12 JAN. 2005

DEMEB
ESSAIS CLINIQUES - LOI HUR

Adjudication Manual of protocol IMP 11528

Once-daily oral direct factor Xa inhibitor BAY 59-7939 in patients with acute symptomatic deep-vein thrombosis. The Einstein-DVT dose-finding study

December 31, 2004

1. Administration

1.1 Abbreviations

AE Adverse event
CIAC Central Independent Adjudication Committee
CRA Clinical Research Associate
CRF Case Report Form
ExCie Executive Committee
SAE Serious adverse event
VTE Venous thromboembolism

1.2 General task

The task of the Central Independent Adjudication Committee (CIAC) is to assess objectively, independently, unaware of treatment allocation and in compliance with this manual, the routine ultrasounds and perfusion lung scans in all patients, and all potential outcome events. The latter include assessments of all cases of venous thromboembolism (VTE), bleeding episodes and mortality in the Einstein DVT dose finding study (IMP 11528).

Tasks and responsibilities as specified in the protocol,

1. with respect to the primary outcome:
- to propose to the executive committee (ExCie) the criteria for:
  - deterioration, improvement or no relevant change on the routine ultrasound and perfusion lung scans
  - VTE
  - cause of mortality
- to apply these criteria after they have been agreed upon by the ExCie
- to adjudicate and evaluate (blindly) on an ongoing basis all reported routine ultrasound and perfusion lung scans, suspected outcomes and deaths

2 with respect to the principal safety outcome:
- to propose to the ExCie extended criteria for major, non-major clinically relevant and trivial bleeding
- to apply these criteria after they have been agreed upon by the ExCie
- to evaluate (blindly) all reported suspicions of bleeding on an ongoing basis

1.3 Membership

The CIAC consists of the following members:
[redacted]s, chairman, Clinical Epidemiology, University Medical Center, Maastricht
[redacted]
[redacted]

All correspondence should be sent to:
ICTOM
W.G. Plein 467
1054 SH Amsterdam
The Netherlands

1.4 Meetings

Meetings will be scheduled monthly or more frequently if indicated by the number of cases to be reviewed. After each meeting, a summary of the events reviewed by the CIAC will be made available within 10 working days.

2. Procedures

2.1 Collection of information and data flow

For each set of routine ultrasound and perfusion lung scans and for each event (i.e. VTE, bleeding or death), an adjudication dossier with the following contents will be compiled:

Table 1 – Contents of adjudication dossiers

Adjudication dossier	Clinical Summary Form	AE/SAE CRF	Other applicable CRFs	Additional information	Baseline and 12 week US+PLS	Adjudication CRF (added by ICTOM)
Routine US+PLS					X	X
Suspected event	X	x	X	X		X
Bleeding	X	x	X	X		X

Applicable CRF pages are to be completed by the investigator. All images/films will be labelled by the investigator or by the CRA using pre-printed labels, identifying study, centre, patient number, and date of examination. Good quality copies of tests will be included in the adjudication package as well as all other relevant information for the CIAC. The adjudication package is sent via ICTOM to the CIAC (see Table 2).

Table 2 – Data flow in case of an event

1	2	3	4	5
Investigator sends notification fax to CRA	CRA collects dossier, checks it for de-blinding & sends it to ICTOM	ICTOM re-checks for de-blinding and completeness; adds (S)AE report (CIOMS form) if applicable and other applicable CRFs and sends dossier to CIAC	CIAC completes adjudication CRFs, and updates list of adjudicated material	Study manager (Bayer) receives adjudication CRFs and sends them for entry into the study database

Time from the date of onset of the event and the receipt of the dossier at the CIAC should not exceed five weeks.

In case a dossier is incomplete or includes inconsistent data, the CIAC will inform the person who is responsible for global monitoring (study manager). Queries will be sent out to the investigators via local CRAs and should be resolved with the site within four weeks, and faxed back to the study manager for communication with the CIAC without delay. The CIAC may ask specific questions to the investigators via the CRAs: no direct contact will take place between CIAC and investigators regarding adjudication of events that took place at the investigator's site. The chairman of the CIAC will participate in ExCie meetings and report the progress of adjudication and specific issues, which may be fed back to investigators through the Study Management and Coordination Committee and/or ICTOM.

All outcomes will be documented on adjudication CRFs and will be stored in the study database. Queries and answers are to be filed in the corresponding dossier. Data validation directives for these CRFs will be described as part of the study validation directives.

2.2 Blinding

Blinding to treatment allocation will be guaranteed by implementing several checks.

1. The investigator is instructed to avoid inclusion of unblinding elements in the adjudication package
2. The local CRA checks the package for de-blinding before shipping it to ICTOM
3. ICTOM checks the package for de-blinding before shipping it to the CIAC
4. Instead of SAE CRFs, the CIAC receives CIOMS forms which are blinded for treatment

2.3 Ajudication process

Cases/events are reviewed by at least three (3) members. In case a member was involved in the actual care or documentation of an event, he or she will not be involved in the review of this event. This will be documented by listing the members involved in the decisions for each individual case. The membership of the committee is such that at lease the chairman and two members will be available without knowledge of the actual care or completion of documentation of an event.

The CIAC will use a priori defined criteria for the events which are to be adjudicated, as detailed in section 3 of this manual.

2.4 Results

The results of adjudication will be reported on specific adjudication CRFs. The chairman of the CIAC will sign all forms or this will be delegated as documented on a signed 'authorized delegation sheet'. This sheet also indicates who completes the CRFs. Discrepancy resolutions can be initiated by the CIAC, based on newly arrived information, internal review, or requests from the sponsors. In case the CIAC requires additional information from study sites, requests will be sent to the person who is responsible for global monitoring (study manager) . The study manager will arrange for the required information/material via the local CRA, informing ICTOM. The process of sending additional information is similar to the process of sending

- associated with a fall in hemoglobin of 2 g/dL (i.e 1,25 mmol/L) or more, or
- leading to a transfusion of 2 or more units of packed red blood cells or whole blood. A red cell unit is defined as the quantity of red cells obtained from or corresponding to approximately 500 mL of whole blood, or
- in a critical organ, intracranial, retroperitoneal, pericardial, or
- contributing to death

Other clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding and including:

- any bleeding compromising hemodynamics, or
- any bleeding leading to hospitalization, or
- subcutaneous (skin) hematoma if the size is larger than 25 cm2, or 100 cm2 if provoked, or
- intramuscular hematoma, or
- epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e. 2 or more episodes of true bleeding, i.e. not spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocoagulation etc), or
- gingival bleeding if it occurs spontaneously (i.e. unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes, or
- hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g. catheter placement or surgery) or the urogenital tract, or
- macroscopic gastro-intestinal hemorrhage: at least one episode of melena/hematemesis, if clinically apparent and hemoccult positive, or
- rectal blood loss, if more than a few spots on toilet paper, or
- hemoptysis, if more than a few speckles in the sputum and not occurring within the context of PE or
- any other bleeding type that is considered to have clinical consequences for a patient.

All other overt bleeding episodes not meeting the criteria for clinically relevant bleeding will be classified as trivial