Name of sponsor: Solvotrin Innovations Ltd	*(For National Authority Use only)*
Name of Finished Product: Eplerenone 25mg tablets (Inspra®) Eplerenone 50mg tablets (Inspra®)	
Name of Active Ingredient: Eplerenone	
Title of Study: Impact of Eplerenone on Asymptomatic Left Ventricular Diastolic Dysfunction in Diabetic Patients	
Investigators: Professor Ken McDonald, St Vincent's University Hospital, Dublin	
Study Centre: The STOP-HF Service, St Michaels Hospital, Dun Laoghaire	
Publication (reference): None available yet	
Study period (years): 33 months **Date of first enrolment:** 28 February 2013 **Date of last completed:** 23 November 2015	**Phase of development:** IIa
Objectives: The primary objective of this study was to investigate the impact of eplerenone on left atrial volume index (LAVI) measured by cardiac magnetic resonance imaging (MRI) in subjects treated with eplerenone compared with untreated patients. The secondary objectives were to evaluate the change in the level of markers of collagen turnover, change in left ventricular mass index, change in doppler-echocardiographic markers of diastolic function including LAVI, mitral valve inflow pattern and tissue doppler signal and change in the level of markers of fibro-inflammation.	
Methodology: This was a proof of concept, randomised, prospective study of open label therapy with oral eplerenone versus no treatment in type II diabetic subjects with asymptomatic left ventricular diastolic dysfunction (ALVDD). After fulfilling all eligibility criteria and following informed consent, subjects were randomised to one of two arms in a 1:1 ratio for 12 months: [1] intervention arm with usual medical care and additional treatment with eplerenone (25mg daily for one month and then uptitrated to 50mg daily for the remaining 11 month study period); or [2] control arm with usual medical therapy, but no eplerenone treatment. Usual medical care means that additional medications or interventions were administered at the discretion of the attending physician and the general practitioner.	
Number of subjects (planned and analysed): The aim was to recruit 60 subjects in total (30 subjects per group). A total of 52 subjects were recruited onto the study. Forth-eight were analysed for the primary endpoint; 24 in each arm. Four patients were withdrawn from the study (three withdrew consent for personal reasons and one subject was withdrawn due to a serious adverse event (SAE)).	
Diagnosis and main criteria for inclusion: Consenting subjects were included if they met the following inclusion criteria: 1. Over 18 years of age	

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2. Ability to give informed consent
3. Type II diabetes mellitus
4. Diastolic dysfunction on doppler-echocardiogram as evidenced by either LAVI >32ml/m^2 and/or e' <10 cm/s

Test product, dose and mode of administration

Subjects randomised to the intervention arm of the study received eplerenone (Inspra®) 25mg daily for 4 weeks. The dose was then increased to 50mg daily for the remainder of the study period (providing the increase in creatinine from baseline was no greater than 25% and the potassium level within one week of commencing eplerenone was <5.5 mmol/L). All doses of eplerenone were administered as a single dose, once daily by mouth.

Duration of treatment: 12 months

Reference therapy: None (usual medical care in control group)

Criteria for evaluation:

Efficacy:

- Change in LAVI measured by MRI over the 12-month treatment period (primary endpoint)
- Change in the level of markers of collagen turnover and fibro-inflammation
- Change in doppler-Echocardiographic markers of diastolic function including LAVI, mitral valve inflow pattern, tissue doppler signal

Safety:

- Adverse events (AE) to include all deaths and all cause hospitilisations

Statistical methods:

Comparisons between groups were conducted using independent sample Student *t*-test for continuous variables and Wilcoxon (Mann-Whitney) test for non-normally distributed variables (two-sided, $\alpha = 0.05$). Fisher or Chi-squared tests were used to compare categorical variables.

Data are presented as the mean value ± the standard deviation for continuous variables while frequencies and percentages are for categorical variables. All analyses were carried out using R statistical software, version 3.2.3 (CRAN Project).

Efficacy results:

The results show that eplerenone did not change the LAVI on cMRI compared with control over the duration of this study.

Safety results:

Fifty-two subjects were enrolled into this study and 28 were randomised to eplerenone. There were 72 adverse events (AEs) (2.92 per subject year (SY)) in the intervention group vs 22 AEs (0.91 per SY) in the control group (p=0.00). There were six serious adverse events (SAE) in the intervention group (0.24 per SY) and two (0.08 per SY) in the control group (p=0.30). Only one of the intervention

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arm SAEs were considered related to the study drug. The patient was withdrawn from the study as a result. Of the 94 AEs reported, 53.19 % were mild in severity (n=50), 42.55 % were moderate (n=40) and 1.06 % (n=1) was reported as severe. Severity was not reported for three AEs. In conclusion, no new risks or safety concerns were identified with the use of eplerenone in subjects with type II diabetes and ALVDD during this clinical trial. There was a small but significant increase of serum creatinine amongst patients taking eplerenone, although levels were still within normal range.

Conclusion: Chronic treatment with eplerenone for 12 months, resulted in no significant impact on the LAVI measured by cMRI. The therapy was well tolerated with a small but significant increase in serum creatinine observed in the eplerenone group.

Date of report: 23 November 2016