A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-center, event driven study in dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to recombinant human erythropoietin, following a switch from erythropoietin-stimulating agents.;Anemia Studies in CKD: Erythropoiesis via a Novel PHI Daprodustat-Dialysis (ASCEND-D)

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Co-primary (tested in parallel for non-inferiority):- To compare daprodustat to rhEPO for CV safety (non-inferiority)- To compare daprodustat to rhEPO for Hgb efficacy(non-inferiority)

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON50208

Source
ToetsingOnline

Brief title

ASCEND-D 200807

Condition

- Renal disorders (excl nephropathies)

Synonym
Anemia, chronic kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: industrie

Intervention

Keyword: anemia, chronic kidney disease, CKD, dialysis subjects, erythropoietin

Outcome measures

Primary outcome

- Time to first occurrence of adjudicated major adverse cardiovascular event

(MACE) [composite of all-cause mortality, non-fatal myocardial infarction (MI)

and non-fatal stroke]

- Mean change in Hgb between baseline and evaluation period (EP, mean over

Weeks 28 to 52)

Secondary outcome

Time to first occurrence of adjudicated

-MACE

-MACE or a thromboembolic event (vascular access thrombosis, deep vein

thrombosis or pulmonary embolism)

-MACE or a hospitalization for heart failure (HF)

Average monthly IV iron dose (mg)/subject to Week 52

Safety:

-Incidence and severity of AEs and serious adverse events (SAEs) including AEs

of special interest

-Reasons for discontinuation of study treatment

-Absolute values and changes from baseline in laboratory parameters, BP and

heart rate (HR)

Study description

Background summary

Daprodustat (GSK1278863) is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) currently being investigated as a treatment for anemia associated with CKD in both dialysis and non-dialysis (ND) subjects, with adequate safety and efficacy having been demonstrated in clinical trials up to 24 weeks* duration. Both pre-clinical and clinical data show that daprodustat stimulates erythropoietin (EPO) production resulting in increased erythropoiesis and elevation in Hgb concentrations. These increases in Hgb are achieved with peak plasma EPO exposures substantially lower than those observed with rhEPO.

Based on its mechanism of action to stimulate erythropoiesis via inhibition of HIF-prolyl hydroxylase enzymes, daprodustat is postulated to be associated with fewer MACE by raising Hgb without the supraphysiologic EPO concentrations associated with rhEPO therapy, thereby potentially
avoiding blood pressure (BP) elevations and other adverse effects of high EPO levels.
A Phase 2B clinical trial in dialysis subjects with anemia associated with CKD demonstrated that daprodustat can maintain Hgb up to 24 weeks, with minimal effects on plasma EPO concentration. Daprodustat treatment for up to 24 weeks demonstrated an adverse event (AE) profile consistent with the patient population.
This Phase 3 study in dialysis subjects with anemia associated with CKD will evaluate the safety and efficacy of daprodustat compared to rhEPO, the current standard of care, as co-primary endpoints, following switch from ESAs. Both

co-primary endpoints must meet non-inferiority of daprodustat to rhEPO for the study to be successful and for analyses to progress to testing principal secondary endpoints. Data from this trial are intended to support the use of daprodustat for the treatment of anemia associated with CKD in patients on dialysis.

Study objective

Co-primary (tested in parallel for non-inferiority):
- To compare daprodustat to rhEPO for CV safety (non-inferiority)
- To compare daprodustat to rhEPO for Hgb efficacy(non-inferiority)

Study design

- This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center, event-driven study in dialysis subjects with anemia associated with CKD who are currently treated with ESAs2.
- This study will comprise four study periods: a 4-week screening period, a 4-week placebo run-in period, a treatment period and a follow-up period. Prior ESA therapy continues during the screening and run-in periods.
- The treatment period consists of :
1. The stabilization period, defined as the period from Day 1 to Week 28 during which randomized treatment will be dose titrated to achieve the appropriate Hgb target
2. The maintenance period, defined as the period from the end of the stabilization period (Week 28) to the end of treatment (variable per subject), to assess long term safety and efficacy.
o The efficacy evaluation period (EP) is defined as the period from Week 28 to Week 52 during which Hgb efficacy will primarily be assessed.
- The total duration of the study is dependent upon the accumulation of 945 adjudicated first MACE (i.e., it is event-driven) unless review of interim data by the IDMC recommends bringing the study to an earlier close.
- All subjects will remain in the study (including subjects receiving kidney transplant), regardless of whether they continue with randomized treatment (unless consent for any further follow up is withdrawn), until the target number of first adjudicated MACE has occurred. At that point, the sponsor will notify investigators to have subjects come in for an End of Study visit within a pre-defined time period.
- Subjects will be stratified by dialysis type [HD or PD], by region, and by participation in the ABPM sub-study. Dialysis type and region are considered to be stratification factors that are potentially prognostic of study endpoints while participation in the ABPM sub-study is an administrative stratification factor intended solely to ensure a similar number of sub-study subjects in each of the two randomized groups
-Following stratification, subjects will be randomized 1:1 to receive oral daprodustat or rhEPO (IV epoetin alfa for HD subjects and SC darbepoetin alfa

for PD subjects). A central randomization approach will be used to protect against potential selection bias due to the open-label design. The sponsor is blinded to treatment assignment in the main study and ABPM sub-study.
- Both treatment arms (daprodustat and rhEPO) will follow a protocol-specified randomized treatment dose adjustment algorithm to achieve and/or maintain Hgb within the target range of 10-11 g/dL (Section 6.3.3). Dose changes will be made programmatically by the Interactive Response Technology (IRT) system for both randomized treatment arms.
- To ensure subjects remain iron replete and to minimize the potential for iron overload during the study, the investigator will follow the iron management criteria (Section 6.12) from randomization through the end of the study treatment period.
- A rescue algorithm is provided to minimize subjects having an inadequate response to the treatment for their anemia for an extended period of time and to enable consistency in the application of rescue therapy across the study (Section 6.12).

Intervention

oral daprodustat
or rhEPO [intravenous (IV) epoetin alfa or subcutaneous (SC) darbepoetin alfa].

Study burden and risks

The study drug, the reference drugs and the study procedures have certain risks and may lead to discomforts.This protocol employs precautions to mitigate known and potential risks to randomized subjects (please refer to appendix 4). These include the close monitoring of the patient, close monitoring of Hgb, specific guidance for dose adjustments and unblinded monitoring of safety data by an IDMC.

In clinical trials of up to 24 weeks in duration, in subjects with anemia associated with CKD, daprodustat has been shown to treat Hgb to target range. Daprodustat may present several important advantages over rhEPO and other ESAs. It is an oral medication and does not require cold-chain storage as does rhEPO, thus increasing ease of use for patients and health care providers. After administration of daprodustat, data suggest that the increases in Hgb are achieved with EPO exposure lower than those observed with rhEPO. Treatment of anemia of CKD with rhEPO is associated with increased CV risk which is postulated to be related to the associated increases in EPO exposure with rhEPO; therefore, daprodustat has the potential to raise Hgb without the same CV risk associated with rhEPO. Other potential benefits include possibly improving iron availability for erythropoiesis, the potential to successfully treat rhEPO hyporesponders, and the potential to treat anemia without causing rhEPO-induced hypertension.

Given these precautions, as well as the potential benefit that daprodustat holds for the treatment of anemia associated with CKD compared to the current standard, the overall benefit risk balance is considered to be positive.

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

A subject will be eligible for inclusion in this study only if all of the following criteria apply at screening (Week -8) and randomization (Day 1) unless otherwise specified.
1. Age (confirm at screening only): 18 to 99 years of age (inclusive).
2. ESAs: Use of any approved ESA for at least the 6 weeks prior to screening and between screening and randomization.
3. Hgb concentration measured by HemoCue (range is specified in protocol)

4. Dialysis: On dialysis > 90 days prior to screening and continuing on the same mode of dialysis from screening (Week -8) through to randomization (Day 1).
5. Frequency of Dialysis:
* - HD: *2 times/week
* - PD: * 5 times/week
* - Home HD: (*2times/week)
6. Compliance with placebo [randomization (Day 1) only]: *80% and * 120% compliance with placebo during run-in period (NOTE: this is in addition to ESA treatment).
7. Informed consent (screening only): capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

Exclusion criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply at screening (Week -8) or randomization (Day 1), unless otherwise specified.
CKD related criteria
1. Kidney transplant: Planned living-related or living-unrelated kidney transplant within 52 weeks after study start (Day 1).
Anemia related criteria
2. Ferritin (screening only): *100 ng/mL (*100 ug/L).
3. Transferrin saturation (TSAT) (screening only): *20%. If TSAT is 18-20%, then a retest using a new blood sample can be obtained within 7 days of the final laboratory report; the final retest value must be >20% to confirm eligibility.
4. Aplasias: History of bone marrow aplasia of pure red cell aplasia.
5. Other causes of anemia: Untreated pernicious anemia, thalassemia major, sickle cell disease or myelodysplastic syndrome.
6. Gastrointestinal (GI) bleeding: Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding *4 weeks prior to screening through to randomization (Day 1).
CV disease-related criteria
7. MI or acute coronary syndrome: *4 weeks prior to screening through to randomization (Day 1).
8. Stroke or transient ischemic attack: *4 weeks prior to screening through to randomization (Day 1).
9. Heart failure (HF): Chronic Class IV HF, as defined by the New York Heart Association (NYHA) functional classification system.
10. Current uncontrolled hypertension: Current uncontrolled hypertension as determined by the investigator that would contraindicate the use of rhEPO.
11. QTcB (Day 1): QTcB >500 msec, or QTcB >530 msec in subjects with bundle branch block. There is no QTc exclusion for subjects with a predominantly ventricular paced rhythm.

Other disease-related criteria
12. Liver disease: (any one of the following):
- Alanine transaminase (ALT) >2x upper limit of normal (ULN) (screening only)
- Bilirubin >1.5xULN (screening only)
NOTE: Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%.
- Current unstable liver or biliary disease per investigator assessment, generally by the presence of ascites,
encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.
NOTE: Stable chronic liver disease (including asymptomatic gallstones, chronic hepatitis B or C, or Gilbert's syndrome) are acceptable if subject otherwise meets entry criteria.
13. Malignancy: History of malignancy within the 2 years prior to screening through to randomization (Day 1) or currently receiving treatment for cancer, or complex kidney cyst (e.g. Bosniak Category II F, III or IV) > 3cm. Note: The only exception is localized squamous cell or basal cell carcinoma of the skin that has been definitively treated 4 weeks prior to screening.
Concomitant medication and other randomized treatment-related criteria 14. Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (refer to daprodustat IB), or epoetin alfa or darbepoetin alfa (refer to product labeling).
15. Drugs and supplements Use of strong inhibitors of CYP2C8 (e.g., gemfibrozil) or strong inducers of CYP2C8 (e.g., rifampin/rifampicin).
16. Other study participation: Use of other investigational agent or device prior to screening through to randomization (Day 1).
*Note: at screening, this exclusion applies to use of the investigational agent within 30 days or within five half lives (whichever is longer).
17. Prior treatment with daprodustat: Any prior treatment with daprodustat for treatment duration of > 30 days.
General health-related criteria
18. Females ONLY: Subject is pregnant [as confirmed by a positive serum human chorionic gonadotrophin (hCG) test for females of reproductive potential (FRP) only], subject is breastfeeding, or subject is of reproductive potential and does not agree to follow one of the contraceptive options listed in the List of Highly Effective Methods for Avoiding Pregnancy in Appendix 5 of the protocol.
19. Other Conditions: Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance (e.g., intolerance to rhEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-09-2017
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aranesp
Generic name:	Darbepoetin alfa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Daprodustat
Generic name:	Daprodustat
Product type:	Medicine
Brand name:	Procrit®
Generic name:	Epoetin alfa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-11-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-10-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	10-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-000541-31-NL
ClinicalTrials.gov	NCT02879305
CCMO	NL58801.056.16

Study results