Pfizer’s Investigational Vaccine, rLP2086, for Invasive Meningococcal Serogroup B Disease

Laura J York, PhD
Sr Director, International Scientific & Medical Affairs
Serogroup B is now the predominant remaining meningococcal serogroup in several parts of the world.

Note: *Number of cases is an average of 2002-2005. Isolates were collected from 19 countries and the Caribbean Epidemiological Center. Most isolates were from Brazil and Chile.

Age-specific Incidence of Serogroup B Meningococcal Disease in the EU

Data used from: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Slovenia, Switzerland, United Kingdom

EU-IBIS Invasive *N. Menigitidis* in Europe Reports; www.euibis.org
Significant MnB Disease Burden in Adolescents and Young Adults (EU, average number of cases 1999 – 2006)

EU-IBIS Invasive *N. Menigitidis* in Europe Reports; www.euibilis.org
Meningococcal Carriage Rates Are Highest in Adolescents

Vaccination of adolescents has the potential to provide direct and indirect (herd immunity) benefits.

Modified from Christensen et al. (2010). Lancet Infect. Dis. 10: 853-861
Serum Bactericidal Screen Was Used to Identify Pfizer’s MnB Vaccine Candidate

N. meningitidis Serogroup B

Extract and Fractionate

Immunize Mice

hSBA Screen Against Diverse MnB

Important Target Antigen Attributes

Surface exposed
Highly conserved
Expressed universally in diverse strains
Induces serum bactericidal activity

Fletcher et al. 2004; Bernfield et al 2002
LP2086 Is a Factor H Binding Protein and MnB Virulence Factor

- fHBP/LP2086 binds human factor H
- LP2086 expressed during infection
- Factor H binding to LP2086 protects MnB from complement attack
- Functional anti-LP2086 antibodies protect via two mechanisms
  - Inhibition of factor H binding to bacteria
  - Serum bactericidal killing

fHBP/LP2086 Protein Sequences (Variants) Segregate into Two Distinct Subfamilies

- LP2086 gene is present in > 2500 MnB invasive disease strains studied
  - > 200 variants identified
  - Two subfamilies, A & B
    - Sequence identity between subfamilies 60-75%
    - Sequence identity within subfamily >84%
  - Two lipidated LP2086 variants selected (one from each subfamily) to assure immunogenicity and broad strain coverage

Murphy et al. 2009; Jiang et al. 2010
Broad Protection Against Diverse, Invasive MnB Strains Requires an LP2086 Protein From Both Subfamilies

Vaccine: rLP2086A  rLP2086B  rLP2086A and rLP2086B

LP2086 Subfamily A Expressing SBA Strains

LP2086 Subfamily B Expressing SBA Strains

*Vaccine homologous LP2086 Variants

Jiang et al. 2010
Pfizer’s Bivalent rLP2086 Investigational Vaccine Elicits Broad hSBA Activity

Subfamily B
71%

- Strains killed expressing vaccine homologous LP2086 variants

- Strains killed expressing vaccine heterologous LP2086 variants

Subfamily A
29%

McNeil et al. 2009; Jiang et al. 2010
Pfizer’s Development Strategy

Focus on adolescent/young adult population

- Substantial disease burden
- High morbidity and mortality
- Highest meningococcal carriage rates
- Potential to affect disease burden in very young (<6 months of age), and throughout the community
Phase 2 MnB Vaccine Study in Adolescents (B1971005) Proof of Concept

- Randomized, single-blind, placebo-controlled trial conducted in Australia, Spain and Poland

- 535 Healthy Subjects, 11 to 18 Years of Age

- Safety, tolerability & immunogenicity of 3 doses
  - 0, 2, 6 month immunization schedule
  - 60, 120 or 200 µg dose in small sentinel cohorts; randomization 2:1
  - 120 or 200 µg dose in expanded cohort; randomization 2:2:1

- Study Objectives
  - **Primary Objective**
    - Assess immunogenicity of MnB vaccine by hSBA
  - **Secondary Objectives**
    - Assess immunogenicity of MnB vaccine by IgG
    - Assess safety and tolerability of MnB vaccine

Richmond et al 2011
Percentage of Adolescents Reporting Fever (B1971005)

Severities of Fever Within 1-7 days

<table>
<thead>
<tr>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>60 mcg</td>
<td>120 mcg</td>
</tr>
<tr>
<td>1/197*</td>
<td>2/192</td>
<td>1/118</td>
</tr>
</tbody>
</table>

*number of severe reactions/number of immunizations at dose level
No fever >40.0C

Richmond et al 2011
**rLP2086 Was Immunogenic in Adolescents**

* hSBA Responses to MnB Bearing Diverse fHBP Variants,
  Dose Selection for Completion of Clinical Program (B1971005)

<table>
<thead>
<tr>
<th>SBA Test Strain</th>
<th>Control</th>
<th>120 µg dose (0, 2 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% hSBA ≥ 1:4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PD3</td>
<td>PD2</td>
</tr>
<tr>
<td>A05</td>
<td>11.8</td>
<td>89.0</td>
</tr>
<tr>
<td></td>
<td>(6.3, 21.2)</td>
<td>(81.9, 93.5)</td>
</tr>
<tr>
<td>A04*</td>
<td>16.1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(8.6, 28.1)</td>
<td>(93.5, 100.0)</td>
</tr>
<tr>
<td>A56*</td>
<td>15.4</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td>(8.2, 25.3)</td>
<td>(89.2, 98.1)</td>
</tr>
<tr>
<td>B02*</td>
<td>6.3</td>
<td>79.5</td>
</tr>
<tr>
<td></td>
<td>(2.7, 14.3)</td>
<td>(71.4, 85.8)</td>
</tr>
<tr>
<td>B03*</td>
<td>8.8</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>(4.0, 18.3)</td>
<td>(24.9, 43.0)</td>
</tr>
<tr>
<td>B44*</td>
<td>6</td>
<td>70.4</td>
</tr>
<tr>
<td></td>
<td>(2.0, 13.5)</td>
<td>(61.2, 78.6)</td>
</tr>
</tbody>
</table>

* MnB strains expressing fHBP/LP2086 variant heterologous to vaccine antigen

Richmond et al 2011
rLP2086 Was immunogenic in Adolescents
hSBA Responses to MnB Bearing Diverse fHBP Variants
(US Study 2001, subjects 11 to 18 Years of Age)

% of subjects with hSBA titer ≥ 1:4

* MnB strains expressing fHBP/LP2086 variant heterologous to vaccine antigen

Jansen MRF Conference 2011
rLP2086 Was immunogenic in Young Adults
hSBA Responses to MnB Bearing Diverse fHBP Variants
(US Study 1004, subjects 18 to 25 Years of Age)

% of subjects with hSBA titer ≥ 1:4

Data generated using sera from a subset of subjects (n~ 20)
* MnB strains expressing fHBP/LP2086 variant heterologous to vaccine antigen
Bivalent rLP2086 Investigational Vaccine Induces hSBA Responses in Adolescents and Young Adults

Subfamily B

- Strains expressing vaccine homologous LP2086 variants
- Strains expressing vaccine heterologous LP2086 variants
- POC and exploratory strains

Subfamily A

Genetic Distance
### Bivalent rLP2086 Phase 2/3 Vaccine Clinical Development Plan (Ongoing and Planned Clinical Studies)

<table>
<thead>
<tr>
<th>STUDY DESCRIPTION</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent Safety &amp; Immunogenicity</td>
<td>Adolescents</td>
</tr>
<tr>
<td>Safety &amp; Immunogenicity 2-dose schedules</td>
<td>Adolescents</td>
</tr>
<tr>
<td>Safety &amp; Immunogenicity Concomitant Repevax</td>
<td>Adolescents</td>
</tr>
<tr>
<td>Safety &amp; Immunogenicity &amp; Concomitant Menactra/Adacel</td>
<td>Adolescents</td>
</tr>
<tr>
<td>Safety &amp; Immunogenicity &amp; Concomitant Gardasil</td>
<td>Adolescents</td>
</tr>
<tr>
<td>Large Scale Safety Study</td>
<td>Adolescents + Young adults</td>
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<tr>
<td>Young Adult Safety &amp; Immunogenicity</td>
<td>Young adults</td>
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<tr>
<td>Lot Consistency &amp; Pivotal Immunogenicity</td>
<td>Adolescents</td>
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Summary

- Pfizer’s investigational MnB vaccine is based on LP2086, a surface-exposed factor H binding protein (fHBP), important for survival of the organism \textit{in vivo}

- Demonstrated hSBA activity against >160 epidemiologically relevant invasive MnB strains provides evidence for killing across the diversity of variants within the two fHBP subfamilies

- Phase 1 and 2 clinical studies in adolescents and young adults have shown that the bivalent rLP2086 investigational vaccine
  - has an acceptable safety profile
  - elicits a response that is broadly active against diverse MnB strains

- A comprehensive clinical development program is ongoing to support licensure in adolescents and young adults to protect against invasive MnB disease
Acknowledgements

Clinical Investigators
- P. Richmond, University of Western Australia School of Paediatrics and Child Health, Australia
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Pfizer Colleagues
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- J. Eiden, J L. Perez, J. Beeslaar, Ann Wouters, D. Giorgio, W. Gruber, D. Morgenstern
- N. Tatsis, B. Abbott
rLP2086 Was Well Tolerated in Adolescents
Reported Injection Site Induration, B1971005

Severity of Induration Within 1-7 days

- **severe**
- **moderate**
- **mild**

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<td>1/193</td>
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<td>Dose 3</td>
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* number of severe reactions/number of immunizations at dose level

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www.euibis.org  data, 1999-2006