Burkholderia study patients was extremely low (Shannon Index <1), but higher in the *Pseudomonas* study (Shannon Index >1).
Conclusion: Microbiota analysis provided a holistic view of lung infection during the trials. For Bcc infection significant alterations of the microbiota were associated with patient sex, diabetes status and specific Bcc species were observed for the first time. Treatment with OligoG shows a trend towards reduction in microbial burden for certain CF patients.

61

A randomised, double-blind, placebo-controlled, parallel-group, dose-escalation phase I study in healthy volunteers (HV) of inhaled single doses (SD) of POL6014, a potent and selective reversible inhibitor of human neutrophil elastase

P. Barth[1], A. Wach[1], E. Chevalier[1], O. Sellier Kessler[1], B. Huber[2], D. Kappeler[2], W. Timmer[2], L. Hooftman[1]. [1]*Polyphor Ltd, Allschwil, Switzerland;* [2]*Inamed GmbH, Gauting, Germany*

Objectives: Neutrophil elastase (NE) is a key proteolytic enzyme implicated in the pathogenesis and progression of chronic pulmonary diseases such as Cystic Fibrosis. This first-in-man study investigated the safety, tolerability and pharmacokinetics (PK) of single ascending doses of inhaled POL6014, a novel Protein Epitope Mimetic (PEM) NE inhibitor, in healthy adult male subjects.
Methods: The study consisted of six ascending dose groups (20, 60, 120, 240, 480 and 960 mg). 8 subjects per group were randomized to POL6014 or placebo in a 6:2 fashion. Inhalation was performed with a Pari eFlow® nebuliser. Safety, tolerability and PK were assessed over a 24 hr period. PK included monitoring of POL6014 levels in plasma and urine. Escalation to the next dose was executed after evaluation of all safety data of the preceding dose level.
Results: Inhaled POL6014 was clinically safe and very well tolerated including the highest dose level tested (960 mg), however, at this dose inhalation time was up to 60 min. Clinical chemistry, ECG's and blood pressure measurements did not demonstrate any abnormalities; no serious adverse events occurred. Plasma concentration profiles showed clear linear kinetics for POL6014; C_{max} values ranged between 0.2 and 2.5 µM and AUC values were between 2 and 20 h×µM. T_{max} was reached approximately 3 h after inhalation.
Conclusion: The results of this study indicate that there are no safety concerns when POL6014 is administered to healthy volunteers as SD in doses ranging between 20 and 960 mg. Dose limiting toxicity with POL6014 in this trial was not reached and the agent was well tolerated; however, the 960 mg dose required too long an inhalation time. Further exploration of this treatment in the given dose ranges in patients with neutrophil-driven respiratory diseases, in particular CF, is well founded.

62

Correlated changes in inflammation biomarkers from a phase 1 study of acebilustat in adult cystic fibrosis patients

E. Springman[1], S. Ahuja[1], L. Bhatt[1], T. Van[1], R. Grosswald[1], G. MacGregor[2], A. Horsley[3], D. Bilton[4], J.S. Elborn[4]. [1]*Celtaxsys, Inc., Atlanta, United States;* [2]*West of Scotland CF Centre, Manchester, United Kingdom;* [3]*Manchester Adult Cystic Fibrosis Centre, Manchester, United Kingdom;* [4]*Royal Brompton Hospital, Department of Respiratory Medicine, London, United Kingdom*

Objectives: In cystic fibrosis (CF) patients, the interplay between inflammation and infection plays a central role in the progression of lung disease, resulting in a rapid decline in lung function. The need for safe, effective anti-inflammatory treatments for CF remains high. A previously reported study showed that once-daily oral acebilustat, a leukotriene A4 hydrolase inhibitor (LTA4Hi), reduced markers of lung and systemic inflammation over the course of two weeks of treatment in adult CF patients. Here, a further analysis examines correlations between markers for the treated population.
Methods: Twelve patients, two groups of 6, were treated with 50 mg or 100 mg oral once-daily acebilustat for 15 days. Sputum biomarkers were measured before and after treatment, including: leukotriene B4 (LTB4), neutrophil count (PMN), white blood cell count (WBC), neutrophil DNA (DNA), neutrophil elastase (NE). Serum C-reactive protein (CRP) was also measured.
Results: Across the acebilustat treated patients, NE was highly correlated with both LTB4 ($r^2 = 0.6$) and DNA ($r^2 = 0.8$). WBC was generally well-correlated with LTB4 and NE, with the notable exception of 2 outliers which are discussed. Surprisingly, CRP was well-correlated with LTB4 ($r^2 = 0.4$) but not with WBC or NE, suggesting a potentially different, possibly systemic, mechanism for the LTB4-CRP interaction.
Conclusion: Together, these results suggest that reducing LTB4 confers a strong propensity for comparable reductions in NE, DNA and CRP and provide a direct link between acebilustat mechanism and observed biomarker effects. In summary, analysis of correlations between independent measures of anti-inflammatory response suggest that acebilustat treated CF patients achieving significant reduction in sputum LTB4 and/or sputum WBC are likely to exhibit response across most or all inflammation biomarkers. These results provide support for the potential of once-daily oral acebilustat in the treatment of CF lung disease.

63

TORPEDO-CF – completion of recruitment to trial of optimal regimen for eradication of new infection with *Pseudomonas aeruginosa*

S. Langton Hewer[1], H. Hickey[2], A. Jones[2], M. Blundell[2], A.R. Smyth[3], on behalf of the TORPEDO-CF contributors. [1]*Bristol Royal Hospital for Children, Bristol, United Kingdom;* [2]*University of Liverpool, Liverpool, United Kingdom;* [3]*University of Nottingham, Nottingham, United Kingdom*

Objectives: TORPEDO-CF is a Trial of Optimal TheRapy for Pseudomonas EraDicatiOn in Cystic Fibrosis. The key objective was to randomise 280 CF patients to either oral ciprofloxacin or intravenous ceftazidime with tobramycin, both groups also receiving 3 months of nebulised colistin. The primary outcome measure is successful eradication of *P. aeruginosa* infection three months after allocated treatment has started, remaining infection free through to 15 months.
Methods: This trial is open in 66 UK adult and paediatric CF centres and one site in Italy (Genoa). Feasibility data suggested that 25% of patients would be adults. Eligible patients are over 28 days of age and have either the first ever growth of *P. aeruginosa* or the first growth for greater than a 12 month period. Consenting patients are randomly allocated to either treatment arm in a 1:1 ratio using simple block randomisation with random variable block length.
Results: Recruitment has been slower than expected. Screening data (Nov 2016) showed 1420 patients have been screened of whom 904 were eligible (63.7%). Consent was sought from 727 patients of whom 259 consented (35.6%). The commonest reasons for failure to consent (n = 468) were preference not to have IV therapy (n = 304, 65.0%), preference against oral therapy (n = 34, 7.3%) and family circumstances (n = 17, 3.6%). The protocol has been revised, now to the 9th edition, mainly to address barriers to recruitment.
284 patients have now been randomised.
Conclusion: Minor alterations to protocol, the opening of additional sites including international sites and persistent reminders to participating centres from members of the Trial Management Group (TMG) have now led to complete recruitment to the original target. The TMG, supported by the independent Trial Steering Committee, have maintained that the original recruitment target should be attained in order to provide a satisfactory answer to the original objective.

64

Differences in research priorities within the CF community

E. Crane[1], N.J. Rowbotham[1], P.A. Leighton[1], A.R. Smyth[1]. [1]*University of Nottingham, Nottingham, United Kingdom*

Objectives: We undertook a James Lind Alliance (JLA) Priority Setting Partnership (PSP) to identify the top 10 research questions in CF. Through an initial survey we asked for submission of ideas. Not all responses were suitable for clinical research but all submissions gave a valuable insight into important issues faced by the CF community. Here we explore differences between the concerns of lay and professional participants.
Methods: We undertook a framework analysis of the original PSP data, comparing lay and professional groups. We received 1122 responses, of which 1031 contained useful narrative, from which we identified 23 themes. We chose 6 themes with either clear concordance or marked