4. New Therapies

77 Potential of denufosol as an early intervention in CF lung disease: efficacy in patients with minimal pharmacotherapy in a US phase 3 clinical trial

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Introduction: Early onset of lung disease in CF necessitates early intervention with disease-modifying agents. Denufosol, a novel ion channel regulator, stimulates CT transport, inhibits Na+ absorption and increases ciliary beat frequency regardless of CFTR genotype. The potential of denufosol as an early intervention agent was explored in patients (pts) on limited background pharmacotherapy.

Methods: Denufosol was studied in pts on 0 to 2 concurrent pharmacotherapies for CF lung disease from a Phase 3, placebo (PL)-controlled double-blind (DB) trial (TIGER-1) in pts on US standard of care ≥5 yrs with FEV1 ≥75 % pred. The 24-wk DB phase was followed by a 24-wk denufosol-only open label extension (OLE).

Results: The demographics of PL (n = 34) and denufosol (n = 37) pts with 91% and 93% pred. FEV1 were similar to intent-to-treat population (ITT). In DB, the denufosol treatment resulted in net FEV1 improvement over PL of 5.7% (p = 0.028) or 100 ml (p = 0.059) (% change from baseline [CFB] or CFB). The net improvement over PL was 6.4 % (p = 0.011) in % pred. FEV1. In OLE, the pts on 48 wks of denufosol improved in FEV1 by 12% (183 ml) and by 4% pred. FEV1. These treatment effects were greater than observed in ITT where >50% of pts used at least 4 pharmacotherapies. Denufosol was well tolerated with comparable safety profile to PL.

Conclusions: Due to its mechanism of action designed to correct the ion transport defect, denufosol may be an ideal early intervention treatment in CF lung disease. The clinically meaningful improvement in pts on denufosol who are >90% predicted and on limited medications highlights the potential of denufosol as a first line agent in CF pts.

78 Aerosol and pharmacokinetic properties of denufosol support its use for early intervention in CF lung disease

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Introduction: Early onset of CF disease in small airways calls for disease-modifying therapies that treat small airways and possess a favorable safety profile. Denufosol, an inhaled ion channel regulator, increases CT transport, inhibits Na+ absorption and stimulates ciliary beat frequency regardless of CFTR genotype. This work examines denufosol's aerosol and PK properties and their impact on its clinical ability to nebulize denufosol to smaller airways. Following inhalation, there was little to no systemic exposure to denufosol, no evidence of liver damage or changes in biochemistry. Conclusion: Denufosol's median droplet size (3.4 to 3.8 μm, 2.4 μm MMAD) is suitable for reaching small airways. Statistically significant improvement in FEV1,75 over PL in pts <110% pred. FEV1 (p = 0.025) supports the in vitro data suggesting clinical ability to nebulize denufosol to smaller airways. Following inhalation, there was little to no systemic exposure to denufosol after the first dose, no evidence of accumulation with chronic TID dosing and a favorable safety profile.

Conclusion: Denufosol is an investigational treatment designed to correct the ion transport defect in CF lung disease. Denufosol nebulized in LC STAR is suitable for delivery to the smaller airways as supported by FEF25−75 results. The ability to treat small airways and the lack of systemic exposure make denufosol a promising early intervention therapy for CF lung disease.

79 Phase III study of inhaled dry powder mannitol (Bronchitol®) in cystic fibrosis – results from the 6 and 12 month open label phase

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Background: Inhaled dry powder Mannitol (DPM) is an osmotic agent that increases water content of the ASL, improves mucociliary clearance and cough clearance [1]. A 6 month-double blind (DB) phase III trial of DPM (400 mg bd), in a broad representative CF population, demonstrated a sustained clinically meaningful FEV1 improvement (6.5% from baseline) irrespective of concomitant rhDNase use [2]. This open label phase (OLP) aimed to further assess safety and efficacy of DPM for 12–18 months. Methods: 198 patients (112 DPM, 86 control) who completed the DB phase were given the option of entering the OLP and receiving DPM at 400 mg bd. The OLP followed patients at week 38, 52, 64 and 78 to assess lung function, safety and review pulmonary exacerbations.

Results: 85.9% of patients who completed the DB phase elected to continue into the OLP. Preliminary data showed that patients on DPM maintained the increase in FEV1 seen in the DB phase throughout the OLP (Table 1). Control group patients had an absolute mean FEV1 % predicted improvement of 5.4% (p < 0.05) after switching to DPM. The final 12 month OLP patient visit (wk 78) will be March 2010 and additional data from this OLP will be presented.

Table 1. Preliminary FEV1% predicted OLP results

<table>
<thead>
<tr>
<th>Group</th>
<th>Start of the first OLP (week 26)</th>
<th>End of the first OLP (week 52)</th>
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<tbody>
<tr>
<td>Mannitol-Mannitol</td>
<td>67.6% (SD ±16.31) (n = 97)</td>
<td>67.8% (SD ±17.3) (n = 82)</td>
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<tr>
<td>Control-Mannitol</td>
<td>61.7% (SD ±17.0) (n = 71)</td>
<td>67.8% (SD ±25.5) (n = 52)</td>
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Conclusions: DPM shows sustained improvement in FEV1. Control subjects who changed to DPM in the OLP showed a similar improvement in FEV1, as seen for patients on DPM in the DB phase, further confirming the efficacy and safety of DPM therapy in patients with CF.

Reference(s)

80 Commercial garlic preparations inhibit quorum sensing lasB and pqsA gene expression in Pseudomonas aeruginosa clinical strains

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Background: There are no new antibiotics in development to address infections caused by Pseudomonas aeruginosa (PA). PA is an environmental organism that causes chronic destructive lung infection in patients with CF. Quorum sensing (QS), an intercellular signaling mechanism coordinating gene expression has a key role in PA's virulence, resistance and immune system evasion. Inhibiting QS may reduce the virulence of this devastating pathogen.

Aim: To determine the in vitro efficacy of a garlic supplement upon the inhibition of PA in clinical strains of PA.

Methods: A laboratory strain (PA01) and clinical isolates from the spuTa of 5 children with CF and chronic pulmonary PA infection were tagged using chromosomal transcriptional lacZ-based fusions (CTX:lasB) to the QS controlled genes pqsA and lasB. Isolates were grown in control media or media infused with garlic oil. Growth and luminescence of the transcriptional fusions were measured. The reduction in expression was calculated between the difference in expression in garlic and expression in control media.

Results: See the table.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Mean reduction of QS target gene expression when grown in garlic-infused media [absolute value; relative luminescence units - 104 standard error of mean]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA01</td>
<td>8.44 (1.53)</td>
<td>10.57 (1.86)</td>
</tr>
<tr>
<td>PA03</td>
<td>1.86 (0.21)</td>
<td>4.06 (0.34)</td>
</tr>
<tr>
<td>PA06</td>
<td>4.27 (0.43)</td>
<td>4.06 (0.23)</td>
</tr>
<tr>
<td>PA09</td>
<td>8.91 (0.62)</td>
<td>27.53 (2.54)</td>
</tr>
<tr>
<td>PA15</td>
<td>5.82 (0.41)</td>
<td>7.48 (0.30)</td>
</tr>
<tr>
<td>PA21</td>
<td>0.91 (0.08)</td>
<td>2.16 (0.16)</td>
</tr>
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*Experiment repeated in triplicate – all values significant, p < 0.05.

Conclusion: Garlic oil reduces the expression of two genes which represent major loci of control of QS in all clinical strains tested. This further advances the potential for translation as a therapeutic candidate.