Randomized, active-controlled, double-blind, parallel design study to evaluate the efficacy and safety of a once-a-week prophylaxis treatment with BAY 79-4980 compared to three times-per-week prophylaxis with rFVIII-FS in previously treated patients with severe hemophilia A

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The primary objective is to evaluate the effect of a once-a-weekprophylaxis regimen with BAY 79-4980 on the protection from all bleeds compared to a three times-per-week prophylaxis regimen with rFVIII-FSWFI.

Ethical review	Approved WMO
Status	Pending
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON33645

Source
ToetsingOnline

Brief title
IMP 12781/LIPLONG

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
Hemophilia A

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer B.V.

Intervention

Keyword: bleeding, Hemophilia A

Outcome measures

Primary outcome

The primary efficacy variable will be the percentage of subjects with less than

9 total bleeds per year. The three weeks run-in phase will not be considered

for efficacy analyses.

Secondary outcome

Secundary study parameters/outcome of the study (if applicable):

Secondary efficacy variable will be

- the percentage of subjects with less than 5 joint bleeds per year

- the number of joint bleeds per subjects per year in responders (i.e.

subjects with less than 9 total bleeds per year)

A joint bleed is defined by the following symptoms:

- pain (mild, moderate or severe)

- restriction of motion (minimal, moderate or major restriction)

- swelling (minimal, moderate swelling or mayor effusion)

- increased temperature as compared to the contralateral joint

- symptoms resolve with FVIII treatment (within 24 h for minor bleeds, failure

to resolve within 24 hours are defined as major bleeds)

In some instances, a spontaneous bleed is preceded by a subjective

aura. At least one of the above mentioned symptoms must be present

for the definition of a joint bleed. The feeling of an aura as single

symptom is not defined as a joint bleed.

Study description

Background summary

BAY 79-4980 could have a clinical advantage to the hemophilia patient by extending the protection duration against hemorrhages, and therefore reducing the total amount of injections.

Study objective

The primary objective is to evaluate the effect of a once-a-week prophylaxis regimen with BAY 79-4980 on the protection from all bleeds compared to a three times-per-week prophylaxis regimen with rFVIII-FSWFI.

Study design

Multicenter, multinational, randomized, active-controlled, double-blind study with 2 parallel treatment arms and equal randomization after stratification for presence or absence of target joints and age (> 18years and <= 18 years). The two arms are double-blinded by employing POPCLiposomes, a reconstitution solvent for rFVIII-FS making it unidentifiable from BAY 79-4980 and excipient reconstituted with WFI making it unidentifiable from rFVIII-FS reconstituted with WFI. POPC-Liposomes will be used for one of the 3 weekly injections in the rFVIII-FS arm. Patients in the BAY 79-4980 arm will receive 2 dummy injections with excipient in WFI.
Total trial duration 52 - 56 weeks (52 weeks treatment)
N = 250 patients

Intervention

Test Drug: BAY 79-4980, 35IU/kg 1x/week plus 2 dummy injections/week.
Comparator: rFVIII-FS, 25IU/kg 3x/week (one injection with rFIII-FSPOPC).

Treatment of bleeds: BAY 79-4980 or rFVIII-FS-POPC up to a daily maximum of 70IU/kg (max. 50IU/kg/injection) and over maximal 5 days (weekly maximum 350IU/kg).
Administration: The first injection (either BAY 79-4980 or rFVIII-FS-POPC) will be administered under medical supervision by the Investigator or designated personnel. The injection rate for the first 5 mL will be around 0.5 mL/min. The next 5 mL will be slowly injected at a rate of about 0.8 mL/min, the remaining volume will be slowly injected at a rate of about 1 mL/min, or faster, so that the total injection time for the first injection will be between 15-30 minutes, depending on body weight and total volume.
If the first injection is well tolerated, then the total injection time for the second and third injections administered by the subjects will be reduced to approx. 5-10 minutes, depending upon the total volume and an injection rate of approx. 1-2 mL/min.

Study burden and risks

There are in total 9 visits at the investigator (including screening visit) and 1 follow-up phone call.
Any joint bleed must be verified by the subject and study personnel via a phone call with documentation of the symptoms

Almost 100 subjects have already received BAY 79-4980 and the following side effects related to the
liposomes have been recorded in some cases: warmth in the throat, nausea, flushing, headache,
abdominal pain, back pain, dizziness, shortness of breath or increased breathing rate, infection of the
outer ear, slight temporary increase in cholesterol in blood.
Based on previous experience with other FVIII products the risks of injecting BAY 79-4980 may also
include the following very rarely serious allergic reactions which have occurred in very young patients
or patients who had previously reacted to other FVIII products:
- in very rare cases hypersensitivity reaction (e.g. tightness of the chest, general feeling of being
unwell, dizziness and nausea, mildly reduced blood pressure which may make you feel faint upon
standing)
- in rare cases rash/itchy red welts or hives at the injection site (e.g. burning sensation, temporary
redness)
- in rare cases shortness of breath
- unusual taste in the mouth
- fever
If an allergic or hypersensitivity reaction occurs during the injection, the injection should be stopped

immediately.
As with any factor VIII, the development of inhibitors (a reaction of the body that blocks either partially
or totally the given FVIII) is a known complication. The risk of developing inhibitors is usually
correlated to the exposure and is highest within the first 20 exposure days. Rarely, inhibitors may
develop after 100 exposure days to a FVIII. By now, no patient treated with BAY 79-4980 has
developed an inhibitor.

Contacts

Public
Bayer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Males aged 18 to 70 years
- Subjects with severe hemophilia A (< 1% FVIII:C)
- Subjects with equal or greater than 150 EDs with any FVIII in total
- Subjects who have been on-demand treatment (no more than 40% of patients and at least 20% are high-frequency bleeders [>=20 bleeds/year]) with an average of minimum 1 relevant bleed per month or have been on secondary prophylaxis treatment with not more than a 3x/week schedule with the history of minimum 12 relevant bleeds per year prior to be on secondary prophylaxis treatment
- Subjects with bleeding events and/or treatments during the last 6 months prior to study entry which are documented in the subjects medical records.
- Subjects with no measurable inhibitor activity using the Nijmegen-modified Bethesda assay (>0.6BU/mL is considered positive) in two consecutive samples and absence of clinical signs or symptoms of decreased response to FVIII administration.
- Subjects with no history of FVIII inhibitor antibody formation. (>=0.6BU/mL using the Nijmegen-modified Bethesda assay)
- Subjects who complete an EPD (electronic patient diary) device training and demonstrate the ability to correctly use it

Exclusion criteria

- Subjects who are receiving primary prophylaxis (start of prophylaxis before or directly after the first joint bleed without relevant interruptions)
- Subjects on prophylaxis with documented requirements of > 75 IU/kg/week
- Subjects with any other bleeding disease beside hemophilia A (i.e., von Willebrand disease)
- Subjects with thrombocytopenia (platelets < 100,000/mm3)
- Subjects with abnormal renal function (serum creatinine > 2.0 mg/dL)
- Subjects with elevated hepatic transaminases (AST or ALT > 5xULN)
- Subjects on treatment with immunomodulatory agents within the last 3 months prior to study entry or during the study (the following drugs are allowed: interferon-alpha-treatment for HCV, HAART therapy for HIV and/or a total of two courses of pulse treatment with steroids for a maximum of 7 days at 1mg/kg or less)
- Subjects with an absolute CD4 lymphocyte cell count < 250 cells/mm3
- Subjects with positive Lupus Anticoagulant antibodies or history thereof
- Subjects with known hypersensitivity to the active substance, mouse or hamster protein, liposomes or PEG
- Subjects with severe dyslipidemia of all causes LDL-C >= 190 mg/dl)
- Subjects who are receiving or had received other experimental drugs within 3 months prior to study entry
- Subjects who require any pre-medication for FVIII injections (e.g. anti-histamines)
- Subjects with uncontrollable hypertension (diastolic blood pressure > 100 mmHg)
- Subjects with known unstable coronary artery angina and/or with known history of myocardial infarction.

- Subjects who are unwilling to comply with study visits or the treatment regimens
- Subjects who have planned major surgery (including orthopedic) or radioisotopic synovectomy during the study
- Subjects who are not suitable for participation in this study for any reason, according to the Investigator

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-01-2008
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BAY 79-4980
Generic name:	n.v.t.
Product type:	Medicine
Brand name:	Kogenate® Bayer (rFVIII-FS)
Generic name:	n.v.t.
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-12-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-04-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-05-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-06-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-08-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-12-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-03-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-06-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-08-2009

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-12-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-02-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2007-003718-32-NL
CCMO	NL20623.042.07