A Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad Versus Standard of Care Treatment in Controlling Parenchymal Bleeding During Elective Hepatic Surgery

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The objective of this study is to evaluate the safety and hemostatic effectiveness of FP versus SoCtreatment in controlling parenchymal bleeding during hepatic surgery.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON34280

Source
ToetsingOnline

Brief title
The Fibrin Pad Liver Study

Condition

- Hepatobiliary therapeutic procedures

Synonym
Haemostasis; bleeding from the liver

Research involving
Human

Sponsors and support

Primary sponsor: Omrix Biopharmaceuticals
Source(s) of monetary or material Support: Johnson & Johnson Medical Ltd.

Intervention

Keyword: Fibrin Pad, Hepatic Surgery, Parenchymal Bleeding, Standard of Care

Outcome measures

Primary outcome

The primary endpoint will be the proportion of subjects achieving hemostasis at the TBS at 4-miniutes following randomization and with no re-bleeding requiring treatment at the TBS any time prior to the initiation of wound closure (last point in time where FP will be visible to confirm hemostasis).

Secondary outcome

The secondary endpoints of this study include:

- Proportion of subjects achieving hemostatic success at 10 minutes following randomization;
(defined as achievement of hemostasis at 10 minutes and no further bleeding requiring retreatment prior to wound closure);
- Absolute time to hemostasis (defined as the absolute time to achieve hemostasis at or after 4 minutes from randomization);
- The proportion of subjects who after initial hemostatic success at 4 minutes

have

breakthrough bleeding requiring treatment;

- The proportion of subjects who after the initial establishment of hemostasis

(after 4 minutes)

have breakthrough bleeding requiring treatment;

- Incidence of adverse events potentially related to re-bleeding at the TBS;

- Incidence of adverse events that are potentially related to thrombotic events;

- Incidence of adverse events.

Study description

Background summary

Bleeding during surgical procedures may manifest in many forms. It can be discrete or diffuse from a large surface
area. It can be from large or small vessels* arterial (high pressure) or venous (low pressure) of high or low volume. It
may be easily accessible or it may originate from difficult to access sites. The bleeding tissues may be firm or friable.
For challenging severe bleeding, immediate control may be necessary to avoid unwanted haemodynamic
consequences.

Conventional methods to achieve control of bleeding (haemostasis) include use of surgical techniques, sutures,
ligatures or clips, and energy*based coagulation or cauterisation. When these conventional measures are ineffective
or impractical, adjunctive haemostasis techniques and products are typically utilised, including topical absorbable haemostats
(agents used to control bleeding which are applied to the surface of the tissue) such as oxidised regenerated
cellulose, gelatin, or collagen and active haemostats such as topical thrombin or fibrin sealants.

While fibrin sealants have proven efficacious in controlling slowly bleeding foci, diffuse oozing, bleeding from needle
puncture sites, and diffuse parenchymal organ haemorrhage they are not as

effective in the control of severe or active
bleeding. The requisite preparation time for lyophilised products can be impractical and furthermore the use of fibrin
sealants can complicate the application of pressure to the bleeding site, in that applied pressure can disrupt the
sealant bond or cause the sealant to adhere to gloves or gauze. Application of fibrin sealants to actively bleeding sites
can result in the sealant lifting or floating off the target site, particularly in high volume or high pressure bleeding.
There is a need for products or techniques to rapidly control challenging severe and active bleeding when treatment
with conventional surgical techniques or conventional adjunctive haemostatic products is either ineffective or
impractical. The ideal agent would be effective in a wet field, with active bleeding, would rapidly and effectively control
severe bleeding of high or low pressure, and would afford ease of operative handling and storage.

This clinical study is the third pivotal clinical trial for FP, and is designed to determine the safety and efficacy of FP when
used in controlling bleeding from the liver during hepatic surgery.

Study objective

The objective of this study is to evaluate the safety and hemostatic effectiveness of FP versus SoC
treatment in controlling parenchymal bleeding during hepatic surgery.

Study design

This is a randomized, controlled, superiority, study evaluating the effectiveness of the FP compared with SoC methods utilized to control bleeding in hepatic parenchyma for which standard methods of achieving hemostasis are ineffective, impractical or inappropriate. Qualified subjects are stratified based on the typeof hepatic parenchyma (Normal vs. Abnormal) and are randomized on a 1:1 basis, FP vs. SoC control.

Intervention

The appropriate TBS will be identified following transection of the hepaticpar enchyma. This will be the site assessed for hemostatic effectiveness.

FOR SUBJECTS TO BE TREATED WITH FIBRIN PAD
After placement of the treatment article, firm manual compression sufficient to stem all bleeding at the TBS will be applied continuously and will be

maintained until 4 minutes post-randomization. The surgeon may use a surgical sponge (laparotomy pad or surgical gauze) to assist in providing adequate pressure over the entire FP surface area (including pressure over the area of FP overlap).
Hemostasis will be assessed at 4 minutes following randomization by carefully releasing manual compression and removing the surgical sponge (if used) without disturbing the hemostatic product. The FP should not be removed once bleeding has been stopped.
If breakthrough bleeding occurs at the TBS during the 4-minute treatment period, the surgeon may re-treat with FP if clinically appropriate. After re-treatment application, manual compression must be applied for 2-3 minutes, after which hemostasis will be assessed. Under any circumstance, hemostasis must be assessed at 4 minutes post-randomization. If breakthrough bleeding requiring treatment other than FP occurs at anytime, the surgeon will revert to SoC and the subject will be considered a treatment failure for the primary efficacy parameter.
If hemostasis is achieved at 4 minutes post randomization with FP but the surgeon feels that additional treatment is required to assure durability of hemostasis then such treatment should be applied. This will be considered a treatment failure.

Hemostasis at the TBS will be assessed again at 10 minutes from randomization. The TBS will be observed until completion of the surgery immediately prior to initiation of final fascial closure.
FP may be used in other areas of the resected plane of the parenchyma. These additional areas treated with FP will not be assessed for TTH. A maximum of four units (4 x 4 inches) of FP may be implanted (left in place at the bleeding site/s) per subject assigned to be treated with FP.

FOR SUBJECTS RANDOMIZED TO STANDARD OF CARE (SoC)
SoC will be initiated with 4 minutes of continuous firm manual compression following randomization with or without gauze or sponge and with or without a topical absorbable hemostat (TAH) i.e. SURGICEL
Patient safety in this control SoC group is protected since during manual compression there should be no ongoing blood loss based upon this TBS definition and if break through bleeding requiring treatment occurs at anytime, the surgeon will revert to whatever his/her standard treatment would be. This will be considered as a treatment failure for the primary efficacy parameter.
Hemostasis will be assessed at 4 minutes post-randomization. If hemostasis has not been achieved at 4 minutes, the surgeon will continue to treat the bleeding according his/her SoC. Hemostasis at the TBS will be assessed again at 10 minutes following randomization. The TBS will be observed until completion of the surgery and immediately prior to initiation of final fascial closure. If hemostasis is achieved at 4 minutes post randomization with manual compression but the surgeon feels that additional treatment is required to assure durability of hemostasis then such treatment should be applied. This

will be considered a treatment failure.
If bleeding requiring re-treatment at the TBS occurs anytime after the 4-minute assessment, the surgeon should control bleeding according to his/her SoC and the subject will be considered a treatment failure for the primary efficacy variable.

Study burden and risks

The additional burden for patients participating in this study is minimal. Study-related examinations are generally done during the visits associated with the standard treatment of this patient group, with the exception of perhaps the 30 and 60 day visits.
The risks involved in the study are the same as patients who undergo standard liver surgery. The additional risk that participants have is the chance of developing a viral infection because of the use of the investigational product. As described elsewhere, this product is manufactured under the strictest safety measures but can not guarantee 100% certainty that no viruses are transmitted. A viral safety test is taken from every patient.

However, the small chance of developing a viral infection outweights, in the perspective of the researcher, the
adverse effects of CSF leakage, i.e. need for renewed surgical intervention, wound infection, meningitis and
delayed wound healing.

The risks associated with participation are the same as those noted in section E9, which are:

Possible risks and discomforts that may be expected include any of the standard risks and discomforts associated with the elective surgical procedure each subject is undergoing.

In addition the possibility of passing on infection by using the Fibrin Pad cannot be totally excluded because this medicine is made from human blood.

Contacts

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Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects aged 18 years or over, requiring elective or urgent open hepatic surgery
2. Presence of an appropriate bleeding parenchymal Target Bleeding Site (TBS) as identified intraoperatively by the surgeon.
3. Subjects must be willing to participate in the study, and provide written informed consent.

Exclusion criteria

1. Subjects with any intraoperative findings identified by the surgeon that may preclude conduct of the study procedure*
2. TBS is from large defects in arteries or vein where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of the FP to blood flow and pressure during healing and absorption of the product*
3. TBS with major arterial bleeding requiring suture or mechanical ligation*
4. Subjects admitted for trauma surgery*
5. Subject is a transplant patient for fulminant hepatic failure*
6. Subject with TBS within an actively infected field*
7. Bleeding site is in, around, or in proximity to foramina in bone, or areas of bony confine.
8. Subjects with known intolerance to blood products or to one of the components of the study product*
9. Subjects who are known, current alcohol and / or drug abusers*
10. Subjects who have participated in another investigational drug or device research study

within 30 days of surgery*
11. Female subjects who are pregnant or nursing.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-03-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fibrin Pad
Generic name:	Fibrin Pad

Ethics review

Approved WMO

Date:	27-07-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	15-12-2010
Application type:	First submission
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	EUCTR2010-019427-58-NL
CCMO	NL32612.042.10