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A phase 2 pilot study of the safety, pharmacokinetics, and pharmacodynamics of ARC1779 injection in patients with von Willebrand factor-related platelet function disorders

Submission date	Recruitment status	[ ] Prospectively registered
11/03/2008	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
16/04/2008	Completed	[X] Results
Last Edited	**Condition category**	[ ] Individual participant data
07/02/2019	Haematological Disorders	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT00632242

Secondary identifying numbers
ARC1779-004

Study information

Scientific Title
A phase 2 pilot study of the safety, pharmacokinetics, and pharmacodynamics of ARC1779 injection in patients with von Willebrand factor-related platelet function disorders

Study objectives
The pathophysiologic basis of thrombotic thrombocytopenic purpura (TTP) is an excess of ultra-large multimers of von Willebrand Factor (vWF) resulting from inborn or acquired deficiency of the activity of the ADAMTS13 enzyme which is responsible for proteolytic degradation of vWF. These ultra-large multimers are especially avid for binding platelet membrane glycoprotein Ib (GPIb), and give rise to disseminated platelet thrombi in the microvasculature of many organs in the body. The pathophysiologic basis of vWD-2b is that these patients produce a variant of the normal vWF protein with a "gain-of-function" mutation in the A1-domain which increases its affinity for the platelet GPIb and permits vWF-mediated platelet aggregation to occur abnormally in the absence of endothelial damage and hemodynamic shear forces. The increased affinity of these A1-domain-mutated vWF molecules is such that they effectively completely coat the circulating pool of platelets in the bloodstream and render them functionally unavailable to mediate platelet adhesion and initiation of platelet thrombus formation at sites of vascular injury, thereby predisposing to bleeding.

ARC1779 is an aptamer that inhibits the pro-thrombotic function of vWF by binding to the A1 domain of vWF and thereby blocking its interaction with the platelet GPIb receptor. Based on the mechanism of action defined for ARC1779 and the mechanism of thrombosis defined for TTP, ARC1779 is expected to normalise platelet dysfunction and prevent the thrombotic end-organ complications of TTP. Similarly, based on the mechanism of action of ARC1779 and the mechanism of desmopressin-induced thrombocytopenia in vWD-2b, ARC1779 is expected to increase platelet counts in that setting.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee of the Medical University of Vienna and the General Hospital of the City of Vienna. Approved on 22/02/2008.

Study design
Uncontrolled, open-label study followed by a randomised, blinded, double-dummy, and placebo-controlled study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)

Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
von Willebrand factor-related platelet function disorders

Interventions
Study design:
Four cohorts of TTP patients as an uncontrolled, open-label study. Patients with vWD-2b will be enrolled in an additional cohort in a randomised, blinded, double-dummy, and placebo-controlled study.

TTP Remission Cohort 1: Initial stepwise infusion of 0.23 mg/kg given over 30 minutes and subsequent continuous infusion of an additional 0.24 mg/kg given over 4 hours at a rate of 0.001 mg/kg/min.

TTP Remission Cohort 2: Initial stepwise infusion of 0.23 mg/kg over 30 minutes and subsequent continuous infusion of an additional 1.44 mg/kg given over 24 hours at a rate of 0.001 mg/kg /min.

TTP Remission Cohort 3: Initial stepwise infusion of 0.46 mg/kg over 30 minutes and subsequent continuous infusion of an additional 2.88 mg/kg given over 24 hours at a rate of 0.002 mg/kg /min.

Acute TTP Cohort 4: Initial stepwise infusion of 0.23 mg/kg given over 30 minutes and subsequent continuous infusion of an additional 1.44 mg/kg given over 24 hours at a rate of 0.001 mg/kg/min to produce a target plasma concentration of 6 mcg/mL. Continuous infusion of ARC1779 Injection may continue for less than or equal to 14 days. After initial 24 hours dose may be titrated to achieve a target plasma concentration of 12 mcg/mL as needed, on the basis of clinical and laboratory data, according to the Investigator's judgment.

vWD-Type2b Cohort 5: In this cohort, all participants will receive the following three treatments. The patients are randomised with respect to the order of the three treatments:

Treatment A: In one period of the sequence, ARC1779 will be administered to all subjects as a stepwise infusion of 0.23 mg/kg over 30 minutes and subsequent continuous infusion of an additional 0.24 mg/kg given over 4 hours at a rate of 0.001 mg/kg/min in combination with a dummy 30-minute infusion of placebo.

Treatment B: In another period, subjects will receive a single infusion of desmopressin at a dose of 0.4 mcg/kg given over 30 minutes in combination with a dummy 30-minute stepwise infusion followed by 4-hour continuous infusion of placebo.

Treatment C: In another period, subjects will receive the combination of desmopressin at a dose of 0.4 mcg/kg given over 30 minutes and ARC1779 given as a stepwise infusion of 0.23 mg/kg over 30 minutes and subsequent continuous infusion of an additional 0.24 mg/kg given over 4 hours at a rate of 0.001 mg/kg/min.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
ARC1779

Primary outcome measure
To establish the overall safety and tolerability of ARC1779 in three varieties of von Willebrand Factor (vWF)-related platelet function disorders (time frame: 28 days)

Secondary outcome measures
1. To characterise the pharmacokinetic (PK) profile of ARC1779 intravenous (IV) infusion in patient groups (time frame: 28 days)
2. To characterise the pharmacodynamic (PD) profile of ARC1779 in patients with vWF-related platelet function disorders with respect to parameters of platelet function and vWF activity (time frame: 28 days)
3. To assess the concentration- and dose-response relationships among ARC1779 PK and PD parameters (time frame: 28 days)

Overall study start date
01/01/2008

Completion date
31/08/2008

Eligibility

Key inclusion criteria
1. Aged 18 - 75 years
2. vWD-2b confirmed diagnosis, or
3. TTP Remission prior episode(s) of primary acute TTP, or
4. Acute TTP - any episode, first or relapse, with presence of all of the following:
4.1. Microangiopathic hemolytic anaemia (schistocytosis present, Coombs test negative)
4.2. Severe thrombocytopenia
5. Clinical diagnosis of either a primary or secondary form of TTP:
5.1. Primary TTP: e.g., familial TTP (Upshaw-Schulman syndrome), or acquired idiopathic TTP, or atypical HUS
5.2. Secondary TTP: e.g., TTP occurring post-bone marrow transplant, drug-induced TTP, lupus-related TTP, etc.
6. Negative qualitative urine drug test at screening, and no history of alcohol or drug abuse
7. Not considering or scheduled to undergo any surgical procedure during the duration of the study
8. Has not donated or lost more than a unit of blood within 30 days prior to screening visit
9. Has not received an experimental drug within 30 days prior to screening
10. Female patients must be non-pregnant (for TTP Remission and vWD-2b Cohorts, a serum pregnancy test at screening and a urine pregnancy test at Day 1 pre-dose must be negative; for the Acute TTP Cohort, a serum pregnancy test at Day 1 pre-dose must be negative), and willing

to use effective, redundant methods of contraception (i.e., for both self and male partner) throughout the study and for at least 30 days after participation. If possible, the treatment will be initiated within 5 days of the cessation of the preceding menstrual period
11. Male patients must agree to use a medically acceptable contraceptive (abstinence or use of a condom with spermicide) throughout the study and for at least 30 days after participation
12. Patients must be capable of understanding and complying with the protocol and must have signed the informed consent document prior to performance of any study-related procedures

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
10 - 28

Key exclusion criteria
1. History of recent surgery or trauma
2. Any major, active health problem, e.g., cancer or heart disease, which could render the patient medically unstable during the period of participation in the study

Date of first enrolment
01/01/2008

Date of final enrolment
31/08/2008

Locations

Countries of recruitment
Austria

United States of America

Study participating centre
Archemix Corp.
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Sponsor information

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Sponsor type
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Funder(s)

Funder type
Industry

Funder Name
Archemix Corp. (USA)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results from TTP patients	01/03/2011	07/02/2019	Yes	No
Results article	results from vWD patients	01/09/2010	07/02/2019	Yes	No