Update on PROWESS-SHOCK

V. Marco Ranieri MD
B. Taylor Thompson MD

Co-PIs
PROWESS-SHOCK
Disclosures

Ranieri

Lilly
• Co-PI for PROWESS-SHOCK

Hemodec
• PI Enhance Lung Protection Trial

Faron Pharmaceuticals
• SC member of the FPCLI002 study (Recombinant Human Interferon Beta-1 in ARDS)

Thompson

Lilly
• Co-PI for PROWESS-SHOCK

Astra Zeneca
• DMC Cytofab for sepsis

Hemodec
• Co-I Enhanced Lung Protection

NHLBI ARDS Net
• Medical Director, CCC
PROWESS-SHOCK
Background
PROWESS: 4 Day Infusion of APC for Severe Sepsis

Survivors (%) vs Days from Start of Infusion to Death

- Drotrecogin alfa (activated) (N=850)
- Placebo (N=840)

P=0.006

PROWESS: Biomarkers

IL-6 Change from Baseline

D-Dimer Change from Baseline

Pre-infusion 1 2 3 4 5 6 7

IL-6 Change (pg/mL) (Median)

D-Dimer Change (µg/mL) (Median)

Placebo
Drotrecogin alfa (activated)

Subgroups – Disease Severity Measures

Primary
APACHE II
1st Quartile
2nd Quartile
3rd Quartile
4th Quartile
Cardiovascular Organ Failure
Yes
No
Cardiovascular SOFA
0 or 1
2 to 4
Shock Within 6 Hours
Yes
No
Any Shock
Yes
No
Respiratory Organ Failure
Yes
No
Respiratory SOFA
0 or 1
2 to 4
Mechanical Ventilation
Yes
No

Relative Risk of Death (Point Estimate and 95% CI)
Subgroups – Disease Severity Measures

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APACHE II
- 1st Quartile
- 2nd Quartile
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Relative Risk of Death (Point Estimate and 95% CI)
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  Yes
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  Yes
  No

Respiratory SOFA
  0 or 1
  2 to 4

Mechanical Ventilation
  Yes
  No

Relative Risk of Death (Point Estimate and 95% CI)

N       Trt     Plc
1690 24.7 30.8
433 15.1 12.1
440 22.5 25.7
366 23.5 35.8
451 38.1 49.0
1214 25.1 32.0
476 23.8 27.6
494 19.1 26.6
1196 27.3 32.4
1200 26.3 34.2
490 21.0 22.3
1362 26.0 32.5
328 19.7 23.3
1272 25.6 31.6
418 22.0 28.5
184 12.9 26.4
1479 26.4 31.7
1275 27.3 33.1
415 17.6 22.9

www.fda.gov, Ely CCM 2003
**ADDRESS: APC for low risk severe sepsis**

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28 d

Abraham NEJM 2005
ADDRESS: APC for low risk severe sepsis

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RR 1.94 (1.0-3.82) with 3 Organ Failures

Abraham NEJM 2005
The Regulatory Request

European Medicines Agency *Post-
Evaluation of* 
Medicines for Human Use

London, 22 February 2007

Product name: **XIGRIS**

Procedure No: **EMEA/H/C/000396/S/0021**

“Therefore a placebo-controlled study in patients ... with severe sepsis and documented organ failure (e.g. MOD or vasopressor dependent septic shock) when treated within a strictly defined time window, should be performed to assert the benefit/risk profile of Xigris.”
PROWESS-SHOCK
Design
Steering Committee

Co-Principal Investigators:

**Marco Ranieri M.D.**
Ospedale San Giovanni Battista, Turin, Italy

**B. Taylor Thompson, M.D.**
Mass General Hospital, Harvard Medical School, USA

**Philip Barie MD**
Cornell University, USA

**Ivor Douglas MD**
University of Colorado, USA

**Andrew Rhodes MD**
St George Hospital, London UK

**Simon Finfer MD**
University of Sydney, Australia

**John Marshall, MD**
University of Toronto

**Bengt Gardlund MD**
Karolinska University, Sweden

**Jean-Francois Dhainaut MD**
Cochin University, Paris, France
PROWESS-SHOCK

- Adults, 2/4 SIRS, *clear evidence of infection*, study drug initiated within Rx w/in 24 h of shock onset
- *Persistent septic shock after* 30 mL/kg IV fluids and requiring norepi $\geq 5$ mcg/min $\times$ 4h and evidence for hypoperfusion (renal, acidosis, hepatic)
- Conditionally powered for mortality reduction from 35 to 28% (1,500 – 2,000)
- Academic Statistical Center (Duke CRI) for primary and secondary analyses, publication of the results by the SC, public access to the database.
Why Septic Shock?

• Readily identifiable syndrome

• A subset with a strong efficacy signal in PROWESS

• Recent academic trials have focused on septic shock and report a high mortality (35-40%):
  VASST, CORTICUS, CATS
10% Mortality Reduction in the Shock Subset of PROWESS

<table>
<thead>
<tr>
<th>PROWESS (NEJM 2001)</th>
<th>Placebo</th>
<th>DAA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>31%</td>
<td>25%</td>
<td>0.005</td>
</tr>
<tr>
<td>High risk of Death- Multiple organ failure</td>
<td>34%</td>
<td>27%</td>
<td>0.006</td>
</tr>
<tr>
<td>High risk of death- APACHE II ≥ 25</td>
<td>44%</td>
<td>31%</td>
<td>0.002</td>
</tr>
<tr>
<td>Shock, vasopressors, hypoperfusion</td>
<td>39%</td>
<td>29%</td>
<td>0.0003</td>
</tr>
</tbody>
</table>
Efficacy Measures

Primary endpoint is 28-day all-cause mortality

Secondary endpoints include

- Mortality in the subset with low protein C
- Changes in organ function over time
- 90-day and 180-day mortality
- Quality of life as measure by Euro-QoL-5 and SF-12 scales after 6 months
- Safety
PROWESS-SHOCK
Preliminary Results
PROWESS-SHOCK Results

• Enrollment began in April of 2008 and was completed in August 2011

• International participation
  • Europe
  • North and South America
  • India
  • Australia and New Zealand

• Adaptive design: sample size increased from 1,500 to 1,696 (per protocol) when aggregate mortality after 750 patients was lower than expected (27% vs 32%)

Thompson et al ICM 2010
PROWESS-SHOCK
Baseline Characteristics

Age* 63 ± 16
Male 56.4%
Location Prior to Hosp.
  Home, no support 58%
  Other Acute Hosp 18%
  Home with support 16%
Recent Surgery 37%

* n=1696; Mean ± SD
### PROWESS-SHOCK
Baseline Characteristics

<table>
<thead>
<tr>
<th>Primary Site of Infection</th>
<th>%</th>
<th><em>(%)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>44%</td>
<td>(54%)*</td>
</tr>
<tr>
<td>Abdomen</td>
<td>30%</td>
<td>(20% )</td>
</tr>
<tr>
<td>Urinary</td>
<td>12%</td>
<td>(10% )</td>
</tr>
<tr>
<td>Skin</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

* PROWESS
<table>
<thead>
<tr>
<th># of Organ Failures</th>
<th>Percentage</th>
<th>(Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5%</td>
<td>(25%)*</td>
</tr>
<tr>
<td>2</td>
<td>13%</td>
<td>(32%)</td>
</tr>
<tr>
<td>3</td>
<td>34%</td>
<td>(26%)</td>
</tr>
<tr>
<td>4</td>
<td>38%</td>
<td>(14%)</td>
</tr>
<tr>
<td>5</td>
<td>13%</td>
<td>(4%)</td>
</tr>
</tbody>
</table>

* Mean ± SD

* PROWESS
### PROWESS-SHOCK
#### Baseline Characteristics

<table>
<thead>
<tr>
<th>APACHE II*</th>
<th>25.3 ± 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE ≥ 25</td>
<td>50%</td>
</tr>
<tr>
<td># of Organ Failures</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.5% (25%)*</td>
</tr>
<tr>
<td>2</td>
<td>13% (32%)</td>
</tr>
<tr>
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* Mean ± SD

* PROWESS
## PROWESS-SHOCK

### Baseline Characteristics

Mean SOFA

<table>
<thead>
<tr>
<th>Component</th>
<th>Mean SOFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV</td>
<td>3.9</td>
</tr>
<tr>
<td>Resp</td>
<td>2.8</td>
</tr>
<tr>
<td>Renal</td>
<td>1.6</td>
</tr>
<tr>
<td>Coagulation</td>
<td>0.7</td>
</tr>
<tr>
<td>Liver</td>
<td>0.5</td>
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* Mean ± SD
## PROWESS-SHOCK
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Fluids prior to pressors*</td>
<td>3,552 ± 2,372 ml</td>
</tr>
<tr>
<td>CVP</td>
<td>12 ± 5 mmHg</td>
</tr>
<tr>
<td>Norepinephrine dose**</td>
<td>22 ug/min</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>70%</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>82%</td>
</tr>
<tr>
<td>Corticosteroid use for shock</td>
<td>51%</td>
</tr>
<tr>
<td>Severe PC Deficient</td>
<td>40%</td>
</tr>
<tr>
<td>Vasopressor -&gt; Study Drug</td>
<td>17 hours (17.5)</td>
</tr>
</tbody>
</table>

* Mean ± SD  ** Median; used in 88% of subjects
PROWESS-SHOCK 28d Results

• 28-day mortality in Xigris-treated patients was **26.4%** (N=846) compared to **24.2%** in the placebo control group (N=834)
  • p=0.31
  • RR=1.09 (95% CI 0.92-1.28)

• No improvement in mortality in the subset with severe protein C deficiency
Serious Events Reported During Infusion

PROWESS

PROWESS-SHOCK

DAA

Placebo

(%)
Discussion
INDIANAPOLIS, October 25, 2011
PRNewswire

Eli Lilly and Company announces withdrawal of its Xigris(R) [drotrecogin alfa (activated)] product in all markets following results of the PROWESS-SHOCK study...
The Steering Committee’s View

• The Academic Steering Committee's review of the 28 day data reinforced its previously published plan to await the 90 day outcome data after which we will submit a primary manuscript for publication.

“Mortality at 28 days, the primary study endpoint, will be reported to regulatory agencies prior to submitting a manuscript for publication. The primary publication will be submitted following the 90-day data lock and will report both 28-day and 90-day mortality"

Ranieri et al ICM 2010
Preliminary Observations and Conclusions
Preliminary Observations and Conclusions

We enrolled the intended population (resuscitated persistent shock) but mortality was lower than we projected.
Preliminary Observations and Conclusions

We enrolled the intended population (resuscitated persistent shock) but mortality was lower than we projected.

No effect of DAA on 28 day outcomes.
Why the lack of effect of DAA on 28 day outcomes?
Why the lack of effect of DAA on 28 day outcomes?

- DAA was not adequately delivered or was inactive?
  - Administered IV within 24 hours of shock onset
  - Majority completed the 4 day infusion
  - Drug met all manufacturing standards

- Responsive subset not included or was under-represented in the PROWESS-SHOCK study?
  - Nearly all subset analyses negative without adjustment for multiple comparisons (eg. really negative)
  - Responsive subset, if present, may be relatively small (eg diffuse endothelial injury, microcirculatory failure, and DIC) or not recognized by current definitions/phenotypic classifications

- PROWESS was a false positive trial (1/200)?
Preliminary Observations and Conclusions
Preliminary Observations and Conclusions

• Mortality in the *placebo arm* was lower than expected (25% versus 35% expected) even though the enrolled patients had high disease severity with persistent septic shock and multisystem organ failure.
  - Did we exclude mortality patients?
  - Did secular trends in sepsis care improve outcomes?

• If the attributable mortality from sepsis *per se* has been reduced, then:
  - the potential benefit of novel anti-inflammatory/anti-coagulant therapies for sepsis will be relatively smaller, and
  - much larger sample sizes will be needed to detect these relatively smaller effects of new therapies for sepsis
Thank you
28 vs 90 Day Outcomes in ICU Trials of Glycemic Control

Van den Berghe NEJM 2001

Brunkhorst NEJM 2008

Finfer NEJM 2010
28 vs 90 Day Outcomes in ICU Trials of Vasopressin and Cisatricurium

Russell NEJM 2008

P = 0.27 at day 28

Vasopressin

Norepinephrine

Days since Initiation of the Study Drug

No. at Risk
Vasopressin 397 301 272 249 240 234 232 230 226 220
Norepinephrine 382 289 247 230 212 205 200 194 193 191

Papazian NEJM 2010

Probability of Survival

Cisatracurium

Placebo

Days after Enrollment
28-Day Mortality Rates for Septic Shock Patients in Five Trials with Corresponding 95% Confidence Intervals

VAST - Vasopressin
n = 396

VAST - Norepinephrine
n = 382

CORTICUS - Placebo
n = 248

CATS - Norepinephrine + Dobutamine Arm
n = 169

CATS - Epinephrine Arm
n = 161

PROWESS - Placebo
n = 364

ADDRESS - Placebo
n = 151
Inclusion Criteria – Evidence of Infection

- Lower respiratory tract and other infections of the thorax
- Abdominal infection
- Skin or soft tissue infection
- Purpura fulminans
- Bacterial meningitis
- Pyelonephritis
- Bloodstream infections

Finfer et al ICM 2008
Inclusion Criteria

The patient must have a continuous requirement for vasopressor support for at least 4 hours at a minimum dose of at least 1 of the vasopressors shown below:

- norepinephrine \( \geq 5 \text{ mcg/min} \)
- dopamine \( \geq 10 \text{ mcg/kg/min} \)
- phenylephrine \( \geq 25 \text{ mcg/min} \)
- epinephrine \( \geq 5 \text{ mcg/min} \)
- vasopressin \( \geq 0.03 \text{ units/min} \)

Finfer et al ICM 2008
Inclusion Criterion

Patients must remain *vasopressor dependent* throughout the pretreatment period and through the time of randomization at any vasopressor dose with the goal of maintaining a systolic blood pressure of approximately 90 mm Hg or higher or a mean arterial pressure of approximately 65 mm Hg or higher with reasonable attempts made to wean the patient from vasopressor support, if applicable.

Finfer *et al* ICM 2008