A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-center, event driven study in non-dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to darbepoetin alfa;Anemia Studies in CKD: Erythropoiesis via a Novel PHI Daprodustat-Non-Dialysis (ASCEND-ND)

Published: 03-11-2016
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Co-primary (tested in parallel for non-inferiority):-To compare daprodustat to darbepoetin alfa for CV safety (non-inferiority)-To compare daprodustat to darbepoetin alfa 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-OMON50351

Source
ToetsingOnline

Brief title
ASCEND-ND - 200808

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: industry: GSK

Intervention

Keyword: anemia, chronic kidney disease, CKD, 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)

Time to progression of CKD

Veiligheid:

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

of special interest

-Reasons for discontinuation of randomized treatment

-Absolute values and changes from baseline

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 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 rhEPOs. 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 (Major Adverse Cardiovascular Event) 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 ND subjects with anemia associated with CKD demonstrated that daprodustat can correct and 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 will evaluate the safety and the efficacy of daprodustat compared to darbepoetin alfa for the treatment of anemia associated with CKD in ND subjects. Both co-primary endpoints must meet non-inferiority of daprodustat to darbepoetin alfa 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 not on dialysis.

Study objective

Co-primary (tested in parallel for non-inferiority):
-To compare daprodustat to darbepoetin alfa for CV safety (non-inferiority)
-To compare daprodustat to darbepoetin alfa 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 ND subjects with anemia associated with CKD.
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 erythropoietin-stimulating agents (ESA1) therapy, if present, continues during the screening and run-in periods.

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 Independent Data Monitoring Committee (IDMC) recommends bringing the study to an earlier close.

Subjects will be stratified by region, by whether they are currently using an ESA, and by participation in the ambulatory blood pressure monitoring (ABPM) sub-study.
Following stratification, subjects will be randomized 1:1 to receive oral daprodustat or subcutaneous (SC) darbepoetin alfa.

Both treatment arms (daprodustat and darbepoetin alfa) 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. 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 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.

GSK will provide randomized treatment: daprodustat or darbepoetin alfa.

Intervention

oral daprodustat 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.CKD stage (confirm at screening only): Kidney Disease Outcomes Quality Initiative (KDOQI) CKD stages 3, 4, or 5 defined by eGFR using the CKD Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009]., 3.ESAs: , *Group 1 (not using ESAs): No ESA use within the 6 weeks prior to screening and no ESA use between screening and randomization (Day 1)., *Group 2 (ESA users): Use of any approved ESA (see footnote in protocol) for the 6 weeks prior to screening and continuing between screening and randomization., 4.HemoCue Hgb (range is specified in protocol): Hgb defined by ESA use, 5.Compliance with placebo [randomization (Day 1) only]: *80% and *120% compliance with placebo during run-in period (NOTE: for ESA users, this is in addition to ESA treatment)., 6.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) and randomization (Day 1), unless otherwise specified. , CKD related criteria, 1.Dialysis: On dialysis or clinical evidence of impending need to initiate dialysis within 90 days after study start (Day 1)., 2.Kidney transplant: Planned living-related or living-unrelated kidney transplant within 52 weeks after study start (Day 1)., Anemia-related criteria, 3.Ferritin (screening only): *100 ng/mL (*100 ug/L)., 4.Transferrin saturation (TSAT) (screening only): *20%. If the laboratory

report indicates TSAT is 18-20%, then up to two retests can be obtained using a new blood sample. These retests may occur during screening and run-in up to two weeks prior to anticipated randomization (Day 1); the final retest value must be >20% to confirm eligibility., 5.Aplasias: History of bone marrow aplasia or pure red cell aplasia., 6.Other causes of anemia: Untreated pernicious anemia, thalassemia major, sickle cell disease or myelodysplastic syndrome., 7.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, 8.MI or acute coronary syndrome: *4 weeks prior to screening through to randomization (Day 1)., 9.Stroke or transient ischemic attack: *4 weeks prior to screening through to randomization (Day 1)., 10.Heart failure (HF): Chronic Class IV HF, as defined by the New York Heart Association (NYHA) functional classification system., 11.Current uncontrolled hypertension: Current uncontrolled hypertension as determined by the investigator., 12.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, 13.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 defined 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., 14.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, 15.Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (refer to daprodustat IB) or darbepoetin alfa (refer to product labeling). , 16.Drugs and supplements: Use of strong inhibitors of CYP2C8 (e.g., gemfibrozil) or strong inducers of CYP2C8 (e.g., rifampin/rifampicin)., 17.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)., 18.Prior treatment with daprodustat: Any prior treatment with daprodustat for a treatment duration of >30 days., General health-related criteria, 19.Females ONLY: Subject is pregnant [as confirmed by a positive urine 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. , 20.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 darbepoetin alfa) 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):	06-11-2017
Enrollment:	30
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

Ethics review

Approved WMO Date:	03-11-2016
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:	02-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-12-2018
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:	17-06-2019
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:	11-11-2019
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:	17-01-2020
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:	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	EUCTR2016-000542-65-NL

Register	ID
ClinicalTrials.gov	NCT02876835
CCMO	NL58802.056.16