Clinical Trials of a Recombinant Hepatitis E Vaccine

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Topics:

- Development of the candidate recombinant hepatitis E vaccine (p239)
- Phase I/II clinical trial
- Phase III clinical trial
Recombinant HEV Structural Proteins

Xing et al Virol 1999
# Quality Control of p239

**Product:** HEVAC  
**Mfg. Date:** Apr 2003  
**Batch No:** 20030401  
**Pack size:** 0.5 ML

<table>
<thead>
<tr>
<th>S.No</th>
<th>Tests</th>
<th>Specifications</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fill volume</td>
<td>0.5 – 0.6 ml</td>
<td>Passes</td>
</tr>
<tr>
<td>2</td>
<td>Appearance</td>
<td>White turbid liquid</td>
<td>Whitish turbid liquid</td>
</tr>
<tr>
<td>3</td>
<td>Identity–ELISA</td>
<td>Should identify</td>
<td>Identifies</td>
</tr>
<tr>
<td>4</td>
<td>Al+++ content</td>
<td>Al(OH)₃ 1.4~1.8 mg / ml</td>
<td>0.56 mg / ml</td>
</tr>
<tr>
<td>5</td>
<td>Thiomersal content</td>
<td>39.0 – 67.0 μ g / ml</td>
<td>50 μ g / ml</td>
</tr>
<tr>
<td>6</td>
<td>pH</td>
<td>6.1-7.4</td>
<td>6.65</td>
</tr>
<tr>
<td>7</td>
<td>Sterility</td>
<td>Shall comply</td>
<td>Passes</td>
</tr>
<tr>
<td>8</td>
<td>Abnormal toxicity</td>
<td>Shall comply</td>
<td>Passes</td>
</tr>
<tr>
<td>9</td>
<td>Bacterial endotoxins</td>
<td>Less than 10 EU / 0.5ml</td>
<td>Passes</td>
</tr>
<tr>
<td>10</td>
<td>Relative potency (ED50)</td>
<td>Less than 1.5 μ g</td>
<td>0.113</td>
</tr>
</tbody>
</table>
Serology in General Population of the Field

<table>
<thead>
<tr>
<th>地区</th>
<th>n</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>crude</td>
</tr>
<tr>
<td>LY</td>
<td>1047</td>
<td>58.4</td>
</tr>
<tr>
<td>XA</td>
<td>1037</td>
<td>60.4</td>
</tr>
<tr>
<td>GL</td>
<td>542</td>
<td>57.8</td>
</tr>
<tr>
<td>LC</td>
<td>981</td>
<td>42.2</td>
</tr>
<tr>
<td>TD</td>
<td>377</td>
<td>45.6</td>
</tr>
<tr>
<td>BY</td>
<td>1106</td>
<td>31.1</td>
</tr>
<tr>
<td>LS</td>
<td>1230</td>
<td>21</td>
</tr>
<tr>
<td>LZ</td>
<td>964</td>
<td>43.1</td>
</tr>
<tr>
<td>Total</td>
<td>7284</td>
<td>43.3</td>
</tr>
<tr>
<td>M</td>
<td>3440</td>
<td>45.8</td>
</tr>
<tr>
<td>F</td>
<td>3844</td>
<td>41</td>
</tr>
</tbody>
</table>

## One-Year Follow-Up Serology

<table>
<thead>
<tr>
<th>Area</th>
<th>n</th>
<th>Anti-HEV%</th>
<th>Positive conversion % (n)</th>
<th>Negative conversion % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2003</td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>LY</td>
<td>738</td>
<td>62.2</td>
<td>78.2</td>
<td>17.9 (50)*</td>
</tr>
<tr>
<td>XA</td>
<td>533</td>
<td>63.6</td>
<td>65</td>
<td>3.1 (6)</td>
</tr>
<tr>
<td>GL</td>
<td>340</td>
<td>58.2</td>
<td>59.4</td>
<td>4.2 (6)</td>
</tr>
<tr>
<td>LC</td>
<td>455</td>
<td>44.4</td>
<td>44.9</td>
<td>2.0 (5)</td>
</tr>
<tr>
<td>TD</td>
<td>166</td>
<td>48.2</td>
<td>46.9</td>
<td>1.2 (1)</td>
</tr>
<tr>
<td>BY</td>
<td>657</td>
<td>30.6</td>
<td>31.8</td>
<td>1.8 (8)</td>
</tr>
<tr>
<td>LS</td>
<td>542</td>
<td>19.4</td>
<td>20.1</td>
<td>0.7 (3)</td>
</tr>
<tr>
<td>T</td>
<td>3431</td>
<td>46.2</td>
<td>49.1</td>
<td>4.3 (79)</td>
</tr>
<tr>
<td>M</td>
<td>1597</td>
<td>48.5</td>
<td>52.1</td>
<td>5.0 (41)</td>
</tr>
<tr>
<td>F</td>
<td>1834</td>
<td>44.1</td>
<td>46.5</td>
<td>3.7 (38)</td>
</tr>
</tbody>
</table>

![Positive seroconversion rate (%)](chart1.png)

![Negative seroconversion rate (%)](chart2.png)

Progression through the dose scheduling study of the HEV 239 vaccine

Group A assigned 20µg studied vaccine in 0/1/6 schedule

- 155 enrolled
  - 141 received 3 doses
  - 4 missed Dose 2
  - 14 missed Dose 3
- 0 lost to follow-up post vaccination
- 13 missed 2m serum
- 22 missed 6m serum
- 21 missed 7m serum
- 33 missed 13m serum
- 128 completed immunogenicity follow-up to 7m
- 102 completed 13m follow-up of anti-HEV

Group B assigned 20µg studied vaccine in 0/6 schedule

- 151 enrolled
  - 135 received 2 doses
  - 16 missed Dose 2
- 0 lost to follow-up post vaccination
- 17 missed 1m serum
- 29 missed 6m serum
- 25 missed 7m serum
- 109 completed immunogenicity follow-up to 7m

Group C assigned control vaccine in 0/1/6 schedule

- 151 enrolled
  - 145 received 3 doses
  - 1 missed Dose 2
  - 6 missed Dose 3
- 0 lost to follow-up post vaccination
- 20 missed 1m serum
- 14 missed 6m serum
- 6 missed 7m serum
- 20 missed 13m serum
- 131 completed 7m follow-up of anti-HEV
- 104 completed 13m follow-up of anti-HEV

457 subjects enrolled and randomized

Zhang et al. Vaccine 2009, 27:1869-74
Progression through the dosage escalation study of the HEV 239 vaccine

155 subjects enrolled and randomized

**Group E** assigned
10µg studied vaccine
in 0/1/6 schedule

- 45 enrolled
- 43 received 3 doses
- 2 missed Dose 2
- 1 missed Dose 3
- 0 lost to follow-up post vaccination
- 3 missed 1m serum
- 2 missed 6m serum
- 2 missed 7m serum
- 40 completed immunogenicity follow-up

**Group F** assigned
20µg studied vaccine
in 0/1/6 schedule

- 49 enrolled
- 49 received 3 doses
- 0 missed Dose 2
- 0 missed Dose 3
- 0 lost to follow-up post vaccination
- 1 missed 6m serum
- 1 missed 7m serum
- 48 completed immunogenicity follow-up

**Group G** assigned
30µg studied vaccine
in 0/1/6 schedule

- 41 enrolled
- 39 received 3 doses
- 0 missed Dose 2
- 2 missed Dose 3
- 0 lost to follow-up post vaccination
- 2 missed 6m serum
- 3 missed 1m serum
- 1 missed 7m serum
- 38 completed immunogenicity follow-up

**Group H** assigned
40µg studied vaccine
in 0/1/6 schedule

- 20 enrolled
- 20 received 3 doses
- 0 missed Dose 2
- 0 missed Dose 3
- 0 lost to follow-up post vaccination
- 1 missed 1m serum
- 0 missed 6m serum
- 0 missed 7m serum
- 19 completed immunogenicity follow-up

Zhang et al. *Vaccine* 2009, 27:1869-74
Reactogenicity of the p239 Hepatitis E Vaccine

<table>
<thead>
<tr>
<th>Vaccination group</th>
<th>Dose</th>
<th>No.</th>
<th>Age Mean ± SD(range)</th>
<th>M/F</th>
<th>% Total (grade 3) AE/Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Total (grade 3) AE/Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Local</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1. Dose schedule</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>3×20 µg</td>
<td>155</td>
<td>30.1±12.3(17~55)</td>
<td>0.67</td>
<td>447 8.5 (1.6) 7.6(0)</td>
</tr>
<tr>
<td>B</td>
<td>2×20 µg</td>
<td>151</td>
<td>32.8±12.5(17~55)</td>
<td>0.66</td>
<td>286 5.2(0) 4.9(0)</td>
</tr>
<tr>
<td>C</td>
<td>3×5 µg Ctrl</td>
<td>151</td>
<td>33.6±12.5(16~55)</td>
<td>0.74</td>
<td>446 2.0(0)* 5.6(0)</td>
</tr>
<tr>
<td><strong>2. Dosage escalation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>3×10 µg</td>
<td>45</td>
<td>18.0±0.62(17~19)</td>
<td>0.36</td>
<td>132 8.3(0) 15.2(0.8)</td>
</tr>
<tr>
<td>F</td>
<td>3×20 µg</td>
<td>49</td>
<td>18.0±0.56(17~19)</td>
<td>0.58</td>
<td>147 6.8(0) 12.9(0)</td>
</tr>
<tr>
<td>G</td>
<td>3×30 µg</td>
<td>41</td>
<td>17.9±0.66(17~19)</td>
<td>0.58</td>
<td>121 8.3(0) 9.9(0)</td>
</tr>
<tr>
<td>H</td>
<td>3×40 µg</td>
<td>20</td>
<td>17.9±0.45(16~19)</td>
<td>0.67</td>
<td>60 8.3(1.7) 11.7(1.7)</td>
</tr>
</tbody>
</table>

Zhang et al. *Vaccine* 2009, 27:1869-74
## Imunogenicity of the p239 Hepatitis E Vaccine

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Serum IgG anti-HEV level (U / ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>group</td>
</tr>
<tr>
<td>1. Dose schedule</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>128</td>
</tr>
<tr>
<td>B</td>
<td>109</td>
</tr>
<tr>
<td>C</td>
<td>131</td>
</tr>
<tr>
<td>2. Dosage escalation</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>40</td>
</tr>
<tr>
<td>F</td>
<td>44</td>
</tr>
<tr>
<td>G</td>
<td>38</td>
</tr>
<tr>
<td>H</td>
<td>19</td>
</tr>
</tbody>
</table>

Zhang et al. *Vaccine* 2009,27:1869-74
Anti-HEV IgG level

- General population (n=105)
- Asymptomatic infection (n=10)
- Acute HE (n=114)

- E. 3 × 10 μg (n=45)
- F. 3 × 20 μg (n=49)
- G. 3 × 30 μg (n=41)
- H. 3 × 40 μg (n=20)
- A. 3 × 20 μg, 0/1/6m (n=128)
- B. 2 × 20 μg, 0/6m (n=110)

Zhang et al. Vaccine 2009, 27:1869-74
## Occurrence of New Infection

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Infection Case Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>groups</td>
<td>No.</td>
</tr>
<tr>
<td>----------</td>
<td>-----</td>
</tr>
<tr>
<td><strong>During vaccination (0m-6m)</strong></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>131</td>
</tr>
<tr>
<td>B</td>
<td>109</td>
</tr>
<tr>
<td>A</td>
<td>128</td>
</tr>
<tr>
<td><strong>After vaccination (7m-13m)</strong></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>104</td>
</tr>
<tr>
<td>B</td>
<td>78</td>
</tr>
<tr>
<td>A</td>
<td>102</td>
</tr>
</tbody>
</table>

Zhang et al. *Vaccine* 2009, 27:1869-74
3. Phase III Clinical Trial

- Primary end-point
  - Efficacy against hepatitis E
  - Safety in large scale population

- Secondary end-point
  - Immunogenicity
  - Antibody persistence
Field for phase III——DT, Jiangsu province
Establishment of Survey System for Acute Hepatitis in DT

- **2006.10~; 8 townships: 310,000 residents**
- **2007.1~; 10 townships: 480,000 residents**

**Survey point:**
- Village clinical site
- Town hospital
- Country hospital

**Clinical inclusion standard:**
- Fatigue or lost appetite \( \geq 3d \)

**Laboratory diagnosis**
- ALT
- IgM anti-HEV
- Elevation of IgG anti-HEV
- Serum RT-PCR
Phase III Clinical Trial

- **Target subjects age**: 16-65
- **IIIa**: To confirm vaccine *immunogenicity & safety* for general population. (Volunteers in phase II clinical study were all HEV seronegative subjects.)
- **IIIb**: To determine *protection efficiency* against hepatitis E over 12 months after completing vaccination course;
  - To re-confirm vaccine safety
Sample Size Calculation

- **IIIa.** 2x ~1000 subjects per group.

- **IIIb.** 2x ~50,000 subjects per group

  - $\alpha = 0.05$; $\beta = 0.8$
  - Efficacy: > 80%
  - Incidence rate in control group: 3.5 / 10,000
  - Three doses (complete vaccination) rate: 80%
  - Cannot be followed up: < 15%
Study Design – Blinding & Randomization

- Placebo: commercial HB vaccine
- Blinding: vaccines were labeled with **A/D/K/Y** by manufactory, two for HE vaccine, two for HB vaccine
- Block randomization for vaccine

Label on the ampoule

Label on the external package
Publications: