Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with Pseudomonas aeruginosa (ORBIT-3 and ORBIT-4)

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Appendix/Supplement

Inhaled liposomal ciprofloxacin (ARD-3150) in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa*: results of two phase III randomized controlled trials (ORBIT-3 and ORBIT-4)

This supplement includes the following materials:

Supplemental item 1

Inclusion criteria

1. Willing and able to provide written informed consent.
2. Male or female, ≥18 years of age, and able to walk.
3. Confirmed diagnosis of NCFBE per computerised tomography (or high resolution computerised tomography) showing bronchial wall dilatation (internal bronchial lumen diameter greater than accompanying pulmonary artery or lack of tapering) with or without bronchial wall thickening.
4. Documented history of at least two PEs treated with courses of antibiotics within the past 12 months.
5. FEV_1 ≥25% of predicted values at the Screening Visit (Visit 0).
6. Positive documented *P. aeruginosa* in a sputum/deep-throat swab culture (or bronchoalveolar lavage [BAL] or bronchoscopic specimen) before the Screening Visit (Visit 0). Subjects without documented *P. aeruginosa* before screening who met all other eligibility criteria must have had at least two sputum samples or deep-throat swabs collected 3–4 or more weeks apart from each other during the 42-day Screening Phase. Two of the samples collected must have tested positive for *P. aeruginosa*. These two positive tests must have been from samples taken a minimum of 3–4 or more weeks apart.
7. Positive *P. aeruginosa* in the sputum/deep-throat swab culture collected at the Screening Visit (Visit 0) with at least one *P. aeruginosa* isolate non-resistant to ciprofloxacin. As of Protocol V3.0, if the sputum sample was negative for *P. aeruginosa* or only showed resistant *P. aeruginosa* isolates, the sputum/swab culture could have been repeated multiple times during screening to document *P. aeruginosa* presence. In subjects without documented *P. aeruginosa* before screening who met all other eligibility criteria and who had two or more sputum cultures or deep-throat swab cultures obtained 3–4 or more weeks apart from each other during screening, at least one *P. aeruginosa* isolate taken after 3–4 or more weeks must have been non-resistant to ciprofloxacin for the subject to have been considered eligible for randomisation. The qualifying sputum culture results had to be available within the 42-day Screening Phase.
8. Clinically stable and capable of performing the 6-Minute Walk Test (6MWT) without supplemental oxygen. Note: During the study, subjects who needed to initiate continuous oxygen were allowed to forgo 6MWT testing.
9. Willing and able to comply with the requirements for participation in the study.
10. Female subjects of childbearing potential had to have a negative pregnancy test at the Screening Visit and must have used an acceptable method of contraception for at least 3 months before the first dose of study drug and for 28 days after the last dose of study drug. Acceptable methods of contraception for women included orally administered or implantable or injectable hormonal contraceptives, surgical intervention, and intrauterine device (IUD). Sexual abstinence was allowed as an acceptable contraceptive method.
11. To be considered “not of childbearing potential”, female subjects had to have been postmenopausal for at least 1 year as confirmed by an elevated follicle-stimulating hormone (FSH) level (≥30 mIU/ml) at screening and 1 year of amenorrhoea, or to have been irreversibly surgically sterilised by hysterectomy, oophorectomy, or bilateral tubal ligation for at least 3 months before the first dose of study drug. Male subjects whose female partners were of childbearing potential (defined as above) had to agree to use an acceptable method of birth control for the duration of study treatment and for 28 days after the last dose of study drug.

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the trial:

1. PE during the Screening Phase (between signing the informed consent form and randomisation), defined as requiring acute treatment with inhaled, oral, or IV antibiotics.
2. Clinical diagnosis of CF.
3. Primary diagnosis of Chronic Obstructive Pulmonary Disease (COPD) related to smoking history of greater than 10 pack years.
4. Current diagnosis of active allergic bronchopulmonary aspergillosis.
5. Received any IV, oral or inhaled anti-pseudomonal antibiotic (except chronic macrolides erythromycin, clarithromycin, or azithromycin with a stable dose) within 28 days before Visit 1.
6. Allergy to ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, or norfloxacin.
7. Known allergy to soy products.
8. Used tizanidine within 28 days before Visit 1 and anticipated need to use tizanidine during the study (tizanidine was contraindicated due to a PK interaction with ciprofloxacin).
9. Initiated supplemental oxygen within 28 days before Visit 1.
10. Used any IV or intramuscular corticosteroid or used oral corticosteroid >10 mg/day or >20 mg every other day (prednisone or prednisolone equivalents) within 28 days of Visit 1.
11. Had changes in either the treatment regimen or initiation of treatment with any of the following medications within 28 days before Visit 1:
    a. Macrolides, eg, azithromycin, clarithromycin, or erythromycin
    b. Inhaled hypertonic saline or inhaled mannitol
    c. Mucolytics
    d. Bronchodilator medications
    e. Oral corticosteroid
12. Had changes in pulmonary rehabilitation, chest physiotherapy technique or frequency within 28 days before Visit 1.
13. History of solid organ (eg, lung) transplantation.
14. Non-tuberculous mycobacterial infection and currently receiving antibiotic treatment or anticipated to require initiation of antibiotic treatment during the study.
15. Active tuberculosis.
16. Serum creatinine levels ≥2.0 × upper limit of normal (ULN) at the Screening Visit (Visit 0).
17. Serum transaminase levels >3 × ULN at the Screening Visit (Visit 0).
18. Febrile illness within 1 week before Visit 1.
19. Massive haemoptysis (greater than or equal to 300 ml or requiring blood transfusion) within 6 months before Visit 1.
20. Received an investigational drug or device within 42 days before Visit 1.
21. Malignancy or any other serious or active medical illness with a life expectancy of less than 12 months.
22. Any serious or active medical or psychiatric illness, which in the opinion of the investigator, would interfere with subjects' treatment, assessment, or compliance with the protocol.
23. History or suspicion of unreliability, poor cooperation, or non-compliance with medical treatment.
24. Unable to use nebulisers during the course of the study.
25. Unable either to understand the instructions for use of the study drug or to complete the QOL-B questionnaire at Visit 1.

26. Previous randomisation in this study.
27. Pregnant or planned to become pregnant during this study; nursing mothers; or unwilling to use an acceptable method of contraception for the duration of the study.
28. Any other condition that, in the opinion of the investigator, prohibited the subject from participating in the study.

Supplemental item 2.

Methodological and statistical details

Randomisation scheme details

At study entry, each subject was assigned a unique screening identification number. After a subject met all entry criteria, sites accessed SynteractHCR's interactive web randomization system (IWRS) system, which assigned a randomization number to the subject. Subjects were randomly allocated to receive ARD-3150 or placebo treatment in a 2:1 manner. Central randomization was used to protect the overall intended 2:1 allocation of subjects to ARD-3150 and placebo treatment, respectively, in the Double-Blind Phase of the study.

Treatment assignment was accomplished by a computer generated random sequence implemented through the IWRS. The study coordinator accessed the IWRS during visits when study drug was dispensed (i.e., at Visits 1, 4, 6, 8, 10, 12, and 14) to register the visit and obtain the study drug kit assignment for the subject.

Subjects who were withdrawn from the study after randomisation and who received at least one dose of inhaled study drug were not replaced. Patients who withdrew after randomisation but did not receive study drug were replaced.

Blinding

The 48-week Double-Blind Phase of this study was performed in a double-blind manner. Neither the investigator nor the subject knew the subject's treatment assignment. The study drug was supplied in 5-mL vials color coded with red and blue vial caps to ascertain that each dose was a mixture of the liposomal and non-liposomal components.

Aradigm staff and designees involved in clinical management, data management, and statistical evaluation remained blinded until a database lock memo was issued and identification of the analysis populations was agreed upon and documented.

Definition of a new PE

A PE was defined as new if the next course of antibiotics was started ≥14 days after stopping the previous course as long as the PE defining symptoms had resolved. If the PE occurred <14 days after completing the previous course of antibiotics, it was considered part of the original PE.

Adjudication of a discrepancy in the assessment of a PE

In the case of a discrepancy between the investigator's assessment and the protocol-defined criteria of a PE or its severity, an adjudication was performed by a three-member committee, which was blinded to the patient's study group assignment. The committee was composed of an independent chair and two principal investigators of the studies. If the adjudication committee members disagreed in their assessment of a PE occurrence or severity, the majority opinion (two of the three members) prevailed.

Additional antibiotic testing

P. aeruginosa in vitro susceptibilities to amikacin, aztreonam, cefepime, ceftazidime, gentamicin, meropenem, piperacillin, ticarcillin/clavulanate, and tobramycin were also assessed at each study visit.

Statistical details

Pre-specified analyses included the probability distribution of time to first PE (primary endpoint), which was estimated using the Kaplan–Meier method. For each trial, a stratified unweighted log-rank test was performed to compare the probability distribution between treatments using the stratification factors at randomisation (sex and the number of PEs [2–3, ≥4] in the prior 12 months). Owing to a very small number of current smokers in the trials, stratification for smokers was not applied in the analyses, in agreement with regulatory authorities. The rates of PE per patient were estimated and compared between treatment groups using stratified negative binomial regression, a test that assumes that serial PEs are independent events. Data were analysed for each trial separately and the data from the two trials combined for pooled analyses. The QOL-B Respiratory Symptoms Domain[1] was analysed using the stratified mixed model for repeated measures (MMRM) analysis. Statistical analyses were performed with SAS Version 9·4 or higher (SAS Institute, Cary, NC, USA).

Where presented, means and percentages were computed using the Means and FREQ procedures in SAS. Survival analysis and the counting process analyses were performed using the PHREG procedure. Comparison of two survival distributions was accomplished using the Lifetest procedure. Longitudinal data analyses were performed using the Mixed (for continuous outcome measures) and GENMOD (for binary outcomes or responses that could be counted) procedures. The per-protocol analysis of the number of PEs was performed using a negative binomial analysis model in SAS. Within all of these procedures, SAS options were available to report point estimates and confidence intervals for specified analysis models. Graphical presentations of cumulative incidence curves used the Kaplan–Meier method of estimation, and graphical presentations of counts presented by calculating the step-function using the ordered counts (without regard to the subject ID) and for each treatment arm.

Survival analysis and counting process analysis models used the proportional hazards assumption for estimation of model parameters.

Mixed models used the subject ID to identify repeated measures from an individual and treatment differences were assumed to be random effects. A compound symmetry covariance assumption was used to model the repeated measures.

For GEE models, a log-link odds ratio function was used to estimate parameters for the required model. Distributional assumptions were specified to be binary, Poisson, or negative binomial depending on the type of variable and analysis being carried out. Where necessary, the distributional assumptions are indicated when reporting the analysis results.

Statistical significance for the first of the three secondary endpoints defined in the protocol, the number of PEs per subject, was only to be assessed if the primary endpoint was significant at the 0·05 level two-sided alpha. A combination of hierarchical and step-down approaches was to be used to maintain the Type I error at the overall two-sided 0·05 significance level. If significance of the primary analysis at the two-sided 0·05 level was obtained, then the significances of the three secondary analyses were to be assessed, also at the overall 0·05 two-sided level. First, significance of the number of PEs was to be assessed at the 0·05 two-sided level. If significant, the remaining two protocol-specified secondary endpoints (number of severe PEs per subject, and QOL-B Respiratory Symptoms Scale score) were to be tested, using the Holm–Bonferroni step-down procedure to maintain the overall significance of these two tests at the overall two-sided 0·05.

Supplemental item 3. PE endpoints analysed when British Thoracic Society criteria for changes in sputum are used to define occurrence of PE

All PE-related primary, secondary, and other endpoints were also analysed in those patients who met PE criteria as defined by the British Thoracic Society (BTS) with respect to sputum changes.[2] The sputum changes include increase in volume, increase of viscosity, increased purulence, and haemoptysis.

The PE endpoints analysed by BTS criteria consisted of the following:

1. Time to the first PE from baseline (day of randomisation) to week 48.
2. Number of PEs per patient from baseline (day of randomisation) to week 48.
3. Number of severe PEs per patient from baseline (day of randomisation) to week 48.
4. Duration of PE: sum of the duration of all PEs per patient from baseline (day of randomisation) to week 48.
5. Number of mild PEs per patient from baseline (day of randomisation) to week 48.
6. Number of moderate PEs per patient from baseline (day of randomisation) to week 48.
7. Number of PEs requiring hospitalisation per patient from baseline (day of randomisation) to week 48.
8. Number of PEs requiring IV antibiotics per patient from baseline (day of randomisation) to week 48.
9. Number of patients experiencing at least one severe PE from baseline (day of randomisation) to week 48.
10. Number of patients experiencing at least one PE from baseline (day of randomisation) to week 48.
11. Number of patients initiating antibiotics to resolve a PE from baseline (day of randomisation) to week 48.
12. Number of patients initiating IV antibiotics to resolve a PE from baseline (day of randomisation) to week 48.
13. Number of patients with hospitalisation for PE from baseline (day of randomisation) to week 48.

Supplemental item 4. Safety assessments

Safety parameters evaluated in this study included treatment-emergent AEs (TEAEs) and serious AEs (SAEs), clinical safety laboratory test results, vital signs measurements, serial spirometry test results, physical examination findings, including the 6-Minute Walk Test[3] (change in distance walked from baseline [day 1] to week 48), and electrocardiogram (ECG) results. Data from single-breath DLCO, was performed on patients randomised at sites capable of performing DLCO testing. Illnesses that existed before entry into the study were not considered AEs unless they worsened during the treatment phase.

Adverse events of special interest (AESI) were defined as any irritation of the airway, and included bronchial hyper-reactivity, bronchospasm, increased cough, dry throat, dysphonia, dyspnoea, oropharyngeal pain, painful respiration, pharyngeal oedema, pleuritic pain, respiratory tract irritation, tachypnoea, throat irritation, upper airway cough syndrome, wheezing, pleurisy, throat ache, laryngitis, pharyngitis, and itchy (itching) throat.

Spirometry endpoints evaluated from baseline (day 1) to week 48 consisted of the following:

1. Absolute and percentage change in FVC (in litres [L]).
2. Absolute and percentage change in FVC % predicted.
3. Absolute and percentage change in FEV_1 (L).
4. Absolute and percentage change in FEV_1 % predicted.

Supplemental item 5.

Supplemental table S1: **Concomitant medications allowed in ORBIT-3 and ORBIT-4**

Category
Antibiotics
Fluoroquinolones
Macrolides
Penicillins, combinations (including beta-lactamase)
Cephalosporins, third generation
Penicillins with extended spectrum
Tetracyclines
Combinations of sulphonamides and trimethoprim, including derivatives
Aminoglycosides
Carbapenems
Corticosteroids
Glucocorticoids*
Corticosteroids*
Bronchodilators
Selective beta-2-adrenoreceptor agonists
Adrenergics in combination with other corticosteroids or other drugs, excluding anticholinergics
Anticholinergics
Adrenergics in combination with anticholinergics
Mucolytics
Mucolytics

*Includes all routes of administration.

Supplemental item 6.

Supplemental table S2: **Endpoint analysis by BTS criteria**

	ORBIT-3				ORBIT-4			
Endpoint	**ARD-3150 (n=183)**	**Placebo (n=95)**	**HR (95% CI)**	**p value**	**ARD-3150 (n=206)**	**Placebo (n=98)**	**HR (95% CI)**	**p value**
Time to the first PE (days)*	267	232	0·95 (0·67–1·33)	0·75	296	173	0·67 (0·48–0·91)	0·0109
Number of PEs per patient†	0·96	1·16	0·84 (0·63–1·13)	0·25	0·87	1·39	0·60 (0·45–0·79)	0·0004
Number of severe PEs per patient†	0·20	0·25	0·79 (0·38–1·65)	0·53	0·12	0·28	0·39 (0·20–0·73)	0·0037
Duration of all PEs (days)	39·99	39·87	-	0·98	52·03	57·13	-	0·51
Number of mild PEs per patient†	0·16	0·16	1·11 (0·58–2·12)	0·75	0·18	0·17	0·95 (0·50–1·81)	0·88
Number of moderate PEs per patient†	0·60	0·75	0·81 (0·56–1·16)	0·24	0·57	0·94	0·60 (0·43–0·84)	0·0028
Number of PEs requiring hospitalisation per patient†	0·17	0·20	0·85 (0·39–1·88)	0·69	0·11	0·16	0·61 (0·30–1·23)	0·17
Number of PEs requiring IV antibiotics per patient†	0·17	0·21	0·87 (0·39–1·95)	0·73	0·12	0·24	0·42 (0·22–0·80)	0·0078
Number of patients experiencing at least one severe PE, n (%)‡	27 (14·8)	15 (15·8)	-	0·84	19 (9·2)	22 (22·4)	-	0·0019
Number of patients experiencing at least one PE, n (%)‡	101 (55·2)	52 (54·7)	-	0·81	105 (51)	62 (63·3)	-	0·0539
Number of patients initiating antibiotics to resolve a protocol-defined PE, n (%)‡	86 (47·0)	46 (48·4)	-	0·85	88 (42·7)	55 (56·1)	-	0·0397
Number of patients initiating IV antibiotics to resolve a protocol-defined PE, n (%)‡	24 (13·1)	12 (12·6)	-	0·90	20 (9·7)	20 (20·4)	-	0·0102
Number of patients with hospitalisation for PE, n (%)‡	24 (13·1)	13 (13·7)	-	0·90	19 (9·2)	15 (15·3)	-	0·11

*Stratified unweighted log-rank test. †Stratified negative binomial regression analysis. ‡Stratified logistic regression analysis. CI=confidence interval; HR=hazard ratio; IV=intravenous; PE=pulmonary exacerbation.

Supplemental item 7.

Supplemental table S3: **Absolute change from baseline in spirometry parameters (pooled ORBIT-3 and ORBIT-4)**

	FEV_1 (L)		FEV_1 % predicted		FVC (L)		FVC % predicted	
Absolute change from baseline to:	**ARD-3150 (N=389)**	**Placebo (N=193)**	**ARD-3150 (N=389)**	**Placebo (N=193)**	**ARD-3150 (N=389)**	**Placebo (N=193)**	**ARD-3150 (N=389)**	**Placebo (N=193)**
Baseline, n	320	153	320	153	320	153	320	153
Mean	1·540	1·432	60·1	57·9	2·453	2·343	72·3	71·1
(SD)	(0·6511)	(0·5815)	(21·74)	(19·90)	(0·8647)	(0·7985)	(19·08)	(17·90)
Week 24, n	285	137	285	137	285	137	285	137
Mean	–0·011	–0·033	–0·5	–1·2	–0·025	–0·058	–0·9	–1·5
(SD)	(0·1724)	(0·1374)	(6·41)	(5·52)	(0·2470)	(0·2325)	(7·44)	(7·37)
Week 48, n	265	127	265	127	265	127	265	127
Mean	–0·047	–0·064	–1·8	–2·5	–0·042	–0·084	–1·1	–2·4
(SD)	(0·1897)	(0·1751)	(6·82)	(6·86)	(0·2893)	(0·2601)	(8·21)	(8·39)

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; SD=standard deviation.

Supplemental item 8.

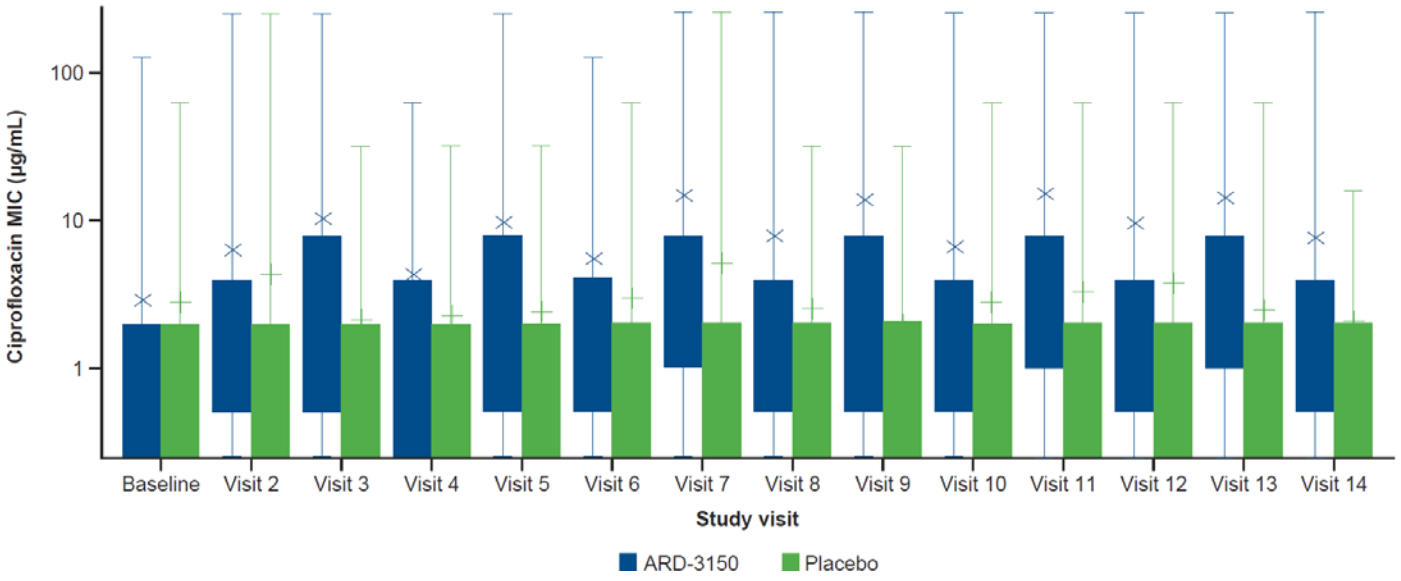
Supplemental figure 1: **Clinical trial sites**

In ORBIT-3, 514 patients were screened from 16 countries (Australia, Canada, Germany, Hungary, Ireland, Israel, Italy, Latvia, Poland, Romania, South Africa, South Korea, Spain, Taiwan, United Kingdom (UK), and the US) and 93 sites randomised at least one patient. ORBIT-3 began on April 22, 2014 and was completed on August 17, 2016.

In ORBIT-4, 533 patients were screened from 16 countries (Australia, Canada, France, Georgia, Hungary, Israel, Italy, New Zealand, Peru, Poland, Romania, Serbia, South Korea, Spain, the UK, and the US and 88 sites randomised at least one patient. ORBIT-4 began on June 6, 2014 and was completed on August 11, 2016.

Supplemental item 9.

Supplemental figure S2: **Highest ciprofloxacin MIC for *P. aeruginosa* isolates by visit (pooled ORBIT-3 and ORBIT-4).**
Includes data from one isolate per patient per visit, based on the highest MIC result at a visit. MIC=minimum inhibitory concentration.



References for supplementary data

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2 Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; **65**: i1–i58.

3 Lee AL, Button BM, Ellis S, et al. Clinical determinants of the 6-Minute Walk Test in bronchiectasis. *Respir Med* 2009; **103**: 780–5.