European Medicines Agency

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ASSESSMENT REPORT
FOR
Xigris

International Nonproprietary Name:
drotrecogin alfa (activated)

Procedure No. EMEA/H/C/396/S/29

Marketing Authorisation Holder/Applicant: Eli Lilly Nederland B.V.

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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I. SCIENTIFIC DATA PROVIDED BY THE MARKETING AUTHORISATION HOLDER

1.1 Chemical and pharmaceutical aspects

No additional data have been provided with this submission.

1.2 Preclinical aspects

No additional data have been provided with this submission.

1.3 Clinical aspects

The MAH has submitted the following documents to support the 7th annual re-assessment of Xigris:

- data from completed and ongoing clinical studies that have become available during the past 12 months
- publications occurring during the reporting period
- update on spontaneous safety data from the market

1.3.1 Update on clinical trials during the past annual re-assessment

As of 21 August 2009, a total of up to 7711 adult patients have been exposed to Xigris in completed and ongoing clinical trials (7243 on 21 July 2008). One cohort study was finished in November 2007 and is discussed below (F1K-US-EVDA). There are 2 ongoing trials: RESPOND and PROWESS-SHOCK (discussed below).

F1K-US-EVDA

Study F1K-US-EVDA was a prospective, nonrandomized, multicentre, open-label clinical trial of Xigris in patients with septic shock. The study evaluated the vasopressor requirement, haemodynamic response, and measures of tissue perfusion with the administration of Xigris as part of physician-directed therapy in patients with septic shock compared to a control cohort of patients with septic shock in which the physician chooses not to treat with Xigris. A total of 43 patients were entered into the study. The first patient entered the study on 1 February 2006 and enrolment concluded on 5 November 2007. As per company standard operating procedures, the study report for this study was planned to be the published manuscript. However the manuscript has yet to be accepted. This draft manuscript has been submitted for publication and a summary of the study results posted to *clinicaltrials.gov*.

ABSTRACT (adapted by the Assessor)
Introduction: The study investigates whether the vasopressor requirement, as measured by the change in Cumulative Vasopressor Index (CVI), will be reduced in patients receiving drotrecogin alfa (activated) (DrotAA) compared to patients not receiving DrotAA.

Methods: This was a prospective, non-randomized, multi-center, open-label clinical trial of DrotAA in patients with septic shock. Eligible patients were ≥ 18 years of age with severe sepsis and vasopressor-dependent septic shock despite adequate fluid resuscitation, with a catheter for hemodynamic management (N=43). Patient assignment (Drotrecogin Cohort [n=22] vs. Control Cohort [n=21]) was determined by physician-directed DrotAA administration. Patients were excluded if the time from the onset of the first sepsis-induced organ dysfunction to enrollment exceeded 24 hours and for evidence of inadequate right heart filling pressures (pulmonary artery occlusive pressure [PAOP] <12 mmHg, or central venous pressure [CVP] <8 mmHg). Data were collected prospectively for 7 days. The primary endpoint was the CVI, an assessment of hemodynamic support, representing the relative use of vasoactive agents applied to each patient. The study evaluated multiple secondary endpoints (hemodynamic measures, global tissue perfusion, and oxygenation).

Results: There were no significant differences in vasopressor requirements between the cohorts as measured by the CVI at any study time point. The Drotrecogin Cohort had significant improvements in Protein C activity at 24 hours and change from baseline to 24 hours, lactate change from baseline at 6 hours, and lower coagulation component Sequential Organ Failure Assessment (SOFA) score as compared to the Control Cohort. No other difference in secondary endpoints was noted. There were 2 serious bleeding events in the Drotrecogin Cohort (1 right-sided hemothorax, 1 intraperitoneal hemorrhage) and no serious bleeding events in the Control Cohort. There were no events of intracranial hemorrhage. The 7-day in-hospital mortality for the overall study population (N = 43) was 4 in the Drotrecogin Cohort and 8 in the Control Cohort.

Conclusions: The CVI, a measure of vasopressor support, was similar at all time points and mean arterial pressure differed only at 12 hours post-DrotAA infusion in favour of DrotAA. While these findings indicate an absence of a clear effect on macro-hemodynamics, the role of DrotAA in microcirculatory regulation deserves further exploration

It is concluded by CHMP that no relevant information can be extracted from this study. The results of larger cohort studies performed across the world have been extensively discussed during the 6th ALR and should be referred to for additional "field" information.

RESPOND (F1K-MC-EVDK) is a Phase 2 exploratory study investigating the potential role of protein C levels as a biomarker to help guide therapy with Xigris, specifically comparing higher doses and longer infusion of Xigris with standard therapy. Recruitment was completed 3 June 2009, and, following completion of 90-day follow up, data lock occurred on 5 October 2009. Full data analysis has not been completed. A full study report will be submitted to the CHMP when completed, which is planned in Q2 2010.

PROWESS SHOCK (F1K-MC-EVDP) – Specific Obligation 051
First patient visit took place 20 March 2008. The current performance of the study was extensively discussed as part of the recently completed 6th ALR. As of 7 October 2009, 476 patients have been randomised, which remains slightly ahead of the most recent plan communicated to the CHMP, and thus recruitment remains on track for a planned completion in Q1 2011. As discussed during the last ALR, the MAH has taken multiple steps to help ensure that recruitment continues to stay on track, including:

- Increasing the total number of sites, particularly in countries and regions that have been recruiting well. This also includes some high recruiting sites (who fulfilled site equipoise criteria) from the recently completed RESPOND study.
- Appointment of more country national coordinator investigators to help motivate sites in their country to recruit.
- Provision of additional resources to enable additional site visits by Lilly study monitors (in addition to Parexcel monitoring visits) to identify and solve potential site recruitment issues.
- Organisation of national and regional investigator meetings.

As of 1 October 2009, the combined serious bleeding rate during the infusion was similar to the combined rate from PROWESS (2.4% Xigris and 1.2% placebo). There has been one fatal bleeding event; no CNS bleeding events have been reported. The combined blinded mortality rate for patients recruited as of 08 September 2009 was presented and reviewed by CHMP.

The CHMP has previously requested that the MAH provide yearly updates on the following in each Annual Reassessment:

(1) the names of centres recruiting patients for that study → approximately 340 centres have been approved,

(2) their worldwide allocation → all regions have been included,

(3) the prescriptions and recommendations concerning the use of Xigris at

each participating centre → see discussion below,

(4) the number of patients included → as of 7 October 2009, 476 patients have been randomised,

(5) and the blinded opt-out rate → of the 476 patients recruited, none have been unblinded by the investigator or received commercial Xigris.

During evaluation of the current 7th ALR, **the MAH was requested to comment** on the overall mortality data*%.* Analysis of the baseline characteristics of *all patients in the database* as of *3 December 2009* (with and without 28-day mortality data, *n=575*; Table 1 in the response) demonstrates that although there are a number of demographic similarities between PROWESS and PROWESSSHOCK, *patients in PROWESS-SHOCK have greater disease severity* as measured by the degree of organ dysfunction (mean of 3.4 in the new study instead of 2.4 in PROWESS; 100% of cardiovascular failure and vasopressor use as these are inclusion criteria; 71% of renal dysfunction instead of 42%, etc.), degree of organ support, total SOFA score, and APACHE II score. These data support that PROWESS-SHOCK, as per its design, is in fact recruiting *a higher disease severity population compared to PROWESS*.

The mean time from onset of vasopressors to start of study drug is 17.2 hours, indicating that patients are being treated reasonably early in the course of their septic shock episode. These data suggest that, from a clinical perspective, *the study is recruiting an appropriately severely ill patient population. Thus the MAH does not plan to make any changes to the study inclusion and exclusion criteria.*

Factors to consider when reviewing mortality rate from an ongoing study compared to sample size assumptions:

- Mortality rates at a particular point in time may reflect *random chance* related to a relatively *small sample size*. As discussed previously with CHMP, mortality rates can fluctuate during the initial stages of a study.
- Over time there may be a general trend of a reduction in mortality in severe sepsis patients treated in the ICU related to general improvements in the standard of ICU care. However, in the recently completed RESPOND study (last patient visit 29 August 2009; study report submitted Q2 2010), the 28-day mortality for Xigris patients was 27%, which is the same as a comparable population from PROWESS (multiple organ dysfunction and protein C less than or equal to the lower limit of normal) that was completed in 2000. The RESPOND study used similar exclusion criteria and definitions of organ dysfunction as PROWESS. Nor was there any change in 28-day placebo mortality rates over time noted in the INDEPTH clinical trial database (Laterre et al. 2007), which included patients recruited into severe sepsis clinical trials between 1996 and 2002. However, the recently published results from the Surviving Sepsis Campaign (Levy et al. 2010), which completed in 2008, reported an *adjusted absolute drop of 5.4% in hospital mortality over 2 years* (95% confidence interval, 2.5 – 8.4) following a campaign to increase compliance with sepsis care bundles.
- the difference in mortality between placebo and Xigris treated patients may be different from that assumed for the sample size calculations.
- Does *not* reflect commercial Xigris use. There have been *no recorded cases of commercial use so far* during the study, so this is not currently an issue.

The MAH has provided a new power calculation. Based on the current situation with no "opt-out" patients, the power of the study with various aggregate mortality rates and sample sizes is provided in Table 2. These data demonstrate that, provided the aggregate mortality remains >24%, the potential sample size increase of up to500 patients can maintain the planned 80% power for the study if the risk ratio is in truth 0.8.

Table 2. Estimated Sample Size based on the Aggregate Mortality Rate

Aggregate Mortality Rate (%)	Placebo Mortality Rate (%)	Drotrecogin Alfa (Activated) Mortality Rate (%)	Sample Size per Treatment Group for 80% Power	Power with 1000 Patients per Treatment Group
30	33.33	26.66	751	89
28	31.11	24.88	827	86
26	28.88	23.11	916	83
25	27.77	22.22	965	81
24	26.66	21.33	1019	79
23	25.55	20.44	1077	76
22	24.44	19.55	1141	74
20	22.22	17.77	1282	69

Note: Power at Last Analysis Using a alpha=0.0479: Conservative Bonferroni Assumption for Group Sequential Monitoring Scheme (using nominal alpha of .0001, .001, and .001 at looks 1-3) with Risk Ratio of 0.8

The MAH proposes to follow the agreed protocol and *await the decision of the Steering Committee on whether to increase the sample size*. This decision is *anticipated in Q2 2010* (i.e. when approximately 375 patients per group will be recruited). Provided that the mortality rate remains greater than 24%, the power of the study will be preserved at 80% provided that the risk ratio is in truth 0.8.

As a **further follow-up question** during the evaluation of the current 7th ALR (March 2010), the MAH was requested to provide (1) the mortality rates by region (USA, Europe, and rest of the world) in PROWESS-SHOCK; (2) written expert's opinions (at least one US and one EU expert) on whether the mortality rate of severe sepsis patients is indeed improving across the world, or in specific areas of the world.

The MAH stated review of the most recent baseline characteristics based on *633 patients* with 28-d follow-up data (*February 2010*) demonstrate *similar high levels of organ dysfunction* and need for organ support as was noted in the January response, indicating that, from a clinical perspective, the study is recruiting an appropriate severely ill patient population. As was noted in the previous response, it is anticipated that the Steering Committee will make a decision as to whether to increase the sample size in *May/June 2010*, when 28-day follow-up data will be available from approximately 750 patients.

Regarding the request to provide mortality rates by region, the MAH states that it is currently only reviewing 28-day aggregate blinded mortality for the overall study population and believes that *it would be preferable not to review regional mortality rates* for several reasons, including the wish to not influence the Steering Committee by changing recruitment now that the first interim analysis has been completed and the fact that PROWESS-SHOCK is continuing to recruit *approximately two thirds of patients from the EU region*, so mortality in this region will be a key determinant of the overall mortality. At this stage, the US will have recruited less than 90 patients and the remaining countries, less than 150 patients, so mortality estimates from these relatively small populations will potentially be unreliable.

Regarding the need for an expert opinion "on whether the mortality rate of severe sepsis patients is indeed improving across the world, or in specific areas of the world…", the MAH has provided a joint letter by Prof Taylor Thompson and Prof Marco Ranieri, the US and EU Principal Investigators for the study, respectively, and the Co-Chairs of the Steering Committee. The authors have quoted the Levy et al. 2010 study already mentioned in the MAH response, showing a 5.4% absolute decrease in hospital mortality in the 15,022 severe sepsis subjects treated between 2005 and 2008, as well as the ANZIC study, demonstrating an even greater reduction in hospital mortality (from 35.6% to 21.2%; n=7,250)

over an eight year period ending in 2005 (Delaney, 2008). The experts have also quoted the results of two clinical trials of sepsis therapies conducted within the past few years and showing lower than expected mortality, including a Ph II North American trial of eritoran in adults with severe sepsis or sepsis requiring mechanical ventilation with a predicted mortality of 53% based on APACHE II scores which showed an actual 28-d mortality of 24 and 25% in the placebo and active arms respectively (Tidswell, 2010). The crude mortality rates between studies are obviously difficult to compare as they rely on different inclusion and exclusion criteria.

In this letter, the two Co-Chairs of the PROWESS-SHOCK Steering Committee reiterate that they have negotiated with the sponsor to provide the additional funds to enroll *up to 2000 subjects using a conditional power design based on aggregate mortality of the first 750 patients* as outlined in the PROWESS-SHOCK protocol. The Steering Committee anticipates having the 28-d outcome data upon which this decision rests in mid-May.

1.3.2 Publications occurring during the reporting period

The CHMP has previously requested that the annual licence reassessment should include a discussion of publications related to Xigris during the reporting period. A list of publications is included in Appendix 2. This list is based upon the MEDLINE database (July 2008 through August 2009) using the search terms: Xigris, drotrecogin alfa (activated), and recombinant human activated protein C. Below is a review of a selection of those that appear to have some clinical relevance to the use of Xigris.

Nonclinical Studies

One study in a mouse model of metastasis by Bezuhly et al. (2009a) showed that rhAPC treatment resulted in a 44% reduction in lung metastases, probably via inhibition of tumour cell adhesion and transmigration. Endothelial cells pretreated with rhAPC at concentrations of 10 to 25 nM (but not at 100 nM) showed significantly decreased adhesion and transmigration of melanoma cells. Endogenous APC may also limit cancer cell extravasation through its sphingosine-1-phosphate receptor-1 (S1P1) signalling properties independent of its anticoagulant activity (Van Sluis et al., 2009). This observation is consistent with previous reports.

However, as seen in last year's literature review, much of the research regarding activated protein C (APC) during this reporting period has focused on APC's activity at the microvascular/ endothelial levels. The effects of APC in severe sepsis, particularly its effect on inflammation and the endothelium, were investigated in several studies.

Elphick et al. (2009) found that rhAPC directly binds to β1 and β3 integrins at the neutrophil surface and inhibits neutrophil migration. This may be a novel target of APC and a potential mechanism by which rhAPC protects against sepsis. Similarly, Yang et al. (2009) discovered that APC ligation to ApoE receptor 2 initiates an intracellular signalling cascade in neutrophils. The ApoE receptor 2 may join EPCR and PAR-1 as candidates for cell receptors or co-receptors that mediate APC's actions. Regarding the crucial role of PAR-1 in these actions, Schuepbach et al. (2009) showed that in endotoxin-challenged mice, APC significantly prevented pulmonary fluid accumulation in wild-type mice, but not in PAR-1 deficient mice. Waerhaug et al. (2008) found that rhAPC alleviates endotoxin (LPS)-induced lung injury in sheep as characterized by improvements in oxygenation, coagulation, and inflammation, as well as by reversal of pulmonary haemodynamic and volumetric changes. Pirrone et al. (2008) showed that rhAPC has a beneficial effect in acute lung injury in endotoxin-induced lung inflammation in Large White pigs and concluded that may depend in part on modulation of lung matrix metalloproteinase activity. APC partially prevented the reduction in blood pressure induced by LPS and improved both vascular reactivity and myocardial performance in a rat endotoxic shock model (Sennoun et al., 2009a). In this study, APC also decreased tissue leukocyte infiltration and activation. Niessen et al. (2009) showed that EPCR/APC PAR-1 signaling by rhAPC or a S1P1 agonist has protective functions and promotes survival by preventing vascular leakage in escalating systemic inflammation.

In addition, Deane et al. (2009), using a mouse brain vascular perfusion technique, showed that APC and reduced anticoagulant variants, 5A-APC and 3K3A-APC, cross the blood brain barrier via EPCR-

mediated saturated transport and reach therapeutic targets in the brain, suggesting that the effect of rhAPC on some neurologic diseases is worth investigating. For instance, Thiyagarajan et al. (2008) showed that mice given tissue-plasminogen activator (tPA) 6 hours after onset of brain ischaemia died within 2 days, whereas mice given APC at 6 or 24 hours after ischemia onset showed significant improvement in functional outcome and reduced spread of the ischaemic lesion. These data suggest that delayed APC administration is neuroprotective.

In an effort to better understand how APC works, recent studies have sought to further understand the relationship between the cytoprotective and anticoagulant properties of APC. This research has been facilitated by the recent development of APC variants with predominantly PAR-1 or anticoagulant effects. Gupta et al. (2009) generated 2 APC variants, one with impaired anticoagulant activity (K193E) and one with impaired ability to modulate PAR-1 (L8W), and demonstrated that PAR-1 agonism, but not the anticoagulant function, reversed systemic hypotension in a rat model of LPS-induced renal microvascular dysfunction while both functions played a role in reversing decreases in renal blood flow and volume. Similarly, Wang et al. (2008) showed that the non-anticoagulant APC variant, 3K3A-APC, exhibited greater neuroprotective efficacy with no risk for bleeding compared with Xigris in a model of middle cerebral artery occlusion in mice. Qureshi et al. (2008) characterized an APC chimera in which the Gla domain of APC was substituted with the Gla domain of factor X (APC-FXGla). Results of this study support the hypothesis that variant residues of the N-terminal Gla-domain are critical for binding of rhAPC to EPCR and that those of the C-terminal domain are involved with specific interactions of APC with protein S.

In other relevant animal models, Bezuhly et al. (2009b) found that systemic APC improved ischemic skin flap survival in rats and modulated genes involved in angiogenesis, inflammation, and apoptosis. In a rat model of heatstroke, Lin et al. (2009) demonstrated that both rats pretreated and treated with rhAPC had significantly increased survival time compared with vehicle-treated rats. Akima et al. (2009) found that rhAPC prevented, in a dose-dependent manner, the instant blood mediated inflammatory reaction (IBMIR) associated with islet cell transplant. Teke at al. (2008) found that APC treatment prevented the delaying effects of intra-abdominal sepsis on the colonic anastomatic wound healing process.

Clinical Studies/Case Series/Case Reports

There have been 5 observational studies published in patients with severe sepsis, including the PROGRESS study. These studies all reported results consistent with other previously published observational studies of Xigris. In the 3 studies that compared Xigris treatment to a control group (unadjusted or adjusted), evaluated treatment using statistical methods (propensity scoring), or compared to a predicted mortality, Xigris treatment was associated with lower mortality. The main clinical results of Xigris published in 2009 were the Edusepsis Study and the PROGRESS registry. The results of other studies are described in the sponsor's documentation.

The Edusepsis Study Group published the results from a large prospective multicenter observational study in severe sepsis (Ferrer et al., Am J Respir Crit Care Med 2009). That study was conducted at 77 intensive care units and enrolled 2796 patients. It evaluated the impact of treatments for severe sepsis recommended in the sepsis guidelines on hospital mortality. The effectiveness of each treatment was estimated using propensity scores. Hospital mortality was 41.6% and the treatments associated with lower hospital mortality were early broad spectrum antibiotic treatment and Xigris (odds ratio, 0.59; 95% confidence interval, 0.41-0.84; P=0.004). Fluid challenge and low dose steroids showed no benefits.

The international PROGRESS registry of severe sepsis reported on Xigris use and patient outcomes (Martin et al., Crit Care 2009). Results from 12,492 patients with complete data showed that 882 (7%) patients overall received Xigris therapy. Although in-hospital mortality was similar for Xigris and non-Xigris patients (49.6% and 49.7%, respectively), after adjusting for imbalances, patients receiving Xigris had a 28% reduction in the odds of death and a relative risk reduction of 17%.

In publications relating to bleeding risks with Xigris, Taylor et al. (2009) reviewed 100 consecutive patients from one hospital who had received Xigris for the treatment of severe sepsis and compared the incidence of bleeding complications in surgical and nonsurgical cohorts. During Xigris administration,

transfusion of greater than 3 units of blood, an intracranial hemorrhage, or other bleeding serious adverse events were considered bleeding complications. They found no significant difference in the rate of bleeding complications between surgical and nonsurgical cohorts, with no mortalities ascribed to bleeding and no intracranial hemorrhage events.

The Gentry et al. (2009) study was discussed during the 6th ALR. It compared outcomes, by retrospective medical record review, of patients receiving Xigris with or without baseline bleeding precautions as defined by the PROWESS trial. Serious bleeding events occurred in 35% of patients with any baseline bleeding precaution versus 4% of patients without any bleeding precautions. Mortality in patients with a baseline bleeding precaution was 65% compared with 25% in patients without any bleeding precautions. Multivariate analysis demonstrated that the presence of a baseline bleeding precaution was the only independent variable associated with occurrence of serious bleeding events. The authors concluded that strict adherence to PROWESS trial exclusion criteria would further limit serious bleeding events associated withthe use of Xigris). The United States FDA (Lorenz et al., 2009) commented on Gentry et al. and provided an explanation of the content and purpose of the sections of the US label questioned by Gentry.

There was one randomized, placebo-controlled study published during this reporting period. Dhainaut et al. 2009 reported results from the EXTEND (Extended Xigris treatment in patients with prolonged septic shock) trial. In this study, extended treatment (an additional 72 hours) with Xigris did not reduce 28-day all cause mortality or in-hospital mortality or improve organ function compared with placebo.

The design, conduct, analysis and reporting of the PROWESS-SHOCK study was discussed by Finfer et al. (2008). It confirmed an academic steering committee will oversee the conduct of the study, write study manuscripts, and conduct the study with maximum possible transparency. The authors concluded that patients will only benefit if clinicians have confidence in the conduct, analysis and reporting of the trial.

There have been a number of results and further reviews of data from previously published randomized trials (Laterre et al., 2008, on ADDRESS and PROWESS; van Ruler et al., 2009, and Vail et al., 2009, on PROWESS; Hodder et al., 2009, on ENHANCE; Shorr & Williams, 2009, and Levy et al., 2009, on XPRESS). These conclusions reached by all these authors have been discussed and agreed upon in previous CHMP's ALR reports on Xigris.

In a retrospective study to assess the health and cost outcomes of Xigris therapy, Chan et al. (2009) found that pharmacist intervention in prescribing Xigris for patients with severe sepsis led to reduced 28-day in-hospital mortality and length of stay as well as earlier initiation of therapy. Durthaler et al. (2009) reported on a survey of critical care nurses regarding adherence to the 17 Surviving Sepsis Campaign (SSC) treatment guidelines. Hospitals most frequently reported adherence to those concerning prompt ordering of cultures, prompt administration of broad-spectrum antibiotics, and prompt initiation of DVT prophylaxis. Among all hospitals, the least followed guideline was prompt initiation of Xigris therapy.
There has also been a number of case reports published describing use of Xigris, the results of which can be found in the sponsor's references. Notably, all reports relate to successful treatment with Xigris and none describes serious bleeding events. For instance, one patient received an accidental overdose, but had no bleeding complications (Bland et al., 2008). Rinaldi et al. (2008) describe their experiences with 5 liver transplantation patients treated for septic shock with Xigris. All patients showed septic shock, with ≥3 organ dysfunctions and thrombocytopenia with impairment of coagulation. No major bleeding occurred; 1 patient experienced minor bleeding events; and all patients were subsequently discharged from ICU.

There were some publications to aid identification of patients who may benefit from Xigris. Schauer et al. (2008) created a patient-specific decision model to estimate the balance between treatment risk and benefit for individual patients to guide clinicians in the use of Xigris therapy. Ahishakiye et al. (2009) developed a model to identify patients in whom Xigris might be administered for periods shorter than the recommended 96 hours. This was done by retrospective chart review of 124 patients treated with a standard 96-hour infusion of Xigris in a 31-bed intensive care unit. The authors found that a simple model based on sequential organ failure assessment score and arterial pH that may help identify patients in whom a shorter duration of Xigris treatment may be justified.

Finally, a number of papers discussing the mechanism of action or physiological role of Xigris in humans were published. Many of them investigated the relationship between Xigris treatment and the evolution of specific inflammatory processes or fibrinolysis.

Reviews/ commentaries

A number of reviews and commentaries have been published that focus specifically on Xigris or on the treatment of sepsis in general. Many of the reviews are positive and focus on the proven benefits of Xigris, others are more cautious and urge careful consideration of patients for treatment, and others are negative, questioning the benefit/risk of Xigris. None of these points are new. A few comments worth mentioning are summarised below.

There were many commentaries on the design, analysis, or evaluation of Xigris use trials. For instance, the November 2008 issue of *Intensive Care Medicine* featured several editorials commenting on a special article in the same issue that described the design of the PROWESS-SHOCK trial (Finfer et al., 2008). Suter and Takala (2008) commented that although the PROWESS-SHOCK trial is a laudable effort to improve collaboration and transparency, the protocol should include unblinded safety monitoring, independent of the request of the data safety monitoring committee. Sweeny et al. (2008) claimed that the need for the PROWESS-SHOCK trial, years after regulatory approval of Xigris use, contains important lessons for health care providers, pharmaceutical industry, and regulatory agencies. The authors contend that 2 beneficial, randomized, controlled trials should be necessary for regulatory approval of any new sepsis therapy, with at least one being a confirmatory trial. In a letter published in the January 2009 issue of the same journal, Paramesh and Zwaal (2009) suggested that any future Xigris trials should be conducted independently, without involvement of the manufacturer or anyone associated with prior trials, in order to dispel any doubt concerning the results from PROWESS-SHOCK. Poole et al. (2009) discussed "errors" in the approval process and post-marketing evaluation of Xigris use during both the FDA and EMEA review processes. The authors noted that subgroup analyses are prone to over-interpretation and questioned their use for drug approval and labelling. They believed the choice of both agencies to license Xigris for use in patients with high risk of death only was in disagreement with their own guidelines and the CONSORT statement guidelines. Further, the authors claim that information gathered in the post-marketing phase was mostly interpreted in the interest of the vendor, which intensifies concerns about the methodologies used by the FDA and EMEA for the drug approval and postmarketing assessment.

Sweeney et al. (2009) commented on the use of Xigris in septic patients with baseline bleeding risks and the implications of a label warning instead of a contra-indication. The authors noted that in 6 of 7 studies of Xigris in patients who received treatment based on the US label, the incidence of serious bleeding was higher than in trials that excluded patients with bleeding risk. In light of these results, the authors concluded that one approach for increasing the safety of Xigris in the United States without compromising efficacy is not to administer it to patients with baseline bleeding risk, effectively changing the labelled warning to a contra-indication.

Other reviews considered the mode of action of APC and other anticoagulants in the treatment of sepsis and other conditions involving activation of the inflammatory or coagulation cascades. Gupta et al. (2009) summarized the emerging data suggesting the potential therapeutic effect of Xigris in the prevention and treatment of acute kidney injury. Levi et al. (2009) offered guidelines for the diagnosis and management of disseminated intravascular coagulation (DIC) and recommended treating patients with severe sepsis and DIC who are not at high risk of bleeding with Xigris at the standard dose of 24 µg/kg/h for 96 hours. In a review of literature published over the last 5 years regarding treatment of severe pancreatitis, Darvis et al. (2008) noted that some treatments aim at reducing systematic inflammatory response and multiorgan dysfunction, and suggested that affecting the coagulation cascade by Xigris can play a role in reducing the inflammatory response.

Finigan (2008) reviewed the major signaling pathways governing endothelial permeability in acute lung injury with a particular focus on the role of endothelial proteins, such as APC. The author described a complex system featuring receptor cross-talk and anti-coagulant/ procoagulant protein interactions. Although the author notes the inconclusive study of APC in patients with acute lung injury cited in last

year's report (Liu et al 2008), he suggests that the APC may provide a protective effect in lung injury. In a review of the potential use of rhAPC variants with altered bioactivity in sepsis therapy, Weiler and Ruf (2008) concluded that activated protein C variants with selectively diminished antithrombotic activity but normal cytoprotective potential may allow more efficient dosing without increasing adverse bleeding effects and therefore provide a safer and possibly more efficient alternative to normal activated protein C.

1.3.3 Update on spontaneous safety data from the market

The last PSUR, submitted in January 2009, covered the period 22 November 2007 to 21 November 2008. Thus a safety report has been included in this submission, which reviews the 9 months safety data from 22 November 2008 to 21 August 2009. As of 21 August 2009, it is estimated that 143,333 patients have been exposed to marketed Xigris worldwide (10,078 within this reporting period). The rate of exposure to Xigris during this period is slightly less than the last PSUR period taking into account the different lengths of the reporting periods. The higher reporting rate from India noted in this reporting period may have influenced some of the inter-regional comparisons with previous PSUR reporting periods.

a) Bleeding/CNS Bleeding Reactions

An increased risk of bleeding is the only adverse event known to be associated with treatment with Xigris. Although there have been some fluctuations in reporting rates between reporting periods, there appeared to have been a general downward trend in the reporting of bleeding events between PSURs, and these rates now appear to have stabilised in the last 3 PSURs and the current reporting period. Rates of non-CNS bleeds are similar between EU and North America (NA), but in this period are higher in the non-EU Non-NA region, which appears to be due to a higher reporting rate noted in India.. Although, as in previous reports, the rate of reporting CNS bleeds remains higher in EU compared to the other 2 regions, the EU reporting rate (17/100,000) is lower than that reported in EU in the last PSUR (44/100,000) but is similar to the preceding 2 PSURs. Although the reporting of bleeding events was higher in the Non-EU Non-NA region this did not translate into an increase in CNS bleeds.

b) Thrombocytopenia Reactions

There have been some fluctuations in reporting rates of thrombocytopenia between reporting periods, and these rates now appear to have remained relatively stable over the last 5 periods. Thrombocytopenia is a common finding in severe sepsis and there does not appear to be a causal association with treatment with Xigris.

c) Convulsions

In response to a CHMP request, a cumulative review of the Lilly safety database was included in PSUR #7 to assess the number of convulsions or seizures reported. The conclusion of that review was that a causal association of convulsion events with Xigris treatment could not be established. There were 4 spontaneous cases reported in this reporting period; two of the events were reported from India. In this patient population, the complexity of the disease processes and treatments confound the ability to ascribe causality of a seizure or convulsion to any one drug or condition.

d) Use of Xigris in Paediatric Patients

During the reporting period, there were 3 reports from paediatric patients, none of which were reported by an EU Member State. Two patients were adolescents, aged 14 and 16 years (originating from Canada, the latter of which was published in a literature article during the reporting period). The other patient was 8 years old and originated from India. None reported haemorrhages.

e) Maladministration

During the reporting period, 5 cases reported Xigris overdose. This rate is within the reporting fluctuations seen between previous PSURs. Two of these 5 cases contained reports of clinical adverse events attributed to the overdose. The overdoses ranged from 2 to 600 times the prescribed dose. The

patient who received a double dose died of an unknown cause, whereas the 600 times dose did not correlate to a reported adverse event.

f) CHMP Feedback on PSUR #9

PSUR #9, covering the period 22 November 2007 through 21 November 2008, was submitted 19 January 2009. On 25 June 2009, the CHMP adopted the request for follow up on 3 questions, the responses to which were submitted 1 September 2009. These responses included a cumulative review of all cases of allergic and anaphylactic reactions, a cumulative review of safety information pertaining to venous thromboembolism (VTE), and the submission of reports related to Study EVBQ and Study O014. These responses are currently under review.

Conclusion

On review of this spontaneously reported data, there does not appear to be any new clinically significant safety information that would warrant any alteration of the current labelling for Xigris.

II. DISCUSSION AND CONCLUSION ON CLINICAL SPECTS

2.1 Discussion on clinical aspects

There is a growing scientific interest in the mechanisms of action of Xigris, and the recent generation of activated protein C variants (single amino acid substitution) with anti-inflammatory effects that are devoid of anticoagulant properties is a useful addition in this regard. Xigris interacts with PAR-1, EPCR, and possibly the ApoE receptor.

A large number of recent publications describe clinical data, most of which comes from observational studies. These data are compatible with a beneficial effect of Xigris and none of them raises new concerns as compared with the assessments of all previous ALRs, especially with regard to the use of Xigris in Europe, which is more constrained than in the US due to additional warnings and contra-indications.

Overall, the worldwide scientific and clinical debate on the optimal use of Xigris continues and many stakeholders are eagerly awaiting the results of PROWESS-SHOCK. If the aggregate mortality rate is lower than 30% at the planned review at approximately 750 patients, the total sample size may have to be increased up to a total maximum sample size of 2000 patients. As agreed in the protocol, this decision will be taken by the Steering Committee when approximately 750 patient have completed day 28 follow up (Q2 2010). The MAH has provided comments on the overall mortality data. Mortality rates in the study may reflect recent changes in clinical practice as well as the particular inclusion and exclusion criteria in PROWESS-SHOCK. Based on their own responses ("*The MAH understands that demonstrating a statistically significant mortality difference in PROWESS-SHOCK is the expectation to assert the benefit/risk profile of Xigris*"), the MAH is well aware that the absence of a statistically significant effect of Xigris in a septic shock population, despite a low mortality rate, will have serious consequences regarding the marketing authorisation status of this medicinal product which remains under exceptional circumstances.

In summary, the decision of the PROWESS-SHOCK Steering Committee whether to increase the sample size is expected in Q2 2010. **The MAH has committed to provide the result of the Steering Committee decision to the CHMP as soon as it is available (new FUM 068).**

The CHMP has also requested additional analyses of pharmacogenomic data linked to the effects of Xigris. These data will be provided by the MAH and discussed by the CHMP in coming months.

2.2 Change of the Product Information

The CHMP agreed that no changes in the Summary of Product Characteristics, labelling and package leaflet are warranted as result of evaluation of the 7th ALR.

III. OBLIGATIONS PENDING TO BE FULFILLED OR ONGOING

3.1 Specific Obligations (SOs)

- **SPECIFIC OBLIGATION**

EMEA SOB 051: "Further to uncertain conclusions of the XPRESS study investigating the possible interaction between Xigris and heparin, additional clarifications on the benefit/risk balance of Xigris are required. Therefore the MAH has committed to performing a placebo-controlled study in patients (who were either on low-dose prophylactic heparin or not receiving any thrombosis prophylaxis) with severe sepsis and documented organ failure (e.g. MOD or vasopressor dependent septic shock) when treated within a strictly defined time window, to assert the benefit/risk profile of Xigris". See discussion in previous sections of this report. The commitment is not yet fulfilled.

3.2 Follow-up Measures (FUMs)

Assessment of FUM 063

The following FUM was agreed with the 6th Annual Licence Reassessment (S028):
"*MAH commits to update CHMP on the progress of recruitment in PROWESS-SHOCK every 6 months*".

The first planned interim analysis occurred on 8 February 2010. The Data Monitoring Committee reviewed data from approximately *500* patients with complete 28-d follow-up and *recommended that the study continue with no changes*. As of *28 February 2010, 735* patients have been randomised, which meets the recruitment plan communicated to the CHMP in September 2009. Recruitment remains on track for a planned completion of enrolment of 1500 patients in Q1 2011. Figure 1 shows the projected and actual enrolment in the study. When approximately 750 patients have been recruited, i.e. some time in Q2 2010, the Steering Committee will make a decision on increasing the sample size based on the aggregate mortality rate. **Thus, the first part of FUM 063 can be agreed.**

The second part of FUM 063 (an update of the recruitment rate) is expected in September 2010.

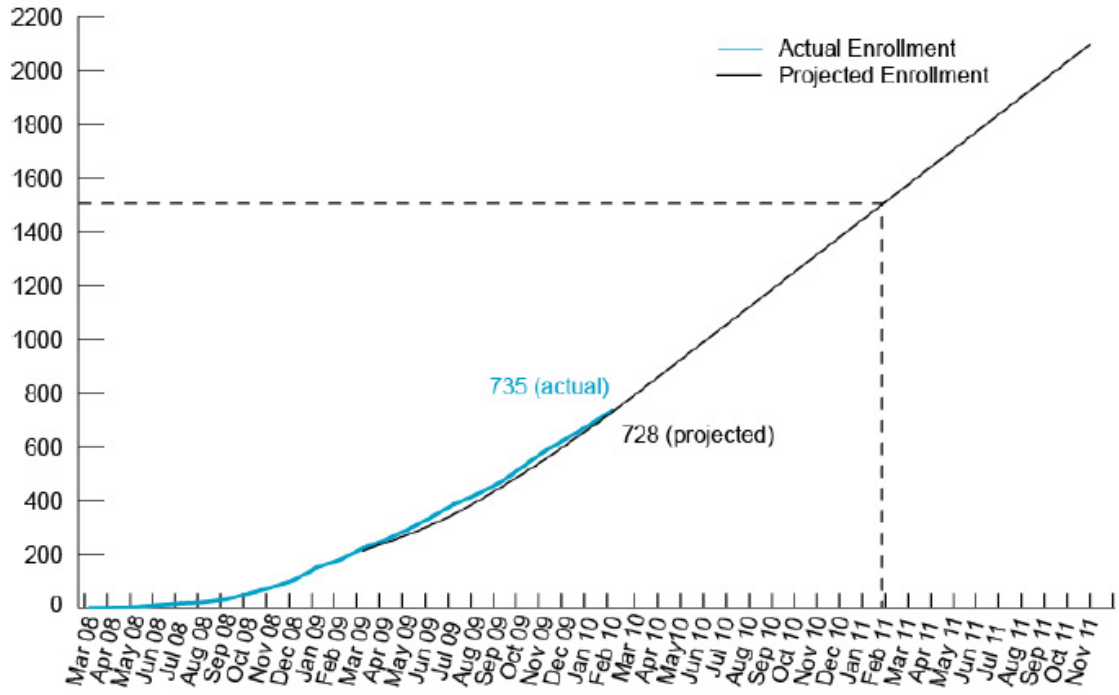

Figure 1. **Actual and projected enrolment in PROWESS-SHOCK.**

IV. BENEFIT/RISK ASSESSMENT

The CHMP concluded that since the 6th annual re-assessment, no further data has become available that would alter the B/R of Xigris. The CHMP has reiterated the importance of completing the PROWESS-SCHOCK study within the shortest possible timeframe as this study will assert the benefit/risk profile of Xigris. This study remains on track to complete recruitment in Q1 2011. However, following review of blinded 28-day mortality, the sample size may have to be increased to a total maximum sample size of 2000 patients. This would obviously have an impact on the reporting timelines. The decision of the study's Steering Committee whether to increase the sample size is expected in Q2 2010.

The product remains licensed under exceptional circumstances while waiting for the update on recruitment status in the ongoing PROWESS-SHOCK study as well as for the results of that study which are now planned for Q2 2011. There is a need for further information on the pharmacogenetic data that were not part of this submission but are considered important for the annual reassessment of the benefit/risk balance of Xigris.

V. OVERALL CONCLUSION AND RECOMMENDATION

The CHMP concluded by majority that, on the basis of the data submitted since the 6th annual re-assessment, the benefit/risk profile for Xigris in the "*treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. The use of Xigris should be considered mainly in situations when therapy can be started within 24 hours after the onset of organ failure"* remains positive.

However the CHMP concluded that there was still a Specific Obligation that remained to be fulfilled. The assessment of the pending commitments will form the basis of the next annual re-assessment. Therefore the Marketing Authorisation for Xigris will remain under exceptional circumstances.

On 22 April 2010, the CHMP adopted an Opinion by majority on the 7th annual re-assessment of the benefit/risk profile of Xigris, subject to the additional commitments undertaken. The Icelandic/Norwegian CHMP members agreed with the above mentioned recommendation of the CHMP.

A revised Letter of Undertaking dated 22 April 2010 including the amended list of Follow-up Measures has been adopted accordingly by the CHMP