A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of JTT-251 Administered for 24 Weeks to Participants with Heart Failure with Reduced Ejection Fraction

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• To evaluate the efficacy of JTT-251 in participants with heart failure with reduced ejection fraction (HFrEF)• To evaluate the safety and tolerability of JTT-251 following administration for 24 weeks in participants with HFrEF• To evaluate the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON48915

Source
ToetsingOnline

Brief title
AT251-G-17-005

Condition

- Heart failures

Synonym
Decompensatio cordis, Heart failure

Research involving

Human

Sponsors and support

Primary sponsor: Akros Pharma
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Heart Failure, JTT-251, Reduced Ejection Fraction

Outcome measures

Primary outcome

Efficacy Parameters

• Change from baseline to end of treatment (EOT) in:

o LVEF as assessed by two-dimensional echocardiography (2D-echo)

o Left ventricular end-systolic volume (LVESV) index as assessed by 2D-echo

o Left ventricular end-diastolic volume (LVEDV) index as assessed by 2D-echo

o NT-pro-BNP

o 6MWD test

o NYHA functional class

Exploratory Parameters

• Change from baseline to EOT in:

o Supplementary cardiac function estimates as determined by echocardiography

o Health-related quality of life (QoL) assessment as determined by the Kansas

City Cardiomyopathy Questionnaire (KCCQ)

o HbA1c and fasting plasma glucose

o Branched-chain amino acids (BCAAs), alanine, pyruvic and lactic acid

o Cardiac troponin I, suppression of tumorigenicity 2 (ST2) and galectin-3

o eGFR and cystatin C

o Albumin-to-creatinine ratio (ACR)

o Serum myostatin and brain-derived neurotrophic factor (BDNF)

• All-cause death, cardiovascular death and heart failure hospitalizations up

to EOT

Pharmacokinetic and Pharmacodynamic Parameters

• JTT-251 trough plasma concentrations will be measured at Visit 5 (Week 4),

Visit 7 (Week 12) and Visit 10 (Week 24)

• JTT-251 plasma concentrations (post-dose) will be measured at Visit 5 (Week 4)

• Relationship between JTT-251 exposure and efficacy, and safety parameters

Safety Parameters

The number of participants with adverse events (AEs), type and severity of AEs,

change from baseline in safety laboratory, vital sign and electrocardiogram

(ECG) parameters and AEs leading to permanent discontinuation of study drug.

Secondary outcome

See above.

Study description

Background summary

JTT-251 is a novel, oral PDHK inhibitor being developed for the treatment of HFrEF. Based on the MoA of PDHK inhibitors together with available nonclinical

data, JTT-251 is expected to ameliorate cardiac function via improving cardiac work efficiency with a different MoA from that of existing drugs without directly affecting systemic hemodynamics in patients with HFrEF. It is recognized that the objectives of new HF treatments should be to improve survival, prevent deterioration of clinical status and hospitalizations, ameliorate symptoms and improve quality of life (QoL). However, Phase 2 studies are seldom powered for these outcomes, but rather are powered to explore dose, safety and other markers of efficacy. In addition, this is the first study to assess efficacy and safety of JTT-251 in patients with HFrEF and will employ multiple mechanistic endpoints such as LVEF, six minute walk distance (6MWD), New York Heart Association (NYHA) functional class, natriuretic peptides (NP) and QoL assessments.

Study objective

• To evaluate the efficacy of JTT-251 in participants with heart failure with reduced ejection fraction (HFrEF)
• To evaluate the safety and tolerability of JTT-251 following administration for 24 weeks in participants with HFrEF
• To evaluate the blootstelling-response of the efficacy and safety of JTT-251 in participants with HFrEF
• To evaluate the pharmacokinetics (PK) of JTT-251 in participants with HFrEF

Study design

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 28-week study to assess the safety, tolerability, efficacy and PK of three doses of JTT-251 (50 mg, 150 mg or 300 mg) in participants with HFrEF. Participants must be on stable, guideline-directed medical therapy for heart failure (HF), consistent with American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA) or European Society of Cardiology (ESC) guidelines.
Eligible participants will be randomized to receive one of the three doses of JTT-251 or placebo once daily (QD) for 24 weeks followed by a ~ 4-week Follow-up Period. Randomization will be stratified by region at Visit 2.

This study will randomize ~ 400 participants and includes 11 study visits. At the Screening Visit (i.e., Visit 1), participants will undergo initial safety and specific diagnostic assessments to determine study eligibility. Participants who meet the screening eligibility criteria will be randomized upon final confirmation of eligibility at Visit 2 (i.e., Day 1) in a 1:1:1:1 ratio to receive double-blind treatment with one of the three doses of JTT-251 or placebo QD for 24 weeks. A Follow-up Visit (i.e., Visit 11) will occur at ~ Week 28 for participants who complete the doubleblind treatment period. For participants who discontinue study drug prematurely, the Early Termination (ET) Visit should occur as close to the time of the last dose of study drug as

possible and the Follow-up Visit should occur ~ 4 weeks after the last dose of study drug.

Intervention

Approximately 400 participants will be randomized into one of four groups: JTT-251 50 mg, 150 mg, 300 mg or placebo QD in a 1:1:1:1 ratio; ~ 100 participants per group.

Study burden and risks

See overview in protocol.
Questionnaires 4 times
6MWD 5 times

P-gp substrates and JTT251 intake (time and dosage) will be noted in a diary by the patient.
P-gp substraten en JTT-251 inname (tijd en dosering) worden door de patient bijgehouden in een dagboekje.

Some of the most common side effects and discomforts reported in clinical studies with JTT-
251 included headache, nausea and vomiting. Other reported side effects included
• diarrhea
• decreased absolute neutrophil count
• dizziness
• abdominal discomfort
• abdominal distension
• feeling hot
• sleepiness

JTT-251 intake may lead to reductions in white blood cells. JTT-251 intake may also cause reduction of glucose in plasma when administered to type 2 diabetes mellitus patients

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female, age 18 to 85 years (inclusive), at the Screening Visit;
2. Participants with a clinical diagnosis of symptomatic HF >=3 months prior to the Screening Visit;
3. Participants with NYHA functional class II or III at the Screening Visit;
4. Participants must be on stable, guideline-directed medical therapy for HF, consistent with AHA, ACC, HFSA or ESC guidelines for at least 30 days prior to the Screening Visit. These therapies include an ACEI or ARB with/without a neprilysin inhibitor, in combination with an evidence-based β-blocker and a MRA, in appropriate participants, or documentation justifying why optimal therapy is not being used (e.g., intolerance, contraindication, participant preference or physician*s judgement);
5. Participants must have a documented history of LVEF <=35% within 6 months prior to the Screening Visit using any of the following modalities: echocardiography, single-photon emission computed tomography (SPECT), multigated acquisition (MUGA), computed tomography (CT) scanning, magnetic resonance imaging (MRI) or ventricular angiography; if more than one measurement was performed, then the most recent one should be used for eligibility;
Note: If LVEF measurement was obtained >6 months prior to the Screening Visit, a local echocardiography measurement and interpretation will be used to determine eligibility (i.e., LVEF <=35%).
6. Participants with a plasma NT-pro-BNP level >=900 pg/mL at the Screening Visit;
7. Females may participate if they meet one of the following criteria:
• surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or

• post-menopausal, as defined by: 1) Permanent cessation of menstruation for >=12 months without an alternative medical cause [regardless of follicle-stimulating hormone (FSH) value] at the Screening Visit, or 2) Cessation of menstruation for <12 months and FSH >40 mIU/mL at the Screening Visit.
All other females will be considered of childbearing potential and must either:
a. practice abstinence, or
b. have same-sex partner, or
c. use one highly effective contraceptive method of birth control, which includes intrauterine devices, male partner sterilization (at least six months prior to screening with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate, and the vasectomized male partner should be the sole partner for that participant), tubal ligation, bilateral tubal occlusion, intrauterine hormone-releasing systems, or
d. use a double-barrier method of birth control, which includes a combination of male condom with either diaphragm, cervical cap or vaginal sponge, all with spermicide.
Note: Concomitant use of a female condom and a male condom is not considered an acceptable double barrier method of contraception for the study.
The above-described contraception methods must be maintained during treatment and until 30 days after the last dose of study drug.
8. Males must either practice abstinence, have same-sex partner, use a barrier contraceptive method with spermicide (for the duration of the treatment period and until 30 days after the last dose of study drug), or be sterilized at least six months prior to screening (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
Notes: Males with sterile or post-menopausal female partners are not required to use contraception if said female partner is the sole partner for that participant. Males must not donate sperm for the duration of the study and for 30 days after the last dose of study drug.
9. Able and willing to give written informed consent.

Exclusion criteria

1. Participants with confirmed acute MI (i.e., Type 1) within 30 days prior to the Screening Visit or unstable angina, a history of coronary revascularization (percutaneous coronary intervention and/or coronary artery bypass grafting) or other cardiovascular surgery within 90 days prior to the Screening Visit;
2. Participants whose HF is due to congenital heart disease, active myocarditis or constrictive pericarditis;
3. Participants who have received a heart transplant or are on a transplant list or who have a history of LV assist device implantation;
4. Participants with severe stenotic valvular disease or severe outflow tract obstruction;
5. Participants with a history of stroke or cerebral transient ischemic attack within 30 days prior to the Screening Visit;
6. Participants who started cardiac resynchronization therapy within 90 days prior to the Screening Visit;
Note: Implantable cardioverter defibrillator (ICD) placement alone or generator change is acceptable.

7. Participants with planned cardiovascular surgery and/or cardiac resynchronization therapy during the double-blind treatment period;
8. Participants who were admitted to hospital for HF within 30 days prior to Visit 2;
9. Participants with known active liver disease or with aminotransferases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >3.0x upper limit of normal (ULN) or total bilirubin >1.5x ULN at the time of screening;
Note: Participants with documented benign liver condition that can result in elevated bilirubin levels (e.g., Gilbert*s Syndrome) are eligible to participate in the study.
10. Participants unable to perform a six minute walk distance (6MWD) test at Visit 2;
11. Participants with resting symptomatic hypotension or uncontrolled hypertension (i.e., systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg) at the Screening Visit;
12. Participants with clinically significant chronic renal insufficiency (i.e., estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2 using the 4-variable Modification of Diet in Renal Disease [MDRD] formula) or who are on or indicated to start renal dialysis within the next 90 days;
eGFR (in mL/min/1.73 m2) = 175 × Serum Creatinine -1.154 × age -0.203 × 1.212 (for black participant) × 0.742 (for female participant)
13. Diabetic participants with hemoglobin A1c (HbA1c) >10% measured at the Screening Visit;
14. Participants with hemoglobin <8 g/dL at the Screening Visit;
15. Participants currently receiving or have received an investigational product (including an investigational drug or other investigational therapeutic intervention) within 28 days, five half-lives or twice the duration of the biological effect of the investigational product, if known (whichever is longer) prior to the Screening Visit;
16. Participants with a history of recreational drug abuse within six months of the Screening Visit;
Note: Medical marijuana prescribed by a physician is acceptable.
17. Participants with a history of alcohol abuse within six months of the Screening Visit;
18. Participants with an ANC <1200/µL at the Screening Visit;
19. Participants with systemic effects of untreated active infection(s) (e.g., fever >=100.4°F [38.0°C]) at Visit 2;
Note: Participants with successfully treated infections or infections that required antibiotics will be permitted if resolved >7 days prior to Visit 2.
20. Participants who test positive for human immunodeficiency virus (HIV) antibodies at the Screening Visit;
21. Participants with current malignancies or who are receiving or require active cancer treatment (exceptions include adequately treated or excised non-metastatic basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ);
22. Participants who have unstable physical or major psychiatric conditions (e.g., schizophrenia, clinically unstable major psychiatric disorder) that would put the participant at risk, or would interfere with study procedures according to the Investigator*s clinical judgement;
23. Females who are pregnant as determined by a positive serum human chorionic gonadotropin (hCG) test result at the Screening Visit or urine hCG at Visit 2;
Note: Any positive urine pregnancy test result at Visit 2 must be verified with a serum pregnancy test prior to randomization.

24. Females who are lactating at the Screening Visit or at Visit 2;
25. Participants who are unwilling or unable to comply with the requirements of the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	JTT-251 monohydrate
Generic name:	JTT-251

Ethics review

Approved WMO

Date:	06-12-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	22-02-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	137287
EudraCT	EUCTR2017□005093□19-NL
CCMO	NL65965.078.18