Clinical development of Synflorix™
(Pneumococcal non-typeable Haemophilus influenzae protein D-Conjugate Vaccine)

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Vice President & Head
Clinical R&D and Medical Affairs
Latin America and the Caribbean
**Synflorix™ innovative clinical development**

1997

4 valent-PD

6B, 14, 19F, 23F

1999

11 valent-PD

1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F

2006

10 valent-PD-Di-T

1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F

2008

1st license in Canada

**Pneumococcal Otitis Efficacy Trial**

*Prymula et al. The Lancet 2006*

Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study

Synflorix™ regulatory status 18 November 09

- Chosen for the UMV program of Brazil
  - 3.7 million Latin American children
- Used in the immunization programs of Canada (Ontario, Quebec, Prince Edwards, territories) and selected Australian and Sweden provinces.
- First PCV with WHO pre-qualification

*Approved for the prevention of NTHi AOM

47 APPROVALS

27 EU countries
Norway
Iceland

Canada

Serbia and Montenegro
Moldova
Bosnia-Herzegovina
Croatia

Russia
Ukraine
Kazakhstan

Taiwan
Indonesia
Malaysia
Thailand
Korea
Singapore

Hong Kong
Philippines
Malaysia

Australia
New Zealand

Uruguay
Panama
Peru
Honduras
Costa Rica
Dom Rep.
Guatemala

Ethiopia
Morocco
Ivory Coast
Gabon
Congo
South Africa
Tanzania

Kuwait
S. Arabia
Israël
Qatar
Pakistan
Lebanon

Turkey
UAE
Bahrain
Kenya

China
India

*Mexico
*Chile
Colombia
Brazila
*Argentina
Venezuela
*Ecuador

UAE
Bahrain
Kenya

3.7 million Latin American children

Used in the immunization programs of Canada (Ontario, Quebec, Prince Edwards, territories) and selected Australian and Sweden provinces.

First PCV with WHO pre-qualification
Synflorix™ clinical study sites distribution

- Czech Republic
- Denmark
- Finland
- France
- Germany
- Greece
- Netherlands
- Norway
- Poland
- Slovakia
- Spain
- Sweden
- Argentina
- Chile
- Colombia
- Mexico
- Panama
- Kenya
- Mali
- Nigeria
- South Africa
- India
- Korea
- Malaysia
- Philippines
- Singapore
- Taiwan

**4 continents, 27 countries**
Clinical Development Program in Latin America

About 25,000 subjects in clinical and epidemiological studies

AOM epidemiology studies

AOM Etiology
- Mexico - DONE
- Colombia - DONE
- Venezuela
- Costa Rica
- Chile

Incidence and Costs
- Mexico (Mar 2010)
- Brazil (Jan 2010)

IPD & CAP studies
- Chile - DONE
- Argentina - DONE
- Brazil - DONE
- Panama - DONE
- Colombia - DONE

Phase IIA clinical trials
- Chile (10-PN-PD-DIT005) - DONE
- Chile (10-PN-PD-DIT009-BST005) - DONE

Phase III clinical trials
- Mexico (10-PN-PD-DIT029) DONE
- Argentina (10-PN-PD-DIT028) COMPAS
- Colombia (10-PN-PD-DIT028) COMPAS
- Panama (10-PN-PD-DIT028) COMPAS

Phase IV clinical trial
- Brazil

Health economics studies
- Mexico - DONE
- Chile
- Brazil - DONE
- Colombia
- Peru
AOM etiology studies in Latin America

- **Mexico**
  - (Mar 2008 – Apr 2009)
  - 126 subjects
  - 74% samples (+)

- **Caracas** (Dec 2008 – ongoing)
  - 56 subjects
  - 75% samples (+)

- **Colombia**
  - (Feb 2008 – Jan 2009)
  - 102 subjects
  - 67% samples (+)

- **Panama** (Sept 2007)
  - 7000 subjects under surveillance

Data on GSK file – in preparation for publication
**H. influenzae** represents ~50% \((101/203)\) of bacterial strains isolated in AOM

Data on GSK file – in preparation for publication

* Enrollment is ongoing  
**DATA FROM POSITIVE TESTS*
Burden of pneumococcal disease in children ≤5 years

From global to regional: The importance of pneumococcal disease in Latin America

Ciro A. de Quadros*

Albert B. Sabin Vaccine Institute (SVI), 2600 Pennsylvania Ave., N.W., Suite 7100 Washington, DC 20006, United States

Comparative estimates of the global burden of pneumococcal disease.

<table>
<thead>
<tr>
<th>Region</th>
<th>Population (millions)</th>
<th>Annual number of cases</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Meningitis</td>
<td>Bacteremia</td>
<td>Pneumonia (hospitalised)</td>
</tr>
<tr>
<td>United States</td>
<td>231a</td>
<td>2,000</td>
<td>8,000</td>
<td>106,000–175,000</td>
<td>3,100,000</td>
</tr>
<tr>
<td>Asia</td>
<td>3634</td>
<td>25,865</td>
<td>103,459</td>
<td>1,517/283–4,263,186</td>
<td>40,090,391</td>
</tr>
<tr>
<td>Africa</td>
<td>757b</td>
<td>5,459</td>
<td>21,836</td>
<td>289,331–477,659</td>
<td>8,461,566</td>
</tr>
<tr>
<td>Europe</td>
<td>729b</td>
<td>5,189</td>
<td>20,754</td>
<td>2/4,996–454,004</td>
<td>8,042,3490</td>
</tr>
<tr>
<td>Latin America</td>
<td>511b</td>
<td>3,637</td>
<td>14,548</td>
<td>192,761–318,238</td>
<td>5,637,367</td>
</tr>
</tbody>
</table>

*These data were extrapolated from the number of cases of invasive pneumococcal disease reported for the United States (Centers for Disease Control and Prevention, Manual for the surveillance of vaccine-preventable diseases, 4th ed. 2008 [4]) and extrapolated against populations for other geographic regions (United Nations. The world at six billion. Available at: http://www.un.org/esa/population/publications/sixbillion/sixbilpart1.pdf [6]).


The value of immunization for \textit{S. pneumoniae} includes invasive and non-invasive disease

Estimates for Latin America

<table>
<thead>
<tr>
<th>Disease</th>
<th>Volume of cases</th>
<th>Deaths</th>
<th>Sequels</th>
<th>Hospitalization Costs</th>
<th>Antibiotics &amp; resist.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>3,637 (1x)</td>
<td>192,761-318,238 (53-87.5x)</td>
<td>20,200 deaths/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteriemia</td>
<td>14,548 (4x)</td>
<td>5,637,367 (1550x) (94%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>192,761-318,238</td>
<td>5,637,367 (1550x) (94%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>5,637,367 (1550x)</td>
<td>5,637,367 (1550x) (94%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Synflorix™ contains 9 of 11 most frequent serotypes in Latin America and Caribbean, and is expected to confer cross-protection against ST 6A.

Percentage of pneumococcal serotypes related to IPD in children less than 6 years old

### Years 2000-2005
- 03: 29.9%
- 04: 9.3%
- 19F: 7.2%
- 18C: 6.3%
- 23F: 5.9%
- 6A/6C: 5.1%
- 19A: 4.7%
- 7F: 4.2%
- 9V: 3.7%
- 3: 3.1%
- 4: 2.6%
- Other: 1.6%

### Years 2006, 2007 and 2008
- 03: 14%
- 04: 6B: 5%
- 1: 19F: 1%
- 18C: 1%
- 19F: 18C: 1%
- 23F: 7F: 1%
- 6A/6C: 9V: 1%
- Other: 14.3%

Additional coverage of Synflorix™: 17%

(*) ST6A included in coverage

Years 2000-2005 IPD in children less than 6 y.o.
Years 2006, 2007 and 2008 IPD in children less than 5 y.o.

The value of immunization for *NTHi* includes invasive and non-invasive disease

<table>
<thead>
<tr>
<th>NTHi status</th>
<th>Estimates for Latin America</th>
<th>Immunization basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive and non-invasive disease</td>
<td><strong>3,637</strong> (1x)</td>
<td>Severity Deaths Sequels</td>
</tr>
<tr>
<td></td>
<td><strong>14,548</strong> (4x)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>192,761-318,238</strong> (53-87.5x)</td>
<td>Hospitalization Costs Deaths</td>
</tr>
<tr>
<td></td>
<td><strong>5,637,367</strong> (1550x) (94%)</td>
<td>Volume of cases Costs Antibiotics &amp; resist</td>
</tr>
</tbody>
</table>


Invasive disease due to NTHi = 532

Diseases: meningitis, bacteriemia/sepsis, pneumonia

Isolation site: CSF, hemoculture

A next generation PCV: *PHiD-CV*

**S. pneumoniae**

**Non-typeable H. influenzae (NTHi)**

**Protein D**

carrier protein

**Polysaccharides**

8 serotypes conjugated to protein D;
18C to tetanus toxoid, 19F to diphtheria toxoid

Includes 10 pneumococcal serotypes (1, 5 and 7F + PCV7 serotypes)

Inclusion of the carrier protein NTHi-Protein D:
- to help minimize risk of interference with co-administered vaccines
- expected to offer protection against NTHi by virtue of Protein D carrier protein, based on clinical experience (POET)

ImmunoLogic licensure criteria proposed by WHO and endorsed by European CHMP:

1. Non-inferiority of post-primary ELISA antibody responses compared to PCV7 (based on % of subjects reaching pre-set thresholds)

2. Demonstration of functional capacity of antibodies (OpsonoPhagocytic Activity - OPA)

3. Induction of immunological memory

Clinical development of Synflorix™

- Immunogenicity compared with PCV7 1–3,6–9
- Functional responses (OPA) 1–3,6,8,9
- Boostability of primary responses 1,2,8,9
- Co-administration with routine vaccines 4
  - DTPa-HBV-IPV/Hib, DTPa-HBV-IPV and DTPa-IPV/Hib 1–3,6,8,9
  - MenC-CRM, MenC-TT and Hib-MenC
  - DTPw-HepB/Hib and OPV 3
  - MMRV (with booster dose) 7
  - Rotavirus vaccine 8
- Safety & tolerability profile similar to PCV7 5
- Interchangeability (Synflorix™ booster after PCV7 priming) 1
- Immunisation schedules
  - 2-3-4 mo1; 3-4-5 mo8; 2-4-6 mo2,3,6; 3-5-11 mo9; 6-10-14 weeks3

Primary immunogenicity study

Randomization 3:1

**Synflorix™ + DTPa-HBV-IPV/Hib (N=1200)**

**PCV7 + DTPa-HBV-IPV/Hib (N=400)**

Dose 1
2 months of age

Dose 2
3 months of age

Dose 3
4 months of age

ELISA all subjects
OPA subset of 25%

1 month post dose 3
blood sample

Single blind, controlled trial in Finland, France and Poland

Study 10PN-PD-DIT-001 (NCT00307554)
Antibody & OPA responses of Synflorix™ vs PCV7


Percent 22F-ELISA antibody ≥0.2 µg/mL one month post-dose 3

Percent OPA titre ≥8 one month post-dose 3
Cross-reactive Serotypes (6A & 19A) (Primary Immunisation)

Subjects (%) with OPA ≥ 1:8

- **Synflorix™ + DTPa-HBV-IPV/Hib**
- **7vCRM + DTPa-HBV-IPV/Hib**
- **Synflorix™ + MenC-CRM + DTPa-HBV-IPV/Hib**
- **Synflorix™ + MenC-TT + DTPa-HBV-IPV/Hib**
- **Synflorix™ + Hib-MenC-TT + DTPa-HBV-IPV**
- **7vCRM + Hib-MenC-TT + DTPa-HBV-IPV**

Synflorix™ is a trademark of the GlaxoSmithKline group of companies.


Antibody GMCs one month post-dose 3, pre- and post-booster

OPA GMTs one month post-dose 3, pre- and post-booster
Synflorix™ co-administration with DTPw-HBV/Hib + OPV

Randomization 3:1

Synflorix™ + DTPw-HBV/Hib + OPV (N=300)

PCV7 + DTPw-HBV/Hib + OPV (N=100)

Dose 1
6 weeks of age

Dose 2
±10 weeks of age

Dose 3
±14 weeks of age

1 month post dose 3 blood sample

ELISA all subjects OPA subset of 25%

Double blind, controlled trial in Philippines

Study 10PN-PD-DIT-012 (NCT00344318)

DTPw-HBV/Hib = Tritanrix™ is a trademark of the GlaxoSmithKline group of companies
Immunogenicity of PHiD-CV when co-administered with DTPw

Percentage of subjects with anti-pneumococcal antibody concentration ≥ 0.2 µg/ml one month post-dose 3 (22F-ELISA)

Bernal N et al. PIDJ 2009;28:89-96
PHiD-CV - Pneumococcal non-typeable *haemophilus influenzae* protein D conjugate vaccine; Synflorix™; DTPw-HBV/Hib: Tritanrix™-HepB/Hiberix™; IPV: Poliorix™ and OPV: Polio Sabin™ are trademarks of the GlaxoSmithKline group of companies; PCV7-CRM: Prevenar™/Prevnar™, Wyeth
Immunogenicity of PHiD-CV when co-administered with DTPw

Anti-pneumococcal antibody concentration one month post-dose 3 (22F-ELISA µg/mL)

PHiD-CV - Pneumococcal non-typeable haemophilus influenzae protein D conjugate vaccine; Synflorix™; DTPw-HBV/Hib: Tritanrix™-HepB/Hiberix™; IPV: Poliorix™ and OPV: Polio Sabin™ are trademarks of the GlaxoSmithKline group of companies; PCV7-CRM: Prevenar™/Prevnar™, Wyeth

Bermal N et al. PIDJ 2009;28:89-96
Immunogenicity of PHiD-CV when co-administered with DTPw

Percentage of subjects with anti-pneumococcal OPA titres ≥8 one month post-dose 3

Anti-pneumococcal opsonophagocytic activity (OPA) titres one month post-dose 3

Bermal N et al. PIDJ 2009;28:89-96
Overall post-primary seroprotection rates for D,T, Hep B and Hib antigens

**Co-administration**

- High levels of seroprotection/seropositivity induced against all targeted diseases
- No evidence of negative interference on the immune response to any of the co-administered vaccine antigens was observed when compared with PCV7

Diphtheria: ELISA cut-off ≥0.1 IU/mL; Tetanus: ELISA cut-off ≥0.1 IU/mL; Hepatitis B (Hep B): AUSAB cut-off ≥10 mIU/mL; Anti-PRP (Hib): ELISA cut-off ≥0.15 mg/mL


NCT00307554/NCT00334334/NCT00344318

*Synflorix™* is a trademark of the GlaxoSmithKline group of companies
Overall per dose incidence (%) of general symptoms after primary dose

<table>
<thead>
<tr>
<th>Doses (%)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C1</td>
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<tr>
<td>C2</td>
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<td>A</td>
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<td>C1</td>
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<tr>
<td>C2</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Synflorix™</td>
<td>7vCRM</td>
<td>Grade 3 intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Safety and reactogenicity profiles of Synflorix™ and PCV7 were within the same range, when administered for primary and booster vaccination in co-administration with other routinely used pediatric vaccines.

Synflorix™ is not licensed in China.
Synflorix™ is a trademark of the GlaxoSmithKline group of companies.


NCT00307554/NCT00344318
Immunogenicity of Synflorix™ in Mexico and Chile

Synflorix™ reactogenicity and immunogenicity

Chile:

- **HAV + DTPa-HBV-IPV/Hib (N = 121)**
- **Synflorix™ + DTPa-HBV-IPV/Hib (N = 119)**

Double blind, controlled, 1:1 randomized trial ¹

Mexico:

- **Synflorix™ + DTPa-HBV-IPV/Hib (N = 230)**

Open, single arm trial ²

- **Dose 1**
  - 2 months of age

- **Dose 2**
  - 4 months of age

- **Dose 3**
  - 6 months of age

ELISA all subjects

OPA subset of 50%

1 month post dose 3

¹ Lagos R. et al. ISPPD6, Reykjavik 2008
² Ruiz-Palacios G. et al. SLIPE, Guayaquil 2009

DTPa-HBV-IPV/Hib = *Infanrix™* hexa, HAV = *Havrix™*

are trademarks of the GlaxoSmithKline group of companies
Post-primary immunogenicity of Synflorix™ in Mexico and Chile

Antibody GMCs one month post-dose 3 (22F-ELISA µg/mL)

Percent 22F-ELISA antibody ≥0.2 µg/mL one month post-dose 3

HAV Chile (N=111)  Synflorix™ Chile (N=117)  Synflorix™ Mexico (N=219)

Lagos et al., ISPPD6, Reykjavik, Iceland 2008; Ruiz-Palacios G. et al. SLIPE, Guayaquil 2009
GSK Clinical Data [Phase II Clinical Study 10PN-PD-DIT-005 (Chile) & 10PN-PD-DIT-029 (Mexico)] Data on file
Post-primary immunogenicity of Synflorix™ in Mexico and Chile

OPA GMTs one month post-dose 3

Percent OPA titre ≥8 one month post-dose 3

HAV Chile (N=111) Synflorix™ Chile (N=117) Synflorix™ Mexico (N=219)

Lagos et al., ISPPD6, Reykjavik, Iceland 2008; Ruiz-Palacios G. et al. SLIPE, Guayaquil 2009
GSK Clinical Data [Phase II Clinical Study 10PN-PD-DIT-005 (Chile) & 10PN-PD-DIT-029 (Mexico) ] Data on file
Immunogenicity of Synflorix™ in Chile and Mexico vs Europe

Anti-pneumococcal antibody concentration one month post-dose 3 (22F-ELISA µg/mL)

*statistical significant difference based on non-overlapping 95%CI

Lagos et al., ISPPD6, Reykjavik, Iceland 2008; Ruiz-Palacios G. et al. SLIPE, Guayaquil 2009; Vesikari et al. PIDJ 2009;28:S66–S76; GSK Clinical Data [Phase II Clinical Study (Chile) 10PN-PD-DIT-005] Data on file; GSK Clinical Data [Phase II Clinical Study (Mexico) 10PN-PD-DIT-029] Data on file
**Synflorix™** anti-Protein D responses compared with POET


*Synflorix* is a trademark of the GlaxoSmithKline group of companies
Synflorix™ immunogenicity following 2-dose priming

Sweden, Denmark, Norway and Slovakia

1 month post-primary

1 month post-booster

ELISA and OPA
In all subjects

Randomization

Synflorix™ + DTPa-HBV-IPV/Hib or DTPa-IPV/Hib (n=175)

Synflorix™ + DTPa-HBV-IPV/Hib or DTPa-IPV/Hib (n=176)

Dose 1

Dose 2

Booster

Dose 1

Dose 2

Dose 3

Booster

Age: 3 mo 4 mo 5 mo 11-12 mo

Study 10PN-PD-DIT-002 (NCT00307034)

DTPa-HBV-IPV/Hib = Infanrix™ hexa (Sweden and Slovakia);
DTPa-IPV/Hib = Infanrix™ IPV-Hib (Denmark and Norway)
are trademarks of the GlaxoSmithKline group of companies
**Synflorix™ 2+1 immunogenicity**
(Antibodies post dose 2 vs post dose 3)

**Antibody GMCs one month post-primary (22F-ELISA µg/mL)**

- **Ab GMC (µg/mL) (Log)**
  - 10
  - 1
  - 0.1
  - 0.01

- **Synflorix™ 2+1 Immunogenicity**
  - 4 6B 9V 14 18C 19F 23F
  - 5 7F

- **Cross-reactive**

**Percent 22F-ELISA antibody ≥0.2 µg/mL one month post-primary**

- **% ELISA Ab ≥0.2 µg/mL**
  - 100
  - 80
  - 60
  - 40
  - 20
  - 0

- **Synflorix™ post dose 2 (N=153)**
- **Synflorix™ post dose 3 (N=153)**

*Statistical significant difference based on non-overlapping 95% CI*

**Synflorix™ 2+1 immunogenicity**
(Antibodies post-booster 2+1 vs 3+1)

**Antibody GMCs one month post-booster (22F-ELISA µg/mL)**

<table>
<thead>
<tr>
<th>株</th>
<th>GMC (µg/mL) (Log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4  6B  9V  14  18C  19F  23F  1  5  7F</td>
<td></td>
</tr>
</tbody>
</table>
|10
d|1
d|0.1
d|0.01
d|0.01
d|0.1
d|1
d|10
d|100
d

**Percent 22F-ELISA antibody ≥0.2 µg/mL one month post-booster**

- **Silfverdal S. et al., Pediatr Infect Dis J, 2009; 28: e276-82**

*statistical significant difference based on non-overlapping 95%CI*
**Synflorix™** immunogenicity following 2-dose priming

- **Synflorix™** + DTPa-HBV-IPV/Hib + MenC-CRM (385)
- **Synflorix™** + DTPa-HBV-IPV/Hib + MenC-TT (387)
- **Synflorix™** + DTPa-HBV-IPV + Hib-MenC-TT (386)

**PCV7 + DTPa-HBV-IPV + Hib-MenC-TT (390)**

- **Dose 1**
  - 2 months of age
- **Dose 2**
  - 4 months of age
- **Dose 3**
  - 6 months of age
- 2 month post dose 2 blood sample
- 1 month post dose 3 blood sample

Open, controlled trial in Germany, Poland, and Spain

Study 10PN-PD-DIT-011 (NCT00334334)
Antibody cumulative reverse curves post 2-dose

Aggregated response post 2-dose for the 7 common serotypes

Study 10PN-PD-DIT-011 (NCT00334334)
Conclusions

- **Synflorix™** meets WHO immunological licensure criteria: ELISA - OPA - Immunological memory and has been licensed based on comparative immunogenicity data versus 7vCRM.

- Across the clinical development program, **Synflorix™** was shown to be highly immunogenic, especially in Latin American children:
  - High antibody concentrations and functional OPA titers are induced against pneumococcal serotypes contained in the vaccine
  - Antibodies and OPA activity against **cross-reactive 6A and 19A serotypes** could also be measured
  - **Synflorix™** can be co-administered with other routinely used pediatric vaccines according to a wide range of immunization schedules
  - High antibody concentrations are induced against the carrier protein D

- Clinical trial data from 11-valent prototype demonstrates **efficacy against NTHi** (35% reduction)\(^1\)

- **Synflorix™** has been selected for the UMV program of Brazil and selected regions of Canada, Australia, and Sweden.

- **Synflorix™** is the first pneumococcal conjugated-vaccine **pre qualified by WHO.**