A Multicenter, Double-blind, Placebo-controlled, Randomized Withdrawal, Parallel Group Study of Patiromer for the Management of Hyperkalemia in Subjects Receiving Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Medications for the Treatment of Heart Failure (DIAMOND)

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To determine if patiromer treatment of subjects who developed hyperkalemia while receiving RAASi medications will result in continued use of RAASi medications in accordance with HF treatment guidelines and thereby decrease the occurrence of the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55106

Source
ToetsingOnline

Brief title
DIAMOND

Condition

- Other condition

Synonym
Hyperkalemia / high potassium in the blood

Health condition

Blood potassium increased

Research involving
Human

Sponsors and support

Primary sponsor: Relypsa, Inc., a Vifor Company
Source(s) of monetary or material Support: industry

Intervention

Keyword: Hyperkalemia, Patiromer, Phase 3b

Outcome measures

Primary outcome

Time to first occurrence of CV death or CV hospitalization

Secondary outcome

• Proportion of subjects on >=50% of guideline-recommended target dose of ACEi,

ARB, or ARNi and >=50% of guideline-recommended target dose of MRA at the EoS

Visit

• Total HF hospitalizations (or equivalent in outpatient clinic)

• Change from randomization in the clinical summary score of Kansas City

Cardiomyopathy Questionnaire (KCCQ) at 8 months

Study description

Background summary

Please refer to background and rational in the protocol: section 1 and 2, page

27-30

Twenty-six (26) million people worldwide have a diagnosis of (HF. In their Heart Disease and Stroke Statistics*2017 Update, the American Heart Association (AHA) reported data from National Health and Nutrition Examination Survey 2011-2014, which estimates that 6.5 million Americans >=20 years of age have HF. Projections show that with improved survival and the aging of the population, the prevalence of HF in the US will increase 46% from 2012 to 2030, resulting in more than 8 million people >=18 years of age with HF. Currently, HF accounts for nearly 1 million annual hospitalizations in the US and more than 3 million physician office visits. By 2030, 1 in every 33 US citizens will have a diagnosis of HF. Accordingly, it is in the public interest that therapies which have shown reductions in cardiovascular (CV) mortality, reductions in HF hospitalizations, and improvements in patient quality of life be optimally implemented.

HF mortality remains high. Approximately 50% of people diagnosed with HF will die within 5 years, but mortality rates have improved in the past 20 years, and this has been primarily because of evidence-based approaches to treating HF risk factors and comorbidities, as well as use of ACEi, BB, MRA, coronary revascularization, implantable cardioverter-defibrillators, and cardiac resynchronization therapeutic strategies.

However, evidence suggests that these treatments are not being implemented as recommended in HF treatment guidelines. Data from the Get With The Guidelines-Heart Failure (GWTG-HF) registry suggests that approximately 47% of individuals admitted to the hospital with HF should have had initiation of at least 1 new medication on discharge. The GWTG-HF registry 2008-2013 collected prescribing, indications, and contraindications for ACEi or ARB, BB, MRA, hydralazine/isosorbide dinitrate, and anticoagulants. The difference between a patient*s medication regimen at hospital admission and that which was recommended by HF quality measures at discharge was calculated. Among 158,922 patients from 271 hospitals with a primary discharge diagnosis of HF, initiation of ACEi/ARB was indicated in 18.1% of all patients, 55.5% of whom had not been receiving ACEi/ARB at admission. BB were indicated in 20.3%, 50.5% of whom had not been receiving BB at admission, and initiation of MRA was indicated in 24.1%, 87.4% of whom had not been receiving MRA at admission. A quarter of patients hospitalized with HF needed to start more than 1 medication to meet HF quality measures, and a significant proportion of these patients were not taking these medications at admission, excluding them from the mortality and morbidity benefits attributed to these treatments which have earned Class I recommendations in the HF treatment guidelines.

Similar findings have been seen in the European Society of Cardiology Heart Failure Long-Term Registry. In patients with chronic HFrEF, renin-angiotensin system blockers, BB, and MRA were used in 92.2, 92.7, and 67.0% of patients,

respectively. About 70% of patients did not receive the target dosage of these drugs. Among reasons for non-adherence or not achieving the target dose with ACEi,
ARB, or MRA were contraindication or lack of tolerance, most often due to worsening renal function, symptomatic hypotension, or hyperkalemia. The reduction in renal function associated with HF, older age, and comorbidities such as diabetes mellitus hampers K+ excretion and so makes patients with HF more likely to develop hyperkalemia. Additionally, the guideline-recommended pharmacologic treatments, which include multiple neurohormonal antagonists of the renin-angiotensin-aldosterone system (RAAS), increase the risk of hyperkalemia, especially when used in combination. Epstein et al., 2015 examined renin-angiotensin-aldosterone system inhibitor (RAASi) dose levels in a US patient population. They investigated the impact of hyperkalemia on RAASi dose and the association between dose levels and clinical outcomes. Patients were classified by comorbidities (chronic kidney disease (CKD), HF, or diabetes) and RAASi dose level at index date, as determined by prescription information (supramaximal = above labeled dose; maximal = labeled dose; submaximal = less than labeled dose; or discontinued). One-third (32.8%) of all qualifying subjects experienced at least 1 hyperkalemic event (serum K+ >5.0 mEq/L). Among subjects with HF and Stage
3-4 CKD, maximum doses were prescribed in 19% of subjects; 64% of subjects were prescribed submaximal doses, and 16% of patients discontinued treatment with RAASi medications as of the index date. Analysis of RAASi dosing before and after hyperkalemia events revealed that a substantial proportion of subjects had changes in their dose following an episode of elevated serum K+, with dose changes occurring more
frequently after moderate-to-severe hyperkalemia events (serum K+ >5.5 mEq/L). Patients on a maximum dose of a RAASi were down-titrated to a submaximal dose or discontinued the RAASi nearly half the time (47%) after moderate-to-severe hyperkalemia events and 38% of the time after mild events. Among patients on submaximal doses of RAASi, moderate-to-severe hyperkalemia events were followed by submaximal dose maintenance in 55% of patients and discontinuation in 27% of patients, compared with dose maintenance in 61% after mild hyperkalemia events and discontinuation in 24% after mild events. Nearly 60% of subjects with HF who discontinued RAASi experienced an adverse outcome or mortality compared with 52.3% of patients on submaximal doses and 44.3% of patients on maximum doses (all comparisons $p<0.05$). Patients on submaximal doses or who discontinued RAASi therapy showed consistently worse outcomes compared with patients on maximum doses, irrespective of comorbidity status (CKD, HF, diabetes mellitus) or patient age, suggesting that patients may benefit from continuing maximal, guideline-directed doses of medications, if hyperkalemia can be managed.

Although these data are taken from a retrospective database analysis with many limitations, they are consistent with other observational and retrospective studies that have reported a meaningful gap between recommendations in guidelines and real-world practice. Closing this gap between the number of

guideline-RAASi-eligible patients with HFrEF and the actual number receiving RAASi may provide an opportunity
to further reduce CV mortality, hospitalizations for CV events (including HF), and healthcare costs.

New treatments for hyperkalemia may offer a solution to intolerance or contraindication due to hyperkalemia while on RAASi medications and may help close this gap. Veltassa® (patiromer) for Oral Suspension is a nonabsorbed, polymeric K+ binder that is approved for the treatment of hyperkalemia.

Study objective

To determine if patiromer treatment of subjects who developed hyperkalemia while receiving RAASi medications will result in continued use of RAASi medications in accordance with HF treatment guidelines and thereby decrease the occurrence of the combined endpoint of cardiovascular (CV) death and CV hospitalization events compared with placebo treatment.

Study design

Prospective Phase 3b multinational, multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study that includes Screening, an up to 12 weeks Run-in Phase (all subjects will have patiromer initiated and RAASi medications, including mineralocorticoid receptor antagonist (MRA), optimized) and a randomized withdrawal Blinded Treatment Phase.

Intervention

All enrolled subjects will be treated with patiromer single-blinded during the Run-in Phase. After the Run-in Phase, eligible subjects will be randomized in a 1:1 ratio to treatment with patiromer or placebo in a double-blinded fashion. The starting dose will be 1 packet/day . Based upon the potassium management algorithms, patiromer/placebo may be increased by 1 packet per day in intervals of at least 1 week (±3 days). For subjects who become hypokalemic, patiromer/placebo may be decreased to a minimum of 0 packets/day.

Doses of patiromer/placebo will be 0 packets/day, 1 packet/day, 2 packets/day, and 3 packets/day (maximum dose).

Study burden and risks

For full details see schedule of assessments in the protocol page 17-18
The patient participation in this study will last approximately 2.5 years. During this time the patient will visit the hospital
approximately 13-20 times. The visits will take about hours.

During these visits the following tests and procedures will take place:
- physical examinations will be done and questions will be asked about medical history.
- ECGs will be done
- weight, height, blood pressure, temperature, heartbeat will be measured
- blood and urine sampling will be taken.
- The research physician will also test female participants of childbearing potential for pregnancy.
- Subjects need to complete several questionnaires
Possible side effects that are already known are described in the IB and patient information letter.

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. Subject provides written informed consent prior to study participation
2. Age at least 18 years or greater
3. Current New York Heart Association (NYHA) Class II-IV
4. Left ventricular ejection fraction <=40%, measured by any echocardiographic, radionuclide, magnetic resonance imaging (MRI), angiographic, or computerized tomography method in the last 12 months (without subsequent measured ejection fraction >40% during this interval)
5. Receiving any dose of a beta blocker (BB) for the treatment of HF or unable to tolerate BB (reason documented)
6. Estimated glomerular filtration rate (eGFR) >=30 mL/min/1.73 m2 at Screening (based on a single local laboratory analysis of serum creatinine and calculation using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; see Section 9.2)
7. Hyperkalemia at Screening (defined by 2 local serum K+ values of >5.0 mEq/L each obtained from a separate venipuncture, e.g., one in each arm or two separate venipunctures in the same arm) while receiving ACEi, ARB, ARNi, and/or MRA
OR
Normokalemia at Screening (defined by 2 local serum K+ >=4.0 <=5.0 mEq/L each obtained from a separate venipuncture, e.g., one in each arm or two separate venipunctures in the same arm) but with a history of hyperkalemia documented by a usual care serum K+ measurement >5.0 mEq/L while on RAASi treatment in the 12 months prior to Screening leading to a subsequent and permanent dose decrease or discontinuation of one or more RAASi medications
8. Females of child-bearing potential must be non-lactating, must have a negative pregnancy test at Screening, and must agree to continue using contraception (see Section 9.8) throughout the study and for 4 weeks after study completion
9. With hospitalization for HF or equivalent (e.g., emergency room or outpatient visit for worsening HF during which the patient received intravenous medications for the treatment of HF) within the last 12 months before Screening
a) Without atrial fibrillation at Screening, BNP level must be greater than 150 pcg/mL (18 pmol/L) or N-terminal pro b-type BNP (NT proBNP) must be greater than 600 pcg/mL (71 pmol/L)
b) With atrial fibrillation at Screening, BNP level must be greater than 300 pcg/mL (35 pmol/L) or NT proBNP must be greater than 1,200 pcg/mL (142 pmol/L)
OR
Without hospitalization for HF or equivalent (e.g., emergency room or outpatient visit for worsening HF during which the subject received intravenous medications for the treatment of HF) within the last 12 months before Screening
a) Without atrial fibrillation at Screening, BNP level must be greater than 300 pcg/mL (35 pmol/L) or NT proBNP must be greater than 1,200 pcg/mL (142 pmol/L)
b) With atrial fibrillation at Screening, BNP level must be greater than 600

pcg/mL (71 pmol/L) or NT proBNP must be greater than 2400 pcg/mL (284 pmol/L)

Exclusion criteria

1. Current acute decompensated HF within 4 weeks before Screening. Subjects with a discharge from a hospitalization for acute decompensation of HF longer than 4 weeks before Screening may be included
2. Symptomatic hypotension or systolic blood pressure <90 mmHg
3. Significant primary aortic or mitral valvular heart disease (except secondary mitral regurgitation due to left ventricular dilatation)
4. Heart transplantation or planned heart transplantation (i.e., currently on a heart transplant waiting list) during the study period
5. Diagnosis of peripartum or chemotherapy-induced cardiomyopathy or acute myocarditis in the previous 12 months
6. Implantation of a cardiac resynchronization therapy device in the previous 4 weeks before Screening
7. Restrictive, constrictive, hypertrophic, or obstructive cardiomyopathy
8. Untreated ventricular arrhythmia with syncope in the previous 4 weeks
9. History of, or current diagnosis of, a severe swallowing disorder, moderate to severe gastroparesis, or major gastrointestinal (GI) surgery (e.g., bariatric surgery or large bowel resection)
10. A major CV event within 4 weeks prior to Screening, including acute myocardial infarction, stroke (or transient ischemic attack), a life threatening atrial or ventricular arrhythmia, or resuscitated cardiac arrest
11. Note: This exclusion criterion is included in the new Inclusion Criterion 9
12. Liver enzymes (alanine aminotransferase, aspartate aminotransferase) >5 times upper limit of normal at Screening based on the local laboratory
13. Diagnosis or treatment of a malignancy in the past 2 years, excluding non melanoma skin cancer and carcinoma in situ of the cervix, prostate cancer with Gleason score <7, or a condition highly likely to transform into a malignancy during the study
14. Presence of any condition (e.g., drug/alcohol abuse; acute illness), in the opinion of the Investigator, that places the subject at undue risk, or prevents complete participation in the trial procedures, or potentially jeopardizes the quality of the study data
15. Use of any investigational product for an unapproved indication within 4 weeks prior to Screening or currently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
16. Known hypersensitivity to patiromer (RLY5016) or its components
17. Note: This exclusion criterion is modified and partially incorporated in Exclusion Criterion 18
18. Subjects currently being treated with or having taken any one of the following medications in the 7 days prior to Screening: sodium or calcium polystyrene sulfonate or sodium zirconium cyclosilicate, or patiromer
19. An employee, spouse, or family member of the Sponsor (Relypsa, Vifor

Pharma), investigational site or the Contract Research Organization (CRO)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-01-2020
Enrollment:	82
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Veltassa
Generic name:	Patiromer
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	30-07-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-02-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-09-2021
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
EudraCT	EUCTR2018-005030-38-NL
ClinicalTrials.gov	NCT03888066

Register	ID
CCMO	NL69752.078.19

Study results

Date completed: 04-08-2021

Results posted: 16-08-2022

First publication
01-01-1900