Results From Two Completed Phase I Studies With POL6014-A Novel Inhaled Neutrophil Elastase Inhibitor

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Background

In chronic inflammatory conditions of the lung, neutrophils are abundantly present in the tissue and sputum. Excessive release of neutrophil-derived proteolytic enzymes will accelerate lung tissue damage, leading to progressive decline in lung function [1–5].

POL6014 is a novel, potent and selective neutrophil elastase (NE) inhibitor in development by Santhera Pharmaceuticals (acquired from Polyphor in February 2018). POL6014 is an orally inhaled, investigational compound that is administered as a nebulized drug via the Pari eFlow® system.

Pre-clinical data provide evidence that POL6014 inhibits NE in enzymatic assays and reduces neutrophils as well as inflammatory markers in animal models of neutrophilic inflammation.

Additionally, POL6014 has been shown to inhibit NE in ex-vivo bronchoalveolar lavage (BAL) and sputum of subjects with cystic fibrosis (CF). Toxicology studies performed in rats and non-human primates at micromolar exposures showed excellent safety and tolerability. Consequently, first in human (FIH) studies with POL6014 were initiated as single ascending (inhalation) dose (SAD) studies, first in healthy volunteers (HV) and then in CF subjects.

Objectives

Evaluate safety, tolerability and pharmacodynamics of POL6014 in two Phase 1 studies

Methods

- Both HV and CF SAD studies were single center, randomized, double-blind, placebo-controlled, parallel-group studies with 8 subjects per dose randomly allocated to POL6014 or placebo in a 3:1 (active:placebo) fashion.
- In the HV study (n = 48), the following POL6014 single doses were used: 20, 60, 120, 240, 480, and 960 mg; subsequently in the CF study (n = 24), subjects received single ascending doses of 80, 160, and 320 mg.
- Inhalation was performed using an eFlow® nebulizer (Pari Pharma GmbH, Gräfelfing, Germany) around 9:00 am.
- In CF subjects, spontaneous sputum collection was performed pre-dose, between 1 to 3 h and 24 h after inhalation of POL6014 or placebo.

Results

Table 1: Subject demographics (HV and CF)

	Healthy Volunteers			CF Subjects		
	N	Mean	SD	N	Mean	SD
Age (yrs)	48	30.8	7.2	24	31	6.4
Body weight (kg)	48	77.7	7.59	24	70	12.9
Body height (cm)	48	179.8	6.1	24	177.0	8.6
Body Mass Index	48	24.1	2.36	24	22.3	2.68

Subject demographics are presented in Table 1.

Safety in healthy volunteers (HVs)

- No serious adverse events (SAE) occurred in the HV study.
- A total of 27 AEs were reported, 24 were treatment-emergent AEs (TEAE) recorded in 13 subjects (27.1%)- all subjects had received active drug (POL6014).
- No AEs were reported in subjects receiving placebo.
- The most frequently reported AE was ‘cough’ (5 events).

Safety in CF subjects

- No SAEs occurred during the course of the CF study. No inhalation-related AEs were reported and no subjects withdrew from the study due to an AE.
- Most frequently reported AEs were ‘dizziness’ and ‘headache’.
- In total, TEAEs were recorded in 6 subjects. Five of these subjects (83.3%) were on active drug: 80 mg POL6014 (1 subject), 160 mg (2 subjects), and 320 mg (2 subjects). All 6 TEAEs were determined not to be related to POL6014.
- None of the TEAEs were rated as severe.
- Half of the subjects receiving POL6014 experienced a small and non-clinically significant decline in FEV_1 that was observed 30 min after dosing. In the majority of these subjects, FEV_1 returned to baseline (pre-dose) or above within 24 h. At no time did any patient report dyspnea, wheezing or any other respiratory symptoms. Clinical parameters, including oxygen saturation, remained stable throughout the study in all subjects.
- All POL6014 doses were safely administered in CF subjects, including the highest dose (320 mg).
- All subjects receiving POL6014 rated the overall tolerability as “good” (3/18) or “very good” (15/18).

Table 2: PK parameters (Mean ± SD) for POL6014 after inhalation of single ascending doses of POL6014 in HVs and CF subjects ranging from 20 to 960 mg

	Healthy Volunteers			CF Subjects		
Dose	C_{max} (ng/mL)	AUC (ng*h/mL)	$T_{1/2}$ (h)	C_{max} (ng/mL)	AUC (ng*h/mL)	$T_{1/2}$ (h)
20 mg	70.0 (39.2)	405 (235)	2.9 (0.5)			
60 mg	276.5 (69.5)	1529 (412)	3.3 (0.4)			
80 mg				314.8 (321.1)	1743 (1710)	4.1 (1.3)
120 mg	418.0 (192.0)	2212 (823)	3.1 (0.3)			
160 mg				441.0 (180.2)	2776 (1164)	3.5 (0.4)
240 mg	743.6 (124.9)	5775 (1594)	3.5 (0.6)			
320 mg				694.1 (291.9)	5199 (2193)	3.8 (0.5)
480 mg	1977.6 (676.3)	13698 (3987)	3.4 (0.4)			
960 mg	3603.1 (2055.2)	26845 (13727)	6.0 (0.9)			

- Similar absorption and elimination patterns were observed in CF subjects given doses ranging from 80 mg to 320 mg.
- POL6014 showed a dose linear PK profile in both HVs and CF subjects with C_{max} between 0.2 to 2.5 µM in HVs and between 0.2 to 0.5 µM in CF subjects.
- T_{max} was reached at approximately 2-3 h.
- Mean POL6014 levels in sputum rapidly reached 1000 µM and were above 10 µM at 24 h.

Conclusion

- **In two Phase I SAD studies there were no serious AEs in either the HVs or CF subjects.**
- **In single doses ranging from 20 and 480 mg in HV and 80 to 320 mg in CF subjects no clinical symptoms were observed.**
- **POL6014 was safely administered in doses ranging from 20-480 mg.**

Acknowledgments

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Conflict of interest

J Karafilidis, R Persinger and K Nygren are employees of Santhera Pharmaceuticals. O Sellier-Kessler is an employee of Polyphor LTD.

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