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Journal of Cystic Fibrosis xx (2017) xxx – xxx
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

# KB001-A, a novel anti-inflammatory, found to be safe and well-tolerated in cystic fibrosis patients infected with *Pseudomonas aeruginosa*☆

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Received 16 October 2017; revised 13 December 2017; accepted 14 December 2017
Available online xxxx

**Abstract**

*Background:* Chronic *Pseudomonas aeruginosa* (*Pa*) airways infection, exuberant local inflammation, and progressive lung function loss are hallmarks of cystic fibrosis (CF). KB001-A is an anti-PcrV PEGylated monoclonal antibody fragment to the Type III secretion system of *Pa*.

This 16-week study evaluated KB001-A associated effect on time-to-need for antibiotics for worsening respiratory signs and symptoms, as well as safety, and treatment-associated changes in symptom scores, inflammatory markers, and spirometry.

*Methods:* This was a randomized, double-blind, placebo-controlled, repeat-dose study in CF subjects with *Pa.* Intravenous 10 mg/kg KB001-A or placebo infusions were administered at baseline and weeks 2, 4, 8, and 16, with a 4-week follow-up. Sputum inflammatory markers were assessed in a sub-study. Time-to-need for antibiotics was compared between groups by Kaplan Meier analysis and Cox proportional hazards modeling adjusting for randomization strata.

*Results:* Of 182 subjects, 169 received at least one infusion of KB001-A ($n$ = 83) or placebo ($n$ = 86). KB001-A was generally safe and well-tolerated as compared to placebo, with no significant emergent adverse effects other than one serious adverse event of elevated hepatic enzymes of unclear etiology. Time to need for antibiotics did not differ between groups (HR: 1.00; 95% CI: 0.69, 1.45, $p$ = 0.995). A 3.2 increase in ppFEV$_1$ from placebo favoring KB001-A was observed at week 16 (95% CI: 1.12, 5.30, $p$ = 0.003). Mean changes from baseline in $\log_{10}$ sputum neutrophil elastase (NE) had a non-significant decrease (−0.27, 95% CI: −0.58,0.04, $p$ = 0.084) while IL-8 concentrations at week 16 were significantly lower (−0.27, 95% CI: −0.55,0.00, $p$ = 0.048) among KB001-A subjects ($n$ = 16) relative to placebo ($n$ = 13).

*Conclusions:* KB001-A was safe and well-tolerated and associated with a modest FEV$_1$ benefit and reduction in select sputum inflammatory markers (IL-8). KB001-A was not associated with an increased time to need for antibiotics. The lack of efficacy seen with KB001-A may be due, in

☆ Supported by KaloBios Pharmaceuticals, Inc. and the Cystic Fibrosis Foundation Therapeutics Development Network.
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https://doi.org/10.1016/j.jcf.2017.12.006
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Please cite this article as: Jain R, et al, KB001-A, a novel anti-inflammatory, found to be safe and well-tolerated in cystic fibrosis patients infected with *Pseudomonas aeruginosa*, J Cyst Fibros (2017), https://doi.org/10.1016/j.jcf.2017.12.006

part, to the low levels of the type III secretion proteins previously reported in sputum of CF patients chronically infected with Pa.
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*Keywords:* *Pseudomonas aeruginosa* infection; Cystic fibrosis; Anti-inflammatory; Type III secretion system

## 1. Introduction

Cystic fibrosis (CF) is a life-limiting genetic disease that results in progressive irreversible airway obstruction and respiratory failure. CF airway disease is characterized by chronic infection and inflammation [1]. Activated neutrophils are considered primary effector cells for CF pulmonary pathology because they release neutrophil elastase (NE) and other products that cause lung damage. IL-1β, tumor necrosis factor alpha (TNF-α), and NE are pro-inflammatory and can stimulate IL-8 production, which serves as a chemokine to sustain neutrophilic influx [2–4]. The characteristic inflammatory response of the CF lung is exaggerated in amplitude and duration; this response is believed to account for progressive lung damage and loss of lung function [1].

*Pseudomonas aeruginosa (Pa)* is one of the most common pathogens found in the airways of CF individuals with a prevalence approximating to 80% in adults with CF [5]. *Pa* is also significant for its association with accelerated CF lung disease progression [6,7] and earlier mortality [8–11]. *Pa* infection can occur in infancy, with >97% of children with CF having evidence of exposure to *Pa* by age 3 years [12]. Because of the importance of chronic *Pa* infection in CF, the use of chronic, intermittent, inhaled anti-*Pseudomonal* antibiotics in *Pa*-infected CF individuals has become a mainstay of treatment [13].

An important mediator of virulence of *Pa* infection is the type III secretion system (TTSS). TTSS facilitates exotoxin release [14] and contributes to the cytotoxicity of *Pa* toward epithelial cells, neutrophils, and macrophages. Sera from adults with CF who are chronically infected with *Pa* recognize TTSS antigens [15]. In addition, type III secretion from *Pa* isolated from subjects with CF was previously reported to be inversely correlated with forced expiratory volume in 1 s ($FEV_1$) ($r = -0.35$, $p = 0.02$) and in first infections, 82% of cultures grew either all (44%) or no (48%) type III–positive *Pa* [16]. However, only 11% of adults chronically infection with Pa had TTSS secreting isolates [16].

KB001-A is a modified, PEGylated, recombinant, anti-*Pa* PcrV Fab' antibody that specifically binds to and inhibits the function of the PcrV protein [17]. PcrV is a protein near the tip of the TTSS that is important in the transport of *Pa* exotoxins into host immune and epithelial cells. Inhibition of the function of the PcrV protein and the subsequent release of potent cytotoxins involved in the establishment and maintenance of *Pa* infections represents a new therapeutic approach to treating infection and inflammation in CF.

Animal studies demonstrated the protective effect of immunization against PcrV in acute *Pa*-induced lung injury models and reduced neutrophilic lung inflammation [18,19]. Anti-PcrV antibody treatment in a chronic Pa-infection model similarly showed a lower fraction of neutrophils in bronchoalveolar lavage fluid (BALF) and significantly lower concentrations of inflammatory cytokines including macrophage inflammatory protein-2 (MIP-2), IL-1β, and TNF-α after 21 days when compared with animals receiving control antibody [20]. Safety and pharmacology studies in rats and guinea pigs at doses up to 106 mg/kg revealed no adverse effects (human equivalent dose (HED) of 17.1 and 23 mg/kg, respectively), and no tissue binding was detected in a mouse tissue cross-reactivity study of KB001. Animal safety studies supported the conduct of 3 clinical studies of KB001: a Phase 1, single-dose study in healthy adult volunteers (KB001-02); a Phases 1–2, single-dose study in adults with CF who were infected with *Pa* (KB001-03); [17] and a Phases 1–2, single-dose study of KB001 in adults receiving mechanical ventilation who were at risk of developing *Pa* pneumonia (KB001-04). In all three clinical studies, KB001 was administered in doses up to 10 mg/kg intravenously, over approximately 1 h. Overall, KB001 was safe and well tolerated, with no drug-related deaths or life-threatening AEs. In the study of subjects with CF, all patients had Pa TTSS expression in their sputum, and there was no significant differences noted for changes in Pa density, symptoms or spirometry. However, there was a trend toward a dose-dependent decrease in sputum MPO, IL-1 and IL-8. There were significant reductions in neutrophil elastase and absolute neutrophil counts supporting the use of KB001 at 10 mg/kg [17].

The goals of this study (KB001A-05) were to confirm and extend the KB001-03 findings of an airway anti-inflammatory effect in individuals with CF with chronic *Pa* airway infection, and to determine if this effect translated into clinical benefit with repeat doses of KB001-A. This study tested the hypothesis that KB001-A would increase the time-to-need for antibiotics (intravenous, inhaled, or oral) for worsening of respiratory tract signs and symptoms.

## 2. Methods

### 2.1. Design

This study was a 16-week safety and efficacy randomized, multi-center, double-blind, placebo-controlled, repeat-dose clinical trial in subjects with CF infected with *Pa* conducted at over 60 centers globally. The primary endpoint was time-to-need for antibiotics for worsening respiratory signs and symptoms. The study consisted of a 2-week Screening Period, a 16-week Treatment Period, and a 4-week Follow-up Period (Fig. 1). Eligible subjects were randomized 1:1 to receive up to 5 intravenous infusions of 10 mg/kg KB001-A ($N = 83$) (maximum dose of 800 mg) or placebo ($N = 86$) during the 16-week Treatment Period (Fig. 2). All subjects continued their regularly

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