A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Study of Fostamatinib Disodium in the Treatment of Warm Antibody Autoimmune Hemolytic Anemia

Published: 09-10-2019
Last updated: 09-04-2024

* The primary objective of this study is to compare the proportion of warm antibody autoimmune hemolytic anemia (wAIHA) subjects whoachieve a durable hemoglobin response between the fostamatinib and placebo groups.* The secondary objectives of this...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52459

Source
ToetsingOnline

Brief title
Fostamatinib in treatment of wAIHA

Condition

- Haematological disorders NEC
- Autoimmune disorders

Synonym
Warm antibody autoimmune hemolytic anemia

Research involving
Human

Sponsors and support

Primary sponsor: Rigel Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Sponsor Rigel Pharmaceuticals;Inc.

Intervention

Keyword: Efficacy, Fostamatinib, Warm Antibody Autoimmune Hemolytic Anemia

Outcome measures

Primary outcome

The primary efficacy endpoint is achievement of durable hemoglobin response (Yes/No) defined as achieving a hemoglobin level * 10 g/dL with an increase from Baseline in hemoglobin level of * 2 g/dL on 3 consecutive available visits during the 24-week treatment period, in which hemoglobin measurements eligible for this definition occurred outside a Rescue Treatment Visit Exclusion Period.

Secondary outcome

Secondary Efficacy Endpoints:

The secondary efficacy endpoints within the 24 weeks of treatment are:

* Hemoglobin response on at least one visit (Yes/No)

* Achievement of a change from Baseline in hemoglobin level of 2 g/dL or greater (Yes/No)

* Change in hemoglobin value from Baseline to End of Treatment (Week 14 to Week 24)

* Use of permitted rescue medications after Week 4 (Yes/No)

* Change from Baseline to Week 24 in FACIT-F

Additional efficacy will be evaluated and detailed in the SAP.

Safety Endpoints:

The following safety endpoints will be evaluated:

* Incidence and severity of treatment-emergent adverse events (TEAEs)

* Incidence and severity of TEAEs of interest

* Change from Baseline for select laboratory tests over time (e.g., hematology, chemistry)

* Change from Baseline in blood pressure over time

* Change from Baseline in absolute neutrophil count (ANC) over time

* Change from Baseline in liver function tests (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST]), total bilirubin, direct and indirect bilirubin) over time.

Pharmacokinetic Endpoints:

Plasma concentration of the active component of fostamatinib (R406) relative to the date and time of last dose of study drug, at Weeks 2, 4, 12 and 18 of the treatment period.

Study description

Background summary

Autoimmune hemolytic anemia (AIHA) is an acquired disorder manifested by autoantibody-mediated red blood cell (RBC) destruction. The estimated incidence is 0.8-3 per 100,000/year with a mortality rate of 11%. AIHA is subclassified as either warm or cold, some 80% of cases
are warm AIHA, and can be either primary or secondary to an underlying disease such as autoimmune disease, 20%, lymphoproliferative disorder, 20%, or infections and tumors.
The diagnosis of AIHA is typically made when hemolysis is associated with a positive direct antiglobulin test (DAT), indicating that RBC autoantibodies and/or complement proteins are bound to red cells. Additional abnormalities

include a reduced serum haptoglobin level, an increased indirect bilirubin, and an elevated lactate dehydrogenase (LDH).
The first-line treatment of AIHA generally consists of steroids. Up to 85% of patients will respond, however fewer than 20% of patients will be cured. Splenectomy has traditionally been the second line therapy of choice for this disease, with 60-70% of patients having a sustained response. Other therapeutic approaches that can be used, following the failure of front-line treatment, include rituximab, IVIg, cyclosporine, mycophenolate mofetil, azathioprine, and cyclophosphamide. The availability of these alternative therapies has challenged the role of splenectomy as the preferred second-line treatment.
Fc receptor * (FcR*) signaling in monocytes and macrophages plays an important role in the initiation and propagation of autoimmune responses. The activating FcR* is associated with a signaling subunit, referred to as the FcR* chain, whose phosphorylation subsequent to receptor activation results in the recruitment and activation of spleen tyrosine kinase (Syk). Syk is an important component of the signaling system of activated Fc receptors, as well as the B-cell receptor (BCR).
Aggregation of the Fc receptors, induced by antibody-antigen complexes, can activate a multitude of cellular functions (including degranulation, arachidonic acid metabolism, antibody dependent cellular cytotoxicity, phagocytosis and cytokine secretion) depending on the cell type, and leads to tissue damage and the propagation of inflammatory responses. FcR* have been implicated in immune destruction of RBCs. Accelerated clearance of circulating IgG-coated RBCs via FcR*-bearing macrophages in the spleen and liver is believed to be a pathogenic mechanism in AIHA. Fostamatinib (R788) is the prodrug of R940406 (R406), a potent and relatively selective inhibitor of Syk and, consequently, of the FcR and BCR signaling pathways.
R406 inhibits Syk and FcR signaling at concentrations generally achieved with fostamatinib doses of 100-150 mg twice daily (bid) and above, and nonclinical data have affirmed its activity in AIHA.

Study objective

* The primary objective of this study is to compare the proportion of warm antibody autoimmune hemolytic anemia (wAIHA) subjects who achieve a durable hemoglobin response between the fostamatinib and placebo groups.

* The secondary objectives of this study are:
o To compare the proportion of subjects with hemoglobin response on at least one visit between the fostamatinib and placebo groups.
o To compare the proportion of subjects who achieve a change from Baseline in hemoglobin level of * 2 g/dL between the fostamatinib and placebo groups.
o To compare the change in hemoglobin value from Baseline to the End of Treatment between the fostamatinib and placebo groups.
o To compare the proportion of subjects who use permitted rescue medications

after Week 4 between the fostamatinib and placebo groups.
o To compare the change from Baseline to Week 24 in Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-F).

* The safety objective is to assess the safety of fostamatinib in subjects with wAIHA.

* Additional efficacy and pharmacoeconomic objectives will compare the fostamatinib and placebo groups for the endpoints noted on protocol section 4.5.

Study design

This is a Phase 3 multi-center, randomized, double-blind, placebo-controlled, parallel group study to investigate the efficacy of 24 weeks of treatment with fostamatinib (R935788) vs. placebo in achieving a durable hemoglobin response in subjects with wAIHA who have failed at least one prior treatment regimen. After qualifying for the study, approximately 90 subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups: fostamatinib 100 mg by mouth (PO), twice a day (bid), or matching placebo. Subjects will self-administer the study drug in the morning and evening throughout the 24-week treatment period.
Randomization will be stratified by concomitant steroid use at baseline (*20 mg and <20 mg daily) and by severity of anemia at screening (baseline hemoglobin <9 vs. *9 g/dL).
Starting at Week 4, the initial fostamatinib dose of 100 mg PO bid or matching placebo will be increased to fostamatinib 150 mg PO bid or matching placebo if subjects have adequately tolerated the study drug in the investigator*s judgment. The dose may be reduced at any time to a dose as low as fostamatinib 100 mg PO once daily (qd) or matching placebo if dose-limiting adverse events are observed per the dose adjustment table
below.
Dose Adjustment
Starting Dose Dose Level -1 Dose Level -2 Dose Level -3
Dose Level -4
100 mg PO bid 150 mg PO qd 100 mg PO qd discontinue ----
150 mg PO bid 100 mg PO bid 150 mg PO qd 100 mg PO qd
discontinue
Over the course of the study, subjects will be expected to visit the clinic approximately 15 times. Safety assessments and hemoglobin levels will be performed at each visit to evaluate the safety and efficacy of study drug (fostamatinib or placebo), and to determine if a dose adjustment is required. The end of the trial will be when the last subject has completed either the Week 24 visit or their last study visit, whichever is later.

Intervention

All patients will receive the following interventions:
- ECG
- Vital signs and physical examination
- Urine collection
- Pregnancy test (for females of childbearing potential only)
- Blood draws for safety (hematology and chemistry)
- Blood draws for PK
- Blood draws for Biomarkers (optional)
- Questionnaires

Study burden and risks

Potential Benefit-Risk Summary
Nonclinical data support the potential benefit of fostamatinib, a SYK inhibitor, in wAIHA. SYK plays a central role in FcR*-bearing macrophage clearance of circulating IgG-coated RBCs, which is believed to be a pathogenic mechanism in AIHA (Section 3.1).(2) Fostamatinib administration in an animal model of wAIHA showed protection from anemia.
As described in Section 3.4 of the Protocol V5.0 (p25), an interim data cut of the open label Phase 2 study assessing fostamatinib in treatment of wAIHA patients who failed at least one prior therapy showed that 8/17 subjects (47%) in the Efficacy Evaluable Population responded during the 24-week evaluation period (lower bound of the exact 95% confidence interval is 23%); one additional subject met the response criteria in the extension period (after 24 weeks of dosing) for an overall response rate of 53% (9/17) on fostamatinib (lower bound of the exact 95% confidence interval is 31%). Thus preliminary data indicate that fostamatinib may benefit wAIHA patients who have failed at least one prior therapy.
The risks of fostamatinib have been characterized and consistent across programs including, healthy subjects, and patients with ITP, rheumatoid arthritis (RA), malignancies, IgA nephropathy and wAIHA (see Investigator*s Brochure). The AEs most commonly related to fostamatinib include effects on blood pressure, hepatic transaminase elevations, gastrointestinal complaints (especially diarrhea) and neutrophil counts. These AEs are mostly mild to moderate in intensity. They are reversible and manageable with appropriate safety monitoring, medical intervention and at times fostamatinib dose reduction, interruption or discontinuation. The safety results from the Phase 2 wAIHA interim datacut (described in Section
3.6.1 of the Protocol V5.0 (p26)) are consistent with those in the entire fostamatinib safety database. SAEs in the Phase 2 wAIHA study were often related to the underlying disease or its treatment and complications. None of these SAEs were judged by investigators as related to fostamatinib.
In sum, the potential benefit of fostamatinib treatment in wAIHA patients outweighs the risks and supports the conduct of a Phase 3 study in this indication.

Contacts

Public
Rigel Pharmaceuticals, Inc.

Veterans Boulevard 1180
South San Francisco CA 94080
US
Scientific
Rigel Pharmaceuticals, Inc.

Veterans Boulevard 1180
South San Francisco CA 94080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject must be willing and able to give written informed consent by signing an IRB approved Informed Consent Form prior to undergoing any study-specific procedures.
2. Subject must have a diagnosis of primary or secondary wAIHA as documented by a positive direct antiglobulin test (DAT) specific for anti-IgG or anti-IgA. Eligibility may be based on a historical DAT obtained within 12 months of the screening visit from a local laboratory, provided that specific IgG or IgA positivity is documented; otherwise, this assay will be done at screening by a central laboratory.
3. Has failed or not tolerated at least one prior wAIHA treatment, e.g., steroids, rituximab, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil (MMF), danazol, vincristine, ESA or splenectomy (folate,

iron or other supplements do not fulfill this criterion).
4. Has haptoglobin <LLN or total bilirubin >ULN or lactate dehydrogenase (LDH) >ULN.
5. At screening, subject*s hemoglobin level must be *9 g/dL
OR
If the hemoglobin value is >9 g/dL and <10 g/dL, subject must be on an allowed wAIHA treatment (see Allowed AIHA Therapy table) AND the subject must have documented symptoms related to anemia (e.g., weakness, dizziness, fatigue, shortness of breath, chest pain).
6. Male or female at least 18 years of age at screening.
7. Karnofsky performance status (KPS) *70.
8. Subject*s concurrent treatment for wAIHA may consist of no more than two of any of the following agents: azathioprine, steroids, ESAs, mycophenolate mofetil, dapsone or danazol at a stable dose, as defined in the Allowed AIHA Therapies table. Subject has not taken any disallowed therapies in the intervals defined by the protocol.
9. Female subjects must be either post-menopausal for at least 1 year or surgically sterile; or, if of childbearing potential, must not be pregnant or lactating and must agree to use a highly effective method of birth control throughout the duration of the trial and for 30 days following the last dose. Acceptable methods of birth control are defined as: hormonal contraception (pill, injection or implant) used consistently for at least 30 days prior to screening, an intrauterine device (IUD), or intrauterine hormone-releasing system (IUS), or true abstinence (i.e. abstinence is in line with the preferred and usual lifestyle of the subject).
10. In the investigator*s opinion, the subject has the ability to understand the nature of the study and any hazards of participation and to communicate satisfactorily with the investigator.

Exclusion criteria

1. Subject with other types of AIHA (e.g., cold antibody AIHA, cold agglutinin syndrome, mixed type AIHA, or paroxysmal cold hemoglobinuria).
2. Subject has AIHA secondary to autoimmune disease, including systemic lupus erythematosus (SLE), or lymphoid malignancy if the underlying disease is not stable or is not well-controlled on current therapy, per investigator medical judgment.
3. Subject has a history of or active, clinically significant, cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, psychiatric, musculoskeletal, genitourinary, dermatological, or other disorder that, in the investigator*s opinion, could affect the conduct of the study or the absorption, metabolism or excretion of the study drug.
4. Subject has uncontrolled or poorly controlled hypertension, defined as systolic blood pressure *135 mmHg or diastolic blood pressure *85 mmHg, whether or not the subject is receiving anti-hypertensive treatment.

5. Subject has one or more of the following laboratory abnormalities at screening: neutrophil count of <1,000/µL or platelet count of <30,000/*L, unless due to Evans syndrome; transaminase levels (i.e., alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >1.5 x ULN.
6. Has documented HIV infection or active hepatitis B or hepatitis C infection or HIV infection.
7. Subject is currently enrolled in an investigational drug or device study or has used an investigational drug or device within 30 days or 5 half-lives (whichever is longer) of Day 1.
8. In the judgment of the investigator, the subject may not be able to fully comply with study requirements.
9. Subject has been treated with fostamatinib previously for any indication.
10. Subject has a known allergy and/or sensitivity to the test article or its components.
11. Subject has had a splenectomy within the past 4 weeks.

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:	Recruitment stopped
Start date (anticipated):	03-08-2020
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	NA
Generic name:	Fostamatinib Disodium

Ethics review

Approved WMO Date:	09-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2018-004774-97-NL
CCMO	NL69121.018.19