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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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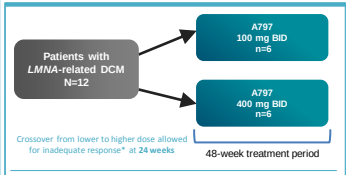
INTRODUCTION

- *Lamin A/C* (*LMNA*)–related heart disease is a progressive dilated cardiomyopathy (DCM) caused by dominant mutations in *LMNA* and characterized by poor prognosis.
  - Approximately 70% of patients experience cardiac death, heart transplant, or major cardiac event by age 45.[1]
- *LMNA*-related DCM occurs in ~8% of familial DCM.[1,2]
  - There are estimated to be 6,000–10,000 affected patients in the US;[3] estimates are similar in Europe.
  - The number of patients currently identified with a molecular diagnosis is likely to be less than this estimate because of underutilization of genetic testing.
- There is no effective, disease-specific therapy for *LMNA*-related DCM.
- Rationale for A797 treatment of *LMNA*-related DCM
  - In animal studies, loss of functional lamin proteins produces strong cellular stress signals that activate the p38 mitogen-activated protein kinase (MAPK) pathway.[4]
  - Downstream consequences of p38 MAPK activation include decreased contractility, enhanced cardiomyocyte apoptosis, cardiomyocyte hypertrophy, and increased expression of brain natriuretic peptide (BNP).[5-8]
  - A797 is an oral, potent, selective p38 MAPK inhibitor that reverses cardiac dysfunction in an animal model of *LMNA*-related DCM.[4]

METHODS

Study Design and Overview

Figure 1. Study Design (ClinicalTrials.gov, NCT02057341)



BID=twice daily; DCM=dilated cardiomyopathy; *LMNA*=lamin A/C.
*Inadequate response: <15% improvement in the 6-minute walk test, no improvement in other efficacy assessments per the investigator's discretion, and no grade 3/4 treatment-related adverse events with 100 mg BID A797.

- Key eligibility criteria
  - ≥18 years of age with stable New York Heart Association class II–IIIa congestive heart failure
  - Gene positive for a pathogenic mutation in the *LMNA* gene, as determined by a Clinical Laboratory Improvement Amendments (CLIA)–certified clinical laboratory before study enrollment
  - Receiving stable heart failure treatment with no dose reduction >50% or dose increase >100% in the past 3 months
  - Distance completed on the 6-minute walk test (6MWT) indicating functional impairment
    - Screening: ≥100 m and ≤350 m and/or ≥100 m and ≤450 m, provided the value is ≤60% predicted distance[9] and the patient is symptomatic for DCM, per investigator judgment
    - Day –1 and baseline (day 1): ≥100 m and ≤400 m (with the greater value within 10% of the lesser value) and/or ≥100 m and ≤475 m (with the greater value within 10% of the lesser value), provided the value is ≤65% predicted distance[9] and the patient is symptomatic for DCM, per investigator judgment
- Patients received oral A797 at starting doses of 100 mg twice daily (BID) or 400 mg BID.
  - Patients were assigned to starting dose cohorts on an alternating schedule.
  - Patients in the 100-mg BID dose cohort could be dose escalated to 400 mg BID at the 24-week visit in case of inadequate response.
- Endpoint assessments were conducted at 4, 12, 24 (28 if crossover occurred), 36, and 48 weeks.
- Option to roll over to continuing treatment protocol after 48 weeks (ClinicalTrials.gov: NCT02351856)
- Data shown are from the combined 100-mg BID and 400-mg BID dose cohorts, with the exception of dose-response analyses.

Endpoints

- Primary endpoint: change from baseline in 6MWT at 12 weeks
  - To minimize potential training effects, 6MWT was assessed 3 times before treatment (screening, day −1, and day 1)
- Secondary endpoints included
  - Changes from baseline in 6MWT over time
  - Changes from baseline in levels of N-terminal pro-brain natriuretic peptide (NT-proBNP)
  - Echocardiographic measures of left and right ventricular function
  - Patient-reported outcomes using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12, 24, 36, and 48 weeks

RESULTS

Patients

- 12 patients were enrolled **(Table 1)**.
- 8 patients completed and 4 patients discontinued the study.
  - The 8 completed patients enrolled in the rollover continuing treatment protocol at 48 weeks. Preliminary data for 6MWT and NT-proBNP from 4 of the 8 patients on the rollover protocol are presented.

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	Total (N=12)
Male sex, n	7
Age, y	
Mean (SD)	50 (11)
Range	30–72
Atrial fibrillation, n	9
Complete atrioventricular block, n	1
Pacemaker, n	3
Implantable cardioverter defibrillator, n	11
LVEF, mean %	36.7
Current concomitant HF medications, n	
Beta blocker	8
ACE inhibitor or angiotensin 2 blocker	10
Loop diuretic	6
Aldosterone antagonist	7

ACE=angiotensin-converting enzyme; HF=heart failure; LVEF=left ventricular ejection fraction

RESULTS (continued)

6-Minute Walk Test

- Improvement with A797 treatment was rapid, with a mean absolute change from baseline on the 6MWT of 69 m at week 12 **(Table 2)**.

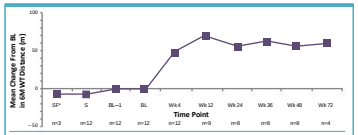
Table 2. Absolute and Percentage Change From Baseline Data Show Early and Sustained Improvements in 6MWT Distance With A797 Treatment

6MWT	Wk 4 (n=12)	Wk 12 (n=9)	Wk 12* (n=12)	Wk 24 (n=8)	Wk 36 (n=8)	Wk 48 (n=8)	Wk 72 (n=4)
Change from BL, m							
Mean (SD)	47 (49)	69 (72)	71 (68)	54 (63)	63 (44)	55 (52)	59 (57)
Median	24	47	51	30	52	41	36
Change from BL, %							
Mean (SD)	15 (18)	17 (23)	23 (23)	18 (23)	21 (16)	19 (19)	19 (18)
Median	7	13	13	10	17	14	13

6MWT=6-minute walk test; BL=baseline.
*Includes imputed data from 3 patients not completing the week 12 visit; the last-observation-carried-forward method was employed.

- 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 (n=4; **Figure 2**).

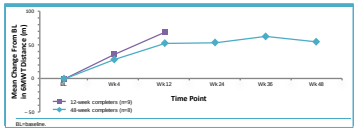
Figure 2. Improvements on the 6MWT Were Sustained Over Time With A797 Treatment



6MWT=6-minute walk test; BL=baseline; BL–1=day −1 (1 day before BL); S=screening; SP=screen fail.
*3 patients who failed screening were allowed to rescreen for this study. Their data are represented above in the "SF" group.

- A completers analysis of patients who completed 12 weeks and 48 weeks showed results consistent over time with the overall patient population **(Figure 3)**.

Figure 3. Completers Analysis of 6MWT Performance: 12 Weeks (n=9) vs 48 Weeks (n=8)

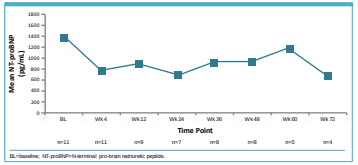


BL=baseline.

Additional Efficacy Endpoints

- Decreases in NT-proBNP mirrored changes in the 6MWT and were also sustained over time **(Figure 4)**.

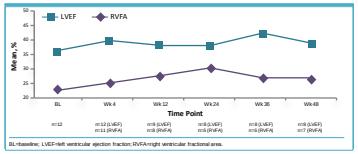
Figure 4. Improvements in Mean NT-proBNP Levels With A797 Treatment



BL=baseline; NT-proBNP=N-terminal pro-brain natriuretic peptide.

- Measurement of left ventricular ejection fraction (LVEF) and right ventricular fractional area suggested overall stability of, or slight improvements in, left and right ventricular function with A797 treatment **(Figure 5)**.

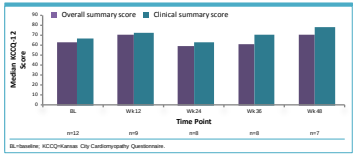
Figure 5. Mean Percentage LVEF and RVFA Were Generally Stable With a Trend Toward Improvement With A797 Treatment



BL=baseline; LVEF=left ventricular ejection fraction; RVFA=right ventricular fractional area.

- KCCQ overall summary and clinical summary scores showed improvements of >5 points at 12 weeks and 48 weeks with A797 treatment **(Figure 6)**.
  - Improvements >5 points are generally recognized as indicative of clinical benefit.[10]

Figure 6. Median KCCQ Overall Summary Scores and Clinical Summary Scores Improved With A797 Treatment



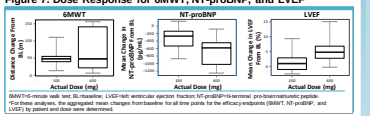
BL=baseline; KCCQ=Kansas City Cardiomyopathy Questionnaire.

- A post hoc analysis of patients with baseline KCCQ overall or KCCQ clinical summary scores of 95 or less showed
  - 71%, 50%, and 50% of patients at 12, 24, and 48 weeks, respectively, experienced a ≥5-point increase in clinical summary score.
  - 63%, 57%, and 43% of patients at 12, 24, and 48 weeks, respectively, experienced a ≥5-point increase in overall summary score.

Dose Response

- Dose-response relationship analyses for 6MWT, NT-proBNP, and LVEF favored the 400-mg BID dose of A797 over the 100-mg BID dose, although the number of patients per dose level was small **(Figure 7)**.

Figure 7. Dose Response for 6MWT, NT-proBNP, and LVEF*



6MWT=6-minute walk test; BL=baseline; LVEF=left ventricular ejection fraction; NT-proBNP=N-terminal pro-brain natriuretic peptide.
*For these analyses, the aggregated mean changes from baseline for all time points for the efficacy endpoints (6MWT, NT-proBNP, and LVEF) by patient and dose were determined.

Safety

- A797 was well tolerated at both dose levels.
- A total of 63 adverse events (AEs) were reported in 11 patients.
  - AEs, regardless of assessed causality, reported in >1 patient were: stomatitis (n=3), acne (n=2), atrial fibrillation (n=2), pyrexia (n=2), upper respiratory tract infection (n=2), abnormal liver function tests (n=2), and accidental overdose (n=2; each took 2 additional capsules during the study, 1 patient at week 36 and 1 patient at week 48).
- Most patients experienced AEs that were grade 1/2.
  - Grade 3 AEs: 1 each of atrial fibrillation, congestive cardiomyopathy, musculoskeletal pain, neck pain, rash, pyrexia, ventricular tachycardia
  - Grade 4 AEs: 1 each of cardiac failure, abnormal liver function test
- None of the serious AEs or grade 3/4 events were considered to be related to study drug by the investigators.
- AEs resulted in treatment discontinuation in 3 patients; only 1 patient withdrew because of an AE considered to be related to treatment (grade 2 event of mouth sores).

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.
  - Improvements on the 6MWT were mirrored by favorable changes in NT-proBNP levels, LVEF, right ventricular fractional area, and KCCQ scores.
  - Patients who rolled over to the continuing treatment protocol maintained 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, and only 1 patient discontinued the study because of a treatment-related AE.
- These positive findings suggest that A797 merits further clinical investigation as a treatment for *LMNA*-related DCM.

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DISCLOSURES

Dr. Calum A. MacRae has no conflicts to disclose.

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