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Product name: **XIGRIS**
Procedure No**: EMEA/H/C/000396/II/0020**

SCIENTIFIC DISCUSSION

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I SCIENTIFIC DISCUSSION

1.1 Introduction

The active substance of Xigris is a recombinant human Activated Protein C, or drotrecogin alpha (activated), which exerts an antithrombotic effect by inhibiting factors Va and VIIIa, resulting in a negative feedback regulation of coagulation. Moreover, *in vitro* data demonstrate that Activated Protein C has an indirect profibrinolytic activity, due to its ability to inhibit plasminogen activator-1 (PAI-1) and limit the generation of activated thrombin-activatable fibrinolysis inhibitor, and exerts an anti-inflammatory effect.

Xigris was first approved in the United States on 22 November 2001. On 22 August 2002 Xigris was authorised in Europe under exceptional circumstances through the centralised procedure with the following indication: *treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care.* Based on the results of further clinical trials, during its second annual re-assessment, the indication was qualified with the following additional sentence: *the use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure.*

During its third annual re-assessment, the CHMP concluded that on the basis of the data submitted the benefit/risk balance for Xigris in the approved indications remained positive and Xigris should remain under exceptional circumstances until at least the results of study F1K-MC-EVBR (to investigate the possible interaction between Xigris and heparin) have been obtained. Therefore, the following Specific Obligation remained to be fulfilled: "A further clinical study (F1K-MC-EVBR) is being conducted to investigate the possible interaction between Xigris and heparin. The final study report will be provided in April 2006".

The Marketing Authorisation Holder (MAH) provided the final study report of the study F1K-MC-EVBR (now XPRESS study - heparin/Xigris versus placebo/Xigris) within the framework of a type II variation (EMEA/H/C/000396/II/0020), since the results of XPRESS identified the need for changes to the Summary of Product Characteristics (SPC).

1.2 Clinical aspects

1.2.1 Background information on coadministration of heparin and Xigris

There were clinical and theoretical concerns associated with the coadministration of drotrecogin alfa (activated) with prophylactic heparin. Both medications have anticoagulant properties and, therefore, coadministration may increase the rate of serious bleeding associated with either therapy alone. Additionally, a number of *in vitro* studies have documented increased inhibition of Activated Protein C activity by protein C inhibitor in the presence of unfractionated heparin and low molecular weight heparin, albeit under high local concentration conditions (Pratt and Church 1993; Aznar et al. 1996; Friedrich et al. 2001).

Analysis of the PROWESS study data, which served as the basis for the Marketing Authorisation for Xigris, by heparin exposure raised the possibility that heparin may reduce the efficacy of drotrecogin alfa (activated). In PROWESS, approximately 75% of patients received prophylactic unfractionated or low molecular weight heparin sometime during the study drug infusion period. A significant treatment-by-concomitant heparin exposure interaction was observed. However, this analysis was based on a post-baseline covariate, and there was no treatment-by-baseline heparin exposure interaction between Xigris and placebo treatment groups. Baseline prophylactic heparin was administered to 64.5% of patients overall, but to a higher proportion (>80%) in Europe. Furthermore, in an analysis stratified for concomitant prophylactic dose heparin administration, Xigris significantly reduced mortality compared to placebo (p=0.005). Mortality rates and serious bleeding event rates were similar for Xigris patients receiving and not receiving any concomitant heparin.

Nevertheless, the mortality rate by prophylactic heparin exposure during the infusion period in PROWESS raised concerns that Xigris might not be as efficacious in patients receiving heparin for

any reason. These concerns were not supported in further studies such as ADDRESS and ENHANCE, but the potential interaction between heparin and Xigris was important to analyse in a study, such as XPRESS, where the decision to use prophylactic heparin treatment was randomised.

1.2.2 Description of XPRESS study

XPRESS was a randomised, double-blind, placebo-controlled Phase IV trial of prophylactic heparin in patients with severe sepsis and higher disease severity who were undergoing treatment with Xigris.

Study design

At baseline, the administration of prophylactic heparin was at the physician's discretion. Then, eligible patients starting treatment with Xigris at 24 µg/kg/h during 96 h (4 days) were randomised to either: low molecular weight heparin (n=500 planned), unfractionated heparin (n=500 planned), or placebo (n=1000 planned) for 96 h as well. During study drug administration, only mechanical methods of deep venous thrombosis (DVT) prevention, such as graduated pressure anti-embolism stockings or pneumatic calf or foot compression, could be used at any time. Commercial heparin could only be used after the completion or early termination of study drug administration. After study drug administration, all severe sepsis care modalities remained at the discretion of the treating physician, including the choice of DVT prevention method. Thus, patients could be switched back to any type of commercial heparin immediately after the end of the Xigris infusion.

Diagnosis and main criteria for inclusion

Patients were eligible for enrolment if they were adults (≥ 18 years old), were indicated for treatment with Xigris under the approved label in the country where the patient was enrolled, and were receiving treatment for severe sepsis at one of the participating investigative sites. "Higher disease severity", which defines the indication population, was defined as an APACHE II score ≥ 25 in the US and other countries and ≥ 2 organ failures in the EU and other countries. The exclusion criteria were similar to those of the PROWESS study, especially the exclusion of patients who were not expected to survive 28 days given their preexisting uncorrectable medical condition and those with a high risk of bleeding. In addition, in XPRESS, patients were excluded if they were contraindicated for treatment with prophylactic heparin, required a higher dose of prophylactic heparin than specified in the protocol, had acute or chronic renal failure with an estimated creatinine clearance <30 ml/min, or had a concurrent need for other anticoagulant/antithrombotic medication during the Xigris infusion.

Primary and secondary endpoints

The primary endpoint was to demonstrate in adult patients with severe sepsis who received Xigris within its current indication that concomitant treatment with heparin was equivalent to treatment with placebo as determined by 28-day mortality, regardless of the cause of death.

Secondary endpoints were:

(1) to determine the relative incidence of venous thrombotic events in patients who received concomitant heparin versus patients who received placebo during Study Days 0 through 6;

(2) to determine the relative incidence of venous thrombotic events in patients who received concomitant heparin versus patients who received placebo during Study Days 0 through 28;

(3) to evaluate the safety profile of Xigris and prophylactic heparin coadministration as determined by the relative incidence of intracranial hemorrhage, fatal bleeding, nonfatal serious bleeding, heparin-induced thrombocytopenia, and ischemic stroke during Study Days 0 through 28;

(4) to evaluate the safety profile of Xigris and prophylactic heparin coadministration as determined by the occurrence of serious adverse events including serious bleeding events and nonserious bleeding events that occurred during Study Days 0 through 6 that led to or contributed to the need for transfusion of packed red blood cells, study-drug-related nonserious adverse events, and adverse events that led to permanent discontinuation of study drug.

As there was no clear difference between unfractionated heparin and low molecular weight heparin in most analyses, the two heparin groups (unfractionated and fractionated heparin) were combined, but separate analyses were also provided.

Study patients

Two thousand two patients (2002) were enrolled into this study. Eight (8) patients were removed from the database because of informed consent issues, thus 1994 randomised patients were included in the reporting database, of which 1935 received study drug (unfractionated heparin, low molecular weight heparin, or placebo) and 1927 completed the study with known 28-day survival status.

The per-protocol population (PPP) included the patients in the intent-to-treatment (ITT) population who received at least 6 heparin/placebo injections or who discontinued the Xigris infusion for reason of death. The PPP was of 1706 patients (88.2% of the ITT population). The 221 patients excluded from the PPP were balanced between the heparin group (n=101) and the placebo group (n=120), but their mortality rates were quite different.

Statistical analysis

The primary endpoint was to demonstrate that heparin was not appreciably different than placebo in reducing 28-day all-cause mortality in patients with severe sepsis who were receiving Xigris. The equivalence margin was set at ± 6.2%, since in PROWESS, Xigris patients with a baseline APACHE II score ≥ 25 had a 28-day mortality rate of 31% and in equivalence studies, an equivalence boundary of 0.8 to 1.2 is often used (6.2% = 31% × 0.20).

Similar analyses were performed for the secondary endpoints of the incidence of venous thrombotic events.

Baseline characteristics

The main demographic characteristics were:

- Male/female, 58.8/41.2 %.
- Mean age, 59.0; patients ≥ 65 years old, 40.3%; patients ≥ 75 years old, 18.7%.
- Caucasian, 73.3%.
- Europe, 35.1%, US/Canada, 47.1%; other regions, 17.8%.

The main clinical characteristics were:

- Patients with ≤ 1 organ dysfunction, 7.9%, with 2 organ dysfunctions, 28.3%, with 3 organ dysfunctions, 33.1%, with ≥ 4 organ dysfunctions, 30.8%. Of note, the number of organ dysfunctions present at baseline was assessed differently in this study than in previous studies of Xigris. In addition to cardiovascular, respiratory, renal, hematologic and unexplained metabolic acidosis dysfunction, the presence of central nervous system and liver dysfunction at baseline was also collected. When recalculated according to previous criteria with a maximum of 5 organ dysfunctions, 91.2% met the EU Xigris indication criteria of ≥ 2 organ dysfunctions. This proportion was higher than what was observed in the PROWESS and ENHANCE studies. The higher severity of sepsis in XPRESS was confirmed by a higher frequency of vasopressors and ventilator usage.

Median time from first organ dysfunction to Xigris start was 23.3 h, i.e., relatively similar to ENHANCE. The EU SPC for Xigris recommends starting treatment within 24 h of the first organ failure; therefore, only half of the XPRESS population met this criterion.

Baseline prophylactic heparin was used at the physician's discretion in 899/1935 ITT patients (46.5%) or 885/1927 (45.9%) in those who completed treatment. Unfractionated heparin was used in 24.1% of patients and low-molecular weight heparin in 22.4%. These groups were equally well randomised to placebo or to each type of heparin as a study drug; thus, among patients who were randomised to placebo, 45.7% had to stop their prior heparin therapy according to the protocol. Aspirin was used by 7.7% of overall patients at baseline, and other anti-platelet agents by 1.1%.

In general, the combined heparin and placebo treatment groups were well-balanced with respect to baseline characteristics. There were statistically significant differences between the two treatment

groups in site of infection and exposure to aspirin at baseline. Although not statistically significant, there were some numerical imbalances between the two treatment groups. Relative to the placebo group, the heparin group had a greater number of female patients (42.7% *vs* 39.6%) and a greater number of patients who were older than 65 (42.2% *vs* 38.3%), who were older than 75 (20.2% *vs* 17.0%), who came from an acute care hospital (17.8% *vs* 15.0%), and who had a history of DVT (3.3% *vs* 2.0%).

Concomitant treatments
More than half of patients (57%) received a mechanical method of DVT prevention at any time during the study (40% between Days 0 though 6). There were no statistically significant differences between the two treatment groups.

The use of heparin or heparin flush to maintain the patency of vascular access lines during the administration of Xigris was discouraged, but not prohibited. Approximately 17% of patients received heparin flush during the Xigris infusion, but the percentage of patients was similar in both the combined heparin and placebo groups.
Most patients (84.3%) received commercial heparin after the completion of study drug administration, and 48.2% received commercial heparin during Study Days 0 through 6. No imbalance between treatment groups (heparin *vs* placebo) was noted for commercial heparin administration.

1.2.3 Efficacy results

Efficacy primary endpoint
In the prospectively defined primary analysis, an equivalence analysis of 28-day mortality for the combined heparin and placebo groups, the 90% absolute risk difference confidence interval was not within the 6.2% equivalence margin; therefore, the combined heparin and placebo groups were not equivalent. Lower 28-day mortality was observed in the heparin group compared with the placebo group (28.3% and 31.9%, respectively). The absolute risk difference is −3.64% (in favour of heparin). The 90% CI on the absolute risk difference was −7.08% to −0.21%. Of note, the overall 28-day mortality (30.0%) was close to the expected value, i.e. the mortality rates in patients with ≥ 2 organ failures in PROWESS (26.5% for the Xigris group, and 33.9% for the placebo group).

Even though the results were not equivalent, the Kaplan-Meier survival curves for the combined heparin and placebo groups did not show a statistically significant difference in survival between the two treatment groups (p=0.086). The curves tended to separate beyond Study Day 5.
Similar results were observed in the individual heparin treatment groups: equivalence could not be concluded in both the analysis of low molecular weight heparin *vs* placebo and unfractionated heparin *vs* placebo.

Subgroup analyses
Statistically significant, and clinically relevant, treatment-by-subgroup interactions (Breslow-Day p-value <0.10) were noted in the following subgroups:

1. **Gender** (p=0.022). The mortality rate for male patients was similar in the heparin and placebo groups (31.5% and 31.1%, respectively); however, there was higher mortality among female placebo patients compared with female heparin patients (33.2% *vs* 24.0%). The reason for this gender difference was unclear. Female placebo patients might have been slightly more severely ill than female heparin patients: relative to the heparin group, the placebo group had a greater percentage of patients who had three or more organ dysfunctions (67.5% *vs* 59.5%), who were on a ventilator (88.9% *vs* 83.5%), and who had renal dysfunction (46.8% *vs* 40.8%).

2. **Region** (p=0.050). Among patients enrolled in Europe, higher mortality was observed in the heparin group compared with the placebo group (27.8% *vs* 24.4%). In the two other regions, US/Canada and "Other," higher mortality was observed in the placebo group compared with the heparin group (US/Canada: 33.9% *vs* 27.2%; "Other": 41.6% *vs* 32.2%).

3. **Baseline heparin exposure** (p=0.029). Similar mortality was observed in the heparin and placebo groups among patients who did not receive heparin at baseline (29.5% and 28.9%, respectively). Among patients who received heparin at baseline, higher mortality was observed in the placebo group (i.e. where baseline heparin had to be discontinued) compared with the heparin group (35.6% *vs* 26.9%).

4. **Time from the onset of the first sepsis-induced organ dysfunction** to the start of the Xigris infusion quartile (p=0.058). Among patients who started treatment with Xigris early (first and second quartiles), higher mortality was observed in the heparin group compared with the placebo group. Among patients who started treatment with Xigris late (third and fourth quartiles), higher mortality was observed in the placebo group compared with the heparin group.

Efficacy secondary endpoints

In this study, there was a lower than expected occurrence of venous thrombotic events: approximately 5% of patients experienced an event during Study Days 0 through 6 and approximately 6% during Study Days 0 through 28. During both time periods, asymptomatic and symptomatic lower extremity DVT were by far the most commonly occurring venous thrombotic event; pulmonary embolism and symptomatic central venous thrombosis were relatively infrequent events. The number of patients who experienced an asymptomatic lower extremity DVT and a symptomatic lower extremity DVT during Study Days 0 through 6 was nearly identical. Most of the DVTs that were discovered during the bilateral compression ultrasound examination were recorded as both an asymptomatic and symptomatic DVT (that is, the same event was reported under both classifications).

Overall, and according to the statistical analysis specified in the protocol (equivalence margin, ± 2.5%), the heparin and placebo groups were equivalent during Study Days 0 through 6, but not equivalent during Study Days 0 through 28. During Study Days 0 through 6, 4.6% of heparin patients and 5.1% of placebo patients experienced a venous thrombotic event; during Study Days 0 through 28, 5.7% of heparin patients and 7.0% of placebo patients experienced an event. This difference was due to the category "symptomatic lower extremity DVT", where the number of events in the placebo group exceeded the number of events in the heparin group by 7 (0.9%).

Efficacy endpoints - analysis of the Per Protocol Population

The PPP (n=1,706) was 88.2% of the ITT population. Demographic and other baseline characteristics did not differ notably from the ITT population, but the excluded population (101 in the heparin group, 120 in the placebo group) had a much worse outcome than the included PPP.

In fact, the primary analysis of the PPP showed equivalence at the 6.2% margin for the 28-day mortality of the combined heparin and placebo groups: mortality rates were 27.3% and 28.1% in the heparin and placebo PP groups, respectively, and the 90% CI on the absolute risk difference was −4.39% to +2.75%. Subgroup analyses of the primary endpoint showed the same treatment-by-subgroup interactions than for the ITT analyses.

In the equivalence and subgroup analyses of venous thrombotic events in the PPP, the results were similar to those seen in the ITT population.

When the non-PPP was analysed, it appeared these patients had a poor outcome, especially in the placebo group: 28-day mortality rates were 36.6% and 58.3% for the heparin and placebo groups, respectively, and the Kaplan-Meier survival curves differed markedly (p=0.0007). The reasons for this difference were not clear.

Therefore, the reasons for terminating Xigris infusion early in the non-PPP and potentially important imbalances between the heparin and placebo PP groups were examined. Mean duration of infusion was ~40 h (38.7 h and 42.1 h in the heparin and placebo groups, respectively) instead of 96 h. Most patients had their infusion terminated because of an adverse event (48% and 42.5% in the heparin and placebo groups, respectively) or "other" reason (44%). Thrombocytopenia was a frequent "other" reason in the placebo group (n=17), more frequent than in the heparin group (n=5). However when combining thrombocytopenia as an adverse event and "other" reason the numbers for both arms were

similar (n=19 and 16, respectively). Seven patients in the heparin group stopped Xigris due to an improvement in clinical status, but only 1 did so in the placebo group. The causes of death were similar between the two groups. No baseline characteristics imbalance seemed to explain the difference in mortality rates, even if there was slightly more COPD (chronic obstructive pulmonary disorder) patients in the non-PP placebo group (16.8% *vs* 11.7% for the heparin group), and if non-PP placebo patients had received baseline prophylactic commercial heparin at a higher frequency than non-PP heparin patients (51.7% *vs* 34.0%, respectively).

Pharmacokinetic analyses

No difference was detected between estimates of Css (steady-state plasma concentration) and CLp (plasma clearance) in the unfractionated and low molecular weight heparin treatment groups (p=0.499 for Css, p=0.502 for weight-normalized CLp); therefore, the two heparin treatment groups were combined and compared to the placebo group. No statistically significant difference was detected between placebo and the combined heparin group (p=0.604 for Css, p=0.862 for weight-normalised CLp); therefore, summary statistics of these parameters were calculated across all three treatment groups combined. These analyses indicate that heparin does not affect Css or weight-normalised CLp of drotrecogin alfa (activated) in patients with severe sepsis. Analysis of PK samples showed that there were no statistically significant differences between the heparin and placebo groups in steady-state plasma concentration and weight-normalised clearance of drotrecogin alfa (activated).

1.2.4 Discussion on efficacy results

The CHMP was not entirely convinced by the study design (study population as well as primary and secondary endpoints): a comparison of Xigris *vs* heparin and *vs* placebo in a new 3-arm trial involving the exact EU target population (severe sepsis with at least 2 organ failures) would have been more appropriate though more difficult to set up. Nevertheless, the CHMP acknowledged that the XPRESS study would be helpful to provide further information on heparin-Xigris interaction (Specific Obligation 1).

The CHMP noted that the baseline characteristics were typical of severe sepsis patients with a higher disease severity and were similar to previous studies of Xigris, including PROWESS. However, in XPRESS, almost all (91.2%) included patients met the criteria of the EU indication (at least 2 organ failures). On the other hand, treatment with Xigris was started relatively late, as the median time from first organ dysfunction to Xigris start was 23.3 h, meaning that almost half of the patients did not meet the EU SPC recommendations to consider Xigris "mainly in situations when therapy can be started within 24 hours after the onset of organ failure".

There was no clinically relevant baseline imbalance between groups. Similarly, there were no clinically relevant imbalances when the heparin treatment groups were analysed separately (low molecular weight heparin and unfractionated heparin).

The proportion of patients who were receiving prophylactic heparin at baseline (46.5%) was relatively low, at least with regard to EU standards. Indeed, in Europe, only 46.1% of XPRESS patients received baseline heparin. The proportion of patients with baseline heparin was similar across all regions (although it varied markedly between countries; for instance, in Germany, 79.1% of patients were on baseline heparin, compared to 30.2% in France). It was also similar across most other parameters such as gender and age.

According to the protocol, about half of the patients randomised to placebo had to stop their prior heparin prophylaxis when they started treatment with Xigris. The CHMP noted that this situation was rather artificial.

The CHMP noted that 68.5% of patients received commercial heparin during Study Days 7 through 14, which means that treating physicians decided to administer commercial heparin in two-thirds of patients immediately, or shortly, after the Xigris infusion ended. Eventually, 84.3% received commercial heparin. These percentages were higher than at baseline (46.5%), a fact which the MAH was requested to comment upon.

The MAH suggested that the lower rate of heparin prophylaxis at baseline in XPRESS (46%) than in PROWESS (67%) and in similar studies may be partly explained by the investigators' awareness that the patient was to be included in a study where heparin treatment would be randomised. After Xigris was stopped, the rate of heparin prophylaxis increased somewhat (55-70%) but remained <70% at any given time. The CHMP noted that evidence from "no heparin" group of XPRESS and from PROWESS showed no increase in the rate of thrombosis once Xigris was stopped and considered the explanation proposed by the MAH acceptable.

Having considered the efficacy results in the subgroup analysis, the CHMP noted that the non-equivalence in mortality rates between heparin and placebo was driven entirely by the results observed in females. The difference in 28-day mortality rates between female heparin and placebo patients was −9.2% (it was −0.4% in males). The reason for this gender difference was utterly unclear. The MAH argued that due to imbalance, female placebo patients might have been more severely ill than female heparin patients: if accepted, this argument leads to the conclusion that heparin and placebo treatments were indeed equivalent. To determine the significance of the interaction "gender" with the therapy, logistic regression was utilised by the MAH in a multivariable model that included significant mortality risk factors identified by previous analysis of the PROWESS data. The multivariate logistic regression analysis showed that the different outcomes in males and females were mostly driven by other prognostic factors such as age, APACHE II scores, number of organ dysfunctions, type of sepsis, and region, rather than by randomisation to heparin or placebo. The CHMP considered this explanation acceptable.

In the post hoc analysis of the subgroup of patients representing the population as per the therapeutic indication of the European SPC, heparin-Xigris coadministration may present a negative benefit/risk balance, since there seemed to be no additional efficacy (in terms of mortality and rates of DVT) of adding heparin prophylaxis to Xigris, and there is a slightly higher risk of bleeding. In the European centres of XPRESS, heparin patients tended to have higher 28-day mortality than placebo patients (27.8% *vs* 24.4%, respectively). It was also noted that among patients treated within 24 h of their first sepsis-induced organ dysfunction, as recommended in the EU SPC, mortality was similar between the heparin and placebo groups (28.9% and 28.0%, respectively). Therefore the MAH was requested to assess the benefit/risk balance of heparin-Xigris coadministration in both the ITT and PP patients meeting the therapeutic indication in the European SPC. A summary of the analysis of the ITT and PP population, with multiple organ dysfunction and treated within 24 hours of first organ dysfunction, split according to baseline heparin prophylaxis, is provided in the tables below.

Table 1: ITT Population – Patients with Multiple Organ Dysfunction Treated within 24 Hours of First Organ Dysfunction

28-day mortality

Overall			Baseline Heparin = No			Baseline Heparin = Yes		
Heparin N=443	Placebo N=447	p-Value[a]	Heparin N=268	Placebo N=265	p-Value[a]	Heparin N=175	Placebo N=182	p-Value[a]
30.25%	26.85%	0.26	30.22%	23.02%	0.06	30.29%	32.42%	0.66

a Analyses attached chi-squared tests unless denoted by "F", which are Fisher's exact test p-values.

Table 2: Per Protocol Population – Patients with Multiple Organ Dysfunction Treated within 24 Hours of First Organ Dysfunction

28-day mortality

Overall			Baseline Heparin = No			Baseline Heparin = Yes		
Heparin N=394	Placebo N=389	p-Value[a]	Heparin N=232	Placebo N=235	p-Value[a]	Heparin N=162	Placebo N=154	p-Value[a]
29.44%	22.37%	0.02	29.31%	17.45%	0.002	29.63%	29.87%	0.96

a Analyses attached chi-squared tests unless denoted by "F", which are Fisher's exact test p-values.

In XPRESS, the EU indicated population represented 443 heparin-treated and 447 placebo-treated patients (total 890 ITT patients). The MAH did not detail the baseline characteristics of these two groups but apparently they were comparable. The mortality rate was lower in the placebo group than in the heparin group in both the ITT and in PP populations: 26.85% *vs* 30.25%, p=0.26, in the ITT population, and 22.37% *vs* 29.44%, p=0.02, in the PP population. This seemed to indicate that the combination of heparin and Xigris was not beneficial, and may even be deleterious, in the EU indicated population. Looking at the subgroups, it appeared that this deleterious effect was concentrated in patients who were not on baseline prophylactic heparin, thus who started heparin and Xigris simultaneously. This combination resulted in a 28-day mortality rate of 30.22%, as compared to 23.02% in patients who started Xigris together with placebo (p=0.06, ITT population; in the PP population, the corresponding numbers are even more striking: 29.31% *vs* 17.45%, p=0.002). The explanation for this deleterious effect of the combination therapy was unclear. It did not seem to be driven by serious bleeding events (the rate of "any bleeding event" was increased with the combination therapy, but this was expected). The MAH suggested that patients randomised to placebo were older and sicker than those randomised to heparin, but the arguments in favour of that hypothesis were considered weak. The CHMP concluded that the results of the XPRESS study cannot be translated into useful recommendations for the use of Xigris in the EU indicated population.

The MAH suggested that when patients were already on prophylactic heparin, this drug should not be stopped when they start Xigris, due to a higher risk of serious adverse events (observed in the multivariate analysis of the overall population, as well as in the EU indicated population with p values <0.001) and to a higher risk of death (observed in the overall population), both of which may be due to rebound cardiovascular events. The CHMP noted that the increased risk of adverse events in patients who stop baseline prophylactic heparin when starting Xigris was also due to an increased rate of bleeding events, which is a paradoxical observation. This contributed also to the CHMP's conclusion not to include in the SPC a warning that prophylactic heparin should not be discontinued, as initially proposed by the MAH, (see section II below).

With regard to the efficacy secondary endpoints, the CHMP noted that the apparent non-equivalence in terms of thrombotic events (difference > 2.5%) was due to a slightly higher rate of symptomatic lower extremity DVT in the placebo group than in the heparin group. When examined more closely, it appeared that "true" symptomatic DVT were present in 3 placebo patients and 2 heparin patients during Study Days 0 through 6, in 3 patients in each group on Day 7, and in 9 placebo patients *vs* 2 heparin patients during Study Days 8 through 28. However, further analysis yielded very confusing information. First, all supplementary cases of symptomatic DVT occurred in patients who were receiving both prophylactic commercial heparin and mechanical compression methods. No single case of thrombotic event occurred during the whole 28-day study period in the 48 placebo patients who received no DVT prophylaxis at all. Secondly, subgroup analyses of venous thrombotic events also yielded confusing results. For instance, among patients with recent surgery, a statistically significantly (Breslow-Day p-value = 0.088) greater percentage of heparin patients experienced a venous thrombotic event compared with placebo patients (6.7% *vs* 4.8%), and among patients with no anticoagulants at baseline, a significantly (Breslow-Day p-value = 0.091) greater percentage of heparin patients experienced a venous thrombotic event compared with placebo patients (5.5% *vs* 4.4%). On the other hand, among patients with baseline prophylactic commercial heparin, a greater percentage of placebo patients experienced a venous thrombotic event compared with heparin patients (5.5% *vs* 4.0% during Study Days 0 through 6, and 2.6% *vs* 1.3% during Days 7 through 28). This reinforced the previous impression, based on mortality data, that patients already on prophylactic heparin, regardless of which type of heparin received at baseline, should not stop this treatment when they were started on Xigris.
The CHMP concluded that based on all the above inconsistencies, the value of the overall "difference" (non-equivalence) in the rate of venous thrombotic events in favour of the heparin study group, as concluded by the MAH, was dubious. The MAH agreed with the CHMP not to include any specific information of that type in the precautions/warning section of the SPC.

Having considered the efficacy endpoints in the PP population, the CHMP noted that the rate of (very) early discontinuation of the study drugs, including Xigris, may not be very high (11.2%), but the non-equivalence in 28-day mortality between the heparin and placebo groups in the ITT population was clearly due to a much worse outcome in the non-PP placebo group (mortality rate, 58.3%) compared with the non-PP heparin group (mortality rate, 36.6%), which meant that non-equivalence relies on reasons for early discontinuation of the study drugs. The heparin and placebo groups gave equivalent 28-day mortality in the PP population. Based on the data provided, there was no clear explanation for the poor outcome in the non-PP placebo group. One possibility was that patients on prophylactic heparin who were randomised to placebo and thus promptly discontinued their heparin anticoagulation were somehow exposed to a higher risk of death while they started treatment with Xigris and that many of these patients discontinued the Xigris infusion due to an apparent adverse event, such as thrombocytopenia, that heralded a fatal outcome. If this was true, heparin and placebo would be equivalent additions to Xigris, but there would be a strong rationale for not stopping heparin prophylaxis when starting Xigris therapy. The MAH was requested to comment on this issue.
To explain why the outcome was worse in the placebo non-PP population than in the heparin non-PP population, the MAH noted that, as for the overall population, patients who stopped baseline prophylactic heparin experienced a higher rate of death and adverse events. The CHMP considered that this explanation can be acceptable for the overall population.

With regard to pharmacokinetic, the CHMP concluded that that there was no apparent PK interaction between heparin, whether unfractionated or low molecular weight heparin, and drotrecogin alpha (activated).

1.2.5 Conclusion on efficacy results

The XPRESS study was a randomised, double-blind, placebo-controlled Phase IV trial of prophylactic heparin in patients with severe sepsis and higher disease severity who were undergoing treatment with Xigris. The XPRESS study was designed to determine the risks of using prophylactic heparin and Xigris concomitantly, depending on the time-course of such a combination. The CHMP noted that the numerically lower mortality rate observed in the overall heparin group (heparin 28.3% *vs* placebo 31.9%, respectively) must be tempered by the opposite results in sub analyses of patients in European centres (heparin 27.8% *vs* placebo 24.4%) and the post hoc analysis of patients in the EU indicated population (patients with multiple organ dysfunction treated within 24 hours of their first sepsis-induced organ dysfunction). Namely, the mortality rate in the EU indicated population was lower in the placebo group than in the heparin group (26.0% *vs* 30.3%, p=0.26). This seemed to indicate that the combination of heparin and Xigris was not beneficial, and may even be deleterious, in the EU indicated population. Considering the subgroups analysis, it appeared that this deleterious effect was concentrated in patients who were not on baseline prophylactic heparin (i.e who started heparin and Xigris simultaneously). This combination resulted in a 28-day mortality rate of 30.2%, as compared to 23.0% in patients who started Xigris together with placebo (p=0.06). The explanation for this deleterious effect of the combination therapy was unclear. It did not seem to be driven by serious bleeding events (the rate of "any bleeding event" was increased with the combination therapy, but this was expected).

Thus, the CHMP concluded that the results of the XPRESS study cannot be translated into useful recommendations for the use of Xigris in the EU indicated population. The CHMP concluded that the XPRESS results did not further clarify the benefit/risk balance of Xigris. On the contrary, uncertainties related to the interactions between heparin and Xigris remain.

1.2.6 Safety results

Two safety endpoints were prospectively defined as secondary endpoints in the study:

- incidence of fatal bleeding, nonfatal serious bleeding, heparin-induced thrombocytopenia, and ischemic stroke, and incidence of central nervous system bleeding;
- incidence of serious adverse events including serious bleeding events and nonserious bleeding events that occurred during Study Days 0 through 6 that led to or contributed to the need for transfusion of packed red blood cells; study-drug-related nonserious adverse events; and adverse events that led to permanent discontinuation of study drug.

Secondary analysis (serious adverse events) – prospectively defined serious bleedings, Central Nervous System (CNS)bleeding, heparin-induced thrombocytopenia (HIT), and ischemic stroke.
There were no statistically significant differences between heparin and placebo patients in the occurrence of fatal bleeds, nonfatal serious bleeds, and heparin-induced thrombocytopenia during both Study Days 0 through 6 and Study Days 0 through 28, although there was a tendency for more frequent fatal bleeding events in the placebo group during Study Days 0 through 28 (1.1% *vs* 0.4% for the heparin group, p=0.065).

A statistically significantly greater number of placebo patients experienced an ischemic stroke during both Study Days 0 through 6 (1.3% *vs* 0.3%; p=0.018) and Study Days 0 through 28 (1.8% *vs* 0.5%; p=0.009) compared with heparin patients. These strokes occurred throughout the study period. Patients who experienced an ischemic stroke were more likely to have a history of hypertension, to be on vasopressors, and to be on a ventilator than the overall population.

The number of patients in the combined heparin and placebo groups who experienced a central nervous system bleeding event was similar during both Study Days 0 through 6 and Study Days 0 through 28 (3 *vs* 3 and 10 *vs* 7, respectively).

Secondary analysis (nonserious but relevant adverse events) – bleedings leading to a need for transfusion, study drug-related nonserious adverse events and adverse events leading to discontinuation of study drug.
For all of these nonserious events, a numerically greater percentage of heparin patients experienced an event compared with placebo patients:

- Nonserious bleeding events that led to transfusion during Study Days 0 through 6 - heparin 5.0%, placebo 4.2%, p=0.372.
- Study-drug-related nonserious adverse events - Study Days 0 through 6: heparin 10.0%, placebo 7.2%, p=0.026; Study Days 0 through 28: heparin 10.1%, placebo 7.9%, p=0.089. The difference was due to an increased incidence of gastrointestinal and renal bleeding events in heparin patients. There was also an increased incidence of thrombocytopenia in heparin patients. The risk of any bleeding event (10.8% *vs* 8.1%; p=0.049) during Study Days 0 through 6 was also higher in heparin compared with placebo patients.
- Adverse events that led to discontinuation of study drug - heparin 8.3%, placebo 7.5%, but this difference was not statistically significant (p=0.519). It was primarily due to an increased incidence of gastrointestinal bleeding events (gastrointestinal haemorrhage) and thrombocytopenia in heparin patients. A statistically significantly greater percentage of heparin patients discontinued study drug because of thrombocytopenia [11 heparin patients (1.1%) and 2 placebo patients (0.2%); p=0.013)], and a gastrointestinal event [26 heparin patients (2.7%) and 13 placebo patients (1.4%; p=0.041)], mostly of the haemorrhagic type, compared with placebo patients. A statistically significantly greater percentage of placebo patients discontinued study drug because of a cardiac event compared to heparin patients [1 heparin patient (0.1%) and 8 placebo patients (0.8%; p=0.018)]. These cardiac events were myocardial infarction (3), atrial fibrillation (2), cardiac arrest (2), and unstable angina (1), whereas 1 case of myocardial infarction was recorded in the heparin group. However, the overall occurrence of serious cardiac events was similar between the heparin and placebo groups. During Study Days 0 through 28, 3.0% of heparin patients and 3.2% of placebo patients experienced a serious cardiac event.

1.2.7 Discussion on safety results

The CHMP noted that among 81 patients who discontinued heparin due to adverse events, 49 did so before receiving at least 6 injections; while in the placebo group among 72 patients who discontinued the study drug due to adverse events, 51 did it before receiving at least 6 injections. However, the CHMP noted that thrombocytopenia was quoted only twice as an adverse event requesting discontinuation of the placebo study drug, while it was mentioned 17 times as an "other" reason for stopping the placebo study drug before 6 injections had been administered (non-PPP). For the heparin group, these numbers were "reversed": 11 cases of thrombocytopenia as an adverse event and 5 as an "other" reason for stopping the study drug very early.
Following the explanation from the MAH on the classification of thrombocytopenia, the CHMP noted that it was indeed quite strange that if the treating physician believed that thrombocytopenia was due to study drug (heparin) or the combination of Xigris and study drug, this event was recorded as an adverse event, whereas if the physician believed that thrombocytopenia was not due to the study drug (but, e.g. to sepsis), then this was not classified as an adverse event but a clinical outcome, and if Xigris was stopped, then the study drug would be stopped as well but not vice versa. Thus, if a patient developed thrombocytopenia while doing relatively well, the physician would probably tend to attribute this event to a potential heparin treatment (and this could indeed be the case, i.e. there seemed to be more heparin-induced than placebo-induced thrombocytopenia), whereas if the patient developed thrombocytopenia in the context of clinical deterioration, all drugs may be stopped. Since placebo patients who had stopped baseline heparin fared less well, the above-mentioned data was compatible with the explanation provided by the MAH. Since this peculiar classification of adverse events did not seem to have introduced any significant bias, the CHMP considered this issue clarified.

The CHMP noted that the frequency of serious or fatal bleeding events through Day 28 was relatively high in XPRESS, both in the placebo group (5.4%) and in the heparin group (3.9%). CNS bleeding events (~1% through Day 28) were similar in both treatment arms. However, there was a small

increase in the "any bleeding event" category for the heparin arm compared with the placebo arm. This increase was statistically significant (10.8% *vs* 8.1%, p=0.049) during Day 0 through 6 only. Thus, prophylactic heparin given concomitantly with Xigris infusion for 6 days, whether or not preceded and/or followed by prophylactic heparin, seemed to slightly increase the risk of bleeding inherent to Xigris administration. This conclusion was based on a comparison with the placebo group in the present study. However, the placebo group in XPRESS may be somewhat artificial, since about half of these patients had to stop the prophylactic heparin they were receiving at baseline by the time they started the Xigris infusion. There was, for example, a potential for rebound thrombosis following heparin cessation, which may have occurred in this study (1.8% of placebo patients experienced an ischemic stroke compared with 0.5% of heparin patients, and placebo patients with baseline commercial heparin experienced more cardiac events and more thrombotic events compared with heparin patients). However, the rebound thrombosis phenomenon remained speculative as it has not yet been specifically studied in the sepsis population.

The CHMP noted that the increased risk of adverse events in patients who stop baseline prophylactic heparin when starting Xigris was also due to an increased rate of bleeding events, which was a paradoxical observation.

The low rate of ischemic strokes in the heparin-Xigris group in XPRESS (0.5% through Day 28) was an interesting finding, but no conclusion can be drawn based on this single study.

The results of the XPRESS study were also discussed at the PhVWP at its November 2006 plenary meeting. The PhVWP compared the safety data from XPRESS, PROWESS and ADDRESS: in XPRESS the rate of serious bleeding during infusion period was 2.3% in the Xigris group (vs 2.5% in the placebo group), which is similar to the rates in PROWESS (2.4%) and ADDRESS (2.4%). The rate of CNS bleeding during the infusion was also similar to other studies (0.3%). However, the additional analysis of the mortality data of the subgroups (baseline heparin or not) of the XPRESS study were unclear and inconsistent.
The PhVWP concluded that the safety data from the XPRESS study overall were very similar to that seen in PROWESS and ADDRESS and it was not possible to conclude any clear benefit from initiating heparin treatment with Xigris. The additional data from subgroup analyses (in severe sepsis patients who are receiving (or not) prophylactic heparin when organ failures develop) could not lead to clear cut conclusions on the interaction between heparin and Xigris.

1.2.8 Conclusion on safety results

The CHMP concluded that in the XPRESS study serious bleeding rates were consistent with those observed in previous studies over the treatment period of 0-6 days, and prophylactic heparin did not increase the risk of serious bleeding compared to placebo (2.3% *vs* 2.5%, respectively), including CNS bleeding (0.3% on both arms). However prophylactic heparin increased the risk of non-serious bleeding compared with placebo (8.7% *vs* 5.7%, respectively; p= 0.0116).

The CHMP also concluded that serious bleeding rates were consistent with those observed in previous studies during the 28-day study period (days 0-28). Prophylactic heparin did not increase the risk of serious bleeding compared to placebo (3.9% *vs* 5.2%, respectively), including CNS bleeding (1.0% *vs* 0.7%, respectively).

Therefore the CHMP concluded that the coadministration of prophylactic heparin with Xigris has an acceptable safety profile.

1.3 Overall discussion on benefit/risk and conclusions

Having assessed the results of the XPRESS study, the CHMP noted that the numerically lower mortality rate observed in the overall heparin group (heparin 28.3% *vs* placebo 31.9%, respectively) must be tempered by the opposite results in sub analyses of patients in European centres (heparin 27.8% *vs* placebo 24.4%) and of patients in the EU indicated population (patients with multiple organ dysfunction treated within 24 hours of their first sepsis-induced organ dysfunction: heparin

30.3% *vs* placebo 26.9%). The results of the XPRESS study cannot be translated into useful recommendations for the use of Xigris in the EU indicated population.

The CHMP noted that the clinical results of the XPRESS study, taken in conjunction with the results from other recent studies, raised concerns on the overall risk/benefit profile of Xigris.

The CHMP concluded that the XPRESS study had not brought a response to the question whether there is a pharmacodynamic interaction between heparin and Xigris on the contrary uncertainties related to the interactions between heparin and Xigris remain. Thus, the XPRESS results did not further clarify the benefit/risk balance of Xigris which was under assessment in the parallel on-going 4th annual re-assessment (EMEA/H/C/000396/S/0021). Therefore, a revised Specific Obligation to further clarify the benefit/risk balance of Xigris was discussed and agreed within the framework of the 4th annual re-assessment of Xigris.

II CHANGES TO THE PRODUCT INFORMATION

Further to the assessment of the proposals of the MAH to amend the Product Information and in light of the assessment of the submitted data, the CHMP agreed with the MAH's proposed changes to sections 4.2 "Posology and method of administration", 4.8 "Undesirable effects" and 5.1 "Pharmacodynamic properties" of the SPC.

With regard to section 4.4 "Special warnings and special precautions for use", the MAH had initially proposed to include a warning that prior to initiating or during treatment with drotrecogin alfa (activated), prophylactic heparin should not be discontinued unless considered medically necessary.
The CHMP noted that the benefit/risk balance of Xigris has not been clarified by the analysis of the XPRESS results. On the contrary, uncertainties related to the interactions between heparin and Xigris remained. The short period of heparin *vs* placebo randomisation (4 days) compared with a relatively extensive use of commercial heparin may be one reason for the confusing results of subgroup analyses. Additionally, the CHMP noted that the increased risk of adverse events in patients who stop baseline prophylactic heparin when starting Xigris was also due to an increased rate of bleeding events, which was a paradoxical observation.

Therefore, the CHMP concluded that the warning to avoid discontinuation of heparin should not be reflected in the SPC. Although the MAH considered that this warning would have been of practical value to clinicians, the MAH accepted the CHMP's request to not include this warning in this section. Thus, the warning to avoid discontinuation of heparin before administering Xigris was also deleted from the MAH's text proposal for the Package Leaflet.

With regard to the changes in section 4.5 "Interaction with other medicinal products and other forms of interaction", the CHMP requested to include the results of mortality of heparin versus placebo observed in patients with multiple organ dysfunction treated within 24 hours of their first sepsis-induced organ dysfunction. The MAH agreed with this request from the CHMP. Furthermore, the CHMP and the MAH agreed to include the results of mortality of heparin versus placebo observed in the subgroup of patients on baseline heparin (see discussion above), highlighting that the reasons for this difference were unknown and could be related to other factors.

For further details on the agreed changes to the SPC refer to the Product Information available in the European Public Assessment Report.

The Product Information includes also the changes from Type II variation EMEA/H/C/000396/II/0022, adopted by the CHMP in its February 2007 plenary meeting, related to an update of sections 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" of the SPC with information on increased risk of serious bleeding events in surgical patients, following the CHMP's assessment of summary data on bleedings events in surgical versus non-surgical patients from the major studies with Xigris. In addition the MAH completed the list of local

representatives in the Package Leaflet to include the two new EU Member States (Bulgaria and Romania).

III CONCLUSION

On 22 February 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics based on the observations and the appropriate conclusions.

The CHMP adopted on 22 February 2007 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation, as amended.

IV REFERENCE LIST

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