CLINICAL STUDY REPORT

Safety and efficacy of TRC4186 in the treatment of stable heart failure associated with HbA1c ≥ 6 % or type 2 diabetes receiving oral hypoglycaemic therapy (with or without additional insulin) as an add-on to conventional treatment for heart failure

1 TITLE PAGE

Investigational Product:	TRC4186
EudraCT Number	2008-006237-27
Indication:	Heart failure associated with impaired glucose metabolism
Sponsor:	Torrent Pharmaceuticals Limited Torrent Research Centre Village Bhat, Dist Gandhinagar Gujarat, India Tel: +91 79 23969100 Fax: +91 79 23969135
Study Number:	CT/P004/HF/08/02_01
Phase of Development:	Phase 2
Study Initiation Date:	17 November 2009
Responsible Medical Officer/ Sponsor Signatory:	Dr Shivani Acharya
Clinical Study Report Date:	

This study was conducted in compliance with Good Clinical Practice

CLINICAL STUDY REPORT PREPARED AND APPROVED BY

I have prepared or read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.	
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2 SYNOPSIS

Name of Sponsor/Company: Torrent Pharmaceuticals Limited **Name of Finished Product:** TRC4186 **Name of Active Ingredient:** TRC4186	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)

Title (CT/P004/HF/08/02_01):

Safety and efficacy of TRC4186 in the treatment of stable heart failure associatedwith HbA1c ≥ 6 % or type 2 diabetes receiving oral hypoglycaemic therapy (with orwithout additional insulin) as an add-on to conventional treatment for heartfailure

Investigators:

The list of investigators is presented in the appendix 16.1.4.

Study Sites:

The study was conducted at 33sites, including28sitesin India, 1 site each in UK, Netherland, Russia, and 2sitesin Serbia.

Publications (reference):

No publications were issuedat the time this report was written.

Study Period:	**Phase of development:**
Date of first patient first visit: 17 November 2009 Date of last patientlast visit: 08 November 2012	Phase 2

Objectives:

The study objectives were to:

- Evaluate safety and efficacy of TRC4186 in treatment of patients with stable heart failure associated with impaired glucose tolerance or type 2 diabetes mellitus as an add on to standard therapy (Proof of Concept)
- Define the recommended dose level for further pivotal studies

Methodology:

This study was a randomised, double-blind, multinational, multi-centre, placebo-controlled, parallel-group study. Patients were divided into three active (TRC4186) and two placebo groups:

- Patients of group 1 received starting dose of 125 mg twice daily for 2 weeks (titration phase) followed by 250 mg TRC4186 twice daily for 46 weeks;
- Patients of group 2 received starting dose of 500 mg twice daily for 2 weeks (titration phase) followed by 1000 mg TRC4186 twice daily for 46 weeks;
- Patients of group 3 received starting dose of 1000 mg twice daily for 2 weeks (titration phase) followed by 2000 mg TRC4186 twice daily for 46 weeks;
- Patients of groups 4 and 5 received placebo twice daily for 48 weeks

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At screening after signing the informed consent form, all patients underwent screening procedures. Once screening results were available, a placebo run-in phase of two weeks was started. Once the patient was deemed eligible for participating in the trial, they were randomised to one of the above mentioned groups with a unique randomisation number and undergone baseline procedures.
After completion of treatment, patients were followed-up for 4 weeks.

Safety data, i.e. adverse events (AE), serious adverse events, safety laboratory variables includingN-terminal fragment of brain natriuretic peptide (NT-proBNP), serum electrolytes, heart rate, blood pressure,electrocardiogram(ECG), impedance cardiography (ICG) readings, and concomitant medications, were reviewed by independent data safety monitoring board (DSMB) at regular intervals.

Phase A

The first 30 patients randomised were enrolled into phase A of the study. After randomisation (Day 0), patients were asked to attend for assessment on Days 7 and 14 (end of titration phase), Day 21 (week 3), Day 28 (week 4), Day 56 (week 8), Day 84 (week 12), Day 168 (week 24), Day 252 (week 36) and Day 336 (week 48). A follow-up visit was also conducted 4 weeks after the end of treatment.

Phase B

Patients subsequent to the 30th randomised patient were enrolled into phase B. After randomisation (Day 0), patients were asked to attend for assessment on Days 14 (end of titration phase), Day 28 (week 4), Day 84 (week 12), Day 168 (week 24), Day 252 (week 36) and Day 336 (week 48). Patients with an estimated glomerular filtration rate (eGFR) of ≥30 mL/min but <40 mL/min at the time of screening attended for additional safety evaluations visits on Day 7 (week 1) and Day 21 (week 3). A follow-up visit was conducted 4 weeks after the end of treatment.

Number of Patient:

Total 300 patients were planned to be randomised in this study (60 patients in each group). In total 298 (260 from India & 38 from Europe) patients were randomised in to the study. Out of these 298 patients, 61 patients were enrolled in group 1 (500 mg group), 61 patients in group 2 (2000 mg group), 60 patients in group 3 (4000 mg group) group, 59 patients in group 4 (placebo-1 group) and 57 patients in group 5 (placebo-2 group), according to the randomisation procedure.

In June 2012, the PEACH-F steering committee(SC) decided to discontinue further administration of investigational medicinal product (IMP)/placebo based on recommendations from the DSMB. This was due to a trend observed during 10th regular DSMB meeting towards an excess of serious adverse events (SAE) amongst patients receiving the two higher doses of the IMP. At the time of decision to discontinue IMP/placebo, of 298 randomised patients, 140 had completed 48 weeks, 220 had completed 24 weeks & 87 patients were on IMP. The SC suggested discontinuing IMP but continuing follow-up off treatment for safety assessment.

According to the statistical analysis plan, all patients who had taken at least one dose of randomised treatment were considered for the safety analysis. The SC, blind to efficacy data, suggested that all patients who had completed at least 32 weeks of trial should be included in the efficacy analysis.

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Diagnosis and Main Criteria for Inclusion:

Inclusion criteria

Patientswho satisfied the following criteria were included in the study:

1. Male and female patientsaged ≥ 45 years. Female and male patientsmust be of non-childbearing or non-fertile potential, i.e. surgically sterile (bilateral oophorectomy, hysterectomy, bilateral tubal ligation, vasectomy) or post-menopausal for at least one year. Male patients of fertile potential, must use an effective method of birth control
2. Patientswith chronic heart failure stable for last 6 weeks (New York Heart Association [NYHA] class II – III) according to the criteria given in appendix I (see section 15.1) and on stable medication for heart failure for at least 2 weeks prior to screening, with no change in drug or dose in that period
3. Patientswith established type 2 diabetes mellitus (i.e. receiving oral therapy with or without insulin) or an impaired glucose tolerance (HbA1c should be ≥6.0 % at screening)
4. Patientswith NT-proBNP ≥ 400 pg/mL (patients with atrial fibrillation NT-proBNP ≥ 1200 pg/mL)
5. Patientsreceiving a loop, thiazide or thiazide like diuretic (Metolazone, Chlorthalidon, Indapamide and Xipamide) for treating heart failure (HF)
6. Patientswho were able to undergo cardiopulmonary exercise testing
7. Patientswho were able to communicate well with the investigator and to comply with the requirements of the entire study
8. Patientswho were willing to give written informed consent (prior to any study-related procedures being performed) and were able to adhere to the study restrictions and assessments schedule

Exclusion criteria

Patientswere excluded from the study if they met any of the following criteria:

1. Congestive heart failure caused by myocarditis, cor pulmonale, congenital heart disease, constrictive pericarditis, or hypertrophic or restrictive cardiomyopathy
2. Significant important haemodynamic disease in the investigators opinion, e.g. mitral regurgitation and/or planned for surgery
3. Acute coronary syndrome or coronary revascularization within 3 months
4. Angina as symptom limiting treadmill/bicycle exercise
5. Evidence of myocardial ischemia which in the investigator’s opinion requires investigation by angiography with a view to coronary revascularization
6. Presence of a left ventricular (LV) aneurysm
7. Patients with a history of ventricular fibrillation or symptomatic sustained ventricular tachycardia without clear reversible precipitating cause (eg:-Severe hypokalemia [Serum potassium <3.0 mmol/L] or acute myocardial ischemia/infarction) in past 12 months unless treated with an implantable defibrillator
8. Patients with second-degree or third-degree heart block (unless treated with a pacemaker)
9. Patients scheduled for cardiac resynchronisation therapy (CRT) or who had received CRT in past 3 months
10. Patient with LV assist device (or an activated minute ventilation pacemaker)

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11. Patient with gross obesity (body mass index (BMI)>40 kg/m^2)
12. Pulmonary function forced expiratory volume within 1 second less than 60 % of predicted or requiring long-term corticosteroids
13. Patients with type I diabetes
14. Severe joint disease or peripheral arterial disease sufficient to impede exercise testing
15. Patient with a history of systemic and other vascular inflammatory disease
16. Patient with uncontrolled hypertension (Systolic blood pressure [SBP] ≥ 160 mmHg under antihypertensive treatment)
17. Screening liver enzyme test [Aspartate amino transferase (AST) or Alanine amino transferase (ALT)] exceeding 3 times the upper limit of normal range or hepatic impairment of Child-Pugh class C
18. Patients witheGFR<30 mL/min
19. Patients with haemoglobin (Hb) <10.0 gm/dL
20. Patients with HbA1c >10 %
21. Gastrointestinal disorder that could interfere with study drug absorption
22. Patients with a medical history of chronic hepatitis B, C
23. Patients with a medical history ofhuman immuno deficiency virus seropositivity
24. Pregnancy or nursing females
25. Any cancer disease, except non-invasive skin cancer (e. g. actinic keratosis or basal cell carcinoma), or any other condition that might preclude full participation in the study or that limit survival
26. Prior history of radiation and chemotherapy for malignancies
27. Known hypersensitivity to any ingredient of the study medication
28. Current participation (including prior 30 days) in any other therapeutic clinical trial
29. Patients who were unwilling or unable to comply with protocol

Test & Reference Product, Dose and Mode of Administration:

TRC4186 was the test product in this study containing 125 or 500 or 1000 mg of It is Pyridinium,3-[[2-(methylsulfonyl)hydrazino]carbonyl]-1-[2-oxo-2-(2 thienyl)ethyl] chloride. The batch used for TRC4186 was as follows:

	TRC4186 Tablets 125 mg	**TRC4186 Tablets 500 mg**	**TRC4186 Tablets 1000 mg**	**Placebo**
Batch No.	BF730001	BF740001	BF750001	BF76000
Batch No.	BF731001	BF741001	BF751001	BF768001
Batch No.	BF738001	BF748001	BF758001	

Dose and Mode of Administration

Patients were instructed to take 1 tablet of TRC4186 or Placebo during the titration period i.e, half of the planneddose of each treatment group and 2 tablets during the treatment period every morning and evening at least 2 hours after a meal and 1 hour before the next meal in addition to their usual treatment.

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Dosing Schedule

	Medication		
Dose group	**Placebo run-in 14 days**	**Titration period 14 days**	**Dosing period 46 weeks**
Low dose of TRC4186 (500 mg/day)	2 x (1 x placebo)	2 x (1 x125 mg)	2 x (2 x 125 mg)
Medium dose ofTRC4186 (2000 mg/day)	2 x (1 x placebo)	2 x (1 x 500 mg)	2 x (2 x 500 mg)
High dose of TRC4186 (4000 mg/day)	2 x (1 x placebo)	2 x (1 x 1000 mg)	2 x (2 x 1000 mg)
Group 4 and 5: 2 placebo groups	2 x (1 x placebo)	2 x (1 x placebo)	2 x (2 x placebo)

All patients had to document date and time of dosing in a diary provided to them.

Duration of Treatment:

The maximum duration of participation in the study for each patient was 56 weeks, including a 2 week screening period, 2 week placebo run-in phase, 48 weeks of randomised treatment and 4 week post treatment follow-up.

Criteria for Evaluation:

Efficacy Assessments

Primary efficacy parameters:

- Physical dimension of Minnesota living heart failure questionnaire (MLHFQ)
- Oxygen uptake efficiency slope (OUES)

Secondary efficacy parameters:

- NT-proBNP levels
- Peak VO2
- NYHA classification
- Significant & persistent change in diuretic dosage, anytime during the therapy persistence: 2 weeks
  - dose changes : loop diuretics - ≥ 40 mg furosemide and ≥ 1 mg bumetanide, toresemide ≥ 10 mg, or change from thiazides to loop diuretics, or combination of thiazides and loop diuretic
- ICG parameters in response to exercise
- Conventional and tissue Doppler echocardiography (at rest)
- Oxygen cost diagram (OCD)

Pharmacokinetics Assessments

The pharmacokinetic assessments were beyond the scope of this CSR and will be reported separately.

Plasma concentration of TRC4186 and its metabolites were determined at selected sitesin 10 patients of each

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treatment group (overall 50 patients) on baseline (Day 0); pre-dose level and week 12 (Day 84), after the start of randomised treatment prior to and 0.5, 1.0, 1.5, 2, 4, 6, 8 and 12 hours after morning dose. Patients were instructed to remainin fasting conditions for 2 hours prior and 2 hours after study medication.

Safety Assessments

Primary safety parameters:

- Morbidity/hospitalisation for cardiac reasons
- Mortality
- eGFR

Secondary safety parameters:

- ICG safety parameters
- Safety laboratory parameters
- AE and concomitant medication

Statistical Methods:

Efficacy Analyses

The primary efficacy analyses were conducted on Full Analysis Set (FAS) and Per Protocol (PP)population. Secondary efficacy analyses were conducted only on Full Analysis Set (FAS) population.For efficacy evaluation, all randomized patients who receive at least one dose of study drug at least one post-baseline efficacy measurement will be included. Patients who did not complete all the visits due to withdrawal from the study or study termination will be assessed as follows:patients with at least Week 18 data will be included in the Week 24 evaluation(FAS 24 dataset). Patients with at least Week 32 data will be included in the Week 48 evaluation, by carrying forward the Week 32 value if the Week 48 value is not available (FAS 48 dataset)

Primary and secondary efficacy endpoints were evaluated descriptively by parameter and time point. Continuous variables were summarised by descriptive statistics. Change or %change from baseline was presented using line graphs or tables of Mean/standard error of mean (SEM). Categorical variable were summarised by number of observations and their percentages supported by %. Values (raw data and changes from baseline) were also listed by treatment group, patient and measurement time.

Formal statistical comparisons between treatments were performed only for the primary & secondary efficacy endpoints and only for the results obtained after 24 and 48 weeks of randomised treatment with TRC4186 or placebo (week 24 and 48).

90 % confidence intervals (CI) were presented for major efficacy parameters (OUES, Physical dimension MLHFQ, NT-proBNP, E/E') along with the forest plots for comparison of treatment relative to placebo. The 2 placebo groups were pooled for all presentations of efficacy parameter.

The below mentioned statistical analysis of the respective parameters was planned for the study:

Physical dimension of MLHFQ

The change from baseline of the physical dimension of MLHFQ were determined for each patient and these changes were compared between treatments at 24 (or follow-up visit 6 weeks prior to Week 24) and 48 [or 32/end of study (EOS) visit] weeks of treatment. Since the scores were assumed as not following a normal distribution, nonparametric methods were used. The Wilcoxon rank sum test for independent samples was used to compare each of the active treatments to placebo. Hodges-Lehmann estimates of the between-treatment differences were derived together with 90 %CI.

OUES

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Thechange from baseline in OUES at Week 24 (or 6 weeks prior to Week 24) and Week 48 (or 16 weeks prior to Week 48) were analysed using the least-square means and 90 % CI from the ANOVA model. Pair-wise comparisons between each dose and placebo were made using the difference in least-square means, 90 % CI and p-values from the ANOVA model.

In absence of normality, between treatment analysis on % change over baseline in OUES at Week-24 and Week-48 (respective End of study data), analysis were carried out using Kruskal-Wallis test (non-parametric) while verifying assumptions of normality to corroborate the results of the parametric analyses.

The assumption of normality on the residuals and homogeneity of variances were tested using the Shapiro-Wilks test and the Levene's test, respectively. If the assumptions were violated, Kruskal-Wallis test (non-parametric) was used to corroborate the results of the parametric analyses. Statistical significance was defined as a 2-sided p-value <0.10.

Peak VO2, NT-proBNP, ICG parameters, echocardiography parameters and OCD

Selected secondary efficacy variables like NT-proBNP, OCD, Peak VO2, exercise time, ICG parameters (Supine position) like Cardiac Index, stroke index(SI),systemic vascular resistance index (SVRI), left ventricular ejection time (LVET) and thoracic fluid content index (TFCI), ECHO parameters: LV end-diastolic volume-index , E/E', left ventricular ejection fraction (LVEF), left atrial diameter (LAD), TR Velocity, LVmass, Left atrial volume index (LAVI), E', Ejection time (ET), diastolic filling time , Left ventricular end-systolic volume index (LVESVI), Minimum variance-Adur-ARD difference and exploratory parameter like peak systolic velocity (PSV)were assessed and analysed in the same manner as detailed above for OUES. Log transformation was done to normalise the data, when required.

Note: ECHO volume measures were normalised for BSA

Change in NYHA Classification

The changes in NYHA class (shift) were summarised at Weeks 24 and 48 by treatment group.

Exploratory Analyses

Based on the suggestions of the SC, additional exploratory analyses were performed on the efficacy parameters (Physical dimension score of MLHFQ, OUES, E/E' and NT-proBNP). These efficacy parameters were further analysed or presented graphically using forest plots of 90 % CI for difference between Placebo and treatment for the following subgroups.

i) Age: below/above median
ii) Gender (Male/Female)
iii) Country: India/ex-India
iv) BMI: below/above median
v) IHD: yes/no
vi) Prior MI: yes/no
vii) Patient having sinus rhythm
viii) eGFR: below/above median
ix) LVEF by median or by three group (<30%, 30-40%, >40%)
x) Patients on β-Blockers (+/-RAS)
xi) Patients on RAS (+/-βB)

Responder Analysis (FAS set)

Proportion of patients who achieved the criteria of minimal effect and cleareffect in selected efficacy

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parameters were computedfor FAS set

Safety Analyses

The safety evaluation included all patients in the safety population. The placebo groups were pooled together for all presentations.

Additionally, for certain key safety endpoints: SAEs, cardiovascular morbidity/hospitalisation and mortality, the summaries were also presented separately for each of the placebo groups.

The SAEs and AEs were coded according to Medical dictionary for regulatory activities(Version 17.0) and tabulated by system organ class, preferred term and lower level term. All AEs were listed by treatment-dose level, patient, SOC and preferred term. The emergence of AE was specified in the listing. If a given patient presents several AEs with same preferred term during the same treatment period, only one event was counted in summary tables. If the AE becomes serious during the treatment period, it was considered serious under this treatment period.

AEs were also summarised by severity (mild, moderate, severe) and by relationship to study medication (unrelated, unlikely, possibly, probably, definitely) in a similar way. The severity was highest recorded severity for all episodes. The drug relationship was the highest drug relationship recorded for all episodes.

Treatment emergent adverse events (TEAEs) are AEs with an onset at or after the administration of study drug during the administration period or if present before, worsened when exposed to study drug administration during the administration period. TEAEs were listed by treatment group, SOC and preferred term as well as serious AEs and AEs leading to withdrawal.

All safety parameters (AEs, eGFR, physical examination, vital signs, ECG parameters, biochemistry/haematology evaluations, coagulation parameters, coagulation parameters for patients not on anticoagulants) were summarised descriptively by treatment for the randomised phase. Quantitative variables were described by n, mean, standard deviation, median, and range. Qualitative variables were described by frequency tables containing counts and percentages. Change from baseline was summarised using descriptive statistics by treatment group and measurement time. Additionally, shift tables were provided for the safety laboratory parameters (within, below or above normal range) from pre-study to follow-up. The summary tables of the laboratory parameters were displayed using the units of the central laboratory.

Laboratory values (raw data and changes from baseline) were also listed by treatment group, patient and measurement time and laboratory abnormal values with investigator’s remark on Clinical significance/Non-significance wherever available.

Vital Signs, ICG and 12-lead ECG at Rest

Raw data and changes from baseline were described by treatment group, visit and measurement time. Tableof mean ± SEM over time by treatment group and measurement time was provided for change from baseline. Values (raw data and changes from baseline) of vital signs and 12-lead ECG (Including QTc) were also listed by treatment group, patient and measurement time with investigator’s remark on Clinical significance/Non-significance wherever available.

Exploratory Safety Analysis as Suggested by SC

The cardiovascular morbidity/hospitalisation and mortality was further classified i.e. CV event and Non CV event. CV events would be further classified as Acute coronary syndrome (ACS), Sudden death, Heart failure, other CV.

Event Specific Baseline Characterisation

Classification of Fatal/Non-fatal events as CV, Non CV, HF for various subgroups based on baseline characteristics, (eg Beta blocker (+/-RAS inhibitor), RAS inhibitor (+/- Beta blocker), LVEF<30%, 30-40%

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and >40%).

Proportion of patients who used concomitant medication during the study period were computed by treatment group, classified by World Health Organisationpreferred terms.

No formal statistical analysis was performed on the safety data. Safety data was presented by dose level.

Pharmacokinetic Analysis

There were only 10 patients (6-placebo, 2-Low dose, 2-Medium dose) who had given samples for Pharmacokinetic at week 12. Analysis of pharmacokinetics (PK) data was not carried out as insufficient patients participated in PK study.

Changes from Protocol

However, based on the recommendation of DSMB and or SC, there was early termination of study due to excess of SAEs in medium and high dosage groups of TRC4186 and the following parameters were assessed in the study:

- The definition of the Full Analysis Set was modified to include patients with major protocol violations and study discontinuations. In addition, the Per-Protocol set was defined as a secondary efficacy analysis set to corroborate the results from the primary analysis performed on the FAS
- Patient completing 32 week follow-up were qualified for end of study evaluation along Week-48 data for primary efficacy analysis. Patient completing 18 week follow-up were qualified for end of study evaluation along Week-24 data for primary efficacy analysis
- Exploratory efficacy analyses by subgroups based on baseline characteristics was added after SC's suggestion
- SAE's adjudicated by DSMB were captured. The difference compared to direct coding, was documented and reported.
- As per the protocol differences of at least 10 % for OUES was considered clinically meaningful, however based on the descriptive summary SC's suggestion, difference over baseline of 5 %was considered as minimal and 15 % was taken for improvement for clear effect. Also based on preliminary efficacy analysis and literature review, the cutoff for MLHFQ scores was modified to a clear improvement of 3 points instead of 5 points.
- Due to discontinuation of study, as end of study visit was notof the same duration of treatment exposure, so OUES analysis approach on actual data along 'time' factor was dropped. The changes from baseline were separately evaluated at Week-24 and End of study.
- After the decision was taken to stop IMP, un-blinded interim descriptive summary was presented to SC; however on termination, since no further modification to study conduct was intended. Also conduct and data management team remained blinded, the multiplicity adjustment was not required.
- PK sampling was planned for total 50 patients however in actual PK sampling was carried out with only 10 patients and which was not in scope of this CSR and was reported separately.
- Due to the poor image quality all the exploratory ECHO parameters as mentioned in protocols from each case/record was not extracted or remained in-evaluable, an attempt was made to extract and derive essential parameters within and beyond the purview of protocol and same has been reported. Conventional ECHO parameters were not analysed due to higher inter and intra individual variability. ECHO parameters of only core lab were evaluated for efficacy.
- Measurement of peripheral perfusion and O2 Saturations by oxygen to seemachine as well as exercises ICG was not carried out due to difficulties in conduct of experiment at sites and many

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missing data due to machine interruption respectively. Only supine CI, SI, SVRI, LVET and TFCI were analysed for efficacy evaluation.

- Bio-analysis of samples collected for renal marker was not done due to logistic and feasibility issues.
- For compliance, patients/sites where IMP distribution done in stage wise manner at week2 and week 4 was pooled together.
- Changes in diuretic doses during treatment were not assessed due to insufficient data collection. So this end point was not analysed.
- Selected major secondary efficacy parameters were also analysed as per SC suggestions.
- Hierarchical strategy meant to maintain an overall error rate of 5 %, was dropped and flexibility was adopted and brought-in, in order to make it more exploratory for comparing treatment to placebo for selecting appropriate dose for future studies.

EfficacyResults:

Disposition and Demographic Characteristics

A total of 926 patients were screened for the study. Of these, 298 patients were randomised in the study and the remaining 628 patients were considered as screen failures due to inability to meet the eligibility criteria. These 298 patients were randomised in 1:1:1:1:1 ratio to 5 treatment groups, low-dose (n = 61), medium-dose (n = 61), high-dose (n = 60), placebo 1 (n = 59), placebo 2 (n = 57).

Subject Disposition, n (%)	Placebo 1 (N=59)	Placebo 2 (N=57)	Low-Dose (N=61)	Medium-Dose (N=61)	High-Dose (N=60)	Overall (N=298)
Randomized population	59	57	61	61	60	298
FAS 24 dataset (including subjects completed at least 18 weeks of treatment)	55 (93.2)	46 (80.7)	54 (88.5)	42 (68.9)	41 (68.3)	238 (79.9)
FAS population at Week 48 (including subjects completed at least 32 weeks of treatment)	43 (72.9)	38 (66.7)	41 (67.2)	25 (41.0)	31 (51.7)	178 (59.7)
Safety population	59 (100.0)	57 (100.0)	61 (100.0)	61 (100.0)	60 (100.0)	298 (100.0)

The demographic characteristics were comparable across 5 treatment groups.

The majority (190 [63.8%]) of patients had the medical history of diabetes mellitus followed by the history of hypertension in 19 (6.4 %) patients.

(Statistical significance was shown for each dose group compared to pooled placebo)

Primary Efficacy Endpoints

Physical Dimension of MLHFQ

In both FAS and PP datasets, physical dimension of MLHFQ significantly declined from baseline to week 48

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in the medium-dose group (Week 48: p = 0.0283 and 0.0435 for FAS and PP set respectively) as compared to the pooled placebo group.

OUES

There was a statistical significant decline in OUES from baseline to week 24 in the low-dose group compared to pooled placebo in the FAS 24 dataset (p = 0.0380). There was a statistical significant decline in OUES from baseline to week 24 in the low-dose and medium-dose groups compared to pooled placebo in the FAS 48 (p = 0.0239 and p = 0.0408 respectively) and PP 48dataset. (p = 0.0270; and p = 0.0386 respectively).

However, change in OUES from baseline to week 48 was not significantly different in any dose groups as compared to pooled placebo for FAS 48 and PP 48 datasets. It is to be noted that the cardiorespiratory capacity decreased till week 24 and then improved in low and medium dose groups compared to the pooled placebo group (Figure 3).

Secondary Efficacy Endpoints

Peak VO2

There was no statistical significant change in peak VO_2 adjusted by weight from baseline to weeks 24 and 48 in the active dose groups compared to pooled placebo group in the FAS 24 and 48 datasets.

NT-proBNP

There were no statistical significant changes in the level of NT-proBNP for subjects with sinus rhythm and NT-proBNP between the dosing treatment groups and pooled placebo at weeks 24 and 48 in the FAS 24 and 48 datasets

NYHA Class

There was an improvement in physical activities from baseline to weeks 12, 24, and 48 in all the treatment groups in the FAS 24 and 48 datasets.

OCD

There were no statistical significant changes in OCD between the dosing treatment groups and pooled placebo at weeks 24 and 48 in the FAS 24 and 48 datasets.

ICG parameters

There was a statistical significant decline in LVET from baseline to Week 24 in the high dose group (p = 0.0340) in the supine position compared to the pooled placebo group in the FAS 24 dataset

However, no significant change was observed for baseline to week 48 for supine CI, SI, SVRI, LVET and TFCI for any dose group compared to pooled placebo in FAS 48 dataset.

ECHO parameters

There was a statistically significant decline in E/E' value from baseline to week 48 in the medium dose group and increase inhigh-dose group compared to the pooled placebo group in the FAS 48 dataset (p = 0.0421 and p = 0.0359 respectively).

There was a statistical significant decline in Fraction shortening (FS) from baseline to week 24 in the high dose group (p = 0.0349) in the FAS 24 dataset and from baseline to week 48 in the low-dose group in the FAS 48 dataset (p = 0.0139).

There was a statistical significant increase in LAD from baseline to week 24 in the high-dose group in the FAS 48 dataset (p = 0.0143).

There was a statistical significant increase in LAV-I from baseline to week 48 in the medium-dose group in the FAS 48 dataset (p = 0.0366).

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Additional Efficacy parameters

MLHFQ parameters

There was a statistically significant decline in MLHFQ score for fatigue (Q13) from baseline to week 48 in the medium-dose group compared to the pooled placebo group in FAS 24 and FAS 48 datasets (p=0.0174 in both datasets).

ICG Parameter (Supine Position)

FAS 24 dataset

There was no statistically significant change in ICG parameter in supine position in the FAS 24 dataset except the following statistical significant changes:

Low-dose group

- Increase in SBP from baseline to week 24 compared to pooled placebo group (p = 0.0024; mean ± standard deviation (SD): 7.15 ± 15.219 (mmHg) vs 4.38 ± 17.245(mmHg))
- Increase in diastolic blood pressure from baseline to week 24 compared to the pooled placebo group (p = 0.0180; mean ± SD: 3.62 ± 9.338(mmHg) vs 2.70 ± 9.129(mmHg))

FAS 48 dataset

There was no statistically significant change in ICG parameter in supine position in the FAS 48 dataset except the following statistical significant changes:

Low-dose group

- Increase in SBP from baseline to week 24 compared to the pooled placebo group (p = 0.0297; mean ± SD: 6.00 ± 16.583(mmHg) vs 4.89 ± 21.747(mmHg))
- Body Weight

There was a statistically significant increase in body weight from baseline to week 24 in the low-dose group compared to pooled placebo group in the FAS dataset at week 48 (1.36 ± 2.712 (kg) vs 0.28 ± 2.661(kg), p = 0.0479). However it was not clinically significant.

Laboratory parameters

Clinically significant changes were not observed in hematology and biochemistry parameters at week 24 and week 48 for FAS 24 and FAS 48 datasets. However, statistically significant increase in WBC from baseline to week 24 in the medium-dose group compared to the pooled placebo group in the FAS dataset at weeks 24 and 48 were observed (1.06 ±1.643 vs -0.07 ± 1.945 (X 10^9/liter), p<0.0001; and 0.94 ± 1.288 vs -0.02 ± 1.990(X 10^9 /liter), p=0.0028).

Responder Analysis

In the FAS 24 dataset, the higher proportion of the patients on RAS inhibitors and beta blockers did not have any change in OUES, NT-proBNP, left ventricular end-diastolic volume index, E', CI, E/E', OCD, peak VO2, from baseline to week 24 in any treatment group. The similar results were reported in the FAS 48 dataset.

There were no major changes in different parameters at week 24 in the FAS 24 dataset and at weeks 24 and 48 in the FAS 48 dataset between the treatment groups for patients with LVEF < 30 %, 30-40 %, and > 40 %.

Exploratory Analyses:

Based on the suggestions of the steering committee, additional exploratory analyses were performed on physical dimension score of MLHFQ, OUES, NT-proBNP and ECHO parameters (E/E') with respect to the following parameters: age (below/above median); gender (male/female); country (India/ex-India); BMI (below/above median); IHD (yes/no); prior MI (yes/no); subject having sinus rhythm; eGFR (below/above

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median); LVEF (by median or by three group [< 30 %, 30-40 %, > 40 %]); subjects on β-blockers (+/-RAS); subjects on RAS (+/-β-blockers).

Physical Dimension Score of MLHFQ

For FAS 24 dataset, there was a statistical significant decline in physical dimension score of MLHFQ from baseline to :

- Week 24 in the low-dose and medium-dose group (low dose: p = 0.0103; and medium-dose: p = 0.0308) in patients with LVEF > 40 %.

For FAS 48 dataset, there was a statistical significant decline in physical dimension score of MLHFQ from baseline to :

- Week 48 in the medium-dose group in patients with median age < 61.28 years (p = 0.0250)
- Week 48 in the low-dose group in non-Indian patients(p = 0.0380)
- Week 48 in the medium-dose group in patients with median BMI ≥ 24.09 (p = 0.0111)
- Week 48 in the medium-dose group in patients with median eGFR ≥ 68.71 (p = 0.0475)
- In patients with LVEF >40% at baseline, there was a statistical significant decline in physical dimension score of MLHFQ from baseline to week 24 and week 48 in the medium-dose group (week 24: p = 0.0224 and week 48: p = 0.0108)

OUES

For FAS 24 dataset, there was a statistical significant decline in OUES from baseline to:

- Week 24 in the medium-dose group in Indian patients (p = 0.0317)
- Week 24 in the low- and medium-dose group in patients with median BMI < 24.06 (low-dose group: p = 0.02; medium-dose group: p = 0.0234)
- Week 24 in the low-dose group in patients with median eGFR ≥ 68.32 (p = 0.0137)
- Week 24 in the medium-dose group in patients on no beta blockers (p = 0.0292)

For FAS 48 dataset, there was a statistical significant decline in OUES from baseline to:

- Week 24 in females of the low-dose group (p = 0.0206)
- Week 24 in the medium-dose group in Indian patients (p = 0.0159)
- Week 24 in the low- and medium-dose group in patients with median BMI < 24.06 (low-dose group: p = 0.0137; medium-dose group: p = 0.0094)
- Week 24 in the median-dose group of patients without ischemic heart disease (p = 0.0438)
- Week 24 in the low- and medium-dose group in patients with sinus rhythm (low-dose group: p = 0.0464; medium-dose group: p = 0.0457)
- In all active treatment groups in patients with median eGFR ≥ 68.71 at week 24 of FAS dataset at Week 48(low-dose: p = 0.0126; medium-dose: p = 0.0378; high-dose: p = 0.0483).
- Week 24 in the high-dose group in patients with median eGFR < 68.71 (p = 0.0394)

However, there was no significant change from baseline to week 48 for any dose group compared to pooled placebo for any of the predefined parameters.

NTproBNP

For FAS 24 dataset, there was a statistical significant decline in NT-proBNP values from baseline to week 24 in females of medium-dose group (p = 0.0205).

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For FAS 48 dataset, there was a statistical significant decline in NT-proBNP values frombaseline to week 24in the medium-dose group in patients on no beta blockers (p = 0.0102).There was a statisticalsignificantincrease in NT-proBNP values from baseline in FAS 48 data set to week 24 in patientswith median age <61.28 years in the medium-dose group (p = 0.0319).

ECHO parameters

In the FAS 24 dataset, there was a statistical significant decline in E/E' from baseline to week 24 in:

- Patients of low-dose group with median age < 61.77 years (p = 0.0081)
- Indian patients of the medium-dose group (p = 0.0317)
- Patients with median BMI ≥ 24.06 in the low-dose group (p = 0.0465)
- Patients on beta blockers in the low-dose group (p = 0.0464)

In the FAS 48 dataset, there was a statistical significant decline in E/E' from baseline to:

- Week 48 in patients of high-dose group with median age < 61.28 years (p = 0.0494)
- Week 24 in Indian patients of the medium-dose group (p = 0.0159)
- Week 48 in patients with median BMI < 24.06 in the medium-dose group(p = 0.0111)
- Week 48 in patients without ischemic heart disease (p = 0.0093) and MI (p = 0.0384) in the medium-dose group
- Week 48 in patients with sinus rhythm in the medium-dose group (p = 0.0159)
- Week 48 in patients with LVEF > 40 % in the medium-dose group (p = 0.0234)
- Week 24 in patients on beta blockers in the low-dose group (p = 0.0251)

There was a statistical significant increase in E/E' from baseline to week 48 in patients with median eGFR ≥ 68.71 (p = 0.0447), without ischemic heart disease (p = 0.0135), without MI (p = 0.008), with sinus rhythm (p = 0.0466), without beta blockers (p = 0.0358), and in patients on RAS inhibitors (p = 0.0356) in the high-dose group in FAS 48 dataset.

Subgroup Analysis (Based on baseline LVEF)

Subgroup analysis based on baseline LVEF data (LVEF < 30 %, LVEF 30-40 %, and LVEF > 40 %) was added after SC suggestion.

Demographic Characteristics

The demographic parameters were compared between the treatment groups in patients with LVEF < 30 %, LVEF 30-40 %, and LVEF > 40 %; the higher proportion of patients were males and of Indian origin. The mean age was comparable between the active treatment groups and the pooled placebo group.

Efficacy Parameters

Minnesota Living with Heart Failure Questionnaire score

Total score of MLHFQ

In patients with LVEF >40 %, there was a statistical significant decline in total score of MLHFQ from baseline to:

- Week 24 in the low- and medium-dose groups in the FAS 24 dataset(low-dose: p = 0.0056; medium-dose: p = 0.0169)
- Weeks 24 and 48 in the medium-dose group in the FAS 48 dataset, (week 24: p = 0.0169; week 48: p = 0.0062)

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Similar results were reported for physical dimension score of MLHFQ in patients with LVEF > 40 %.

Minnesota Living with Heart Failure Questionnaire scorefor Ankle Swelling, Climbing Stairs, Breathlessness, and Fatigue

LVEF < 30 %

There was a statistical significant decline in MLHFQ score for breathlessness (Q13) from baseline to week 24 in the low-dose group compared to the pooled placebo group in the FAS 24 dataset, (p = 0.0227).

In the FAS 48 dataset, there was a statistical significant decline in MLHFQ score for:

- Ankle swelling from baseline to week 48 in the medium-dose group (p = 0.0323).
- Breathlessness from baseline to week 24 and 48 in the low-dose group (week 24: p = 0.0132; week 48: p = 0.0020)

LVEF 30-40 %

There was a statistical significant decline in MLHFQ score for breathlessness (Q13) from baseline to week 24 in the low-dose group in FAS 24 dataset (p = 0.0041). In the FAS 48 dataset, there was a statistical significant decline in MLHFQ score for breathlessness from baseline to week 24 in the low-and high-dose groups compared to the pooled placebo group (low-dose: p = 0.0179; high-dose: p = 0.0232).

LVEF > 40 %

There was a statistical significant decline from baseline to week 24 in MLHFQ score for climbing stairs in the medium-dose group and fatigue compared to the pooled placebo group in the FAS 24 dataset(climbing stairs: p = 0.0247; fatigue: p = 0.0280). In the FAS 48 dataset, there was a statistical significant decline in MLHFQ score for climbing stairs and fatigue from baseline to week 48 in the medium-dose group compared to the pooled placebo group (climbing stairs: p = 0.0299; fatigue: p = 0.0323).

ICG Parameters

There was a statistical significant decline in TFCI from baseline to week 24 in the high-dose group in patients with LVEF > 40 % in the FAS 24 dataset(p = 0.0137). In the FAS 48 dataset, there was a statistical significant decline in LVET from baseline to week 24 in the low-dose group in patients with LVEF > 40 % (p = 0.0218).

Body Weight

There was a statistical significant increase in body weight from baseline to week 24 in the high-dose group in patients with LVEF > 40 % in the FAS 24 (2.18±1.747 kg, P=0.0143) and FAS 48 (2.48±1.940 kg, P=0.0167)datasets. However, significant change was not observed from baseline to week 48 in any dataset.

ECG

In patients with LVEF 30-40 %, there was a statistical significant decline in heart rate and an increase in QTc from baseline to week 48 in the low-dose group (heart rate: p = 0.0078; QTc: p = 0.0108). In patients with LVEF >40 %, there was a statistical significant increase in QRS duration from baseline to week 24 in the high-dose group (p = 0.0348). However, it was not clinically significant change.

Laboratory Parameters

Clinically significant changes were not observed among any subgroup for any dose group for hematology and biochemistry. However statistically significant results were described below.

Haematology

In patients with LVEF < 30 %, there was a statistical significant increase in WBC from baseline to week 24 in the medium-dose group in FAS 24 and FAS 48 datasets(1.679 ± 1.4289 vs -0.020 ± 1.4289 (X 10^9 /liter), p = 0.0003 and1.100 ± 1.1068 vs -0.031 ± 1.4086 (X 10^9 /liter),p = 0.0068, respectively). In patients with LVEF

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30-40 %, there was a statistical significant decrease in Hb from baseline to week 24 in the high-dose group in FAS 24 and FAS 48 datasets(-8.620 ± 14.7796 vs 0.685 ± 8.4224 (g/dl),p =0.0312 and -8.620 ± 14.7796 vs 1.587 ± 8.9789 (g/dl), p = 0.0243, respectively). In patients with LVEF > 40 %, there was a statistical significant increase in Hb from baseline to week 24 in the FAS 24 dataset (11.583 ± 12.2137 vs -1.688 ± 11.7585(g/dl), p = 0.0060) and to week 48 (12.700 ± 12.3473 vs -0.614 ± 15.0730 (g/dl), p = 0.0147) in the FAS 48 dataset in the high-dose group compared to pooled placebo group. However these changes were clinically non-significant.

Biochemistry

FAS 24 dataset

There was a statistical significant decrease in:

- AST from baseline to week 24 in the medium-dose group in patients with LVEF < 30 % (p = 0.0095)
- eGFR from baseline to week 24 in the medium-dose group in patients with LVEF > 40 % (p = 0.0361)

FAS 48 dataset

There was a statistical significant change in:

- Decrease in AST from baseline to week 24 in the medium-dose group in patients with LVEF < 30 % (p = 0.0047)
- Decrease in eGFR from baseline to week 48 in the high-dose group in patients with LVEF > 40 % (p = 0.0279)
- Increase in albumin from baseline to week 48 in the high-dose group in patients with LVEF > 40 % (p = 0.0270).

HbA1c

There was a statistical significant decrease in HbA1C from baseline to week 48 in the high-dose group compared to pooled placebo group in patients with LVEF < 30 % in the FAS 48 dataset (-0.92%±0.852%, p = 0.0480).

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Safetyresults:

There were no major changes in vital parameters for supine and standing sequence 1, 2, and 3, ECG, and body weight from baseline to each study visit. All 20 clinically significant physical findings were recorded as AEs. All the clinically significant abnormalities in laboratory parameters, including clinical chemistry, haematology, and coagulation were recorded as AEs. The most common concomitant medication was acetylsalicylic acid (199 [66.8 %] patients) followed by Atorvastatin (148 [49.7 %] patients) and Ramipril (128 [43.0 %] patients). The most common beta-blocker and RAS inhibitor used at baseline visit was Carvedilol (87 [45.5 %] patients) and Ramipril (128 [52.5 %] patients), respectively. 1 patient each in the low-dose, medium-dose, and pooled placebo groups had eGFR < 30 mL/min/1.73 m^2 during the study. No patient in the high-dose group had eGFR < 30 mL/min/1.73 m^2 at any study visit.

Overall, 151 (50.7 %) patients (low-dose group: 34 [55.7 %]; medium-dose group: 39 [63.9 %]; high-dose: 30 [50 %]; pooled placebo group: 48 [41.4 %]) reported 339 treatment emergent AEs (TEAEs) (low-dose group: 69; medium-dose group: 101; high-dose: 73; pooled placebo group: 96). There were higher proportion of patients experiencing TEAEs in the medium-dose group as compared to the pooled placebo group. The higher proportion of TEAEs in all the treatment groups were mild, not related to study drug, and were completely resolved.

More than 5 % of patients in all the treatment groups had hyperglycaemia (low-and medium-dose groups), blood creatinine increased (low-dose group), dizziness (high-dose group), cough (high-dose and pooled placebo groups), and dyspnoea (pooled placebo group). The proportion of probable related TEAEs was comparable between the treatment groups. The proportion of possible related TEAEs was lower in the low-dose group (1.4 %) as compared to medium-dose (6.9 %), high-dose (2.7 %), and pooled placebo (5.23 %) groups.

As per SC suggestion, SAEs (8 SAEs) which occurred after 10 days of IMP stoppage were excluded from SAE evaluation. A total of 50 evaluable SAEs were reported by 44 (14.8 %) patients where the proportion of patients with SAEs was higher in the medium-dose group (13 [21.3 %] patients) as compared to other treatment groups (low-dose group: 8 [13.1 %]; high-dose: 9 [15 %]; pooled placebo group: 14 [12.1 %]).A total of 22 (44 %) TEAEs were fatal. The proportion of fatal TEAEs was higher in the medium-dose (10.9 %) and high-dose (8.2 %) groups as compared to the low-dose (4.3 %) and pooled placebo (5.2 %) groups.Causality assessment according to investigator showed 2 possible (Placebo group), 1 not assessable (High dose), 25 unlikely (7 in placebo, 8 in low dose, 7 in medium dose & 3 in high dose) and 22 not related (6 in placebo, 3 in low dose, 8 in medium dose & 5 in high dose) to study drugs.

Exploratory Analyses on Serious Adverse Events

An exploratory analyses was done on overall SAEs in patients on RAS inhibitors, beta blockers, and with LVEF < 30 %, 30-40 %, and > 40 %.

Serious Adverse Events in Patients on RAS Inhibitor

Thirty eight of 244(15.6 %) patients had 43 SAEs. The proportion of patients with SAEs was comparable between the treatment groups. 18 of 43 (41.9 %) SAEs caused all-cause mortality and 25 (58.1 %) SAEs caused all-cause hospitalization.

Out of 43 SAEs, 32 (74.4 %) were cardiovascular events; the proportion of these events was comparable between the treatment groups. Of 32 cardiovascular events, 10 (23.3 %) events were of acute coronary syndrome, 12 (27.9 %) were heart failure events, 9 (20.9 %) were sudden death cases, and 1 (2.3 %) event was other cardiovascular event

Serious Adverse Events in Patients on Beta Blockers

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Thirty one of 191 (16.2 %) patients had 37 SAEs. The proportion of patients with SAEs was comparable between the treatment groups.

Out of 37 SAEs, 28 (75.7 %) were cardiovascular events; the proportion of these events was numerically lower with all TRC4186 treatment groups compared to pooled placebo group (92.9 % events). 15 of 37 (40.5 %) SAEs caused all-cause mortality and 22 (59.5 %) SAEs caused all-cause hospitalization. Of 28 cardiovascular events, 11 (29.7 %) events were of acute coronary syndrome, 10 (27.0 %) were heart failure events, 6 (16.2 %) were sudden death cases, and 1 (2.7 %) event was other cardiovascular event.

Serious Adverse Events in Patients with LVEF < 30 %

Twenty of 115 (17.4 %) patients had 24 SAEs. The proportion of patients with SAEs was numerically higher in medium- and high-dose groups compared to low-dose and placebo groups. 10 of 24 (41.7 %) SAEs caused all-cause mortality and 14 (58.3 %) SAEs caused all-cause hospitalization. Out of 10 fatal AEs, 6 (75 %) were reported in medium-dose group and 4 (80%) in high-dose group.

Out of 24 SAEs, 20 (83.3 %) were cardiovascular events; the proportion of these events was comparable between the treatment groups. Of 20 cardiovascular events, 3 (12.5 %) events were of acute coronary syndrome, 11 (45.8 %) were heart failure events, 5 (20.8 %) were sudden death cases, and 1 (4.2 %) event was other cardiovascular event.

Serious Adverse Events in Patients with LVEF 30-40 %

10 of 73 (13.7 %) patients had 12 SAEs. The proportion of patients with SAEs was numerically less in high-dose group compared to other treatment groups. 5 of 12 (41.7 %) SAEs caused all-cause mortality and 7 (58.3 %) SAEs caused all-cause hospitalization. Out of 5 fatal AEs, 2 (50 %) AEs each were reported in pooled placebo and medium-dose groups and 1 (33.3%) in low-dose group.

Out of 12 SAEs, 9 (75 %) were cardiovascular events; the proportion of cardiovascular event was lower in low-dose group compared to pooled placebo and other 2 treatment groups. Of 9 cardiovascular events, 5 (41.7 %) events were of acute coronary syndrome, 1 (8.3 %) event each was a heart failure and sudden death event, and 2 (16.7 %) events were other cardiovascular event.

Serious Adverse Events in Patients with LVEF > 40 %

9 of 78 (11.5 %) patients had 9 SAEs. The proportion of patients with SAEs was numerically less in medium-dose group and comparable between pooled placebo, low-dose, and high-dose groups. 5 of 9 (55.6 %) SAEs caused all-cause mortality and 4 (44.4 %) SAEs caused all-cause hospitalization. Out of 5 fatal AEs, 3 (75 %) AEs were reported in pooled placebo and 1 (50 %) event each in low-and high-dose groups.

Out of 9 SAEs, 7 (77.8 %) were cardiovascular events where 4 events were reported in the pooled placebo group, 2 in the low-dose group, and 1 in the high-dose group. Of 7 cardiovascular events, 4 (44.4 %) events were of sudden death, 2 (22.2 %) events were of acute coronary syndrome, and 1 (11.1 %) event of heart failure.

Discussion and Conclusions:

The score of physical dimension varied from 0 to 40; where the higher the summed score, the worse was the impact of heart failure on a patient's quality of life (QoL). The score of 0 signified that there was no impact of heart failure on patient's QoL (Pietri G et al., 2004). The change from baseline of the physical dimension of MLHFQ was determined for each patient and these changes were compared between treatments at Week 24 (or follow-up visit 6 weeks prior to Week 24) and Week 48 (or follow-up visit 16 weeks prior to Week 48) of treatment. There was significant improvement in primary end point; the physical domain of MLHFQ scores in mid dose at week 48.

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The maximal oxygen uptake (VO_{2max}), defined as the point at which oxygen uptake reaches a plateau despite additional increases in the intensity of work, is regarded as the most valid objective measure of cardiorespiratory capacity. However, deriving values of cardiorespiratory capacity via symptom-limited graded exercise testing is problematic in older adults with significant physical limitations. Baba and coworkers introduced the OUES approach in 1996 as a method for obtaining an index of cardiorespiratory capacity in children with congenital heart defects. This approach involved deriving the slope of the semi-log plot of minute ventilation (V_e) vs. oxygen uptake (VO_2). As such, the OUES was an estimation of the efficiency of ventilation with respect to VO2, with greater slopes indicating greater ventilatory efficiency. Values of OUES were positively associated with greater cardiorespiratory capacity (VO_{2max}).There was no significant difference in OUES after 48 weeks of treatment in active treatment groups compared to placebo arms. OUES using the rapid ramp-up protocol was not consistent with the physical dimension of the MLHFQ, perhaps because MLHFQ reflects factors limiting submaximal exercise and endurance rather than cardiorespiratory reserve.

Echocardiography was an ultrasound-based imaging technique in which a catheter was positioned in the pulmonary artery and the heart function was assessed via thermodilution, which involved measuring the temperature of blood when a known volume of fluid was injected through the catheter to determine how quickly blood was carried from one part of the catheter to the other. It was performed routinely as a monitoring and diagnostic tool at different times in the course of one cardiac surgery (Arques S et al., 2007). Tissue doppler echocardiography was performed and various parameters were evaluated as described in methodology. Significant improvement (decline) in E/E' in the mid-dose group was observed at week 48. Similar results were observed with exploratory analysis of different subgroups, showing robustness of data. However, there was no significant difference reported in other conventional and tissue Doppler parameters, Peak VO2, NT proBNP and in OCD at week 48 in active arms compared to placebo arms. NYHA class was similar by the end of study in each treatment arm.

Overall TRC4186 was well tolerated by the subjects. Total 50 SAEs (serious adverse event) were reported in 44 patients during the study period, of which 22 were fatal (3 in low dose group, 8 in mid dose group, 6 in high dose group, 5 in pooled placebo group) The numerically greater number of deaths in the treatment arms was not associated with other signs of deterioration in heart failure, such as ventricular or atrial dilatation, rise in NT-proBNP, decrease in eGFR or worsening of other safety variables. Even two deaths in the mid-dose group occurred on day 3 and day 8 of randomised treatment i.e. during titration phase, hence actually on half of the mid-dose. Detailed subgroup analysis revealed that most patients who died in the mid and high dose groups had a LVEF <30% and were not on beta blockers i.e. recommended therapy by guidelines. Mortality was similar in each group for patients receiving guideline-indicated therapy (i.e. angiotensin converting enzyme (ACE) inhibitors and β-blockers) or LVEF >30% at baseline. In addition, hospitalization due to HF (heart failure) and other CV (cardiovascular) cause was lower in the mid-dose group compared to placebo amongst patients receiving β-blockers. Most common treatment emergent AEs were hyperglycaemia, blood creatinine increased, dizziness cough and dyspnea. Other data, such as vital signs and safety laboratory variables, were similar across groups.

Overall conclusion:

- TRC4186 was well tolerated in patients with heart failure and dysglycaemia. However, some safety concerns were observed with TRC4186 only in patients with an LVEF<30% who are not receiving guideline-indicated therapy with ACE inhibitors and beta-blockers.
- Although the numbers were too small to prove efficacy in all parameters, significant improvement inphysical dimension MLHFQ and E/E' in the mid-dose group were observed with lower hospitalization rates.

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- The segment of heart failure patients who might get benefit with this IMP are dysglycaemic patients with :
  - LVEF >30% receiving guideline-indicated therapy with ACE inhibitors
  - LVEF <30% provided they are receiving β-blockers

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