A Randomized, Double-Blind, Placebo-Controlled Study of Liposomal Amikacin for Inhalation in Patients With Recalcitrant Nontuberculous Mycobacterial Lung Disease

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INTRODUCTION

• Increased prevalence of nontuberculous mycobacterial (NTM) lung disease has led to a public health crisis.
• Liposomal formulations of amikacin that are being developed for lung infections due to NTM and PJP are currently undergoing clinical trials.
• First randomized controlled multinational study in patients with NTM lung disease in 1984 in US and UK.
• The objective of the 2010 2D study was to evaluate the safety, feasibility, and efficacy of inhaled amikacin patients with multidrug-NTM lung disease.
• The primary efficacy endpoint was evaluated by calculating the change in baseline on the Lung Abscess Score and Culture Negative for the LAI arm compared with the placebo arm at Day 84.
• One of the key secondary endpoints was the proportion of patients whose culture converted to negative for the LAI arm comp. with the placebo arm at Day 84.

METHODS

Study Design

• Phase 3, placebo-controlled, double-blind, randomized, multicenter study.
• 105 subjects: 90 subjects (1:1) randomized to LAI, 15 subjects randomized to placebo.
• 84-day treatment phase,
• 56-day double-blind phase,
• 28-day follow-up.

Patient Distribution

• Stratified: LAI randomized 45 subjects (15 subjects randomized to placebo).
• 2007 ATS/IDSA criteria with evidence of nodular bronchiectasis and/or fibrocavitary disease by chest CT.
• Optional: 12 and 24 month safety follow-up off treatment.
• Continuing on ATS/IDSA guideline-based therapy.

RESULTS

• Kaplan-Meier Plot of Time to Culture Negative for the LAI arm compared with the placebo arm at Day 84.
• Time to culture conversion showed a significantly greater proportion of patients in the LAI arm becoming culture negative at all visits in the double-blind phase (Days 28, 56, and 84).
• Safety assessments showed that patients in the LAI arm had higher number of adverse events, particularly musculoskeletal events, respiratory events, and ONT events.
• Number of treatment-emergent serious adverse events: 12 events in LAI group and 5 events in the placebo group.

CONCLUSIONS

• Primary Endpoint of change from baseline in the full semi-quantitative scale did not achieve statistical significance although there was a positive trend in favor of the LAI arm.
• Time to culture conversion showed a significantly greater proportion of patients in the LAI arm becoming culture negative at all visits in the double-blind phase (Days 28, 56, and 84).
• Safety assessments showed that patients in the LAI arm had higher number of adverse events, particularly musculoskeletal events, respiratory events, and ONT events.
• No difference between arms in patients with hemoptysis, tracheal, and hoarseness.
• In patients refractory to NTM-regimens for at least 6 months, LAI, an inhaled amikacin formulation, unexpectedly led to significantly greater culture conversion compared to placebo within 84 days.

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