Phase 2 Study of A797, an Oral, Selective p38 Mitogen-Activated Protein Kinase Inhibitor, in Patients With Lamin A/C-Related Dilated Cardiomyopathy

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INTRODUCTION

• Lamin A/C (LMNA)-related heart disease is a progressive dilated cardiomyopathy (DCM) caused by dominant mutations in LMNA and characterized by protein dysfunction.
• Approximately 70% of patients experience cardiac death, heart transplantation, or major cardiac event by age 45.
• LMNA-related DCM occurs in ~9% of familial DCM.1,2
• There are estimated to be 6,000–10,000 affected patients in the US; estimates are similar in Europe.
• The number of patients currently identified with a molecular diagnosis is likely to be too small to estimate with underutilization of genetic testing.
• There is no effective, disease-specific therapy for LMNA-related DCM.
• Palbociclib for A797 treatment of LMNA-related DCM

In animal studies, loss of functional lamin proteins produces cardiac dysfunction in an animal model of DCM, characterized by poor systolic function, increased ventricular wall thickness, increased interstitial fibrosis, and increased expression of beta-myosin heavy chain.3,4 A797 is an oral, selective p38 MAPK inhibitor that reverses cardiac dysfunction in an animal model of LMNA-related DCM.

METHODS

Study Design and Overview

Figure 1. Study Design (ClinicalTrials.gov. NCT02073541)

RESULTS

Table 2. Absolute and Percentage Change From Baseline Data SHOW Early and Sustained Improvements in 6MWT Distance With A797 Treatment

- **A797 treatment was associated with early improvements (week 4) in 6MWT distance, which were enhanced and sustained over time, with modest training effects noted during the run-in period before dosing. In patients on the rollover protocol, increases in 6MWT have been sustained out to 72 weeks of treatment (Figure 2).**
- **KCCQ overall summary and clinical summary scores showed improvements of ≥5 points and were generally well tolerated.**
- **KCCQ overall summary and clinical summary scores showed changes in NT-proBNP levels, LV EF, right ventricular fractional area, right ventricular volume, and right ventricular wall thickness.**
- **KCCQ overall summary and clinical summary scores showed improvements in, left and right ventricular function with A797 treatment (Figure 5).**

CONCLUSIONS

- In this phase 2 study, treatment with A797 resulted in sustained increases in functional capacity and cardiac function in patients with LMNA-related DCM. Significant improvements in the 6MWT were mirrored by hierarchical changes in NT-proBNP levels, LV EF, right ventricular fractional area, and right ventricular volume. Patients who rolled over to the continuing treatment protocol showed enhanced improvements in the 6MWT and NT-proBNP levels through 72 weeks of treatment.
- A797 was generally well tolerated. AEs for most patients were mild to moderate, although the number of patients per dose level was small.

DISCLOSURES

3. applications of LMNA-related DCM.