DATA SAFETY MONITORING BOARD CHARTER

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

PROTOCOL (IMP 11528)

Final version December 9, 2004

1. Responsibilities

The main responsibility of the Data Safety Monitoring Board (DSMB) is to protect the safety of the patients participating in the Einstein DVT dose finding trial (IMP 11528)

The DSMB will review independently the accumulating safety and efficacy data.

The DSMB will make appropriate recommendations to the Executive Committee (Ex Cie) if the DSMB deems there is an undue risk for the safety of the patients especially with respect to major bleeding or recurrence of venous thromboembolic (PE/DVT) disease.

The DSMB will control the dissemination of interim results, in particular these results – except recommendations - will not be shared with anyone outside this committee.

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MEMBERS

The DSMB will consist of three members.
The members are:

[redacted] (Sweden) (chair), [redacted] (Austria) and [redacted] (The Netherlands).

DSMB members will not be investigators in the trial.

2. Organisation

The DSMB is independent from:

- the sponsor, Bayer,
- the investigators,
- the ExCie,
- the Central Independent Adjudication Committee (CIAC).

The DSMB will be blinded to treatment as long as possible. The DSMB will review blinded individual clinical data as well as incidences of events (major/clinically relevant bleeding and PE/DVT recurrence) in the BAY 59-7939 and (LMW)Heparin/VKA treatment groups.

The chairman will play the role of interface between the ExCie and the other DSMB members. The DSMB statistician will be in charge of preparing appropriate documentation within ten working days after receipt of each data transfer from the sponsor. The DSMB statistician will also be responsible for conducting data analyses and the dissemination of results exclusively to the other members of the DSMB (see procedures below).

The DSMB will meet at regular intervals as specified below by telephone or in face-to-face meetings. Within one week after each meeting, the DSMB will recommend to the ExCie that:

- the study should continue as planned, or
- a meeting to discuss possible early termination of the study is called

The DSMB recommendations will not include:
- discontinuation of the study for early demonstration of efficacy and/or a better safety of BAY 59-7939
- re-estimation of the sample size

adjudication packages, i.e. including the processes for assuring blinding of the data before review by the CIAC.

3. Criteria for adjudication

3.1 Baseline and end of treatment compression ultrasound and perfusion lung scans

Compression ultrasound (CUS) and perfusion lung scans (PLS) will be used as diagnostic tests for assessment of efficacy in this study in addition to the clinical outcomes. Baseline and end-of-treatment CUS and PLS will be compared. The results will be classified as normalization, no relevant change, or deterioration.

3.1.1 Compression ultrasound

To allow for a quantitative assessment of test results, the vein diameter under full compression of the common femoral, superficial femoral and popliteal vein will be measured during the CUS procedure. To ensure that the vein diameter measurement at the end of the study period is done at the same anatomical location as at start of the study, a hard copy of the initial examination should be obtained and in addition the findings will be recorded on a standardized anatomical form.

Repeat CUS
The repeat ultrasound procedure at the end of the study is done in an identical way as at baseline. Care must be taken to reproduce the exact anatomical localization of the common femoral, superficial femoral and popliteal vein.
Original hard copies of the baseline and repeat examination as well as the standardized anatomical form will be made available for central adjudication.
The pre- and post-treatment vein diameters of the common femoral, superficial femoral and popliteal vein are scored as:
- **Improvement**, if at the 12 week assessment, the thrombus has disappeared (full compressibility or compressed diameter is reduced to 2 mm or less) or the diameter has decreased by more than 50%
- **Deterioration**, an increase in diameter of 4 mm or more
- **No relevant change**, all other changes that can not be scored as improvement or deterioration

3.1.2 Perfusion lung scan

PLS will be performed according to standard methods. Pre-treatment scans will be compared with post-treatment scans. Repeat PLS should be done in the same way as the initial scan. Original hard copies of the baseline and repeat examination will be made available for central adjudication.

PLS will be adjudicated using the lobe score. With this score each lobe is assigned a weight based on the regional distribution of pulmonary blood flow. For each scan an estimation is made of remaining perfusion of each lobe from 0 (no perfusion), 0.25, 0.50, 0.75 to 1 (normal). The total perfusion score is the sum of the 6 lobes, corrected with a factor 0.45 and 0.55 for the left and right lung, respectively.

- **Improvement,** if at the 12 week assessment, all lobes have a lobe score of 1 or the perfusion defect has decreased by more than 50% compared to the baseline scan
- **Deterioration,** the lobe score is decreased with a value exceeding 0.25 for any individual lobe or for the overall score, i.e. the weighted sum over the six lobes.
- **No relevant change,** all other changes that cannot be scored as improvement or deterioration

3.2 Venous thromboembolism (VTE)

VTE is either:
Symptoms of PE with one of the following findings:

- A (new) intraluminal filling defect in (sub)segmental or more proximal branches on spiral CT scan,
- A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram on the pulmonary angiogram,
- A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy (VPLS),
- inconclusive spiral CT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography.
- fatal PE based on autopsy;
- death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death)

OR
Symptoms of DVT with one of the following findings:

- abnormal CUS where compression had been normal or, if non-compressible at screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression
- an extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography

3.3 Mortality

For all patients who died during the study the CIAC will assign the cause of death to one of the following:

- VTE
- Unknown, but VTE cannot be excluded
- Bleeding
- Other known cause
- Other known cause is to be specified by the CIAC, e.g. cancer.

3.4 Bleeding

All bleeding events will be adjudicated by the CIAC and classified as either major bleeding, non-major clinically relevant bleeding or trivial

Major bleeding is defined as clinically overt and:

3. Procedures

The sponsor will initiate an extra effort to have events adjudicated and adjudication results collected in the data base prior to each DSMB meeting.

DSMB meetings. DSMB meetings will be held either face to face or by phone calls. To be informed about adverse events emerging in the beginning of the trial, the DSMB will review all Serious Adverse Events reported at the time the first patient has completed a follow up of 1 month.
After this first review, next meetings will be held after approximately 100, 200, 300 and 400 patients have been randomised. During these meetings the data listed below will be reviewed. Additional meetings may be requested by the Sponsor, the ExCie, or the DSMB itself.

Data Transfer. Ten working days prior to the DSMB meeting the sponsor's trial statistician will provide the following data from the sponsor's data bases (clinical and pharmacovigilance/drug safety databases) to the DSMB statistician in an agreed electronic format:

1. A file of all randomized patients with patient's number, date of randomization and a blinded treatment allocation code. The key of the codes will be kept by the DSMB in a sealed envelope and may be opened at the discretion of the DSMB in case a recommendation regarding stopping is considered. There is no need informing the ExCie of such an unblinding in case no recommendation of stopping the trial has been made.

2. The main baseline characteristics of the patients (confirmation of qualifying event, demographics, risk factors for PE/DVT)

3. Adjudicated safety and efficacy data: suspected as well as confirmed major/clinically relevant bleedings, PE/DVT recurrences and deaths, occurring 1 month before the DSMB meeting date. Any attempt will be made to adjudicate *also* safety and efficacy events with onset between 0 and 1 month prior to the meeting and to transfer the adjudication results to the sponsor's data base. In addition a list of all suspected safety and efficacy outcopmes regardless of the status of adjudication.

4. A file of all SAEs transmitted to the sponsor at least 10 days before the DSMB meeting. This will include for each SAE:
   - diagnosis or main symptom
   - intensity
   - time period (during vs. after randomized treatment)
   - outcome
   - relationship with study drug.

   Paper copies of SAE forms or CIOMS forms will be transferred, if requested by the DSMB. Any attempt will be made to include *also* SAEs with onset between 0 and 10 days prior to the meeting.

5. A file of all AEs - by body organ - and laboratory AEs, transmitted to the sponsor at least 1 month before the DSMB meeting.

The DSMB may request additional relevant information or documentation at any time up to clinical completion of the trial.

Data analysis. At each meeting, the incidences of confirmed major bleeding, non-major/ clinically relevant bleeding and PE/DVT recurrence as well as the SAE and mortality rates will be calculated by treatment group based on the following denominators:

- For major bleeding, clinically relevant non-major bleeding and symptomatic PE/DVT recurrence and overall mortality *within 12 weeks from randomization* the number of randomized patients in the data base 1 month before DSMB meeting (i.e. demography or adjudication data available).
- For SAE and mortality rate (excluding fatal PE): the number of randomized patients 10 days before data transfer.

Stopping (an arm of) the trial. Although the principal safety outcome is the combination of major and clinically relevant non major bleeding. The stopping rule of the trial takes into account only major bleeding, which is a generally accepted serious adverse outcome for patient receiving anticoagulants. However in reaching a final decision for stopping also the clinically relevant non major bleeding will be taken into account.
Differences in incidences of major bleeding within 12 weeks from randomization will be tested using Fisher's Exact Test. The DSMB should consider recommendation to the ExCie to stop (one arm of) the trial if:

- the incidence in major bleeding in a BAY 59-7939 group is statistically significantly higher than in the (LMW)Heparin/VKA group at a one-sided significance level of 1%.

The BAY 59-7939 to (LMW)Heparin/VKA odds ratio associated with VTE recurrence *within* weeks 12 from randomization and its 95% CI will be calculated. The DSMB should consider recommendation to the ExCie to stop (one arm of) the trial if:

- the lower limit of 95% CI for the odds ratio associated for VTE recurrence is greater than 1.0.

If necessary, the DSMB can unblind treatment allocation without informing the ExCie - in order to make recommendations as described above.

No adjustment on the type I error rate is necessary, since there is no intention to stop the trial for a better efficacy or safety profile with BAY 59-7939 as compared to (LMW)heparin/ VKA.

However, 'No single statistical decision rule or procedure can take the place of well-reasoned consideration of all aspects of the data by a group of concerned, competent and experienced persons' (Facey and Lewis, 1998). Therefore, it is possible for the DSMB to overrule the stopping rule -in either direction- if clinical judgement deems it necessary (Whitehead, 1999). Before making a recommendation to terminate the trial, the DSMB will

review the data in a variety of ways with careful attention to other safety and efficacy outcomes (Ellenberg, 2001).

The DSMB is advisory to the ExCie. Should the DSMB consider recommending early stopping of the study, the following steps must be undertaken:

- a meeting between the ExCie and the DSMB to discuss the issue should be called
- following this meeting, the DSMB will take a decision whether to recommend stopping or not.
- the recommendation is forwarded to the chairman of the ExCie.

If the unusual situation occurs that the ExCie or the sponsor disagrees with the interpretation of data, additional expertise may be consulted at a common meeting. These experts should be mutually agreed upon by the ExCie, the DSMB and the sponsor. In any situation where stopping for benefit is considered, regulatory aspects need to be addressed. Before the decision is taken, the sponsor may need to contact authorities for discussion on the implications for the approval of the drug.

Dissemination of results. After each meeting, minutes will be written documenting the advice (i.e. to continue the study as planned, modify the protocol or terminate the study early for safety reasons) as well as the rationale for the advice. A letter with the recommendation will be sent to the chairman of the ExCie within one week after the meeting. The minutes –as well as all documentation prepared for the meeting– will be archived and shared with the sponsors after the study data base has been locked.

REFERENCES

1. Facey, K.M., and Lewis, J.A. (1998). The management of interim analyses in drug development. Statistics in Medicine 17, 1801-1809.
2. Whitehead, J. (1999). On being the statistician on a data and safety monitoring board. Statistics in Medicine 18, 3425-3434.
3. Ellenberg, S. (2001). Independent data monitoring committees: rationale, operations and controversies. Statistics in Medicine 20, 2573-2583.