Forward study

Short title: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled,

Study of Fostamatinib Disodium in the Treatment of Warm Antibody Autoimmune Hemolytic Anemia

Principal investigator: Dr. Josephine M.I. Vos

Sponsor: Rigel Pharmaceuticals, Inc.

EudraCT nr. (if applicable): 2018-004774-97

Patient population:

Required no. of patients (if applicable): 80

Type of study: Phase 3 double blind randomized

Study objectives:

Primary objectives: to assess the efficacy of fostamatinib in subjects with warm antibody autoimmune hemolytic anemia (wAIHA).

Secondary objectives: to assess the safety of fostamatinib in subjects with wAIHA.

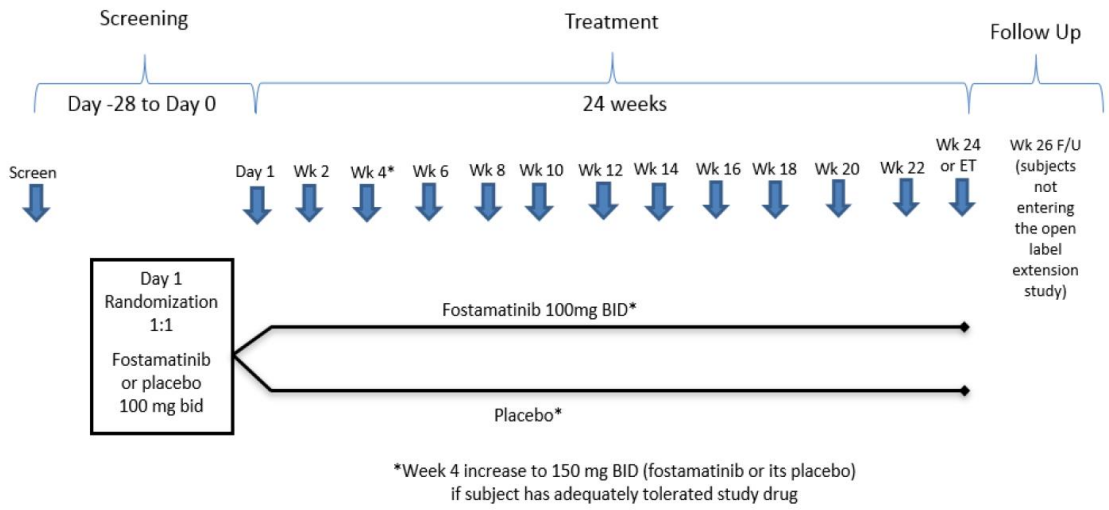
Status: Open for accrual

Participating sites: Amsterdam UMC, location AMC

Contact for more information: Dr. J.M.I. Vos, hemat.trial@amsterdamumc.nl

Summary (optional):

Deze placebo-gerandomiseerde studie is geschikt voor patienten met recidief of refractaire warme AIHA. Fostamatinib is een orale SYK-remmer die effectief is voor de behandeling van ITP en in een eerdere fase 2 studie activiteit heeft laten zien bij AIHA. Na afronding van de studie (behandelduur ongeveer 6 maanden) komen deelnemers in principe in aanmerking voor een open label extensie studie, waarbij zij het middel dus desgewenst kunnen blijven doorgebruiken danwel (in het geval van eerdere loting voor placebo-arm) alsnog kunnen starten.


Screening
Treatment
Follow Up
Day -28 to Day 0
24 weeks
Screen
Day 1
Wk 2
Wk 4*
Wk 6
Wk 8
Wk 10
Wk 12
Wk 14
Wk 16
Wk 18
Wk 20
Wk 22
Wk 24 or ET
Wk 26 F/U (subjects not entering the open label extension study)
Day 1 Randomization 1:1
Fostamatinib or placebo 100 mg bid
Fostamatinib 100mg BID*
Placebo*
*Week 4 increase to 150 mg BID (fostamatinib or its placebo) if subject has adequately tolerated study drug

Subject eligibility criteria:

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 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.

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:

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,

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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/µL, unless due to Evans syndrome; transaminase levels (i.e., alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >1.5 x ULN.

6. Has documented 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.

Disallowed AIHA Therapies: Any of the disallowed therapies below may not be taken within

the indicated interval prior to Day 1.

Drug	**Prohibited Period Prior to Day 1** (from last dose of agent)
RBC transfusion	7 days
IVIg	14 days
Cyclosporine	30 days
Rituximab or other anti-CD20 monoclonal antibody	8 weeks
Ibrutinib or other BTK inhibitor	4 weeks
Chemotherapy agents, e.g. cyclophosphamide, vincristine	6 weeks
Investigational agent	30 days or 5 half-lives, whichever is greater