomized (1:1:1) to one of the three verducatib doses (1 mg, 2.5 mg, 5 mg). After completion of the blinded phase of CLAIRLEAF®, all participants were entered into a longer-term OLE of CLAIRLEAF® where they received verducatib 2.5 mg. Data from this open-label phase are not included in the current analysis.
- **Pooled analysis**
  - We previously reported a pre-specified analysis of the interim pooled data from the AIRLEAF® and CLAIRLEAF® studies.[11] For the current analysis, final data from AIRLEAF® and the blinded phase of CLAIRLEAF® were pooled to allow analyses with observational data up to Week 156. Due to the absence of placebo in CLAIRLEAF®, verducatib 2.5 and 5 mg were compared against the subtherapeutic 1 mg dose, which had a similar effect compared with placebo in AIRLEAF®.[11]
- **Efficacy endpoints (from first verducatib administration):**
  - Time to first PEx up to Week 156
  - Annualized rate of PExs up to Week 156
- **Safety analysis:**
  - The safety analysis set includes all participants who have taken any dose of verducatib treatment, either in AIRLEAF® or CLAIRLEAF®.
  - Safety analysis was not comparative due to the absence of placebo in the pooled analysis.

Baseline characeristics

- Of the 322 participants in AIRLEAF®, 26 participants from the placebo group either discontinued early or did not roll over to the CLAIRLEAF® study. These participants, therefore, did not receive verducatib at any time and were excluded, resulting in 296 participants in the pooled analysis.
- Baseline characteristics were generally similar across verducatib doses.

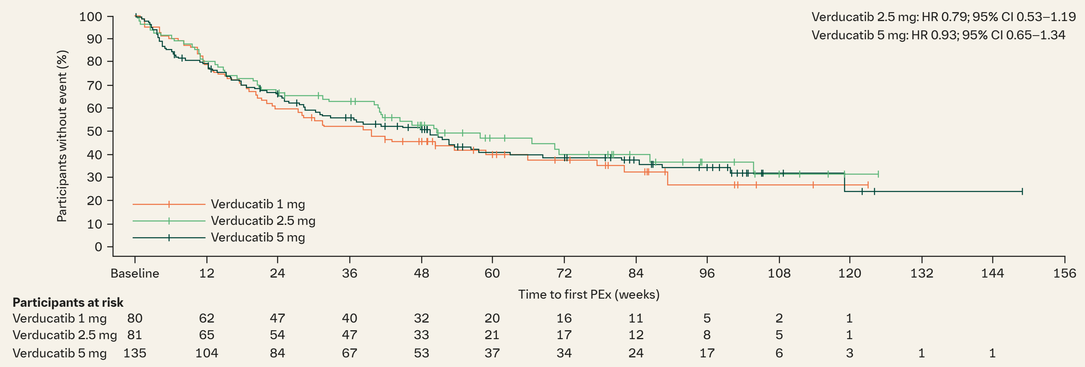
Characteristic	Verducatib (N=296)		
	1 mg (n=80)	2.5 mg (n=81)	5 mg (n=135)
Age, years	58.3±16.5	61.3±14.4	59.7±16.0
Sex, female	49 (61.3)	44 (54.3)	81 (60.0)
Body mass index, kg/m²	23.5±4.5	24.0±5.9	23.8±4.6
Race			
White	68 (85.0)	57 (70.4)	109 (80.7)
Asian	11 (13.8)	21 (25.9)	22 (16.3)
Other[a]	1 (1.3)	3 (3.7)	4 (3.0)
Region			
Eastern Europe	26 (32.5)	18 (22.2)	40 (29.6)
Asia	9 (11.3)	20 (24.7)	17 (12.6)
Western Europe, North/South America, Other	45 (56.3)	43 (53.1)	78 (57.8)
Etiology of BE			
Idiopathic	32 (40.0)	39 (48.1)	57 (42.2)
Post-infectious	18 (22.5)	11 (13.6)	29 (21.5)
Asthma	11 (13.8)	10 (12.3)	13 (9.6)
COPD	5 (6.3)	10 (12.3)	14 (10.4)
Primary ciliary dyskinesia	9 (11.3)	6 (7.4)	11 (8.1)
Connective tissue disease	0 (0)	0 (0)	1 (0.7)
Other[b]	5 (6.3)	5 (6.2)	10 (7.4)
History of PExs in past year			
1	23 (28.8)	27 (33.3)	41 (30.4)
≥2	57 (71.3)	54 (66.7)	94 (69.6)
P. aeruginosa positive	25 (31.3)	34 (42.0)	47 (34.8)
Maintenance use of macrolides	10 (12.5)	16 (19.8)	30 (22.2)
SGRQ Symptoms score	58.4±20.9	60.3±20.9	60.3±20.8

Data are presented as n (%) or mean±standard deviation.
[a]American Indian or Alaska Native, Black or African American, and Native Hawaiian or Other Pacific Islander. [b]Participants with multiple etiologies are grouped into 'Other'.

Efficacy

- **Time to first PEx up to Week 156 (Figure 1)**
  - Compared with the 1 mg dose, the 2.5 mg dose of verducatib was associated with a 21% lower risk of first PEx(HR 0.79; 95% CI 0.53–1.19) up to Week 156. The 5 mg verducatib dose was associated with a 7% lower risk of first PEx (HR 0.93; 95% CI 0.65–1.34) up to Week 156 compared with the 1 mg dose.
- **Annualized rate of PExs up to Week 156 (Figure 2)**
  - Compared with the 1 mg dose, the 2.5 mg dose of verducatib was associated with a 32% reduction in rate of annualized PExs up to Week 156 (RR 0.68; 95% CI 0.46–1.01). The 5 mg verducatib dose was associated with a 3% reduction in rate of annualized PExs up to Week 156 compared with the 1 mg dose (RR 0.97; 95% CI 0.69–1.35).

Figure 1. Kaplan–Meier plot of time to first PEx up to Week 156



Participants at risk

Verducatib 1 mg	80	62	47	40	32	20	16	11	5	2	1		
Verducatib 2.5 mg	81	65	54	47	33	21	17	12	8	5	1		
Verducatib 5 mg	135	104	84	67	53	37	34	24	17	6	3	1	1

Figure 2. Bar plot of number of PExs up to Week 156



Safety

- The pooled safety data were generally consistent with the safety profile established in the AIRLEAF® study.

Participants, n (%) [rate per 100 patient-years at risk]	Placebo AIRLEAF® (n=109)	Verducatib					
		AIRLEAF®			Pooled		
		1 mg (n=53)	2.5 mg (n=53)	5 mg (n=107)	1 mg (n=80)	2.5 mg (n=81)	5 mg (n=135)
Any AE	101 (92.7) [480.0]	45 (84.9) [308.3]	46 (86.8) [300.9]	94 (87.9) [321.8]	70 (87.5) [239.6]	77 (95.1) [347.1]	130 (96.3) [300.2]
Serious AEs	30 (27.5) [43.4]	8 (15.1) [21.6]	6 (11.3) [15.6]	22 (20.6) [31.5]	23 (28.8) [24.4]	26 (32.1) [27.1]	39 (28.9) [25.4]
Investigator-reported drug-related AEs	16 (14.7) [22.5]	8 (15.1) [22.4]	9 (17.0) [25.3]	18 (16.8) [25.3]	11 (13.8) [11.3]	16 (19.8) [16.8]	35 (25.9) [22.2]
AEs leading to treatment discontinuation	6 (5.5) [7.6]	2 (3.8) [4.9]	2 (3.8) [5.0]	5 (4.7) [6.4]	4 (5.0) [3.6]	3 (3.7) [2.7]	11 (8.1) [6.1]
At least one potentially mode of action-related AE informed by PLS[a]	13 (11.9) [17.2]	8 (15.1) [21.2]	4 (7.5) [10.5]	14 (13.1) [19.5]	16 (20.0) [16.6]	14 (17.3) [14.1]	25 (18.5) [15.2]
Skin events	7 (6.4) [9.0]	2 (3.8) [5.1]	3 (5.7) [7.8]	12 (11.2) [16.5]	8 (10.0) [7.7]	7 (8.6) [6.7]	20 (14.8) [12.0]
Periodontal events	5 (4.6) [6.4]	4 (7.5) [10.1]	1 (1.9) [2.5]	3 (2.8) [3.8]	7 (8.8) [6.6]	7 (8.6) [6.6]	8 (5.9) [4.5]
Opportunistic infections	1 (0.9) [1.3]	2 (3.8) [5.0]	0 (0) [0]	1 (0.9) [1.3]	3 (3.8) [2.8]	1 (1.2) [0.9]	1 (0.7) [0.6]

Data are presented as n (%) [rate per 100 patient-years at risk].
[a]PLS is a rare genetic disorder caused by loss-of-function mutations in both alleles of the *DPP1* gene,[12,13] and is characterized by diffuse palmoplantar hyperkeratosis (thickening of the skin of the palms and soles) and severe periodontitis.[12,14] Analysis was based on custom MedDRA PT/HLT groupings (primary pathway only).

Conclusion

This pooled analysis demonstrates consistent positive effects of the 2.5 mg verducatib dose on time to first PEx and annualized rate of PExs over approximately 3 years, and provides supportive evidence for the long-term efficacy and safety of verducatib in people with BE.

Abbreviations
AE, adverse event; **BE**, bronchiectasis; **CatC**, cathepsin C; **CatG**, cathepsin G; **CFBE**, cystic fibrosis bronchiectasis; **CI**, confidence interval; **COPD**, chronic obstructive pulmonary disease; **CT**, computed tomography; **DPP1**, dipeptidyl peptidase 1; **HR**, hazard ratio; **NCFBE**, non-cystic fibrosis bronchiectasis; **NE,** neutrophil elastase; **NSP**, neutrophil serine protease; **OLE**, open-label extension; **PEx**, pulmonary exacerbation; **PLS**, Papillon–Lefèvre syndrome; **PR3**, proteinase 3; **PT**, preferred term; **RR**, rate ratio; **SGRQ**, St. George's Respiratory Questionnaire.

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