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Original Article

Eradication of early *P. aeruginosa* infection in children <7 years of age with cystic fibrosis: The early study

Felix Ratjen [a,*], Alexander Moeller [b], Martha L. McKinney [c], Irina Asherova [d], Nipa Alon [e], Robert Maykut [f], Gerhild Angyalosi [g], EARLY study group:

Olga Bede [1], Katalin Bolbas [2], Vladimir Bulatov [3], Elena Chertok [4], Carla Colombo [5], Michael Fayon [6], Ferenc Gonczi [7], Essam Gouda [8], Jutta Hammermann [9], Anne Munck [10], Melinda Solomon [11], John Tsanakas [12]

[1] *Szegedi Tudomanyegyetem AOK, Gyermekeg. Kozpont, Szeged, Hungary*
[2] *Somogy Megyei Kaposi Mor Oktato, Korhaz, Kaposvar, Hungary*
[3] *Kazan State Medical University, Kazan, Russia*
[4] *Voronezh Burdenko Medical Academy, Voronezh, Russia*
[5] *Fond.IRCCS Ca' Granda, Osp.Maggiore Policlinico Univ.Studi, Milano, MI, Italy*
[6] *Hôpital des enfants groupe Pellegrin, Bordeaux, France*
[7] *Kenezy Gyula Korhaz es, Rendelointezet, Debrecen, Hungary*
[8] *Clinical Research Center, Alexandria, Egypt*
[9] *Universitätsklinikum Carl Gustav, Carvus, Dresden, Germany*
[10] *Hopital Robert Debré, Paris, France*
[11] *Hospital for Sick Children, Toronto, Ontario, Canada*
[12] *General Hospital of Thessaloniki, Hippokrateio, Thessaloniki, GR, Greece*

[a] *Division of Respiratory Medicine, Department of Pediatrics, Translational Medicine, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*
[b] *Division of Respiratory Medicine, University Children's Hospital Zurich, Zurich, Switzerland*
[c] *CHU Ste-Justine, Université de Montréal, Montréal, QC, Canada*
[d] *Yaroslavl's Children's Clinical Hospital, Yaroslavl, Russia*
[e] *Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States*
[f] *RJMMD Consulting, Montreal, QC, Canada*
[g] *Novartis Pharma AG, Basel, Switzerland*

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Abstract

Objective: Antibiotic eradication treatment is the standard-of-care for cystic fibrosis (CF) patients with early *Pseudomonas aeruginosa* (*Pa*)-infection; however, evidence from placebo-controlled trials is limited.

Abbreviations: AE, adverse event; AET, antibiotic eradication treatment; BID, twice daily; CF, cystic fibrosis; CFU, colony-forming unit; DB, double-blind; ITT, intention-to-treat; KIM-1, kidney injury molecule-1; NAG, *N*-acetyl-β-D-glucosaminidase; OL, open-label; *Pa*, *Pseudomonas aeruginosa*; SAE, serious adverse event; TOBI, tobramycin inhalation solution

* Corresponding author at: Division of Respiratory Medicine, Department of Pediatrics, University of Toronto, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.
E-mail address: felix.ratjen@sickkids.ca. (F. Ratjen).

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Methods: This double-blind, placebo-controlled trial randomised CF patients <7 years (N = 51) with early *Pa*-infection to tobramycin inhalation solution (TOBI 300 mg) or placebo (twice daily) for 28 days with an optional cross-over on Day 35. Primary endpoint was proportion of patients having throat swabs/sputum free of *Pa* on Day 29.
Results: On Day 29, 84.6% patients in the TOBI versus 24.0% in the placebo group were *Pa*-free ($p < 0.001$). At the end of the cross-over period, 76.0% patients receiving TOBI in the initial 28 days were *Pa*-free compared to 47.8% receiving placebo initially. Adverse events were consistent with the TOBI safety profile with no differences between TOBI and placebo.
Conclusion: TOBI was effective in eradicating early *Pa*-infection with a favourable safety profile in young CF patients.
Trial registration number: NCT01082367

Keywords: Early eradication; Paediatric patient; Placebo-controlled; Recurrence; Tobramycin inhalation solution

1. Introduction

Respiratory infections, specifically those caused by *Pseudomonas aeruginosa* (*Pa*), are associated with increased morbidity and mortality in cystic fibrosis (CF) patients [1]. Early *Pa* acquisition is associated with reduced lung function [2] and development of bronchiectasis [3]. During the early colonisation phase, *Pa* strains are generally non-mucoid and are usually susceptible to antibiotic eradication treatment (AET). In order to prevent chronic *Pa*-infection, clinicians emphasise the importance of prevention of *Pa* acquisition, early detection of *Pa*-infection and its effective eradication [1,4,5].

Tobramycin inhalation solution (TOBI®) [6] and other inhaled antibiotics are approved for long-term management of chronic *Pa*-infection in CF patients [7]. However, none are approved for CF patients younger than 6 years. Guidelines recommend 'early eradication treatment' as the standard of care for *Pa*-infection. The EU consensus guidelines recommend AET, but no preferred regimen has been specified [8], whereas CF Foundation guidelines recommend tobramycin inhalation solution (300 mg, twice daily [BID], for 28 days) as a favoured regimen [9]. Previously, ELITE [10] and EPIC [11] have demonstrated the efficacy and safety of TOBI in early *Pa*-infection. In addition, combination treatment regimens have been used for treating early *Pa*-infection, such as inhaled tobramycin with oral ciprofloxacin (EPIC) [11] and inhaled colistin with oral ciprofloxacin [12]. Recently, an open-label (OL) study demonstrated that inhaled aztreonam was effective and well tolerated in the treatment of early *Pa*-infection in young paediatric population (age 3 months to <18 years) [13]. However, these previous studies have included only a small number of young patients, particularly those aged <1 year. Moreover, none of them were placebo controlled [10–13]. Several patients aged <6 years cannot use mouthpieces, and therefore, face masks are used for administration of inhaled medication, which may affect the success rate of treatment. In view of spontaneous clearance of early *Pa*-infection, a placebo-controlled study in paediatric CF patients is best suited to evaluate the role of inhaled antibiotics in early *Pa*-infection. This placebo-controlled EARLY study evaluated the efficacy and safety of TOBI for treating early *Pa*-infection in young paediatric CF patients (age 3 months to <7 years). The study was agreed with the European Medicines Agency Paediatric Committee and conducted in line with the TOBI Paediatric Investigation Plan approved by the agency.

2. Materials and methods

Children aged 3 months to <7 years with confirmed diagnosis of CF who had an early infection with *Pa* (either first-ever positive culture isolated or first positive culture after at least 1 year of negative cultures following history of prior *Pa*-infection) at screening and were able to comply with all protocol requirements were included in the study (see Appendix 1 for detailed inclusion/exclusion criteria). Written informed consent on behalf of patients was obtained from their parents/legal guardians.

This was a randomised, double-blind (DB), placebo-controlled, cross-over, multicentre study conducted at 15 centres across nine countries: Canada (2), Egypt (1), France (2), Germany (1), Greece (1), Hungary (3), Italy (1), Russia (3) and Switzerland (1). The study (NCT01082367) was approved by the ethics committee or institutional review board at each centre and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice according to the International Conference on Harmonisation guidelines.

The study was initiated on 28 April 2010 (first patient visit) and completed on 24 June 2015 (last patient visit). The study consisted of a screening period (up to 7 days), a randomisation visit followed by the treatment period (up to Day 91) and a follow-up period (up to 12 months after the treatment period; Fig. 1).

The study comprised an initial 28-day DB treatment randomised 1:1 to TOBI (300 mg/5 mL) or a matching placebo BID. At the end of the first treatment period, patients with *Pa*-negative culture results entered the optional DB cross-over treatment period (Days 35–63), whereas those with *Pa*-positive culture results received OL TOBI BID for 28 days. During the optional DB cross-over period, patients in the TOBI/placebo group (who had received TOBI during the first treatment period) received placebo and those in the placebo/TOBI group (who had received placebo during the first treatment period) received TOBI. The study was designed in a way to allow that every patient could receive active treatment, including patients randomised to initially receive placebo. At

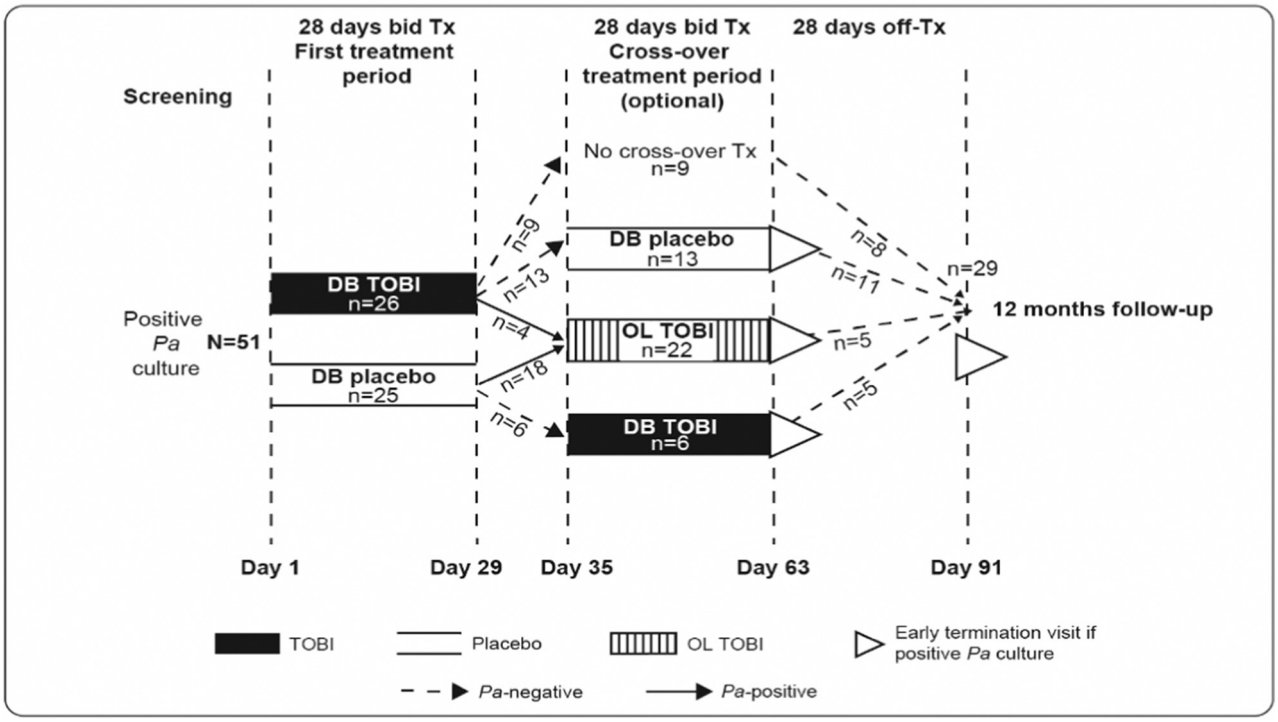

Fig. 1. EARLY study design. Bid, twice daily; DB, double blind; OL, open label; *Pa*, *Pseudomonas aeruginosa*; TOBI, tobramycin inhalation solution; Tx, treatment.

the end of the cross-over or OL TOBI treatment period (Day 63), patients with *Pa*-positive culture results terminated the study and received medical treatment at the investigator's discretion. Patients with *Pa*-negative culture results on Days 63 and 91 entered the follow-up period for up to 12 months in which they received OL TOBI for 28 days if they became *Pa*-positive.

Preservative-free tobramycin 300 mg in 5 mL of excipient (TOBI) or 5 mL of matching placebo consisting of 0.9% saline (NaCl) was delivered through a PARI LC PLUS® jet nebuliser and a suitable compressor, which when attached to the nebuliser and either a mask or mouth piece [14], delivered a flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa. The dose of 300 mg/5 mL has been chosen based on pharmacokinetic and safety results from previous studies [10,15,16]. For rationale of dose selection, see Appendix 1.

The primary efficacy variable was the proportion of patients free of *Pa*, as assessed by sputum/throat swab culture, after completion of the first treatment period (Day 29). The key secondary and exploratory objectives included (i) proportion of patients free from *Pa*-infection, as assessed by sputum/swab culture, 28 days after termination of the cross-over treatment period (Day 91); (ii) duration of persistent eradication of *Pa*-infection (any strain) during the 12-month follow-up period; (iii) proportion of patients free from *Pa* after recurrence (assessed by sputum/throat swab culture 12–24 h after the 28-day TOBI treatment); and (iv) assessment of anti-pseudomonal antibody titres during the 12-month follow-up period, per previously defined criteria [17] (for detailed study objectives see Appendix 2). Definition of persistent eradication was based on repeatedly achieving *Pa*-negative results: patients who had *Pa*-negative sputum/throat swab culture results at any two consecutive visits performed at least 21 days apart were categorised as '*Pa*-infection persistent eradication'. A recurrence was considered to occur when sputum/throat swab results were again *Pa*-positive after persistent eradication [8]. Adverse events (AEs) and serious adverse events (SAEs), with their severity and relationship to the study drug, were collected and monitored across the study. Secondary safety variables included changes in haematology and clinical chemistry parameters from baseline, vital signs, renal injury biomarkers (urinary kidney injury molecule-1 [KIM-1] and *N*-acetyl-β-D-glucosaminidase [NAG]) and audiology testing in a subset of patients.

Throat swab or sputum samples were collected for microbiology culture at all visits. Sputum samples were examined for quantitative growth of *Pa* (colony-forming units [CFUs]/mL). Throat swab samples were examined for semi-quantitative growth of *Pa* (light, moderate or heavy based on growth in quadrants) and organisms other than *Pa*. The minimum inhibitory concentration (MIC) of tobramycin for *Pa* was determined for all specimens to assess any change in pathogen susceptibility to tobramycin before and after treatment.

For sample size calculation, the eradication rate was predicted as 80% for the TOBI group based on previously published OL trials, and 30% for the placebo group, based on data from the ELITE study [10], wherein approximately one third of patients who were *Pa*-positive at screening were found *Pa*-negative at enrolment. Assuming 40 evaluable patients, a

total sample size of 50 provided 86% power for primary analysis based on patients who completed the visit on Day 29. This power calculation is based on the Fisher's exact test with one-sided significance of $\alpha = 0.05$ (nQuery Advisor version 7.0). For more details, see Appendix 2.

The primary efficacy variable (treatment success rate on Day 29) in the intention-to-treat (ITT) population was assessed as a superiority test of TOBI versus placebo. The outcome of eradication was analysed as binary data by using a logistic regression model, including treatment and study drug delivery by facemask or mouthpiece as factors, and age as a covariate. Patients who dropped out before Day 29 were assumed to be non-responders.

All secondary variables were summarised and analysed by treatment for the ITT population during the DB period and for the follow-up safety population during the follow-up period. Time to first recurrence was analysed using Kaplan–Meier methodology. All safety analyses were conducted in the safety population. Safety variables were reported as descriptive statistics.

3. Results

3.1. Baseline demographics and disease characteristics

The median age (range) of the patient population was 39.0 (6.0–82.0) months, and a majority (62.7%) of patients enrolled were in the younger age group (3 months to <4 years; Table 1).

A higher proportion of females (62.7%) were enrolled in the study, and the patients were predominantly Caucasian (96.1%). Most patients (92.2%) enrolled in the study had *Pa* isolated for the first time from deep throat culture or sputum across both treatment groups. Most patients (72.5%) used facemasks for inhalation of the study drug; 76.9% (20/26) of patients in TOBI/placebo group and 68.0% (17/25) of patients in the placebo/TOBI group used a facemask, and the remainder used a mouthpiece. There was a high degree of compliance to the study medication across both treatment arms throughout the treatment period: >99.0% across the treatment groups and 98.7% among the patients receiving OL TOBI (see Appendix 3). Over half of the patients (54.9%) were on short-acting bronchodilators, and few patients (17.6%) reported use of inhaled corticosteroids. In total, five patients from the TOBI/placebo group and four from the placebo/TOBI group were expectorating sputum. As expected in early infection with *Pa*, most patients were colonised with non-mucoid *Pa* isolates, whereas mucoid *Pa* isolates were detected in 19.6% of patients. Among the expectorating patients, one patient from the TOBI/placebo treatment group was *Pa*-negative at baseline but had *Pseudomonas* detected at screening. Among the non-expectorating patients, 24% (9/38) of patients were *Pa*-negative at baseline but had *Pa* detected at screening. These findings were concordant with the false-negative rates observed in other studies, including the ELITE study [10].

Table 1
Baseline demographics and disease characteristics.

Variable	TOBI/placebo N = 26 n (%)	Placebo/TOBI N = 25 n (%)
Age, median (range), months	41.0 (7–82) [a]	36.0 (6–82)
≥3 months to <4 years	16 (61.5)	16 (64.0)
≥4 years to <7 years	10 (38.5)	9 (36.0)
Body weight, mean (SD), years [b]	14.5 (4.5)	13.7 (4.1)
Sex		
Female	15 (57.7)	17 (68.0)
Caucasian	25 (96.2)	24 (96.0)
Episode of *Pa*-infection		
First infection	24 (92.3)	23 (92.0)
Re-infection	2 (7.7)	2 (8.0)
Current use of short-acting bronchodilator	13 (50.0)	15 (60.0)
Current use of long-acting bronchodilator	2 (7.7)	2 (8.0)
Current use of inhaled corticosteroids	4 (15.4)	5 (20.0)
Inhalation device		
Mouthpiece	6 (23.1)	8 (32.0)
Facemask	20 (76.9)	17 (68.0)
Patients with expectorated sputum at baseline	5 (19.2) [c]	4 (16.0)
Patients with mucoid *Pa* isolates at baseline	6 (23.1) [c]	4 (16.0)

SD, standard deviation; TOBI, tobramycin inhalation solution.
[a] Unless otherwise indicated.
[b] Data was missing for one patient.
[c] In one patient, *Pa* was detected before baseline but not at baseline.

3.2. Patient disposition

Sixty-nine patients were screened for the study, and 18 were determined ineligible during the screening period (see Appendix 3 for screen failure): 51 eligible patients were randomised 1:1 into one of the two treatment groups; 26 initially received TOBI (TOBI/placebo group) and 25 received placebo (placebo/TOBI group). Eighteen patients (5 from the TOBI/placebo group and 13 from the placebo/TOBI group) discontinued during the DB period; most of the patients discontinued due to *Pa* positivity. During the DB treatment, one patient from the placebo/TOBI group discontinued the study because of an SAE of bacterial upper respiratory tract infection during the first treatment period (Day 17; Fig. 2).

3.3. Efficacy

3.3.1. Patients free from Pa-infection during the DB period

After the first treatment period (Day 29), a significantly higher proportion of patients from the TOBI group (22/26 patients, 84.6%) were *Pa* free compared with the placebo group (6/25 patients, 24.0%) ($p < 0.001$; odds ratio [95% confidence interval], 21.55 [4.67, 99.52]). The results remained consistent when analysed in the ITT population, excluding one patient with missing data (22/26 patients [84.6%] versus 6/24 patients [25.0%] free from *Pa* in the TOBI/placebo versus the placebo/TOBI groups, respectively; $p < 0.001$, Fig. 3).

At Day 91, more patients receiving TOBI during the initial 28 days (the TOBI/placebo group: 19/25 patients, 76.0%) were *Pa* free compared with those initially on placebo (placebo/TOBI group: 11/23 patients 47.8%).

3.3.2. Time to recurrence after persistent eradication

Patients who had *Pa*-negative sputum/throat swab culture results at two consecutive visits performed at least 21 days

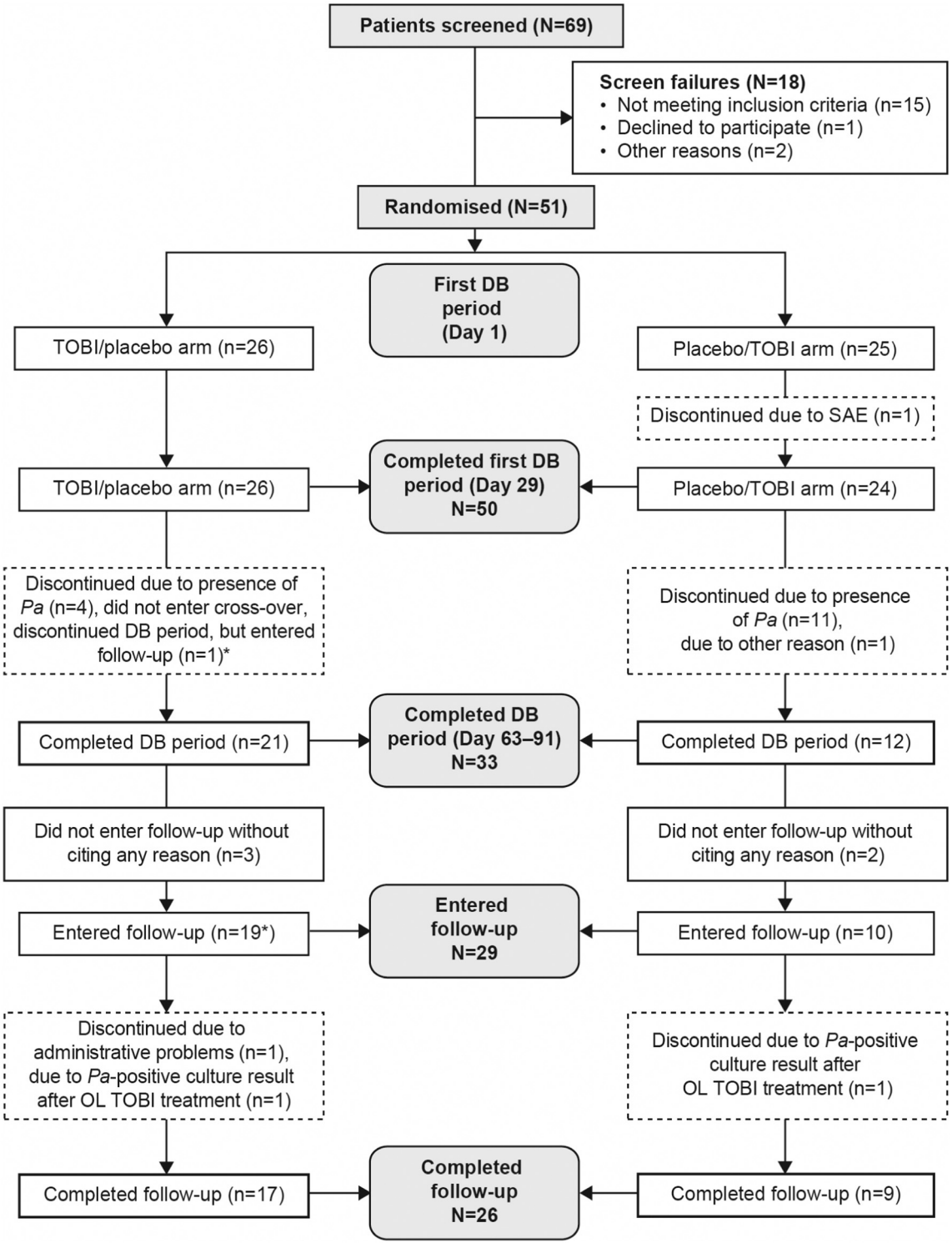

Fig. 2. Patient disposition. *One patient entered the follow-up period after discontinuing the DB period. DB, double-blind; OL, open label; *Pa*, *Pseudomonas aeruginosa*; SAE, serious adverse event; TOBI, tobramycin inhalation solution.

apart were categorised as '*Pa*-infection persistent eradication' (samples collected at Day 29, Day 63 or Day 91). During the follow-up period, a recurrence was considered to occur when sputum/throat swab results in patients were *Pa*-positive after persistent eradication. In fact, persistent eradication of *Pa*-infection was achieved in 28 of the 29 patients who entered the follow-up period. One patient did not meet the persistent eradication criteria at the beginning of the follow-up period and was therefore not included in the analysis for recurrence.

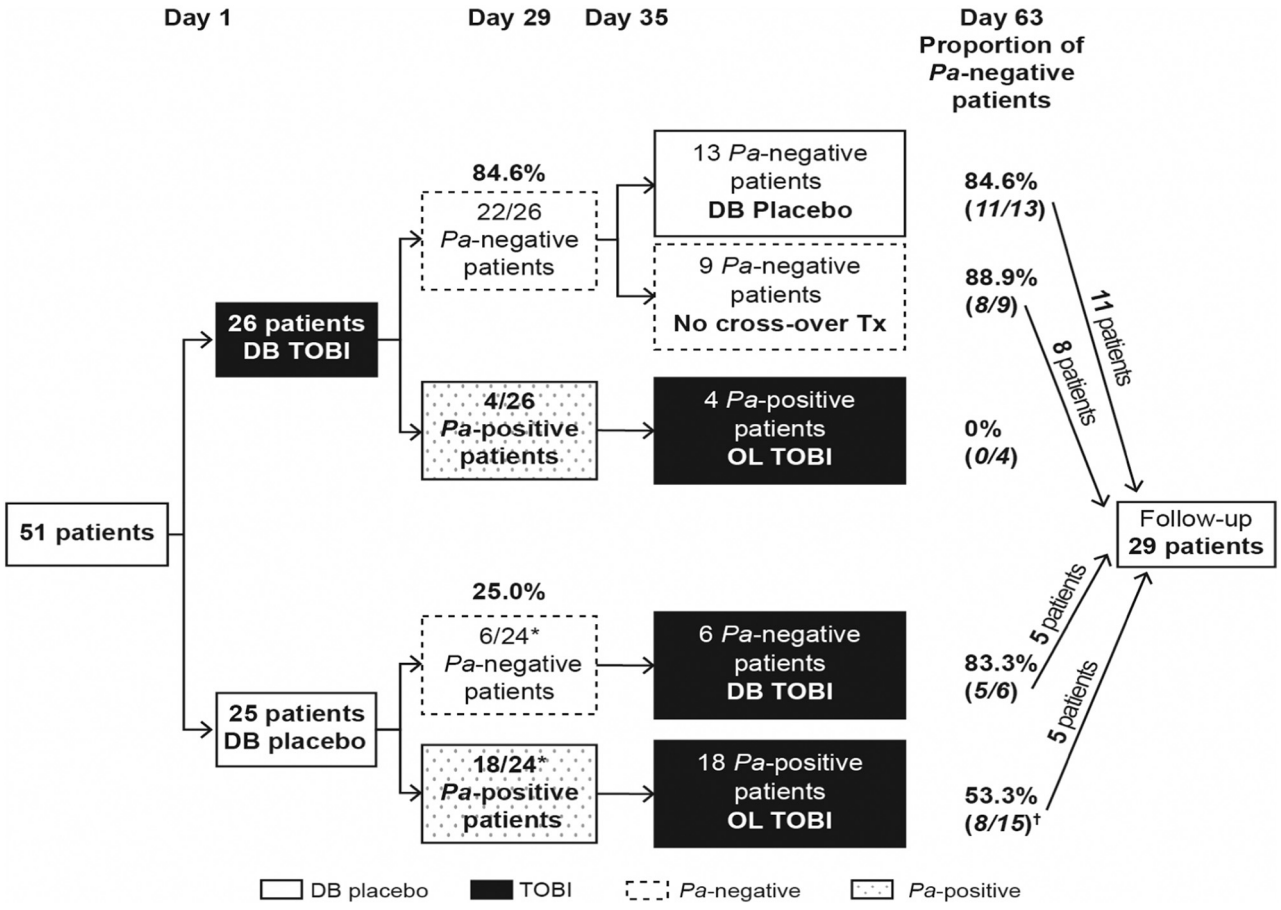

Fig. 3. Proportion of *Pa*-negative patients (observed cases, no imputation). *Of 25 patients from the placebo group, 1 patient discontinued because of serious adverse events. †Of 8 *Pa*-negative patients, only 5 entered follow-up; for the other 3 patients, reason for not entering follow-up was not reported. DB, double-blind; OL; open-label; *Pa*, *Pseudomonas aeruginosa*; TOBI, tobramycin inhalation solution, Tx, treatment.

Furthermore, nine of the 28 patients who entered the follow-up period had recurrence and received OL TOBI, whereas 19 patients remained *Pa*-negative during the follow-up period. Median time to recurrence was 273 (range, 65–379) days (for details see Appendix 4).

Anti-pseudomonal antibody titres were monitored during the study and are summarised in Appendix 5.

3.4. Safety

Overall, 41 (80.4%) patients reported AEs regardless of the treatment period and treatment group. Four (15.4%) patients from the TOBI/placebo group and three (12.0%) from the placebo/TOBI group reported AEs suspected to be related to the study drug during the DB period. AE incidence was lower during the TOBI treatment period than during the placebo treatment. Moreover, a lower proportion of patients reported AEs during the DB TOBI (37.5%) or OL TOBI (45.5%) treatment compared with those on placebo (57.9%) (Table 2; for detailed AEs during the DB period, see Appendix 6).

AEs were of mild severity in a majority of patients during the DB period (Appendix 7). Only two (8%) patients from the placebo/TOBI group reported severe AEs related to *Pa* infection (bacterial disease carrier and lower respiratory tract infection bacterial), during the off-treatment period (after Day

Table 2
Adverse events reported during the double-blind period.

	DB TOBI N = 32 n (%)	DB placebo N = 38 n (%)	OL TOBI N = 22 n (%)
AEs regardless of study drug relationship (reported in at least 2 patients per group)	12 (37.5)	22 (57.9)	10 (45.5)
Preferred term			
Cough	4 (12.5)	6 (15.8)	4 (18.2)
Pyrexia	2 (6.3)	3 (7.9)	2 (9.1)
Rhinorrhoea	1 (3.1)	1 (2.6)	2 (9.1)
Teething	2 (6.3)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	3 (7.9)	0 (0.0)
Respiratory tract infection viral	0 (0.0)	3 (7.9)	0 (0.0)
ALT increased	0 (0.0)	2 (5.3)	0 (0.0)

AE, adverse event; ALT, alanine aminotransferase; DB, double-blind; OL, open label; TOBI, tobramycin inhalation solution.

63). On the other hand, three (3/51, 5.9%) patients experienced SAEs (upper respiratory tract infection bacterial [n = 1], lower respiratory tract infection bacterial [n = 1], bacterial disease carrier [n = 1]) during the DB period; all belonged to the placebo/TOBI group whilst on placebo or during off-treatment. Two (8.0%) patients discontinued the study drug (upper and lower respiratory tract infection bacterial [n = 1] and bacterial disease carrier [n = 1]). During the DB period, no SAEs or discontinuations due to AEs were reported among patients from the TOBI/placebo group or among those treated with OL TOBI. All events suspected to be drug related were mild, except one moderate event (cough) which occurred in a patient from the placebo/TOBI group whilst using placebo. No event suspected to be related to the study medication was serious. No AE leading to study drug discontinuation was reported during the follow-up period, and no deaths were reported during the study.

Renal safety biomarkers were monitored during the study and the results are summarised in Appendix 8.

4. Discussion

This DB, placebo-controlled study was designed to assess eradication after 28 days of TOBI (300 mg/5 mL) BID treatment in young CF patients (age 3 months to <7 years) with early *Pa*-infection. The study was designed to allow every patient to receive active treatment, including those randomised to receive placebo initially. After the first DB period, all *Pa*-positive patients received OL TOBI for 28 days, whereas patients who tested *Pa*-negative on Day 29 were given the option to enter the cross-over period to allow those initially randomised to placebo to receive active medication during the second treatment period; this option was included due to the perceived risk of 'false negativity' in the throat swabs (risk of not detecting *Pa* whilst bacteria are present). This second treatment period was kept as optional, upon investigators' decision.

The baseline demographic and disease characteristics were well balanced across both treatment groups; a majority had *Pa* isolated for the first time. Although most patients from both groups had non-mucoid biotypes, few mucoid isolates were also observed at baseline, possibly due to presence of bacteria that went undetected before the study. The proportion of patients free from *Pa*-infection after 28 days of treatment was significantly higher in the TOBI/placebo group ($p < 0.001$), demonstrating superiority of TOBI over placebo. The overall success rate was consistent with previous studies which included older patients [10,18].

The success rate (84.6%) with TOBI treatment in this study was lower than that reported in the ELITE study (92%) [10], possibly due to the fact that patients with high serum *Pa* antibody titres were not randomised in the ELITE study [10]. Moreover, co-operation with inhalation therapy, which is more challenging in young children, might have contributed to the lower success rate in this study. Furthermore, the smaller sample size of this study may have led to less precise estimate of the effect size because the sample size of the ELITE study was larger. Nevertheless, this study still demonstrated clear benefits of TOBI treatment over placebo. These findings are also consistent with the EPIC study findings [11], which suggested that young children (aged 1–12 years) with early *Pa*-infection have a high likelihood of eradication with TOBI alone, with most patients remaining *Pa* free for a prolonged time period.

A concerning finding in this study was that patients randomised to the placebo/TOBI group exhibited a lower proportion of *Pa* eradication on Day 63 compared with the TOBI/placebo group, even after OL treatment with TOBI. Moreover, at the time when this study was initiated, there was no evidence available in the literature suggesting that postponing treatment by approximately 1 month would affect the success rate of eradication therapy. This suggests that treatment at the earliest opportunity after detecting *Pa*-positive cultures may be more successful and that a short delay of approximately 35 days may impede the success rate of eradication.

These findings support the recommendations of available treatment guidelines [8,9] and provide clinicians with more evidence to guide the selection of an appropriate treatment regimen for paediatric CF patients with early acquisition of *Pa*-infection. To our knowledge, this was the first placebo-controlled study on early eradication of *Pa* wherein patients first randomised to placebo were subsequently treated with inhaled tobramycin and followed up thereafter.

AEs were reported at a lower frequency during treatment with TOBI versus placebo; moreover, very few AEs were suspected to be related to the study drug. Most AEs were mild and transient. No new safety concerns were observed compared with previous studies conducted in patients aged ≥6 years for management of chronic *Pa*-infection [19,20]. Furthermore, the safety profile of TOBI in this age group was consistent with that observed in a similarly aged population from the ELITE study [10] and other studies which included paediatric patients [11,21]. Discontinuations related to AEs were also reported at a lower frequency. Taken together, EARLY study results suggested that TOBI (300 mg/5 mL) BID is well tolerated in children as young as 6 months.

This study has a unique design that tries to address several challenges including a double-blind placebo comparator in a very young patient population. The first treatment period has 1:1 randomised patient population to ensure a robust design for the primary objective (eradication rate at Day 29). The second treatment period has been set-up to allow for flexibility based on physician's decision on whether the patient should undergo further blinded treatment, in light of a recognised false-negative result of *Pa* detection in throat swabs. The open-label treatment ensures that *Pa* positive patients have treatment access.

This is a unique setting and certainly not a recommended model for interventional studies in CF. In vulnerable patient populations where placebo comparator may be problematic, similar study designs may be a practical option to explore, despite the limitations of the data collected beyond the primary endpoint (Day 29). One of the consequences of the optional cross-over design is that the results beyond Day 29 are complex, given the different options that patients have after Day 29. Therefore interpretation of the results beyond Day 29 requires caution.

5. Conclusions

Eradication of early *Pa*-infection with TOBI treatment for 28 days in young paediatric CF patients is feasible by inhalation therapy without the need for systemic antibiotic treatment. The success rate was comparable to that in older children. *Pa* must be identified early and treated as soon as detected because a short delay (approximately 1 month) in treatment initiation results in a significant reduction in the treatment success rate.

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Contributors

Study design and execution, data interpretation and manuscript preparation: FR, AM, GA.

Successful study execution, data interpretation and manuscript preparation: NA, RM.

Successful study execution and manuscript preparation: MLM, IA.

All authors have read, revised and approved the final manuscript for publication. All authors took responsibility for integrity of data analysis.

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Conflict of interests

FR has acted as a consultant to Novartis.

MLM has received research funding from Novartis and has served on Advisory Boards for Novartis.

RM is a former employee of Novartis.

GA and NA are full-time employees of Novartis Pharma AG.

Ethics approval

This study was approved by the ethics committees or institutional review boards at each centre and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice according to the International Conference on Harmonisation guidelines. Written informed consent on behalf of the patient was obtained from their parent or legal guardian.

Appendices. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2018.04.002.

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