Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

Study vaccine number	GSK1024850A
Study vaccines	GlaxoSmithKline (GSK) Biologicals' • 10-valent pneumococcal polysaccharide and non-typeable *Haemophilus influenzae* protein D conjugate (10Pn-PD-DiT) vaccine. • Hepatitis A vaccine (Havrix 720 Junior™). • Hepatitis B vaccine (Engerix B™).
eTrack study number and abbreviated title	111442 (10PN-PD-DIT-043)
EudraCT number	2008-005149-48
Date of protocol	Final 14 October 2008
Date of protocol amendment 1	Amendment 1, 04 February 2009
Date of protocol administrative change	Administrative change 1, 06 July 2010
Date of protocol amendment 2	Amendment 2, 22 August 2011
Title	Evaluation of effectiveness of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A against invasive disease.
Detailed Title	A phase III/IV, cluster-randomized, controlled study to evaluate the effectiveness of GlaxoSmithKline Biologicals' 10-valent pneumococcal and non-typeable *Haemophilus influenzae* protein D conjugate vaccine in reducing the incidence of invasive diseases.
Co-ordinating authors	Co-ordinating authors' names blinded.
Contributing authors	Contributing authors' names blinded.

eTrack study number and abbreviated title	111442 (10PN-PD-DIT-043)
EudraCT number	2008-005149-48
Detailed Title	A phase III/IV, cluster-randomized, controlled study to evaluate the effectiveness of GlaxoSmithKline Biologicals' 10-valent pneumococcal and non-typeable *Haemophilus influenzae* protein D conjugate vaccine in reducing the incidence of invasive diseases.

GSK Biologicals' Protocol DS V 12.5

Note the following minor correction (highlighted in the text) was made to the last amended version (August 22, 2010) of this protocol:
Co-ordinating and contributing authors' names blinded on pages: 1, 105 and 114-116.

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and abbreviated title	111442 (10PN-PD-DIT-043)
EudraCT number	2008-005149-48
Date of protocol amendment 2	Amendment 2, 22 August 2011
Detailed Title	A phase III/IV, cluster-randomized, controlled study to evaluate the effectiveness of GlaxoSmithKline Biologicals' 10-valent pneumococcal and non-typeable *Haemophilus influenzae* protein D conjugate vaccine in reducing the incidence of invasive diseases.
Sponsor signatory:	Dorota Borys, MD, Director, Clinical Development (Pneumococcal Vaccines)
Signature:	_____
Date:	_____

Protocol Amendment 2 Rationale

Amendment number: Amendment 2

Rationale/background for changes:

Amendment 2 was developed for the following reasons:

(1) The study enrolment reached only 50% of the initial recruitment plan; therefore, there has been a need to redefine the conditions for triggering IPD effectiveness analysis:

- The study follow-up period for primary analysis on invasive disease (ID) cases will end on 31 January 2012 (data lock point for ID cases), i.e. at least 30 months after study start. This allows inclusion of an age-related IPD peak at 11-19 months of age in the youngest enrolled subjects and an expected seasonal IPD peak in the fall of 2011 (J. Jokinen, oral communication), thereby increasing the potential to accrue additional IPD cases.
- Reaching a minimum number of 21 culture-confirmed vaccine-type IPD cases in the infant group will no longer be a condition for triggering IPD effectiveness analysis because that minimum number will most probably not be met due to the lower enrolment numbers.

The estimated target number of vaccine-type IPD cases was adjusted accordingly, based on an assumed vaccine efficacy estimate and the currently available information on the total number of IPD cases by age cohort.

Taking into account the lower than expected number of enrolled subjects, associated number of overall IPD cases reported so far and impact on power when considering 80% vaccine efficacy for the 2+1 vaccination schedule, it was decided to evaluate the effectiveness of the 10Pn-PD-DiT vaccine to prevent vaccine-type IPD in the infants assigned to a 2+1 vaccination course as a first secondary objective instead of the second primary objective (sequential) but to keep the pre-defined statistical criteria for success.

(2) Following IDMC recommendation, it was decided to have the chest X-rays from the hospital-diagnosed pneumonia cases in the vaccinated population evaluated by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005] for study purposes. The appropriate sections of the protocol were adjusted to reflect this.

(3) Minor corrections were done.

Protocol Amendment 2 Investigator Agreement

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

eTrack study number and abbreviated title	111442 (10PN-PD-DIT-043)
EudraCT number	2008-005149-48
Date of protocol amendment 2	Amendment 2, 22 August 2011
Detailed Title	A phase III/IV, cluster-randomized, controlled study to evaluate the effectiveness of GlaxoSmithKline Biologicals' 10-valent pneumococcal and non-typeable *Haemophilus influenzae* protein D conjugate vaccine in reducing the incidence of invasive diseases.

Investigator name: _____

_____ _____

Investigator signature **Date**

Synopsis

Detailed Title

A phase III/IV, cluster-randomized, controlled study to evaluate the effectiveness of GlaxoSmithKline Biologicals' 10-valent pneumococcal and non-typeable *Haemophilus influenzae* protein D conjugate vaccine in reducing the incidence of invasive diseases.

Indication/Study population

Active immunization of children from the age of 6 weeks up to 18 months of age at the time of first vaccination, against *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F and *Haemophilus influenzae*.

The immunization schedule will depend on the age at the time of the first vaccination:

- **Between 6 weeks and 6 months of age**: 3-dose primary vaccination with 10Pn-PD-DiT or HBV vaccine with at least 4 weeks interval, or 2-dose primary vaccination with 10Pn-PD-DiT or HBV vaccine with at least 8 weeks interval, followed by a booster dose of the same vaccine with an interval of preferably 6 months since the previous vaccine dose (minimum 4 months).
- **Between 7 and 11 months of age**: 2-dose primary vaccination with 10Pn-PD-DiT or HBV vaccine with an interval of at least 4 weeks, followed by a booster dose of the same vaccine with an interval of preferably 6 months since the previous vaccine dose (minimum 4 months).
- **Between 12 and 18 months of age**: 2-dose vaccination with 10Pn-PD-DiT or HAV vaccine with an interval of at least and preferably 6 months between doses.

Rationale

Pneumococcal conjugate vaccines (PCVs) have enormous potential to reduce burden of *S. pneumoniae* diseases, not only through direct protection provided to the vaccinees but also through indirect protection of the unvaccinated population. In the US, where infants have been vaccinated with the licensed 7-valent CRM197-conjugate vaccine *Prevenar™*(7v-CRM) since year 2000, the incidence of Invasive Pneumococcal Disease (IPD) has decreased considerably in all age groups when compared to the pre-vaccination era. In addition, hospitalization rates for pneumonia have also markedly decreased after routine childhood immunization with 7v-CRM in the US, not only for children younger than 4 years but also for adults aged 18-39 years. However, the decrease in IPD due to the vaccine serotypes has in some regions been accompanied by increases in IPD caused by non-vaccine serotypes. Whilst such changes have been seen in all age

groups for most vaccinated populations there still has been a dramatic net reduction in the overall IPD incidence. It remains unclear to what extent these observed changes are linked to the immunization program or to other epidemiological factors, since results are based on observational time-series data without concurrent controls and may therefore include bias e.g. due to secular trends and changes in treatment practises.

Currently, Prevenar has been introduced in routine childhood immunization in the US and several countries in Europe. The recommended vaccination schedule in the United States and some European countries includes 4 immunizations (i.e., the 3+1 dose schedule, with a 3-dose primary series followed by a booster dose in the second year of life). Other countries (such as Sweden, Denmark, Norway, Belgium, Switzerland and the UK) have recommended a vaccination schedule that includes only 3 doses (i.e., the 2+1 dose schedule, with a 2-dose primary series followed by a booster dose in the second year of life).

GSK Biologicals' 10-valent pneumococcal polysaccharide and non-typeable *H. influenzae* protein D conjugate vaccine (10Pn-PD-DiT) contains 10 serotypes of *S. pneumoniae* and uses Protein D derived from *H. influenzae* as carrier protein for eight of the ten serotype polysaccharides. It is therefore designed to protect against diseases caused by *S. pneumoniae* as well as diseases caused by non-typeable *H. influenzae* (NTHi). The vaccine is licensed in ***more than 100 countries worldwide, including*** Canada***, the European Union and Australia*** and is marketed under the name Synflorix™.
(Amended 22 August 2011)

It is however desirable to assess vaccine effectiveness (VE) against invasive disease post-licensure. In addition, widespread implementation of immunization programs needs to be accompanied by an appropriate surveillance program, in order to identify epidemiological changes potentially related to vaccination, such as decrease in disease incidence due to vaccine serotypes in unvaccinated children (indirect effects also know as herd immunity), or emergence of disease due to pneumococcal serotypes not included in the vaccine, or other bacterial pathogens. In addition molecular typing and antimicrobial resistance patterns of *S. pneumoniae* and *H. influenzae* isolates from invasive disease cases will be evaluated.

This study is designed as a cluster-randomized, double-blind trial and will enable evaluation of the overall effectiveness of

GSK Biologicals' 10Pn-PD-DiT vaccine against invasive disease caused by *S. pneumoniae* or *H. influenzae*, by measuring the effects both in vaccinated children (direct and indirect effects, i.e. total effects) and in unvaccinated population (indirect effects i.e. herd immunity). Effectiveness of immunization according to a 2-dose or 3-dose primary schedule, followed by a booster dose, will be assessed.

The study will also evaluate total and indirect vaccine impact on the incidence of hospital-diagnosed pneumonia, as well as the vaccine impact on tympanostomy tube placement and outpatient antimicrobial prescriptions.

In the Pneumococcal Otitis Efficacy Trial (POET study) conducted with an 11-valent pneumococcal protein D conjugate vaccine, a predecessor of GSK Biologicals' 10Pn-PD-DiT vaccine, a 33% reduction of any clinical AOM and a 42% reduction of any bacterial AOM were measured [Prymula, 2006]. The study demonstrated vaccine efficacy against AOM episodes caused by the serotypes of S. pneumoniae contained in the vaccine and in addition also a reduction of AOM episodes due to NTHi. This suggests that the 10Pn-PD-DiT vaccine could have a significant public health impact especially on non-invasive diseases such as AOM. Therefore, this study will also explore vaccine impact on occurrence of respiratory tract infections (RTIs), including AOM in a subset of subjects in Turku area.

In order to provide a benefit to the control group, two different control vaccines were selected for this study, depending on the age at the time of first vaccination:

- the licensed GSK Biologicals' Engerix B (HBV) vaccine for children < 12 months of age at the time of first vaccination.
- the licensed GSK Biologicals' Havrix 720 Junior (HAV) vaccine for children ≥ 12 months of age at the time of first vaccination.

This study will also serve as basis for conducting a long-term evaluation of the impact of vaccination with GSK Biologicals' 10Pn-PD-DiT vaccine.

Approximately 7000 subjects enrolled in study 10PN-PD-DIT-053 (112595), will contribute to the objectives of the current study. In addition, a detailed evaluation with regard to vaccination impact on carriage, AOM, RTI, safety and immunogenicity (in a subset of subjects) will be performed in

the study 10PN-PD-DIT-053.

Objectives

***P*rimary objective**

To demonstrate the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in clusters assigned to a 3-dose primary vaccination course.

Criteria for effectiveness:

*Effectiveness (VE) in preventing culture-confirmed IPD due to the 10 vaccine serotypes will be demonstrated if the 2-sided p-value calculated for the null hypothesis H0 = (**vaccine-type [VT]** IPD VE = 0%) is lower than 5%.*

(Amended 22 August 2011)

Secondary objectives

- ***To demonstrate the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in clusters assigned to a 2-dose primary vaccination course.***

  Criteria for effectiveness:

  Effectiveness (VE) in preventing culture-confirmed IPD due to the 10 vaccine serotypes will be demonstrated if the 2-sided p-value calculated for the null hypothesis H0 = (VT IPD VE = 0%) is lower than 5%.

  (Amended 22 August 2011)

- To assess the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed invasive disease caused by the bacterial pathogens listed below in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in clusters assigned to a 2- or a 3-dose primary vaccination course, respectively:

  – any and each of the 10 vaccine pneumococcal serotypes

  – any and each of the vaccine-related pneumococcal serotypes

  – any and each of the other pneumococcal serotypes

  - any and each of the *Haemophilus influenzae* types
  - any other bacterial pathogen.

- To assess the effectiveness of 10Pn-PD-DiT vaccine in preventing the culture-confirmed invasive disease caused by the bacterial pathogens listed above, in children vaccinated with at least one dose of vaccine within or beyond the first 7 months of life.
- To assess the effectiveness of a 2- or 3-dose primary vaccination course with 10Pn-PD-DiT vaccine in preventing the culture-confirmed invasive disease caused by the bacterial pathogens listed above, in children starting vaccination within the first 7 months of life and having completed the age-appropriate vaccination schedule. **(Amended 22 August 2011)**
- To assess the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed or probable cases of invasive disease caused by the bacterial pathogens listed above in children vaccinated with at least one dose of vaccine within the first 7 months of life, within or beyond the first 7 months of life, and in children starting vaccination within the first 7 months of life and having completed the age-appropriate vaccination schedule.
- To assess the effectiveness of 10Pn-PD-DiT vaccine in reducing hospital-diagnosed pneumonia cases among children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.
- ***To assess the effectiveness of the 10Pn-PD-DiT vaccine in reducing hospital-diagnosed pneumonia cases with abnormal pulmonary infiltrates on the chest X-ray (CXR pneumonia), hospital-diagnosed pneumonia cases with alveolar consolidation/pleural effusion on the chest X-ray (CXR-AC pneumonia), and hospital-diagnosed pneumonia cases without alveolar infiltrates or pleural effusion on the chest X-ray (CXR-NAC pneumonia), based on chest X-ray (CXR) reading according to WHO criteria, among children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.***

  (Amended 22 August 2011)
- To assess the impact of 10Pn-PD-DiT vaccine on occurrence of tympanostomy tube placements in children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7

months of life.

- To assess the impact of 10Pn-PD-DiT vaccine on outpatient antimicrobial prescriptions for children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.
- Evaluation of antimicrobial susceptibility of S. *pneumoniae* and *H. influenzae* isolated from invasive disease in children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.
- To assess the impact of vaccination with the 10Pn-PD-DiT vaccine on the incidence of lower respiratory tract infections (LRTI) in children starting vaccination below 18 months of age (in a subset of subjects in Turku area).
- To assess the impact of vaccination with the 10Pn-PD-DiT vaccine on the incidence of upper respiratory tract infections (URTI), including AOM in children starting vaccination below 18 months of age (in a subset of subjects in Turku area)
- To assess the indirect effects of 10Pn-PD-DiT vaccine, in terms of:
  - impact on culture-confirmed or probable cases of invasive disease caused by the bacterial pathogens listed above, in the unvaccinated population
  - impact on hospital-diagnosed pneumonia in the unvaccinated population
  - impact on tympanostomy tube placements in unvaccinated children ≤ 7 years of age
  - impact on outpatient antimicrobial prescriptions for unvaccinated children ≤ 7 years of age
- To assess the long-term effects of 10Pn-PD-DiT vaccination.

Study design

- Experimental design: cluster-randomized, controlled study with four parallel groups of clusters:
  - **10Pn_3+1 group of clusters**: subjects enrolled in the 10Pn_3+1 clusters will receive 10Pn-PD-DiT vaccine (± ***16 000*** subjects). Children enrolled in these clusters between 6 weeks and 6 months of age will receive a 3-dose primary vaccination schedule.
  - **10Pn_2+1 group of clusters**: subjects enrolled in the

10Pn_2+1 clusters will receive 10Pn-PD-DiT vaccine (± ***16 000*** subjects). Children enrolled in these clusters between 6 weeks and 6 months of age will receive a 2-dose primary vaccination schedule.

– **Control_3+1 group of clusters**: subjects enrolled in the Control_3+1 clusters will receive Engerix B (HBV) vaccine if < 12 months of age at the time of first study vaccination, or Havrix 720 Junior (HAV) vaccine if ≥ 12 months of age at the time of first study vaccination (± ***8000*** subjects). Children enrolled in these clusters within the first 7 months of life will receive a 3-dose primary vaccination schedule.

– **Control_2+1 group of clusters**: subjects enrolled in the Control_2+1 clusters will receive Engerix B (HBV) vaccine if < 12 months of age at the time of first study vaccination, or Havrix 720 Junior (HAV) vaccine if ≥ 12 months of age at the time of first study vaccination (± ***8000*** subjects). Children enrolled in these clusters within the first 7 months of life will receive a 2-dose primary vaccination schedule.

(Amended 22 August 2011)

Note: The actual immunization schedule to be received by each subject will depend on the age at enrolment as described below, meaning that each group of clusters will contain 3 subgroups of subjects immunized at different ages with different immunization schedules.

- The trial will be conducted in well-baby clinics in Finland.
- Treatment allocation: 2:2:1:1.
- Blinding: double-blind.
- Vaccination schedules will depend on the age at enrolment:
  - **Between 6 weeks and 6 months of age:** 3-dose primary vaccination with 10Pn-PD-DiT or HBV vaccine with at least 4 weeks interval, or 2-dose primary vaccination with 10Pn-PD-DiT or HBV vaccine with at least 8 weeks interval, followed by a booster dose of the same vaccine with an interval of preferably 6 months since the previous vaccine dose (minimum 4 months).
  - **Between 7 and 11 months of age:** 2-dose primary vaccination with either 10Pn-PD-DiT or HBV vaccine with an interval of at least 4 weeks, followed by a

booster dose of the same vaccine with an interval of preferably 6 months since the previous vaccine dose (minimum 4 months).

– **Between 12 and 18 months of age:** 2-dose vaccination with 10Pn-PD-DiT or HAV vaccine with an interval of at least and preferably 6 months between doses.

Note:

1. With the exception of hepatitis A, hepatitis B and/or pneumococcal vaccines, other licensed paediatric vaccines, including vaccinations of the National Immunisation Programme (NIP) may be administered or co-administered during the study period and will not be considered as study vaccines. Additional requests for hepatitis A, hepatitis B and/or pneumococcal vaccines will be managed on a case by case basis, as outlined in Section 6.5.1
2. For catch-up immunization initiated between 12 and 18 months of age, the vaccination schedule for the 10Pn-PD-DiT vaccine was adjusted to the licensed schedule of the control HAV vaccine (i.e. minimum 6 months interval between doses) in order to keep the study vaccination double-blinded.

- Control: GSK Biologicals' Engerix B vaccine (HBV) if < 12 months of age at the time of first study vaccination or GSK Biologicals' Havrix 720 Junior vaccine (HAV) if ≥ 12 months of age at the time of first study vaccination.
- Type of study: self-contained.
- Data source:

  Some subject data will be collected at enrolment at well-baby clinics, for instance personal identity code, consent date, date of first vaccination (if different than consent date), cluster/treatment number and eligibility criteria.

  The Medical Birth Register of the National Institute for Health and Welfare (THL) will be used to collect retrospectively demographic baseline data for the vaccinated and unvaccinated population.

  The following national registers will be used to collect data on:

  – **Invasive disease**: National Infectious Disease Register (NIDR) of the Department of Infectious Disease ***Surveillance and Control*** (***TATO***) of the National Institute for Health and Welfare (THL).

Clinical data for each case of invasive disease notified in NIDR among the study subjects will be retrieved through hospital medical record review. **(Amended 22 August 2011)**

- **Pneumonia**: Finnish Care Register for Social Welfare and Health Care of the National Institute for Health and Welfare (THL).
- **Tympanostomy tube placement**: Finnish Care Register for Social Welfare and Health Care of the National Institute for Health and Welfare (THL) and Social Insurance Institution Reimbursement Register of the Finnish Social Insurance Institution (KELA).
- **Outpatient antimicrobial prescriptions**: Social Insurance Institution Reimbursement Register (KELA).

The Finnish personal identity code is used in all these registers and will be used by THL to link individual data from the different registers, but will not be transferred to GSK Biologicals. Datasets from registers will be collected and stored at THL. Copies of datasets including register data will be transferred in separate batches from THL to GSK Biologicals, without the Finnish personal identity codes.

Register data on health outcomes concerning subjects enrolled in nested study 10PN-PD-DIT-053 (112595) will be also collected by THL and proceeded as described above.

- ***Chest X-rays (CXRs) from the hospital-diagnosed pneumonia cases in the vaccinated population will be collected and assessed by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005].*** **(Amended 22 August 2011)**
- Data on any RTI, including AOM will be collected in a subset of ±1500 subjects in Turku area, using a RTI/AOM diagnosis form. The evaluation of RTI in Turku population is conducted in a respiratory infection subcohort of study "Keys to a Good Childhood" lead by Turku Institute for Child and Youth research.
- The target recruitment time period will be approximately 14 months starting from first subject enrolled but can be adapted according to the decision and timing of introduction of universal mass vaccination with pneumococcal conjugate vaccine in Finland.

- ***Blinded study follow-up for invasive disease will end on 31 January 2012, after at least 30*** months of follow-up from the study start. See section 9.2 for details. **(Amended 22 August 2011)**
- Given the time differences for the availability of register data for secondary endpoints, analyses of data collected for these endpoints during the blinded follow-up period can be done in a second step, after the primary endpoint analysis.
- Register follow-up will continue after unblinding to evaluate the long-term effects on safety and total and indirect effectiveness of the vaccine. This will be reported in an Annex report.

(Amended 22 August 2011)

Number of subjects

Target study population, including subjects from study 10PN-PD-DIT-053 (112595) will be all children aged between 6 weeks and 18 months at the time of first vaccination. Since an annual birth cohort is around 57 000 children, a maximum of 142 000 subjects could be enrolled in this study assuming 14 months of enrolment. Assuming that the annual birth cohort of municipalities included in the trial is 90% of the total annual birth cohort and vaccination coverage will be 80% in the infant cohort starting vaccination below 7 months of age and 60% in the catch-up cohorts starting vaccination from 7 up to 18 months of age, the enrolled study population in this clinical trial may be estimated at approximately 91 000 subjects (± 58 000 subjects starting vaccination below 7 months of age and ± 33 000 subjects starting vaccination from 7 up to18 months of age).

At the time of protocol amendment 2, the final enrolled study population in this trial included approximately 47 000 subjects (approximately 31 000 subjects starting vaccination below 7 months of age and approximately 16 000 subjects starting vaccination from 7 up to 18 months of age).

(Amended 22 August 2011)

Primary endpoint

In children starting vaccination within the first 7 months of life *in clusters assigned to a 3-dose primary vaccination course* (Amended 22 August 2011):

- Occurrence of culture-confirmed IPD due to any of the 10 pneumococcal vaccine serotypes.

Secondary endpoints

In children starting vaccination within the first 7 months of life in clusters assigned to a 2-dose primary vaccination course):

- ***Occurrence of culture-confirmed IPD due to any of the 10 pneumococcal vaccine serotypes.***

(Amended 22 August 2011)

In the vaccinated population:

- Occurrence of culture-confirmed ID caused by any of the bacterial pathogens listed below:
  - any and each of the 10 pneumococcal vaccine serotypes
  - any and each of the vaccine-related pneumococcal serotypes
  - any and each of the other pneumococcal serotypes
  - any and each of the *Haemophilus influenzae* types
  - any other bacterial pathogen.
- Occurrence of probable cases of ID caused by the bacterial pathogens as listed above.
- Occurrence of hospital-diagnosed pneumonia cases.
- ***Occurrence of hospital-diagnosed pneumonia cases with abnormal pulmonary infiltrates on the chest X-ray (CXR pneumonia) based on the CXR reading according to WHO criteria.***
- ***Occurrence of hospital-diagnosed pneumonia cases with alveolar consolidation/pleural effusion on the CXR (CXR-AC pneumonia) based on the CXR reading according to WHO criteria.***
- ***Occurrence of hospital-diagnosed pneumonia cases without alveolar infiltrates or pleural effusion on the CXR (CXR-NAC pneumonia) based on the CXR reading according to WHO criteria.***

  (Amended 22 August 2011)
- Occurrence of tympanostomy tube placements.
- Occurrence of outpatient antibiotic prescriptions.
- Antimicrobial susceptibility of *S. pneumoniae* and *H. influenzae* isolated from invasive disease.
- Occurrence of LRTIs (in a subset of ± 1500 subjects in

Turku area)

- Occurrence of URTIs, including AOM (in a subset of ± 1500 subjects in Turku area).

In the unvaccinated population:

- Occurrence of culture-confirmed ID caused by the bacterial pathogens as listed above.
- Occurrence of probable cases of ID caused by the bacterial pathogens as listed above.
- Occurrence of hospital-diagnosed pneumonia cases.
- Occurrence of tympanostomy tube placements (*only in children ≤7 years of age*).
- Occurrence of outpatient antibiotic prescriptions (*only in children ≤7 years of age*).

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List of Abbreviations

AE	Adverse event
AEFI	Adverse event following immunisation
AOM	Acute otitis media
eCRF	electronic Case Report Form
CAP	Community Acquired Pneumonia
CDC	Centers for Disease Control and Prevention
CRA	Clinical Research Associate
CRM_{197}	Non-toxic cross reacting mutant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197)
CSF	Cerebrospinal fluid
CXR	***Chest X-ray*** **(Amended 22 August 2011)**
CXR pneumonia	***Pneumonia with abnormal pulmonary infiltrates on the chest X-ray*** **(Amended 22 August 2011)**
CXR-AC pneumonia	***CXR pneumonia with alveolar consolidation/pleural effusion on the chest X-ray*** **(Amended 22 August 2011)**
CXR-NAC pneumonia	***CXR pneumonia without alveolar infiltrates or pleural effusion on the chest X-ray*** **(Amended 22 August 2011)**
DT	Diphtheria toxoid (may also be referred to as Di)
DTPa-IPV/Hib	Diphtheria-tetanus-acellular pertussis-inactivated polio virus vaccine to be mixed with a lyophilized *Haemophilus influenzae* type b tetanus conjugate vaccine
EL.U	ELISA units
Engerix™ B	GSK Biologicals'hepatitis B vaccine, referred to as Engerix B or HBV throughout the text.
FDA	Food and Drug Administration, United States
FDR	False Discovery Rate **(Amended 22 August 2011)**
GCP	Good Clinical Practice

GSK	GlaxoSmithKline
GSM	Global Study Manager
HAB	Combined hepatitis A and hepatitis B vaccine
HAV	Hepatitis A vaccine
Havrix™ 720 Junior	GSK Biologicals' hepatitis A vaccine standardised to ensure a viral antigen content of not less than 720 El.U. of viral antigens per 0.5 mL, referred to as Havrix 720 Junior or HAV throughout the text.
H. influenzae	*Haemophilus influenzae*
HBs	Hepatitis B surface antigen
HBV	Hepatitis B vaccine
IB	Investigator Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICU	Intensive Care Unit
ID	Invasive Disease
IDMC	Independent Data Monitoring Committee
IPD	Invasive Pneumococcal Disease
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
KELA	Finnish Social Insurance Institution (Kansaneläkelaitos), Finland
LRTI	Lower respiratory tract infection
KTL	National Public Health Institute (Kansanterveyslaitos), Finland***, now National Institute for Health and Welfare (THL), Finland*** **(Amended 22 August 2011)**
μg	microgram

NCSP	NOMESCO Classification of Surgical Procedures (Pohjoismainen leikkausluokituskoodisto)
NIDR	National Infectious Disease Register (Valtakunnallinen tartuntatautirekisteri) **(Amended 22 August 2011)**
NIP	National Immunisation Programme
NOMESCO	Nordic Medico-Statistical Committee
NTHi	Non-typeable *Haemophilus influenzae*
MedDRA	Medical Dictionary for Regulatory Activities
MEF	Middle-ear fluid
MMR	A combined vaccine against measles, mumps and rubella.
mL	millilitre
PCV	Pneumococcal conjugate vaccine
PD	Protein D is a 42 kD cell-surface lipoprotein which is highly conserved among capsulated and unencapsulated strains of *Haemophilus influenzae*
Pn	Pneumococcal
Prevenar™	7-valent pneumococcal conjugate vaccine with diphtheria CRM_{197} as protein carrier. Serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F (***Pfizer***), referred ***to*** throughout the document as Prevenar **(Amended 22 August 2011)**
RDE	Remote data entry
RTI	Respiratory tract infection
SAE	Serious adverse event
S. pneumoniae	*Streptococcus pneumoniae*
SOP	Standard Operating Procedure
TATO	***Department of Infectious Disease Surveillance and Control*** **(Amended 22 August 2011)**
TT	Tetanus toxoid
THL	National Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos), former National Public Health

	Institute (KTL), Finland
URTI	Upper respiratory tract infection
VE	Vaccine effectiveness
VT IPD	***Vaccine-Type Invasive Pneumococcal Disease*** **(Amended 22 August 2011)**
WHO	World Health Organization
10Pn-PD-DiT	Liquid 10-valent pneumococcal conjugate vaccine with protein D and diphtheria and tetanus toxoids as protein carriers.

Glossary of Terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation (see Section 6.5 for details on observer-blinded studies). When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double blind. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.
Central coordination office	Term used to denote an office in THL Helsinki where the principal investigator, data management, and safety follow-up are located.
Cluster treatment number:	Number identifying the treatment attributed to a cluster, according to the study randomisation or treatment allocation.

Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.4 and 9.2 for details on criteria for evaluability).
Global Study Manager	An individual assigned by GSK Biologicals Headquarters who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Local coordination centre	Term used to denote a centre established for the duration of the study conduct and responsible for the coordination of the operational aspects of the study, including the proper conduct of the procedure to maintain blinding (see section 6.5.1 for details of the procedure to maintain blinding). Members of the local coordination centre are qualified nurses assigned by and located at various THL sites in Finland. Supervision of the local coordination centers and medical expertise will be located in the local coordination center of Tampere.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Personal identity code:	National unique personal identification code given to all new born children in Finland soon after birth.

Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomisation:	Process of random attribution of treatment to clusters in order to reduce bias of selection
Self-contained	Not depending on other studies
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Study Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject according to the study randomisation or treatment allocation.

1. INTRODUCTION

1.1. Pneumococcal diseases

Streptococcus pneumoniae, a gram-positive diplococcus, is a normal inhabitant of the upper respiratory tract of humans and spreads from person to person in droplets of respiratory secretions. Rates of colonization depend on a number of variables including race, age, exposure to young children, and population [Ghaffar, 1999]. The pneumococcus is generally assumed to be the most common cause of community-acquired bacterial pneumonia (CAP) and of blood stream infections (bacteremia and septicaemia), one of the major causes of bacterial meningitis in children, and along with the gram-negative non-typeable *Haemophilus influenzae* (NTHi), the two leading bacterial causes of acute otitis media (AOM) in children.

The highest incidence of invasive pneumococcal disease (IPD) is found in children under two years of age and in elderly adults [Butler, 1996]. The annual incidence of IPD prior to the introduction of pediatric pneumococcal vaccination has been reported to be as high as 160/100 000 in US children under two years of age [Hausdorff, 2000]. Since the introduction of widespread routine immunization with Prevenar in the US (June 2000), the estimated incidence in the US of invasive pneumococcal infections among children aged < 12 months and 12-23 months has fallen with incidences for 2002 of 38.5/100 000 and 31.5/100 000, respectively [CDC, 2002]. In Western Europe, rates of IPD were regarded as being much lower than the IPD rates in the US prior to licensure of Prevenar, possibly due to different blood-culture rates and practices compared to those in the US, leading to an under-reporting of milder cases of pneumococcal bacteraemia [Hausdorff, 2001]. In developing countries, *S. pneumoniae* causes one to two million deaths every year among children under five years of age [Mulholland, 1999], with most cases occurring in the first year of life.

In Finland, the incidence of invasive disease due to *S. pneumoniae* is monitored through the national infectious diseases surveillance system at the National Institute for Health and Welfare (THL), former National Public Health Institute (KTL). The incidence of IPD in Finland was estimated over the years 2004-2007 to be on average:

- 46/100,000 child years among children under 1 year of age
- 87/100,000 child years among 1-year old children
- 36/100,000 child years among 2-year old children

Streptococcus pneumoniae is considered to be the predominant cause of severe pneumonia among children in developing countries and contributes to the major share of pneumonia deaths. In these countries, *S. pneumoniae* causes one to two million deaths every year among children under five years of age [UNICEF, 2006], most of which are due to pneumonia, and a high proportion occurs in the first year of life. The contribution of pneumococci to pneumonia has been difficult to define given the problems of establishing the bacterial etiology of pneumonia [Obaro, 2006]. However, three studies have evaluated the impact of 7- or 9-valent pneumococcal conjugate vaccines on WHO defined “consolidated” radiographic pneumonia (irrespective of the etiological agent) and

showed a 20.5 to 37.0% reduction in radiologically confirmed pneumonia [Black, 2002; Cutts , 2005; Klugman, 2003]. In addition, recent analysis of data from the 9-valent CRM-conjugate pneumococcal vaccine trial in South Africa [Madhi, 2005; Madhi, 2006] has demonstrated that the typical consolidated CAP cases only represent a relatively small proportion of the CAP disease burden that is preventable by pneumococcal vaccines (i.e. the sensitivity of the consolidated CAP case definition is not optimal). This means that the true public health impact (and cost-effectiveness) of a pneumococcal conjugate vaccine may be markedly underestimated if only alveolar consolidation is included. Finally, post-marketing surveillance database analyses in the US following widespread Prevenar introduction have pointed to 20% decreases in (all cause) pneumonia hospitalisations [Grijalva, 2007].

S. pneumoniae is also a major cause of acute otitis media (AOM). The disease is most prevalent in early childhood, with the peak age-specific attack-rate occurring from 6 to 18 months of age. It has been reported that approximately 60% of children have had at least one episode of AOM by one year of age and that more than 20 million cases occur each year in children under two years in the US [Teele, 1989]. In the EU, incidence rates range from 0.2 episodes/child-year in the Netherlands [Jansen, 2006], to 0.4 visits/child-year in the UK [Melegaro, 2004], to 0.45 episodes in the first year of life in Spain [Caceres Udina, 2004] and 1.24 episodes/child-year in Finland [Eskola, 2001]. The latter figure is similar to rates reported in the US [Fireman, 2003]. The England and Wales study [Melegaro, 2004] estimated 270,000 AOM cases would occur annually in children <5 years of age, which would correspond to 2.1 million AOM cases in the 27 member states of the EU.

Studies on the aetiology of AOM are relatively rare since tympanocentesis is not routine clinical practice. Bacteria can usually be isolated in approximately 70% of MEF samples from children with otitis media [Cripps, 2006]. Although case-definitions of AOM are not standardised across studies, *S. pneumoniae* and *H. influenzae* are by far the most common causes of bacterial AOM [Leibovitz, 2004]. Data from the AOM efficacy study conducted in Finland between 1995 and 1999 have shown that 38% and 27 % of all bacterial cases of AOM in children who were not vaccinated with pneumococcal conjugate vaccine were caused by *S pneumoniae* and *H. influenzae* respectively [Eskola, 2001]. In the developed countries, AOM is the most common reason for antimicrobial administration in infants and young children [Leibovitz, 2004]. Although most cases of AOM eventually resolve with (or without) antibiotic treatment, complications of pneumococcal AOM still occur, including secretory otitis media, mastoiditis and meningitis, and often need further interventional therapy [Bluestone, 2000]. Infants with severe and recurrent otitis media with persistent middle ear infection are at risk for behavioural problems and poor development of speech, language and cognitive abilities [Klein, 2001]. In addition, tympanostomy/ pressure equalization tube placement to allow drainage, to aerate the middle ear and restore hearing has become the most common paediatric surgical procedure in many countries [Owings, 1998; Palmu, 2004].

The prevalence of multiple antibiotic resistant pneumococci has increased dramatically over the past decade [Appelbaum, 1996; Whitney, 2000; McCormick, 2003] and this has prompted further efforts to develop vaccination for the prevention of pneumococcal diseases in infants. Vaccination could also be an effective way to decrease the carriage

and spread of antibiotic-resistant pneumococci, especially in crowded settings such as day-care centres [Dagan, 2001].

1.2. *Haemophilus influenzae*

Haemophilus influenzae is a small gram-negative cocco-bacillus exclusively pathogenic for humans, and the infection it causes range from asymptomatic colonization of the upper respiratory tract to serious invasive diseases such as meningitis (Plotkin & Mortimer – Second Edition). Although *H. influenzae* type b disease is now virtually eliminated in areas with high rates of Hib immunization, infections caused by non-typeable *H. influenzae* remain a significant cause of respiratory tract infections.

H. influenzae together with *S. pneumoniae* have been identified as the major pathogens involved in otitis media. Studies performed in Latin America and Europe [Rosenblut, 2001; Arguedas, 2003; Arguedas, 2005; Hausdorff, 2002; Eskola, 2001; Prymula, 2006] to document the etiology of AOM in children, based on culture of middle ear fluid (MEF) samples obtained through tympanocentesis, showed that *H. influenzae* could be isolated in 20-34% of the MEF samples, making it the second most common pathogen after *S. pneumoniae*.

H. influenzae is also an important colonizer of the nasopharynx. In countries worldwide, between 30 and 50% of children around 2 years of age are colonized with this pathogen [García-Rodríguez, 2002]. The reported rates of bacterial acquisition and carriage vary extensively between different studies and geographical areas. These differences have been related to genetic background variables and socio-economic conditions including housing, access to health care, poor hygiene, family size, overcrowded living conditions, day-care contact, number of siblings, etc.

1.3. Pneumococcal vaccine development

The polysaccharide capsule is the most important virulence factor of *S. pneumoniae* and contributes to the progression of the disease by virtue of its antiphagocytic properties [Mitchell, 1997]. Over ninety serologically distinct serotypes of *S. pneumoniae* have been described, varying in the structure of their polysaccharide capsule [Henrichsen, 1995]. Pneumococcal capsular polysaccharide vaccines have been licensed since 1977. The current 23-valent unconjugated plain polysaccharide vaccines are designed to provide coverage of approximately 90% of the most frequently reported isolates in the US and most other countries [Martindale, 1999]. However, a satisfactory immune response is not obtained in children under two years of age, and their use in this age group is therefore not recommended.

Furthermore, the protection provided by polysaccharide vaccines is short-lived, i.e. no immunological memory is induced because of the T-cell independent nature of polysaccharide antigens [Dintzis, 1992]. Polysaccharide antigens can however be made to induce a T-cell-response by their covalent coupling with proteins, resulting in boostable antibody levels after repeated injection, antibody class switching and affinity maturation, and induction of immunological memory. Various carrier proteins are used in licensed or candidate *S. pneumoniae* conjugate vaccines: diphtheria and tetanus toxoids, CRM_{197} (a

non-toxic cross-reacting mutant diphtheria toxin molecule), and lipo-polysaccharide depleted group B meningococcal outer membrane protein complex [Klein, 1999].

To date, ***three pneumococcal conjugate vaccines (Prevenar, Prevenar 13 and Synflorix) have a marketing authorisation*** in several parts of the world. Th***e*** 7-valent pneumococcal conjugate vaccine***, Prevenar,*** comprises serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, each conjugated to CRM_{197}. Its efficacy in preventing vaccine-serotype IPD was 97.4% (95% confidence interval: 82.7–99.9%) [Black, 2000], and although AOM episodes caused by vaccine-serotype pneumococci were reduced by 57% [Eskola, 2001], the overall reduction in clinical AOM episodes was only 6 to 7% [Fireman, 2003; Eskola, 2001]. Since June 2000, the 7-valent pneumococcal conjugate vaccine has been recommended in the US for routine immunization for all children under two years of age and for children aged 24-59 months who are at high risk for pneumococcal infections [CDC, 2004]. In many countries, Prevenar has been recommended for routine immunization. **(Amended 22 August 2011)**

Following licensure of ***Pfizer's*** 7-valent pneumococcal conjugate vaccine (Prevenar) in the USA and in Europe, regulatory approval of new pneumococcal conjugate vaccines will be based on immunological criteria, in comparison to Prevenar. A WHO meeting reached a consensus on criteria that could be used as a basis for licensure: demonstration of non-inferiority to Prevenar based on the percentage of subjects with a pneumococcal antibody concentration above 0.35 μg/mL using an ELISA without adsorption with 22F polysaccharide [WHO, 2005], or equivalent depending on the ELISA technique used (e.g. 0.20 μg/mL using GSK Biologicals' 22F ELISA [Henckaerts, 2006]). **(Amended 22 August 2011)**

GSK Biologicals has produced an 11-valent conjugated pneumococcal vaccine that uses protein D (PD) as carrier (11Pn-PD vaccine) and contains four additional serotypes to those in Prevenar (serotypes 1, 3, 5 and 7F). Protein D is a 42 kD cell-surface lipoprotein which is highly conserved among capsulated and unencapsulated strains of *H. influenzae* and which has shown to enhance clearance of *H. influenzae* in the chinchilla model [Bakaletz, 1999]. The 11Pn-PD vaccine was tested in study Undeca-Pn-010 (POET) conducted in the Czech and Slovak Republics [Prymula, 2006]. This study was designed as a Phase III, double-blind, randomized study using Havrix as control vaccine to assess the efficacy of the 11Pn-PD vaccine in preventing acute otitis media (AOM) caused by pneumococcal serotypes covered by the vaccine. The study also assessed the impact of the vaccine on the incidence of AOM associated with non-typeable *H. influenzae* (NTHi) and, more broadly, the impact on the global incidence of clinical AOM episodes. Results from the POET trial are the first to demonstrate a statistically significant and clinically relevant protective effect of vaccination on the overall AOM disease burden (33.6%, 95%CI: 20.8-44.3), as well as on the number of AOM episodes due to vaccine serotypes *S. pneumoniae* (57.6%, 95%CI: 41.4-69.3) or NTHi (35.3%, 95%CI: 1.8-57.4). The lack of protective efficacy against AOM caused by serotype 3, together with other data indicating an impaired serotype 3 antibody response to the 11Pn-PD booster dose in the second year of life, led the company to decide to remove serotype 3 from the final vaccine formulation to give a 10-valent pneumococcal conjugate vaccine.

GSK Biologicals' 10-valent pneumococcal conjugate (10Pn-PD-DiT) vaccine is using the same protein D (PD) as carrier protein as the previous 11Pn-PD vaccine formulation for 8 of the 10 serotypes contained in the vaccine. In addition, the serotype 18C polysaccharide is conjugated to tetanus toxoid (TT) and serotype 19F polysaccharide is conjugated to diphtheria toxoid (DT).

To date, more than ***22 900*** doses of 10Pn-PD-DiT vaccine have been administered in completed clinical studies. The results of these studies showed that GSK Biologicals' 10Pn-PD-DiT vaccine is safe and well tolerated in infants and toddlers and a good immune response was demonstrated. In addition, more than ***219 000*** doses of the 10Pn-PD-DiT vaccine will be administered in planned and ongoing clinical trials. **(Amended 22 August 2011)**

Please refer to the current Investigator Brochure for the pneumococcal polysaccharide and non-typeable *H. influenzae* protein D conjugate vaccine for a review of pre-clinical and clinical studies of the final 10Pn-PD-DiT vaccine formulation.

1.4. Rationale for the study

Pneumococcal conjugate vaccines (PCVs) have enormous potential to reduce burden of *S. pneumoniae* diseases, not only through direct protection provided to the vaccinees but also through indirect protection of the unvaccinated population. In the US, where infants have been vaccinated with the licensed 7-valent CRM_{197}-conjugate vaccine *Prevenar*™ (7v-CRM) since year 2000, the incidence of Invasive Pneumococcal Disease (IPD) has decreased considerably in all age groups when compared to the pre-vaccination era. In addition, hospitalization rates for pneumonia have also markedly decreased after routine childhood immunization with 7v-CRM in the US, not only for children younger than 4 years but also for adults aged 18-39 years. However, the decrease in IPD due to the vaccine serotypes has in some regions been accompanied by increases in IPD caused by non-vaccine serotypes. Whilst such changes have been seen in all age groups for most vaccinated populations there still has been a dramatic net reduction in the overall IPD incidence. It remains unclear to what extent these observed changes are linked to the immunization program or to other epidemiological factors, since results are based on observational time-series data without concurrent controls and may therefore include bias e.g. due to secular trends and changes in treatment practises.

Currently, Prevenar has been introduced in routine childhood immunization in the US and several countries in Europe. The recommended vaccination schedule in the United States and some European countries includes 4 immunizations (i.e., the 3+1 dose schedule, with a 3-dose primary series followed by a booster dose in the second year of life). Other countries (such as Sweden, Denmark, Norway, Belgium, Switzerland and the UK) have recommended a vaccination schedule that includes only 3 doses (i.e., the 2+1 dose schedule, with a 2-dose primary series followed by a booster dose in the second year of life).

GSK Biologicals' 10-valent pneumococcal polysaccharide and non-typeable *H. influenzae* protein D conjugate vaccine (10Pn-PD-DiT) contains 10 serotypes of *S. pneumoniae* and uses Protein D derived from *H. influenzae* as carrier protein for eight of

the ten serotype polysaccharides. It is therefore designed to protect against diseases caused by *S. pneumoniae* as well as diseases caused by non-typeable *H. influenzae* (NTHi). The vaccine is licensed in ***more than 100 countries worldwide, including*** Canada***, the European Union and Australia*** and is marketed under the name Synflorix™. **(Amended 22 August 2011)**

It is however desirable to assess vaccine effectiveness (VE) against invasive disease post-licensure. In addition, widespread implementation of immunization programs needs to be accompanied by an appropriate surveillance program, in order to identify epidemiological changes potentially related to vaccination, such as decrease in disease incidence due to vaccine serotypes in unvaccinated children (indirect effects also know as herd immunity), or emergence of disease due to pneumococcal serotypes not included in the vaccine, or other bacterial pathogens. In addition molecular typing and antimicrobial resistance patterns of *S. pneumoniae* and *H. influenzae* isolates from invasive disease cases will be evaluated.

This study is designed as a cluster-randomized, double-blind trial and will enable evaluation of the overall effectiveness of GSK Biologicals' 10Pn-PD-DiT vaccine against invasive disease caused by *S. pneumoniae* or *H. influenzae*, by measuring the effects both in vaccinated children (direct and indirect effects, i.e. total effects) and in unvaccinated population (indirect effects i.e. herd immunity). Effectiveness of immunization according to a 2-dose or 3-dose primary schedule, followed by a booster dose, will be assessed.

The study will also evaluate total and indirect vaccine impact on the incidence of hospital-diagnosed pneumonia, as well as the vaccine impact on tympanostomy tube placement and outpatient antimicrobial prescriptions.

In the Pneumococcal Otitis Efficacy Trial (POET study) conducted with an 11-valent pneumococcal protein D conjugate vaccine, a predecessor of GSK Biologicals' 10Pn-PD-DiT vaccine, a 33% reduction of any clinical AOM and a 42% reduction of any bacterial AOM were measured [Prymula, 2006]. The study demonstrated vaccine efficacy against AOM episodes caused by the serotypes of *S. pneumoniae* contained in the vaccine and in addition also a reduction of AOM episodes due to NTHi. This suggests that the 10Pn-PD-DiT vaccine could have a significant public health impact especially on non-invasive diseases such as AOM. Therefore, this study will also explore vaccine impact on occurrence of respiratory tract infections (RTIs), including AOM in a subset of subjects in Turku area.

In order to provide a benefit to the control group, two different control vaccines were selected for this study, depending on the age at the time of first vaccination:

- the licensed GSK Biologicals' Engerix B (HBV) vaccine for children < 12 months of age at the time of first vaccination.
- the licensed GSK Biologicals' Havrix 720 Junior (HAV) vaccine for children ≥ 12 months of age at the time of first vaccination.

This study will also serve as basis for conducting a long-term evaluation of the impact of vaccination with GSK Biologicals' 10Pn-PD-DiT vaccine.

Approximately 7000 subjects enrolled in study 10PN-PD-DIT-053 (112595) will contribute to the objectives of the current study. In addition, a detailed evaluation with regard to vaccination impact on carriage, AOM, RTI, safety and immunogenicity (in a subset of subjects) will be performed in the study 10PN-PD-DIT-053.

2. OBJECTIVES

The following terms are used for study purpose:

- Study vaccines refer to 10Pn-PD-DiT, HAV and HBV vaccines.
- Vaccinated population refers to subjects who received one of study vaccines defined above.
- Unvaccinated population/children refers to the population/children living in the study geographical areas but who do not participate in the present study and have therefore not received any of the study vaccines defined above.

2.1. Primary objective

To demonstrate the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in clusters assigned to a 3-dose primary vaccination course.

Criteria for effectiveness:

*Effectiveness (VE) in preventing culture-confirmed IPD due to the 10 vaccine serotypes will be demonstrated if the 2-sided p-value calculated for the null hypothesis H0 = (**vaccine-type [VT]** IPD VE = 0%) is lower than 5%.*

(Amended 22 August 2011)

Refer to Section 9.1.1 for definition of the primary endpoint.

2.2. Secondary objectives

- ***To demonstrate the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in clusters assigned to a 2-dose primary vaccination course.***

  Criteria for effectiveness:

  Effectiveness (VE) in preventing culture-confirmed IPD due to the 10 vaccine serotypes will be demonstrated if the 2-sided p-value calculated for the null hypothesis H0 = (VT IPD VE = 0%) is lower than 5%.

  (Amended 22 August 2011)

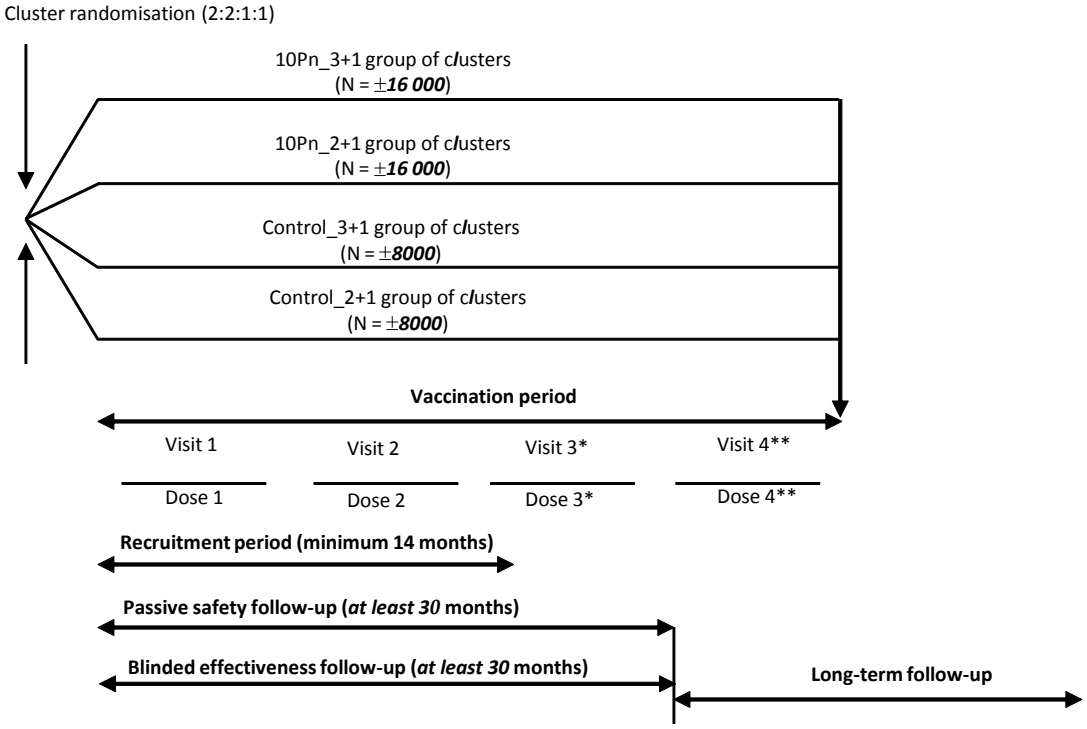
- To assess the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed invasive disease caused by the bacterial pathogens listed below in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in clusters assigned to a 2- or a 3-dose primary vaccination course, respectively:
  - any and each of the 10 vaccine pneumococcal serotypes
  - any and each of the vaccine-related pneumococcal serotypes
  - any and each of the other pneumococcal serotypes
  - any and each of the *Haemophilus influenzae* types
  - any other bacterial pathogen.
- To assess the effectiveness of 10Pn-PD-DiT vaccine in preventing the culture-confirmed invasive disease caused by the bacterial pathogens listed above, in children vaccinated with at least one dose of vaccine within or beyond the first 7 months of life.
- To assess the effectiveness of a 2- or 3-dose primary vaccination course with 10Pn-PD-DiT vaccine in preventing the culture-confirmed invasive disease caused by the bacterial pathogens listed above, in children starting vaccination within the first 7 months of life and having completed the age-appropriate vaccination schedule. **(Amended 22 August 2011)**
- To assess the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed or probable cases of invasive disease caused by the bacterial pathogens listed above in children vaccinated with at least one dose of vaccine within the first 7 months of life, within or beyond the first 7 months of life, and in children starting vaccination within the first 7 months of life and having completed the age-appropriate vaccination schedule.
- To assess the effectiveness of 10Pn-PD-DiT vaccine in reducing hospital-diagnosed pneumonia cases among children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.
- ***To assess the effectiveness of the 10Pn-PD-DiT vaccine in reducing hospital-diagnosed pneumonia cases with abnormal pulmonary infiltrates on the chest X-ray (CXR pneumonia), hospital-diagnosed pneumonia cases with alveolar consolidation/pleural effusion on the chest X-ray (CXR-AC pneumonia), and hospital-diagnosed pneumonia cases without alveolar infiltrates or pleural effusion on the chest X-ray (CXR-NAC pneumonia), based on chest X-ray (CXR) reading according to WHO criteria, among children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.***

  (Amended 22 August 2011)
- To assess the impact of 10Pn-PD-DiT vaccine on occurrence of tympanostomy tube placements in children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.

- To assess the impact of 10Pn-PD-DiT vaccine on outpatient antimicrobial prescriptions for children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.
- Evaluation of antimicrobial susceptibility of S. *pneumoniae* and *H. influenzae* isolated from invasive disease in children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.
- To assess the impact of vaccination with the 10Pn-PD-DiT vaccine on the incidence of lower respiratory tract infections (LRTIs) in children starting vaccination below 18 months of age (in a subset of ± 1500 subjects in Turku area).
- To assess the impact of vaccination with the 10Pn-PD-DiT vaccine on the incidence of upper respiratory tract infections (URTIs) including AOM in children starting vaccination below 18 months of age (in a subset of ± 1500 subjects in Turku area)
- To assess the indirect effects of 10Pn-PD-DiT vaccine, in terms of:
  - impact on culture-confirmed or probable cases of invasive disease caused by the bacterial pathogens listed above, in the unvaccinated population
  - impact on hospital-diagnosed pneumonia in the unvaccinated population
  - impact on tympanostomy tube placements in unvaccinated children ≤ 7 years of age
  - impact on outpatient antimicrobial prescriptions for unvaccinated children ≤ 7 years of age
- To assess the long-term effects of 10Pn-PD-DiT vaccination.

Refer to Section 9.1.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW



(*)Vaccination visit 3 is only applicable for children that are less than 12 months of age when enrolled into the study (either for the 3rd primary dose for infants enrolled in their first 7 months of life in a 3+1 cluster, or for the booster dose in children enrolled in their first 7 months of life in a 2+1 cluster and children enrolled between 7 and 11 months of age).
(**)Vaccination visit 4 is only applicable for the booster dose in infants enrolled in their first 7 months of life in a 3+1 cluster.
N: number of subjects

(Amended 22 August 2011)

- Experimental design: cluster-randomized, controlled study with four parallel groups of clusters:
  - **10Pn_3+1 group of clusters**: subjects enrolled in the 10Pn_3+1 clusters will receive 10Pn-PD-DiT vaccine (± ***16 000*** subjects). Children enrolled in these clusters between 6 weeks and 6 months of age will receive a 3-dose primary vaccination schedule.
  - **10Pn_2+1 group of clusters**: subjects enrolled in the 10Pn_2+1 clusters will receive 10Pn-PD-DiT vaccine (± ***16 000*** subjects). Children enrolled in these clusters between 6 weeks and 6 months of age will receive a 2-dose primary vaccination schedule.
  - **Control_3+1 group of clusters**: subjects enrolled in the Control_3+1 clusters will receive Engerix B (HBV) vaccine if < 12 months of age at the time of first study vaccination, or Havrix 720 Junior (HAV) vaccine if ≥ 12 months of age at the time of first study vaccination (± ***8000*** subjects). Children enrolled in these clusters within the first 7 months of life will receive a 3-dose primary vaccination schedule.

– **Control_2+1 group of clusters**: subjects enrolled in the Control_2+1 clusters will receive Engerix B (HBV) vaccine if < 12 months of age at the time of first study vaccination, or Havrix 720 Junior (HAV) vaccine if ≥ 12 months of age at the time of first study vaccination (± ***8000*** subjects). Children enrolled in these clusters within the first 7 months of life will receive a 2-dose primary vaccination schedule.

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Note: The actual immunization schedule to be received by each subject will depend on the age at enrolment as described below, meaning that each group of clusters will contain 3 subgroups of subjects immunized at different ages with different immunization schedules.

- The trial will be conducted in well-baby clinics in Finland.
- Treatment allocation: 2:2:1:1. Refer to Section 6.4 for a detailed description of the randomisation method.
- Blinding: double-blind. Refer to Section 6.5 for details of blinding procedures.
- Vaccination schedules will depend on the age at enrolment:
  - **Between 6 weeks and 6 months of age**: 3-dose primary vaccination with 10Pn-PD-DiT or HBV vaccine with at least 4 weeks interval, or 2-dose primary vaccination with 10Pn-PD-DiT or HBV vaccine with at least 8 weeks interval, followed by a booster dose of the same vaccine with an interval of preferably 6 months since the previous vaccine dose (minimum 4 months).
  - **Between 7 and 11 months of age**: 2-dose primary vaccination with either 10Pn-PD-DiT or HBV vaccine with an interval of at least 4 weeks, followed by a booster dose of the same vaccine with an interval of preferably 6 months since the previous vaccine dose (minimum 4 months).
  - **Between 12 and 18 months of age**: 2-dose vaccination with 10Pn-PD-DiT or HAV vaccine with an interval of at least and preferably 6 months between doses.

Note:

1. With the exception of hepatitis A, hepatitis B and/or pneumococcal vaccines, other licensed paediatric vaccines, including vaccinations of the National Immunisation Programme (NIP) may be administered or co-administered during the study period and will not be considered as study vaccines. Additional requests for hepatitis A, hepatitis B and/or pneumococcal vaccines will be managed on a case by case basis, as outlined in Section 6.5.1.
2. For catch-up immunization initiated between 12 and 18 months of age, the vaccination schedule for the 10Pn-PD-DiT vaccine was adjusted to the licensed schedule of the control HAV vaccine (i.e. minimum 6 months interval between doses) in order to keep the study vaccination double-blinded.

- Control: GSK Biologicals' Engerix B vaccine (HBV) if < 12 months of age at the time of first study vaccination or GSK Biologicals' Havrix 720 Junior vaccine (HAV) if ≥ 12 months of age at the time of first study vaccination.

- Type of study: self-contained.
- Data source:

  Some subject data will be collected at enrolment at well-baby clinics, for instance personal identity code, consent date, date of first vaccination (if different than consent date), cluster/treatment number and eligibility criteria.

  The Medical Birth Register of the National Institute for Health and Welfare (THL) will be used to collect retrospectively demographic baseline data for the vaccinated and unvaccinated population.

  The following national registers will be used to collect data on:

  – **Invasive disease**: National Infectious Disease Register (NIDR) of the Department of Infectious Disease ***Surveillance and Control*** (***TATO***) of the National Institute for Health and Welfare (THL). Clinical data for each case of invasive disease notified in NIDR among the study subjects will be retrieved through hospital medical record review.
  (Amended 22 August 2011)

  – **Pneumonia**: Finnish Care Register for Social Welfare and Health Care of the National Institute for Health and Welfare (THL).

  – **Tympanostomy tube placement**: Finnish Care Register for Social Welfare and Health Care (THL) and Social Insurance Institution Reimbursement Register of the Finnish Social Insurance Institution (KELA).

  – **Outpatient antimicrobial prescriptions**: Social Insurance Institution Reimbursement Register (KELA).

  The Finnish personal identity code is used in all these registers and will be used by THL to link individual data from the different registers, but will not be transferred to GSK Biologicals. Datasets from registers will be collected and stored at THL. Copies of datasets including register data will be transferred in separate batches from THL to GSK Biologicals, without the Finnish personal identity codes.

  Register data on health outcomes concerning subjects enrolled in nested study 10PN-PD-DIT-053 (112595) will be also collected by THL and proceeded as described above.

- ***Chest X-rays (CXRs) from the hospital-diagnosed pneumonia cases in the vaccinated population will be collected and assessed by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005].*** **(Amended 22 August 2011)**
- Data on any RTI, including AOM will be collected in a subset of ±1500 subjects in Turku area, using a RTI/AOM diagnosis form. The evaluation of RTI in Turku population is conducted in a respiratory infection subcohort of study "Keys to a Good Childhood" lead by Turku Institute for Child and Youth research.
- The target recruitment time period will be approximately 14 months starting from first subject enrolled but can be adapted according to the decision and timing of introduction of universal mass vaccination with pneumococcal conjugate vaccine in Finland.

- ***Blinded study follow-up for invasive disease will end on 31 January 2012, after at least 30*** months of follow-up from the study start. See section 9.2 for details. **(Amended 22 August 2011)**
- Given the time differences for the availability of register data for secondary endpoints, analyses of data collected for these endpoints during the blinded follow-up period can be done in a second step, after the primary endpoint analysis.
- Register follow-up will continue after unblinding to evaluate the long-term effects on safety and total and indirect effectiveness of the vaccine. This will be reported in an Annex report.

(Amended 22 August 2011)

Refer to Appendix B for details of the recruitment plan.

4. STUDY COHORT

4.1. Number of subjects / centres

Target study population, including subjects from study 10PN-PD-DIT-053 (112595) will be all children aged between 6 weeks and 18 months at the time of first vaccination. Since an annual birth cohort is around 57 000 children, a maximum of 142 000 subjects could be enrolled in this study assuming 14 months of enrolment. Assuming that the annual birth cohort of municipalities included in the trial is 90% of the total annual birth cohort and vaccination coverage will be 80% in the infant cohort starting vaccination below 7 months of age and 60% in the catch-up cohorts starting vaccination from 7 up to 18 months of age, the enrolled study population in this clinical trial may be estimated at approximately 91 000 subjects (± 58 000 subjects starting vaccination below 7 months of age and ± 33 000 subjects starting vaccination from 7 up to18 months of age).

At the time of protocol amendment 2, the final enrolled study population in this trial included approximately 47 000 subjects (approximately 31 000 subjects starting vaccination below 7 months of age and approximately 16 000 subjects starting vaccination from 7 up to 18 months of age).

(Amended 22 August 2011)

Refer to Section 9.2 for a detailed description of the criteria used in the justification of the sample size.

This study will be performed in Finland in cooperation with municipal health care centres agreeing to participate in the study and covering the majority of the Finnish population. Refer to Section 4.2.1 for a detailed description of the criteria used in the selection of municipalities.

Details of the recruitment plan are summarized in Appendix B.

Approximately 7000 subjects enrolled in study 10PN-PD-DIT-053 (112595) will contribute to the objectives of the current study.

4.2. Inclusion criteria

4.2.1. Selection criteria for municipalities

Clusters are defined to encompass selected municipalities based on the agreement for study participation obtained from the health care centre responsible for the municipality primary health care and well-baby clinics.

Note:

1. Health care centres with remote location or low annual birth cohorts (for instance the Åland and Northern Lapland municipalities) may not be offered study participation.
2. In some selected municipalities where no collaboration with health care centres has been set up, there is opportunity for parent(s) to let their child participate in study 10PN-PD-DIT-053 and receive the same vaccination as in the current study (see section 6.4.1).

4.2.2. Inclusion criteria for study participants

All subjects must satisfy the following criteria at enrolment:

- A male or female between, and including, 6 weeks to 18 months of age at the time of the first vaccination.
- Written informed consent obtained from the parent/guardian of the subject.

4.3. Exclusion criteria for enrolment

The following criteria should be checked at the time of enrolment. If any apply, the subject must not be included in the study:

- Previous vaccination with any registered, non-registered or investigational pneumococcal vaccine other than the study vaccine, or planned use during the study period. If a child belongs to a high risk group for pneumococcal infections (such as children with an anatomic or functional asplenia, HIV infection, chronic cardiac or respiratory disease (not asthma), diabetes, cochlear implant, CSF fistula or with significant immunodeficiency) for which a licensed pneumococcal conjugate vaccine is made locally available, the subject cannot be enrolled in the study and should be referred to the specific immunization program.
- Previous vaccination against Hepatitis B virus with any registered, non-registered or investigational vaccine, or planned use of such a vaccine other than the study vaccine during the study period.
- Previous vaccination against Hepatitis A virus with any registered, non-registered or investigational vaccine, or planned use of such a vaccine other than the study vaccine during the study period.
- Known severe hypersensitivity to any component of the study vaccines, including neomycin.

- Any medical condition that would contraindicate the initiation of routine immunization outside a clinical trial context.

4.4. Exclusion criteria for further study vaccination

Any vaccination with hepatitis A, hepatitis B and/or pneumococcal vaccine outside of the context of the study, when reported to the well-baby clinic nurse or physician, will be evaluated on a case by case basis in order to determine whether the subject can continue the study vaccination (see section 6.5.1 for details of procedure to maintain blinding).

4.5. Criteria for elimination from analyses

If any of the following criteria become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis for efficacy. See Section 9.2 for definition of study cohorts to be evaluated.

- Use of any pneumococcal vaccine other than the study vaccine.
- Any vaccination with pneumococcal vaccine given in a blinded manner following additional request for pneumococcal vaccination according to the procedures described in Section 6.5.1.

4.6. Contraindications to subsequent vaccination

The following adverse events (AEs) constitute absolute contraindications to further administration of 10Pn-PD-DiT, HAV and/or HBV vaccine:

- Known hypersensitivity to any of component of the study vaccines, including neomycin or signs of hypersensitivity after a previous 10Pn-PD-DiT, HAV or HBV dose.
- Any medical condition that would require discontinuation of routine immunization outside a clinical trial context.

4.7. Warnings and Precautions

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

As with other vaccines, the administration of 10Pn-PD-DiT, HAV and HBV should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication for immunisation.

As for other vaccines administered intramuscularly, 10Pn-PD-DiT, HAV and HBV vaccines should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

10Pn-PD-DiT, Havrix 720 Junior and Engerix B vaccine should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of 10Pn-PD-DiT.

GSK Biologicals' 10Pn-PD-DiT vaccine

10Pn-PD-DiT vaccine will not protect against pneumococcal serogroups other than those included in the vaccine. Although antibody response to diphtheria toxoid, tetanus toxoid and protein D (that is highly conserved in all *H. influenzae* strains) occurs, immunization with 10Pn-PD-DiT does not substitute routine immunization with diphtheria, tetanus or *H. influenzae* type b vaccines. Official recommendations for the immunisations against diphtheria, tetanus and *H. influenzae* type b should therefore also be followed.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Safety and immunogenicity data in children with increased risk for pneumococcal infections (such as sickle cell disease, congenital and acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome) are not available.

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. Data however, suggest that the use of prophylactic paracetamol might reduce the immune response to pneumococcal vaccines. The clinical relevance of this observation, as well as the impact of antipyretics other than paracetamol remain unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born $\leq$ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

GSK Biologicals' Havrix 720 Junior (HAV)

It is possible that subjects may be in the incubation period of a hepatitis A infection at the time of immunisation. It is not known whether HAV vaccine will prevent hepatitis A in such cases.

In haemodialysis patients and in subjects with an impaired immune system, adequate anti-HAV antibody titres may not be obtained after a single dose of HAV and such patients may therefore require administration of an additional dose of vaccine.

GSK Biologicals' Engerix B (HBV)

Because of the long incubation period of hepatitis B it is possible for unrecognised infection to be present at the time of immunisation. The vaccine may not prevent hepatitis B infection in such cases.

The vaccine will not prevent infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

In HIV infected patients, as also in haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titres may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine.

Thiomersal has been used in the manufacturing process of this medicinal product and residues of it are present in the final product. Therefore, sensitisation reactions may occur.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the Declaration of Helsinki, and local rules and regulations of the country.

Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favourable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

5.1.1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. The ICH Harmonised Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. At least one member who is independent of the institution/ study site**.**

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator. A list of the professions of the IRB/IEC members should be obtained by the investigator.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including subject recruitment procedures and information about payments and compensation available to subjects, will be submitted to the IRB/IEC by the investigator. Written and dated unconditional approval/favourable opinion from the IRB/IEC of the protocol and amendment (if any and applicable), written informed consent form, consent form updates (if any), subject recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to subjects must be in the possession of the investigator and GSK before commencement of the study. This approval/favourable opinion must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals' data will be supplied by the investigator to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of the unconditional approval/favourable opinion of the IRB/IEC will be transmitted by the investigator to GSK Biologicals' Study Monitor prior to shipment of vaccine supplies and eCRFs to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval/ favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or where permitted by all applicable regulatory requirements or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s].) Administrative changes and amendments not submitted for approval are submitted to the IRB/IEC for information only. However, written verification that such documents were submitted should be obtained. Approvals/ verifications must be transmitted in writing to GSK Biologicals' Study Monitor by the investigator.

The IRB/IEC must be informed by the investigator of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review,

- serious and/or unexpected adverse events occurring during the study, where required,
- all subsequent protocol administrative changes (for information, except for US studies),
- new information that may affect adversely the safety of the subjects or the conduct of the study,
- an annual update and/or request for re-approval, where required,
- when the study has been completed, where required.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix A for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to the subjects' parent(s)/guardian(s).

Freely given informed consent should be obtained from every subject's parent(s)/guardian(s) prior to clinical trial participation.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

Qualified nurses or physicians at well-baby clinics will describe the study to potential subjects' parent(s)/guardian(s) face to face. The Informed Consent Form will be given to the subjects' parent(s)/guardian(s), but, in any event, nurses or physicians shall give the subjects' parent(s)/guardian(s) ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form. While informed consent information can be presented to groups at an initial information session, each subject's parent/guardian must be given the opportunity to individually pose questions to the qualified nurses prior to the subjects' parent(s)/ guardian(s) dating and signing the Informed Consent Form. A physician responsible for the study at each health care centre can be contacted in case of any questions related to the study.

The informed Consent Form must be in a language fully comprehensible to at least one of the prospective subject's parent(s)/guardian(s). Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by one of the parents/guardians and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been

understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only if the parent'/guardian' incapacity precludes written informed consent, provided that the local legal obligations are fulfilled.

A copy of the signed and dated written informed consent form will be kept at well-baby clinics and the original will be sent to the investigator at ***THL*** on a regular basis (i.e. at least every month but preferably weekly). Each original subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The parent(s)/guardian(s) should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects' parent(s)/guardian(s), and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects' parent(s)/guardian(s). **(Amended 22 August 2011)**

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects' parent(s)/guardian(s) should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subjects' parent(s)'/guardian(s)' responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects' parent(s)/guardian(s) should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects' parent(s)/guardian(s) for participating in the trial.

l. The anticipated expenses, if any, to subjects' parent(s)/guardian(s) for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects' parent(s)/guardian(s) may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification

of clinical trial procedures and/or data, without violating the confidentiality of subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subjects' parent/guardian is authorising such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects' parent(s)/guardian(s) will be informed in a timely manner if information becomes available that may be relevant to the subjects' parent(s)/guardian(s) willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

u. The permission to use the Finnish personal identity code to link individual data from the different registers in Finland, without transferring the personal identity code to GSK Biologicals.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

5.2. General study aspects

5.2.1. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be organised for this study to protect the ethical and safety interests of the subjects recruited, while securing as much as possible the scientific validity of the data. The IDMC will review all-cause mortality and blinded primary endpoint cases.

Responsibilities of the IDMC include the following:

- Review of data collection methods, safety/effectiveness monitoring procedures and making recommendations for additions or adjustments, as applicable.
- Recommendations for maintaining, or breaking the blind where necessary, in the course of reviewing safety results.
- Recommendations for stopping the trial for effectiveness or safety reasons when appropriate.

5.2.2. Disease surveillance

5.2.2.1. Surveillance system for invasive diseases, pneumonia, tympanostomy tube placement and outpatient antimicrobial prescriptions

Data on invasive disease, pneumonia, tympanostomy tube placement and outpatient antimicrobial prescriptions will be collected using 3 main national registers:

- National Infectious Disease Register (maintained by THL)
- Finnish Care Register for Social Welfare and Health Care (maintained by THL)
- Social Insurance Institution Reimbursement Register (maintained by KELA)

All registers indicated above use the Finnish personal identity code in reporting and linking the data. This code is a 11-digit code given automatically to all new born children in Finland soon after birth.

Informed consent will include the permission to use the Finnish personal identity code for study purposes. These codes will however not be transferred to GSK Biologicals. For subjects not enrolled in the study but included in evaluation of herd protection, the permission to use the national register information will be requested from the Ministry of Social Affairs and Health (MoSAH).

1. **The National Infectious Disease Register**

The National Infectious Disease Register (NIDR) will be used to capture cases of invasive disease. This register is maintained by the National Institute for Health and Welfare (THL) Department of Infectious Disease ***Surveillance and Control*** (***TATO***) and includes data on a variety of bacterial pathogens including, but not limited to the following

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Corynebacterium diphtheriae*
- *Neisseria meningitidis*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*

(Amended 22 August 2011)

Cases of invasive diseases due to the bacteria are routinely reported by the laboratories all around Finland. Additionally, the isolates are sent to the THL laboratory for archiving and/or further serotyping. For the study purpose, serotyping using the Quellung method ***and/or PCR-based methodology***, antimicrobial sensitivity testing and molecular typing will be done to better characterise the isolates of *S. pneumoniae* and *H. influenzae.*
(Amended 22 August 2011)

For *S. pneumoniae* and *H. influenzae*, serotyping is usually performed in weekly batches. Overall, the register data accumulates on-line and the data are usually available within approximately 2 weeks.

Additional information in the register includes site of sampling, method of detection, name of the laboratory and name of the treatment facility.

For each ID case retrieved from registers and occurring in the vaccinated population, medical hospital records will be reviewed retrospectively by the investigator or designated study staff member for additional clinical information (focus of infection, intensive care unit (ICU) admission, duration of ICU treatment).

For ID cases occurring in the unvaccinated population, no further investigation in hospital medical records will be performed.

2. **The Finnish Care Registers for Social Welfare and Health Care**

The Finnish Care Registers for Social Welfare and Health Care will provide data on hospital-diagnosed pneumonia (overall clinical diagnoses) and tympanostomy tube placements (TTP). These registers are maintained by the National Institute for Health and Welfare (THL). Information in these registers is based on routine administrative reports of institutional discharges (for pneumonia) and of surgical operations including day-care surgery (for tympanostomy tube placements).

The coverage for day-care surgery conducted in private offices may be incomplete. Therefore, tympanostomy tube placements will also be retrieved from the KELA register (see below).

To ascertain complete case finding of the invasive diseases the clinical syndromes compatible with invasive diseases will also be searched from the Finnish Care Registers for Social Welfare and Health Care and combined with the NIDR data (see above).

ICD10 coding system is used for all the diagnoses in the register (the primary diagnosis as well as up to 2 secondary diagnoses available). The Nordic Medico-Statistical Committee (NOMESCO) has produced the Classification of Surgical Procedures (NCSP). In Finland, the national version is in use (NCSP-F). The applicable code for tympanostomy tube placement is DCA20 [NOMESCO, 2008].

For each identified pneumonia and/or TTP case at least the following information will be retrieved from the Finnish Care register: the current municipality of residence, hospital code, admission and discharge dates, medical specialty of the ward, need of care at discharge. ***CXRs from the hospital-diagnosed pneumonia cases in the vaccinated population will be collected and assessed by an independent review panel according to***

WHO guidelines [WHO, 2001; Cherian, 2005]. No further investigation in hospital medical records will be performed. **(Amended 22 August 2011)**

There is a considerable delay (approximately 11 months for the 2006 data) in the data availability as the data is released in yearly batches after submission of data from the hospitals and data validation.

3. **The Finnish Social Insurance Institution (KELA)**

The Finnish Social Insurance Institution (KELA) will provide data on outpatient antimicrobial prescriptions and tympanostomy tube placements. This register maintains an administrative reimbursement register including data on physicians' prescriptions and pharmacy purchases. Since no systemic antimicrobials are available in Finland without medical prescription, this register includes all outpatient antimicrobial prescriptions.

The register includes data on date of purchase, type of drug, amount purchased and costs incurred, but no structured coding for clinical indication for the prescription.

The coverage of this register is considered complete.

The register also includes the reimbursements for tympanostomy tube placements performed in private practices. These data are expected to be nearly complete as all major private offices use automated electronic reimbursing systems in cooperation with KELA.

5.2.2.2. Surveillance system for RTI

Surveillance of RTI, including AOM, will be done in a subset of ±1500 subjects in Turku area who also participate in a respiratory infection subcohort of study "Keys to a Good Childhood" lead by Turku Institute for Child and Youth research. Data will be collected using a RTI/AOM diagnosis form and will be recorded by the study staff in the study electronic case report form (eCRF).

The Finnish national consensus guidelines (Käypähoito suositus 2004) define the diagnostic criteria for acute otitis media (AOM) as presence of middle ear fluid and abnormal tympanic membrane finding together with a sign or signs of an acute infection (usually signs of concomitant respiratory infection). If tympanostomy tubes have been installed, an acute purulent discharge from ear(s) is also considered as AOM. The diagnosis is always confirmed by otoscopy done by a physician. Evaluation with tympanometer can provide supporting evidence for the presence or absence of AOM, but do not replace the otoscopy as the golden standard method. Otitis media with effusion (OME) is defined as presence of middle ear fluid and abnormal tympanic membrane without signs of an acute infection. While this is considered as part of the normal recovery process following AOM, the prolonged presence of middle ear fluid (over 2 months) is considered as an indication for tympanic tube placement for chronic ear infection/inflammation.

Respiratory tract infections will be diagnosed using ICD-10 coding system.

5.2.2.3. Case definitions

Invasive disease case definition

For study purposes, invasive disease is defined as any disease where *S. pneumoniae* or *H. influenzae* or other bacteria are identified either from normally sterile body fluids using culture or DNA and/or antigen detection tests. The invasive disease will be considered:

- as confirmed when *S. pneumoniae, H. influenzae* or other bacteria are isolated by culture.
- as probable when demonstration of *S. pneumoniae, H. influenzae* or other bacteria is based on DNA and/or antigen detection tests only, without isolation by culture as mentioned above.

To further evaluate ID cases in the vaccinated population, data on the following clinical syndromes of focal invasive disease will be also extracted from the medical records of each case identified in the registers:

- Bacteraemia: isolation of the above-mentioned bacteria from the blood culture but not from the CSF sample (or CSF sample not available).
- Bacteraemia without focus: bacteraemia without any other focus of infection.
- Meningitis: isolation and/or detection of the above-mentioned bacteria from the CSF sample or bacteraemia accompanied by a hospital discharge diagnosis of meningitis.
- Bacteraemic pneumonia: positive blood culture for *S. pneumoniae, H. influenzae* or other bacteria and discharge diagnosis of pneumonia.
- Empyema: isolation of *S. pneumoniae, H. influenzae* or other bacteria from pleural fluid.
- Septic arthritis: isolation of *S. pneumoniae, H. influenzae* or other bacteria from synovial fluid.
- Peritonitis: isolation of *S. pneumoniae, H. influenzae* or other bacteria from peritoneal fluid.
- Osteomyelitis: isolation of *S. pneumoniae, H. influenzae* or other bacteria from bone aspirate.
- Pericarditis: isolation of *S. pneumoniae, H. influenzae* or other bacteria from pericardial fluid.
- Soft tissue infection: isolation of *S. pneumoniae, H. influenzae* or other bacteria from abscess aspirated material or any other sample tissue sample.

No further investigation in hospital medical records will be performed for ID cases occurring in the unvaccinated population.

Pneumonia definitions

The cases of hospital-diagnosed pneumonia will be identified based on hospital discharge diagnosis as defined by the ICD10 diagnosis set by the treating physician.

Chest X-ray ***images from the hospital-diagnosed pneumonia cases in the vaccinated population*** will be ***evaluated by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005]*** for the study purpose. ***The 4 outcomes that could be attributed to the CXRs are (1) consolidation, (2) non-consolidation, (3) no pneumonia or (4) uninterpretable CXR. Based on the outcome attributed to the CXRs, the pneumonia cases will be classified for the purposes of this study based on the concepts and definitions mentioned hereunder.***

CXR pneumonia is defined as a pneumonia case with the presence of abnormal pulmonary infiltrates on the CXR as per the judgement of the independent review panel. These abnormal pulmonary infiltrates can be either with or without alveolar consolidation/pleural effusion.

- ***Pneumonia with alveolar consolidation or pleural effusion (CXR-AC pneumonia) is defined as CXR pneumonia with alveolar consolidation or pleural effusion on the CXR.***
- ***Non-consolidated pneumonia (CXR-NAC pneumonia) is defined as CXR pneumonia without alveolar consolidation (no alveolar infiltrates) or pleural effusion on the CXR.***

No pneumonia is defined as a CXR without abnormal pulmonary infiltrates.

(Amended 22 August 2011)

Outpatient pneumonia diagnosis without subsequent hospitalization will be based on available data in the hospital outpatient clinics (diagnosis data for primary care outpatient clinics not available).

ICD10 diagnosis codes J10.0, J11.0, J12-J18, J85.1 and J86 as the primary, secondary or tertiary diagnosis will be collected into the study database and considered to define the diagnosis of hospital-diagnosed clinical pneumonia. Within this broad definition ICD10 diagnoses of J13, J14, J15, or J18 will be considered as hospital-diagnosed clinical bacterial pneumonia.

Tympanostomy tube placement definition

Tympanostomy tube placement is defined by the applicable NCSP code (DCA20) in the THL and KELA registers. An event of tympanostomy tube placement (defined by the use of the above mentioned code) can refer to an unilateral or a bilateral tympanostomy tube placement procedure.

Lower respiratory tract infection (LRTI)

LRTIs such as, but not limited to, bronchitis, obstructive bronchitis, bronchiolitis, pneumonia, bronchopneumonia, pleural effusion or empyema as diagnosed by a physician and documented in the medical file or other source document.

Upper respiratory tract infection (URTI)

URTIs such as but not limited to: rhinosinusitis, rhinorrhea, conjunctivitis, orbital celullitis, pharyngitis, laryngitis, tonsillitis, epiglottitis or sinusitis as diagnosed by a physician and documented in the medical file or other source document.

AOM

- Level 1 of diagnostic certainty: AOM episode defined as AOM event diagnosed by a physician according to the Finnish AOM management guidelines (confirmed cases) and documented in medical records or other source document (RTI/AOM diagnose form completed by diagnosing physician or copy of medical records available).
- Level 2 of diagnostic certainty: AOM case reported with Level 1 of diagnostic certainty plus positive result of bacteria in middle ear fluid (after spontaneous perforation or tympanocentesis).

Complicated AOM

A complicated AOM episode is defined an AOM episode associated with perforation, mastoiditis, labyrinthitis, Bell's palsy, petrositis, meningitis, epidural abscess, sepsis, cerebral vein thrombosis or any other complication with timely and causal relationship to the AOM as assessed by the investigator.

5.2.3. Data collection and management

Data collected at well-baby clinics

At enrolment, the following data will be collected by nurses or physicians at well-baby clinics on the informed consent form (ICF): personal identity code, consent date, date of first vaccination (if different than consent date), cluster/treatment number, eligibility criteria. Original ICFs will be sent to the investigator on a regular basis (i.e. preferably weekly and at least every month). The investigator and/or designate will enter data from the ICF into the GSK Biologicals' RDE system without the Finnish personal identity codes.

According to the routine vaccination procedure, all vaccination dates are recorded in a vaccination sheet or in the electronic patient records at well-baby clinics. Vaccination data will be sent to the investigator at THL after completion of all study vaccinations. Dates of study vaccination will be entered into the GSK Biologicals' RDE system for:

- all subjects enrolled in the study - date of first vaccination
- a random subset of 2000 subjects (1000 subjects in the infant cohort and 1000 subjects in the catch-up groups) - all vaccination dates
- all subjects reporting ID - all vaccination dates

Collection of adverse events following immunisation (AEFIs) will be performed on ongoing basis through the passive safety surveillance system in Finland (see section 7.1).

Data collected at THL

In addition to data collected by qualified nurses/physicians at well-baby clinics, additional data will be collected at THL:

- data on invasive disease, pneumonia, tympanostomy tube placement and outpatient antimicrobial prescriptions will be collected from the national health registers for the vaccinated and unvaccinated population, as described in section 5.2.2.1:

  For each ID case retrieved from registries and occurring in the vaccinated population, hospital medical records will be reviewed retrospectively by the investigator or designated study staff for additional clinical information (focus of infection, ICU admission, duration of ICU treatment). ***CXRs from the hospital-diagnosed pneumonia cases in the vaccinated population will be collected and assessed by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005].*** For the other health outcome data in the vaccinated population and all health outcome data in the unvaccinated population, no further investigation in hospital medical records will be performed. **(Amended 22 August 2011)**

- demographic baseline data will be collected retrospectively from the Medical Birth Register of the National Research and Development Centre for Welfare and Health (maintained by THL) for the vaccinated and unvaccinated population.

  This register includes a range of variables like infant's gestational age at delivery and weight at birth. The data will allow assessment of potential selection bias during the enrolment period, distribution of confounding factors, and robustness analyses.

Data in the national registers will be collected at THL through linkage of registers using the Finnish personal identity code. Copies of datasets, including registry data, will be transferred in separate batches from THL to GSK Biologicals without the Finnish personal identity codes.

The population centre database will be used to update place of residence for the vaccinated, if needed, and unvaccinated population.

Data collected at "Keys to a Good Childhood" study clinic

Data will be collected at "Keys to a Good Childhood" study clinic in Turku from the children whose parent/guardian has given consent to participate in "Keys to a Good Childhood" study. Data collected include personal identity code, clinical symptoms and otoscopy findings together with their severity, and viral/bacterial culture results from samples taken according to study protocol titled "Recurrent respiratory infections in children: viral-bacterial synergism, environmental factors, and genetic susceptibility".

Data from source documents (such as RTI/AOM diagnosis form) will be encoded by study staff into GSK Biologicals' RDE system using subject identification number without personal identity code.

5.2.4. Recruitment process

As this study is conducted in close collaboration with the health care centres in their facilities, a formal agreement on participating in the trial should be obtained from each health care centre considered for this trial. Once a formal approval is obtained from the health care centre, the municipalities involved (or their defined areas) can be randomly allocated to the different treatment clusters in a blinded fashion with regard to the vaccine that will be administered. Subsequently, informed consent will be obtained at an individual level from parent(s)/guardian(s) from each participating subject.

Refer to Appendix B for details of the recruitment plan.

5.3. Subject identification

A unique study-specific subject identification number will be assigned to each subject enrolled in the study.

5.4. Outline of study procedures

During the study, there will be scheduled visits at well-baby clinics and, only in Turku area, unscheduled visits. Unscheduled visits will take place on an as needed basis, and will be reported in the RTI/AOM diagnosis form (see section 5.4.2).

5.4.1. Scheduled visits and study procedures for all subjects

Table 1 List of study procedures applicable for all subjects

Visit **Vaccination**	**VISIT 1** **Dose 1**	**VISIT 2** **Dose 2**	**VISIT 3(1)** **Dose 3**	**VISIT 4(2)** **Dose 4**
Informed consent	●			
Check inclusion criteria	●			
Check exclusion criteria for enrolment	●			
Check exclusion criteria for further study vaccination		**O**	**O**	**O**
Check warnings, precautions and contraindications	**O**	**O**	**O**	**O**
Identification of cluster treatment according to subject's area of residence	●			
Vaccination with study vaccines	●	**O**(3)	**O**(3)	**O**(3)
Reporting of SAEs	●	●	●	●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
Note:
[1]Vaccination visit 3 is only applicable for children that are less than 12 months of age when enrolled into the study (either for the 3rd primary dose for infants enrolled in their first 7 months of life in a 3+1 cluster, or for the booster dose in children enrolled in their first 7 months of life in a 2+1 cluster and children enrolled between 7 and 11 months of age).
[2]Vaccination visit 4 is only applicable for the booster dose in infants enrolled in their first 7 months of life in a 3+1 cluster.
[3]Vaccination dates will be documented on the vaccination sheet or in the electronic patient records at well-baby clinics and will be transferred to the investigator at THL after completion of all study vaccinations.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed.

Table 2 Intervals between study visits for all subjects

For children enrolled between 6 weeks and 6 months of age and in the 3+1 clusters

Interval	Size of interval	Age range
1 (Visit 1 → Visit 2)	≥ 28 days	-
2 (Visit 2 → Visit 3)	≥ 28 days	-
3 (Visit 3 → Visit 4)	at least 4 months but preferably 6 months	-
Visit 4	-	≥ 11 months of age

For children enrolled between 6 weeks and 6 months of age in the 2+1 clusters

Interval	Size of interval	Age range
1 (Visit 1 → Visit 2)	≥ 56 days	-
2 (Visit 2 → Visit 3)	at least 4 months but preferably 6 months	-
Visit 3	-	≥ 11 months of age

For children enrolled between 7 and 11 months of age

Interval	Size of interval
1 (Visit 1 → Visit 2)	≥ 28 days
2 (Visit 2 → Visit 3)	at least 4 months but preferably 6 months

For children enrolled between 12 and 18 months of age

Interval	Size of interval
1 (Visit 1 → Visit 2)	at least and preferably 6 months

5.4.2. Unscheduled visits and study procedures applicable only for subjects in Turku area

Children who participate in study "Keys to a Good Childhood" and belong to the respiratory infection subcohort of that study are asked to contact "Keys to a Good Childhood" study clinic in Turku in case the child has symptoms of respiratory tract infection. In the study clinic, physical examination including otoscopy will be performed by study physician and data on clinical symptoms and otoscopy findings will be recorded on source documents (such as RTI/AOM diagnosis form) by nurses/physicians of "Keys to a Good Childhood"study. AOM will be diagnosed according to Finnish national consensus guidelines (Käypähoito suositus 2004). Nasal swab will be taken for virology according to study protocol titled "Recurrent respiratory infections in children: viral-bacterial synergism, environmental factors, and genetic susceptibility". Similarly, a MEF sample for microbiological analysis will be collected in case of spontaneous perforation of tympanic membrane or excreting tympanic tube.

5.5. Detailed description of scheduled study visits at well-baby clinics applicable for all subjects

Visit 1 All subjects (first dose)

- Written Informed Consent
- Check inclusion criteria
- Check exclusion criteria for enrolment
- Check warnings, precautions and contraindications to vaccination
- Identification of cluster treatment number as described in section 6.4.1.
- Vaccination: intramuscular administration of one dose of the study vaccine according to the guidelines set out in Section 6.2.

  The nurses will be instructed to observe the vaccinees closely for at least 30 minutes with the appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of any study vaccine.

The nurses will be instructed to describe to the parents the most common anticipated symptoms after vaccinations, e.g. injection site reactions and/or fever or irritability of mild severity. If other and/or more severe symptoms occur after vaccination the subject's parents/guardians will be instructed to contact the well-baby clinic nurse or physician.

- Report to THL serious adverse event with fatal outcome, or other serious adverse events according to the existing routine safety reporting in Finland (see Sections 7.1 and 7.2 for details).

The nurses will be instructed to ask subject's parents/guardians to inform the well-baby clinic nurse or physician if any of the following occur during the study period:

- Use of any hepatitis A, hepatitis B and/or pneumococcal vaccine other than the study vaccine.
- Any additional request for hepatitis A, hepatitis B or pneumococcal vaccines.

Visit 2 - All subjects (second dose)
Visit 3 - Children that are less than 12 months of age when enrolled into the study (either for the 3rd primary dose for infants enrolled in their first 7 months of life in a 3+1 cluster, or for the booster dose in children enrolled in their first 7 months of life in a 2+1 cluster and children enrolled between 7 and 11 months of age).
Visit 4 -For the booster dose in infants enrolled in their first 7 months of life in a 3+1 cluster.

- Check exclusion criteria for further study vaccination
- Check warnings, precautions and contraindications to vaccination

- Vaccination: intramuscular administration of one dose of the study vaccine according to the guidelines set out in Section 6.2.

  The nurses will be instructed to observe the vaccinees closely for at least 30 minutes with the appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of any study vaccine.

The nurses will be instructed to describe to the parents the most common anticipated symptoms after vaccinations, e.g. injection site reactions and/or fever or irritability of mild severity. If other and/or more severe symptoms occur after vaccination the subject's parents/guardians will be instructed to contact the well-baby clinic nurse or physician.

- Report to THL serious adverse event with fatal outcome, or other serious adverse events according to the existing routine safety reporting in Finland (see Sections 7.1 and 7.2 for details).

The nurses will be instructed to ask subject's parents/guardians to inform the well-baby clinic nurse or physician if any of the following occur during the study period:

- Use of any hepatitis A, hepatitis B and/or pneumococcal vaccine other than the study vaccine.
- Any additional request for hepatitis A, hepatitis B or pneumococcal vaccines.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

6.1. Study vaccines

The 10Pn-PD-DiT vaccine to be used has been developed and manufactured by GSK Biologicals. The Quality Control Standards and Requirements for the 10Pn-PD-DiT vaccine are described in separate release protocols and the required approvals have been obtained.

The commercial GSK Biologicals' Havrix 720 Junior and Engerix B vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics (SPC).

Table 3 Formulation of vaccines

Vaccine	Formulation (per dose)	Presentation	Vol. (mL)
Study vaccine: GSK Biologicals' 10-valent Pn-PD-DiT vaccine	Protein D carrier: 1 μg of each capsular PS for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F, and 3 μg for serotype 4 conjugated to PD. Tetanus toxoid carrier: 3 μg of capsular PS of serotype 18C conjugated to TT. Diphteria toxoid carrier: 3 μg of capsular PS of serotype 19F conjugated to DT. Protein carrier content: ~ 12 μg PD, ~ 4.5 μg DT, ~ 7 μg TT. 0.5 mg aluminium (Al^{3+}) as aluminium phosphate adjuvant.	Whitish liquid in vial or pre-filled syringe	0.5
Control vaccine: GSK Biologicals' HBV vaccine (Engerix B™)	HBsAg: 10μg Aluminium as salt: 0.25 mg	Whitish liquid in vial or prefilled syringe	0.5
Control vaccine: GSK Biologicals' HAV vaccine (Havrix™ 720 Junior)	HAV (strain HM 175) 720 EL.U Aluminium as salt: 0.25 mg	Whitish liquid in vial or pre-filled syringe	0.5

6.2. Dosage and administration

Table 4 Dosage and Administration

Visit	Dose	Vaccine	Route	Site
1, 2, 3*, 4**	1, 2, 3*, 4**	10Pn-PD-DiT	Intramuscular	Thigh or Deltoid region of the upper arm[1]
1, 2, 3*, 4**	1, 2, 3*, 4**	HBV	Intramuscular	Thigh or Deltoid region of the upper arm[1]
1, 2	1, 2	HAV	Intramuscular	Thigh or Deltoid region of the upper arm[1]

[1]Only applicable for children aged ≥ 12 months if the size of the deltoid muscle is adequate.
*Vaccination visit 3/Dose 3 is only applicable for children that are less than 12 months of age when enrolled into the study (either for the 3rd primary dose for infants enrolled in their first 7 months of life in a 3+1 cluster, or for the booster dose in children enrolled in their first 7 months of life in a 2+1 cluster and children enrolled between 7 and 11 months of age).
**Vaccination visit 4/Dose 4 is only applicable for the booster dose in infants enrolled in their first 7 months of life in a 3+1 cluster.

The study vaccine will be administered by qualified nurses/physicians at the well-baby clinics. With the exception of hepatitis A, hepatitis B and/or pneumococcal vaccines, other licensed paediatric vaccines may be administered or co-administered during the study period and will not be considered as study vaccines. Additional requests for hepatitis A, hepatitis B and/or pneumococcal vaccines will be managed on a case by case basis, as outlined in Section 6.5.1.

The nurses will be instructed to observe the vaccinees closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

6.3. Storage

Study vaccines will be stored according to the manufacturer's instructions and in accordance with the local regulations and guidance.

All study vaccines to be administered to subjects will be instructed to be stored in a safe and locked place with restricted access.

Study vaccines will be instructed to be stored at the manufacturer's defined temperature range (i.e. +2 to +8°C).

The storage temperature of study vaccines will be monitored using routine surveillance measures in place in the well-baby clinics. The temperature measurements will be recorded during working days, preferably at the same time of the day (e.g. at the beginning of the day). Freezing indication device to be placed close to the vaccines will be provided.

A specific temperature deviation management procedure will be set up and will be described in detail in a separate study-specific ***procedure manual (see latest version)***.

This ***study-specific procedure manual*** will also describe storage conditions for transport of the study vaccines from the warehouse to the dispatching centres (hospital pharmacies and/or medical centre pharmacies) or from dispatching centres to health care centres and well-baby clinics. **(Amended 22 August 2011)**

6.4. Treatment allocation and randomisation

6.4.1. Randomization of clusters

For the purpose of this cluster-randomized study, the municipalities of the participating health care centres will be mapped into 72 clusters with average yearly birth cohort ranging from around 400 to 1350 subjects.

The 72 clusters will be allocated to either

- Forty-eight 10Pn-PD-DiT clusters in which subjects below 7 months of age will receive 10Pn-PD-DiT according to a 2- or 3-dose dose primary vaccination schedule (1:1 randomization ratio of clusters, 24 clusters for each schedule). Subjects living in these 10Pn-PD-DiT clusters and enrolled between 7 and 18 months of age will receive 10Pn-PD-DiT catch-up immunization.
- Twenty-four control clusters in which subjects below 7 months of age will receive HBV vaccine according to a 2- or 3-dose primary vaccination schedule (1:1 randomisation ratio of clusters, 12 clusters for each schedule). Subjects living in these control clusters and enrolled <12 months of age will receive HBV immunization, whereas subjects enrolled ≥ 12 months of age will receive HAV vaccination.

In addition, some selected municipalities such as Espoo, Vantaa and surroundings municipalities and municipalities surrounding Oulu where vaccination is offered only in study 10PN-PD-DIT-053 are organised in 6 additional clusters maintaining the cluster randomization ratio 2:2:1:1. Therefore the total number of clusters is 78.

The complete cluster randomization ratio would thus be 2:2:1:1. The randomization will consist in a blocking scheme randomization stratified according to:

- a dichotomous factor being big cities (urban area) versus complement (rural area). This would approximately split the 72 clusters according to a 1:2 division, where big cities would comprise 1/3 of the 72 clusters,
- the cluster size (below versus above the average size) in order to ensure a reasonable balance of subjects in all treatment groups,
- clusters located in regions participating in study 10PN-PD-DIT-053 (112595) or in the acute otitis media and recurrent respiratory infection cohort study in Turku.

All supplies allocated to a cluster will be identified with a cluster treatment number.

6.4.2. Randomization of subjects

Not applicable.

6.4.3. Randomization of supplies

Not applicable.

6.5. Method of blinding and breaking the study blind

This study will be conducted in a double-blind fashion for vaccine/control clusters applying the same 2+1 or 3+1 infant schedule. Study will be open between infant schedules.

6.5.1. Provisions made to maintain blinding

Additional study supplies will be made available to avoid unblinding in case of medical requests for hepatitis A, hepatitis B and/or pneumococcal vaccination or in case of cluster change (relocation of the family).

In the event that there is a medical request for hepatitis and /or pneumococcal vaccination or a cluster change (relocation), the well-baby clinics nurse or physician will contact the local coordination centre (see contact details in Sponsor Information page) to obtain further details on the vaccine and procedure to be used. Previous vaccination history, including vaccines administered outside the current study, will need to be taken into account when deciding which of the following additional study vaccine supplies can be administered. The medical request for additional vaccination may be managed by provision of additional blinded vaccines in order to maintain the study blinding, or by advising the subjects' parent(s)/guardian(s) to obtain a prescription for commercially

available licensed vaccines to be purchased at the pharmacy by the subject's parent(s)/guardian(s) similar to how the parent(s)/guardian(s) would have proceeded if their child/ward would not have been participating in the study. For more details of the vaccine and procedure applied for these cases refer to Appendix D.

Additional study supplies will be identified by a treatment number and will be given in a blinded manner in the well-baby clinics. Treatment allocation by the THL contact person will be performed using a central randomisation system on internet (SBIR).

After study unblinding, blinded vaccine provided for all ongoing vaccinations due to medical requests will be kept available for completion of vaccination. New medical requests after study unblinding will not require this procedure.

6.5.2. Breaking the study blind

The investigator, or person designated by the investigator, should contact GSK Biologicals' Central Safety physician directly or via the local safety contact (see below and Study Contact for Emergency Code Break in Sponsor Information page) to discuss the need for emergency unblinding. The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s).

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) is to unblind any serious adverse event (SAE) report associated with the use of the investigational product, which is unexpected and attributable/suspected, prior to regulatory reporting. The Clinical Safety physician is responsible for unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs (Refer to Section 7.2.9). Blinded Investigator safety reports will be sent to the investigator.

GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)
Phones for 7/7 day availability: +32 10 85 64 00 (GSK Biologicals Central Safety Physician on-call) Back-up phone contact: +32 10 85 64 01

6.6. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix C for details of supplies).

In case a single vaccine dose is broken or unusable, the nurse at well baby clinics should replace it with another dose of the same cluster treatment number. Although the sponsor need not be notified immediately in these cases (except in the case of cold-chain failure), the use of the replacement vaccine must be appropriately documented.

6.7. Packaging

See Appendix C.

6.8. Vaccine accountability

See Appendix C.

6.9. Concomitant medication/treatment

At any time during the study period, concomitant medication administered for the treatment of a notified SAE must be recorded on the SAE screens in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which SAE), total daily dose, route of administration, start and end dates of treatment. Refer to Section 7 for definition of SAE.

7. SERIOUS ADVERSE EVENTS

The nurses will be instructed to describe to parents the most common anticipated symptoms after vaccinations, e.g. injection site reactions and/or fever or irritability of mild severity. If other and/or more severe symptoms occur after vaccination the subject's parents/guardians will be instructed to contact the well-baby clinic nurse or physician.

Safety reporting will be done through the routine passive safety surveillance in place in Finland, based on spontaneous reporting.

Any additional non-fatal event in the study subject(s) found in health outcome registers and meeting the criteria of seriousness, but not reported to THL via the existing passive surveillance system will not be required to be reported to GSK Biologicals and will therefore not be encoded as SAE in the study database.

For reporting of fatal adverse events, the available register data (e.g. Finnish Care Register and population register data) will also be used as sources of information in addition to the spontaneous reports from well-baby clinic nurses and/or parents. Any additional event with fatal outcome found in registers but not reported to THL via the existing passive surveillance system will be reported to GSK Biologicals and will be encoded in study database.

7.1. Surveillance for adverse events following immunisation (AEFI) in Finland

Health care professionals are responsible for reporting serious and/or unexpected adverse reactions following immunisation (AEFI) to the National Institute for Health and Welfare (THL) by using a specific form (AEFI form) designed for this purpose (decree no. 421/2004 given by the Ministry of Social Affairs and Health).

A list of serious adverse and/or unexpected reactions to be reported by healthcare professionals to the Vaccine Safety Unit of the Department of Vaccines at ***THL*** is provided in Appendix E. **(Amended 22 August 2011)**

The adverse event following immunisation (AEFI) form used routinely in passive surveillance system in Finland will be the primary method for safety reporting to the investigator and/or designate during the study period. The healthcare professional will send the AEFI report form by mail or by fax to the Vaccine Safety Unit of the Department of Vaccines at THL without undue delay. In urgent cases the reporting can be also done by phone. Additional or follow-up information relating to the initial suspected adverse event report is also to be completed and submitted with an AEFI form immediately.

The AEFI form includes among others, the following information: identification of the subject (Personal Identification code, birth date, name), sex, time and place of vaccination, vaccines administered (including vaccine type, trade name, lot number, route of administration, site of injection, number of dose of that specific vaccine), symptoms/findings, start date, time, duration of the symptoms, time from vaccination (separately for each symptom, if more than one), contact information of the physician and the place of treatment. In addition, some extra questions about the location and extent of the symptoms are asked as well as medical history data (i.e. history of previous AEFIs).

There are 23 pre-defined different symptoms/findings listed in the form to make the reporting standardized and easier for the reporter.

The reporting parties are requested to attach a copy of the medical records of the event when sending the reporting form.

The surveillance and investigation of AEFIs has been nationally centralized to the THL. All reports are sent directly to the Vaccine Safety Unit of the Department of Vaccines of THL. This unit enters information on reports to an electronic AEFI register.

Any AEFIs reported to the investigator and/or designate via existing passive surveillance and judged by the investigator and/or designate to meet the definition of a serious adverse event (SAE) as defined in section 7.2.1, will be further reported to GSK Biologicals (see section 7.2).

7.2. Reporting of Serious Adverse Events to GSK Biologicals

7.2.1. Definition of a serious adverse event to be reported to GSK Biologicals

An event is defined as ‘serious’ when it meets one of the pre-defined outcomes described below:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalisation or prolongation of existing hospitalisation,

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

7.2.2. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events and serious adverse events

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, vital signs) that are judged by the investigator and/or designate to be clinically significant will be considered as SAEs if they meet the definition of a SAE, as defined in section 7.2.1. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator and/or designate as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as SAEs.

The investigator and/or designate will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

7.2.3. Time period, frequency, and method of detecting serious adverse events

The investigator and/or designate is required to report to GSK Biologicals, any SAEs notified for subjects enrolled in the study from the day of receipt of first dose of study vaccine until study unblinding. See Section 7.2.6 for instructions for reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs notified to THL for subjects enrolled in the study, that are related to study participation (e.g. protocol-mandated procedures, a change from existing therapy) or are related to a concurrent GSK medication will be recorded from the time the subject consents to participate in the study until study unblinding.

After study unblinding, reporting of individual SAEs to GSK will no longer be required. SAEs notified to THL via the passive safety surveillance system following study unblinding will however be summarized in 6-monthly safety reports to be submitted to GSK Biologicals and IDMC for a period of 18 months after study unblinding (three 6-monthly safety reports).

When the investigator and/or designate becomes aware of a SAE, it is his/her responsibility to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator and/or designate will then record all relevant information regarding a SAE in the SAE screens in the eCRF. It is not acceptable for the investigator and/or designate to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms**.**

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 7.2.6 for details of the back-up reporting system.

7.2.4. Assessment of causality

The investigator and/or designate is obligated to assess the relationship between the investigational product and the occurrence of each SAE notified to THL via the routine

passive surveillance system in place in Finland, for subjects enrolled in the study. The investigator and/or designate will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator and/or designate will follow the recommendations of WHO, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator and/or designate has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator and/or designate always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator and/or designate may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of SAEs to the individual vaccines administered. The investigator should, therefore, assess whether the SAE could be causally related to vaccination rather than to the individual vaccines.

Causality of SAEs should be assessed by the investigator and/or designate using the following question:

Is there a reasonable possibility that the SAE may have been caused by the study vaccines?

NO	:	The SAE is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the SAE.
YES	:	There is a reasonable possibility that the vaccine(s) contributed to the SAE.

If an event meets the criteria to be determined “serious” (see Section 7.2.1 for definition of serious adverse event), it will be examined by the investigator and/or designate to the extent to be able to determine ALL contributing factors applicable.

Other possible contributors include:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

7.2.5. Follow-up of serious adverse events reported to GSK Biologicals and assessment of outcome

After the initial report of a SAE documented as not recovered/not resolved or recovering/resolving, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

Investigators will follow-up subjects with SAEs, until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject must be made available to the Study Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE Report screens in the eCRF. The updated SAE Report screens in the eCRF should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 7.2.6.

In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 7.2.6 for details of the back-up reporting system.

Outcome of any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal.

7.2.6. Prompt reporting of serious adverse events to GSK Biologicals

The SAE screens in the eCRF will be the primary method for reporting SAEs to GSK Biologicals until study unblinding. In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs**.**

7.2.7. Time frames for submitting serious adverse event reports to GSK Biologicals

SAEs notified to THL for subjects enrolled in the study will be reported promptly to GSK Biologicals once the investigator determines that the event meets the protocol definition of an SAE. The investigator and/or designate will complete and submit relevant information on the SAEs in the SAE screens in eCRF **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS.** Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information at THL.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator and/or designate will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting. During the study, the investigator and/or designate should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours) and before using it to report additional information.

7.2.8. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator and/or designate becomes aware of a SAE that occurred in a study subject, the investigator and/or designate will complete and submit the information in the SAE screens in eCRF as outlined in Section 7.2.7. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator and/or designate. If the investigator and/or designate does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional information is received **WITHIN 24 HOURS** as outlined in Section 7.2.7.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 7.2.4.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator and/or designate will report relevant information on SAEs to GSK within the 24 hours as outlined in Section 7.2.7. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator, and forwarded to GSK within the designated time frames. If the investigator and/or designate does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. When occurring during the study period, the investigator and/or designate should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours). When additional information is received on a SAE reported to GSK using the back-up paper SAE Report Form during the study period, the electronic system should be used to report the additional information within 24 hours if the electronic system is working again and only after updating the SAE screens in eCRF once the electronic system was working again.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be resent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information as outlined in Section 7.2.7.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator and/or designate to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used) as outlined in Section 7.2.7.

In the event of a death determined by the investigator and/or designate to be related to vaccination, completion of SAE screens in the eCRF / sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs. Please see Sponsor Information Sheet for contact details of the Study Contact for Reporting SAEs.

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety & Pharmacovigilance Fax: +32 2 656 51 16 or +32 2 656 80 09 **24/24 hour and 7/7 day availability**

7.2.9. Regulatory reporting requirements for serious adverse events

The investigator and/or designate will promptly report all SAEs notified for study subjects to GSK in accordance with the procedures detailed in Section 7.2. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator and/or designate to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.

In order to comply with local regulation, blinded summaries of invasive disease cases will be submitted to Competent Authorities every 6 months as of the time point when the data on ID cases are available to the Sponsor.

Blinded investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

7.2.10. Post-study serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE detection period defined in Section 7.2.3. Investigators are not obligated to actively seek SAEs in former study participants.

However, if the investigator and/or designate learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator and/or designate will promptly notify the Study Contact for Reporting SAEs**.**

After freezing of the study participant's eCRF, if SAE follow-ups or new SAEs have to be reported, the investigators and/or designate should use paper SAE Report Forms and the facsimile (Fax) system.

7.2.11. Treatment of serious adverse events

Treatment of any SAE is at the sole discretion of the physician responsible for the child's medical care and according to current good medical practice. Any medication administered for the treatment of a SAE should be recorded in the SAE section of the subject's eCRF. Refer to Section 6.9.

8. SUBJECT WITHDRAWAL

8.1. Subject withdrawal from administration of study vaccine

A 'withdrawal' from the administration of study vaccine is any subject whose parent(s)/guardian(s) withdraw consent for receiving further study vaccination. For these subjects, no further doses of study vaccine will be administered from the date of consent withdrawal.

A subject withdrawn from the administration of study vaccine will not be withdrawn from further register follow-up. For this subject, information from registers will continue to be collected during the study and used for analysis purposes.

Information relative to withdrawal from further study vaccination will be documented on the medical records at the well-baby clinics.

8.2. Subject withdrawal from register follow-up

A 'withdrawal' from register follow-up is any subject whose parent(s)/guardian(s) withdraw consent for the administration of the study vaccine as well as the register

follow-up. For these subjects, no further dose of study vaccine will be administered and no further information from registers will be collected from the date of consent withdrawal.

Information relative to the withdrawal from register follow-up will be documented on the medical records at well-baby clinics or at THL. In addition, the information on withdrawal from register follow-up will be transferred to the investigator at THL on a regular basis (i.e. at least every month but preferably weekly) and encoded in the study database.

9. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

9.1. Endpoints

9.1.1. Primary endpoint

In children starting vaccination within the first 7 months of life *in clusters assigned to a 3-dose primary vaccination course* (Amended 22 August 2011):

- Occurrence of culture-confirmed IPD due to any of the 10 pneumococcal vaccine serotypes.

9.1.2. Secondary endpoints

In children starting vaccination within the first 7 months of life in clusters assigned to a 2-dose primary vaccination course):

- ***Occurrence of culture-confirmed IPD due to any of the 10 pneumococcal vaccine serotypes.***

(Amended 22 August 2011)

In the vaccinated population:

- Occurrence of culture-confirmed ID caused by any of the bacterial pathogens listed below:
  - any and each of the 10 pneumococcal vaccine serotypes
  - any and each of the vaccine-related pneumococcal serotypes
  - any and each of the other pneumococcal serotypes
  - any and each of the *Haemophilus influenzae* types
  - any other bacterial pathogen.
- Occurrence of probable cases of ID caused by the bacterial pathogens as listed above.

- Occurrence of hospital-diagnosed pneumonia cases.
- ***Occurrence of hospital-diagnosed pneumonia cases with abnormal pulmonary infiltrates on the chest X-ray (CXR pneumonia) based on the CXR reading according to WHO criteria.***
- ***Occurrence of hospital-diagnosed pneumonia cases with alveolar consolidation/pleural effusion on the CXR (CXR-AC pneumonia) based on the CXR reading according to WHO criteria.***
- ***Occurrence of hospital-diagnosed pneumonia cases without alveolar infiltrates or pleural effusion on the CXR (CXR-NAC pneumonia) based on the CXR reading according to WHO criteria.***

  (Amended 22 August 2011)
- Occurrence of tympanostomy tube placements.
- Occurrence of outpatient antibiotic prescriptions.
- Antimicrobial susceptibility of *S. pneumoniae* and *H. influenzae* isolated from invasive disease.
- Occurrence of LRTIs (in a subset of ± 1500 subjects in Turku area).
- Occurrence of URTIs, including AOM (in a subset of ± 1500 subjects in Turku area).

In the unvaccinated population:

- Occurrence of culture-confirmed ID caused by the bacterial pathogens as listed above.
- Occurrence of probable cases of ID caused by the bacterial pathogens as listed above.
- Occurrence of hospital-diagnosed pneumonia cases.
- Occurrence of tympanostomy tube placements (*only in children ≤7 years of age*).
- Occurrence of outpatient antibiotic prescriptions (*only in children ≤7 years of age*).

9.2. Study cohorts to be evaluated

Three cohorts will be considered based on subjects enrolled in study 10PN-PD-DIT-043 and study 10PN-PD-DIT-053 (112595).

9.2.1. Total Vaccinated cohort

The Total Vaccinated cohort will include all subjects enrolled who received at least one dose of study vaccine. The **Infant Vaccinated cohort** will include all subjects vaccinated with first dose of study vaccine below 7 months of age and the **Catch-up Vaccinated cohort** will include all subjects vaccinated with first dose of study vaccine at or above 7 months of age.

The analysis of effectiveness based on this cohort will include all events occurring after vaccination with first dose of study vaccine.

9.2.2. Unvaccinated cohort

The unvaccinated cohort will include all subjects not enrolled in the study but who live in the study cluster areas. The analysis of effectiveness based on this cohort will include all events occurred and diagnosed 6 months after study start.

9.2.3. According-To-Protocol (ATP) cohort for analysis of effectiveness

The ATP cohort for analysis of effectiveness will include all subjects enrolled who received the study vaccine according to the protocol defined immunization schedule for their age group and cluster assignment. Subjects who meet elimination criteria (as defined in Section 4.5) may be eliminated from the ATP cohort for analysis of efficacy.

The analysis of total effectiveness based on this cohort will include for infants: events diagnosed 2 weeks after the last protocol defined primary vaccination dose in infants who received their protocol defined primary doses in the age of 13 months the latest and their booster dose in the age of 20 months the latest. For instance, an event in an infant who received the last primary vaccination dose beyond 13 months of age will be discarded. Likewise an event beyond 20 months of age will be discarded in an infant who did not receive the booster dose before month 20 but any event occurring during the period between 2 weeks after dose 3 and ***20*** months of age will be included. **(Amended 22 August 2011)**

9.3. Estimated sample size

9.3.1. Primary *and first secondary* objectives - Total effect

The power of this study to reach the primary objective ***or the first secondary objective*** is driven by the total number of IPD cases ***that will be reported during the ID follow-up (at least 30 months from study start)***. ***Based on the approximately 31 000 infants enrolled in this study and in the nested study 10PN-PD-DIT-053 (112595), and on revised assumptions of accrual of IPD cases, it is estimated that a total of 23 IPD cases could be collected in the infant cohort in all treatment groups by the end of January 2012 (see Figure 1). Assuming a proportion between 70 and 80% vaccine-serotypes (based on current observations), this translates into around 12 to 18 total VT IPD cases in the infant cohort at the end of the follow-up period.***

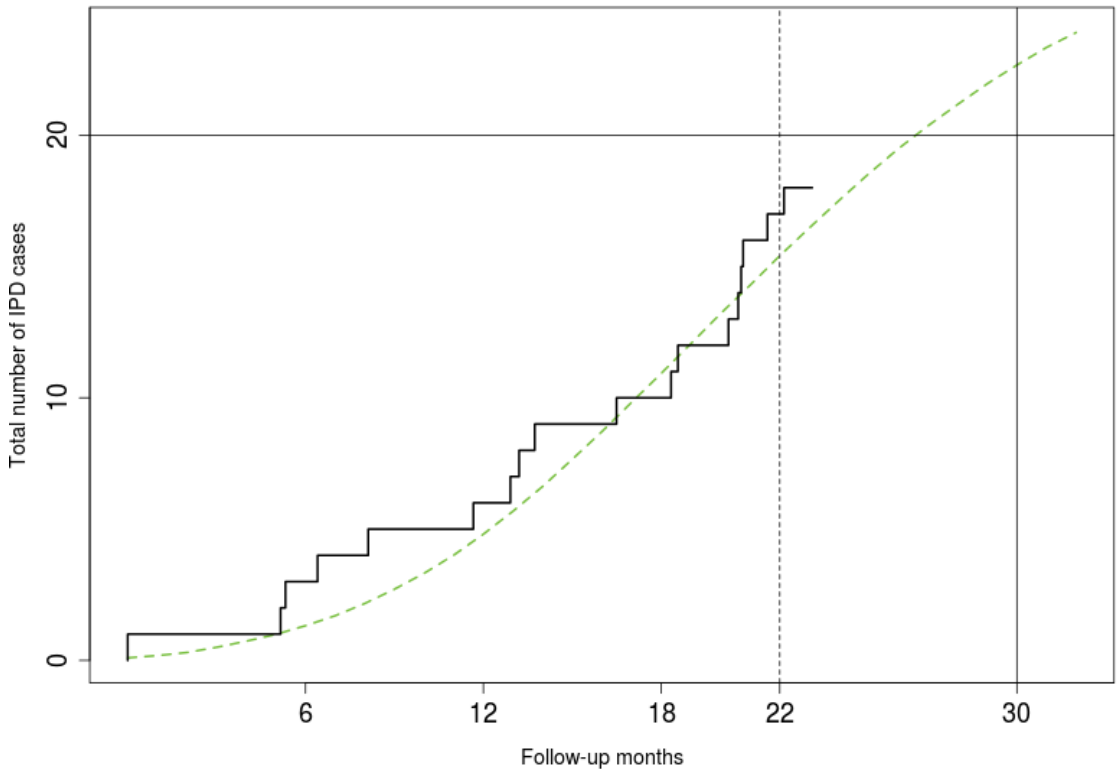
The effectiveness of 10Pn-PD-DiT to prevent vaccine-type IPD cases in subjects vaccinated with at least one dose of 10Pn-PD-DiT according to a ***3***-dose or ***2***-dose primary vaccination course will be computed for each schedule tested in 24 clusters compared to the ***pooled*** 24 control clusters.

Considering for both the ***3***-dose or the ***2***-dose primary vaccination course a 90%, 85% or 80% VE**,** a 0.12 or a 0.38 coefficient of variation between clusters ***and a*** number of ***10 to***

15 vaccine-type IPD cases in the ***pooled*** control group***s, Table 5*** provide***s*** the power ***to demonstrate vaccine efficacy in a 3-dose or 2-dose primary vaccination course***.

(Amended 22 August 2011)

Figure 1 Estimated (dotted line) and actual (solid line) accrual of IPD cases in the infant cohort (all treatment groups, all serotypes) until May 2011.



Note: Assumptions were (i) VT proportion 80% of all IPD; (ii) Vaccine effectiveness 90% on VT IPD; (iii) baseline IPD incidence in Finland before the trial

(Amended 22 August 2011)

Table 5 Power to demonstrate a statistically significant effect of 10Pn-PD-DiT in preventing vaccine-type IPD cases in the Infant Vaccinated cohort: each of both schedules vs Control; 24:24 clusters allocation (2 sided type I error=5%) – Total follow-up

Expected number of cases in *pooled* control clusters (Amended 22 August 2011)	VE	Total Expected number of cases in *pooled* control & one of the two 10Pn group of clusters (Amended 22 August 2011)	Coefficient of variation between clusters	Power[1]
15	90% 85% 80%	16.5 17.3 18.0	12%[2]	95.7% 90.1% 85.8%
12	90% 85% 80%	13.2 13.8 14.4	12%	91.0% 84.3% 76.1%
10	90% 85% 80%	11.0 11.5 12.0	12%	85.9% 77.1% 69.3%
15	90% 85% 80%	16.5 17.3 18.0	38%[3]	95.2% 90.8% 82.9%
12	90% 85% 80%	13.2 13.8 14.4	38%	90.1% 82.6% 73.6%
10	90% 85% 80%	11.0 11.5 12.0	38%	84.2% 73.8% 66.6%

[1] Power based on 1000 simulations using a negative binomial model with equal sized cluster and a log-likelihood ratio test (see analysis section for details).
[2] Estimate from negative binomial model, based on Infectious Disease Register data; IPD aggregated on a cluster level.
[3] Estimate from model for binomial proportions, based on Infectious Disease Register data; IPD aggregated on a hospital district level. **(Amended 22 August 2011)**

9.3.2. Indirect effect

The expected number of IPD cases due to any of the 10 vaccine serotypes in the population starting and older than 5 years, assuming no pneumococcal vaccination is shown per age group in Table 6. A total of 400 cases could be expected in all the population over 5-years old in one calendar year. It is assumed that the recruited clusters will cover 90% of Finland, thus meaning that the expected number of cases in recruited clusters will be 360 per year.

Table 6 Expected number of IPD cases in one calendar year

Age group (years)	Expected IPD cases	Expected vaccine type IPD cases[(1)]
[0,5)	111.25	83.44
[5,10)	9.50	7.12
[10,15)	4.50	3.38
[15,20)	7.50	5.62
[20,25)	13.50	10.12
[25,30)	15.50	11.62
[30,35)	21.50	16.12
[35,40)	29.50	22.12
[40,45)	43.75	28.44
[45,50)	44.75	29.09
[50,55)	47.00	30.55
[55,60)	69.25	45.01
[60,65)	67.00	40.20
[65,70)	54.25	32.55
[70,75)	50.00	30.00
[75,80)	52.00	31.20
[80,85)	42.75	25.65
[85,90)	31.50	18.90
[90,95)	16.00	9.60
[95,100)	2.75	1.65
[100,105)	1.00	0.60
TOTAL in [5,105)	623.50	399.54

(1) Note that the expected number of IPD cases due to any of the 10 vaccine serotypes is estimated assuming a proportion of 10Pn-PD-DiT-serotypes of 75% for [0-40), 65% for [40-60), and 60% for [60-105] year age-groups. Assumed proportions are obtained from the National Infectious Disease Register during years 2004 to 2006.

The estimated indirect vaccine effectiveness (VE) in the unvaccinated population based on study start in 1st quarter of 2009, could be as shown in Table 7. These VEs will be used for power computations.

Table 7 Assumptions of vaccine effectiveness in the unvaccinated population

	VE (%)
2nd half 2009	0
1st half 2010	20
2nd half 2010	30
1st half 2011	40
2nd half 2011	40

Based on a follow-up period of interest starting 6 months after the recruitment start, and ending 24 months after study start, i.e. 1.5 year in total, a coefficient of variation between clusters of 0.12 and the combined 2+1 and 3+1 schedules for the estimation of the indirect effect (i.e. 48 treatment clusters and 24 control clusters) the power for the indirect effectiveness would be 44.7%. Considering an extension of the follow-up up to 30 months after study start, i.e. 2 years in total, this power will become 81.9%.

As part of the 0-5 year old population will also be included in the analysis of the indirect effect on unvaccinated individuals, these powers are conservative estimates (see section 9.5.3.2).

9.4. Derived and transformed data

Not applicable.

9.5. Final analyses

9.5.1. Analysis of demographics/baseline characteristics

Demographic baseline data will be summarized per group and per age strata for each cohort. In addition, baseline data, as well as the vaccination dates for a random subset of 2000 subjects, will be used for robustness analysis of the primary effectiveness results (see Section 9.5.3.1), in order to evaluate possible imbalance due to randomization.

9.5.2. Analysis of safety

The analysis will be performed on the Total Vaccinated cohort.

Serious adverse events (SAEs) will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects with SAE(s) and its exact 95% CI will be tabulated by group and by MedDRA preferred term. The same tabulation will be performed for fatal SAEs and SAEs considered by the investigator to be causally related to vaccination.

Exploratory signal detection will be conducted by comparing the number of subjects with SAE between clusters using a Poisson regression model generalized to account for over-dispersion (i.e. negative binomial regression on number of events with log as link function and log of cluster size as offset). The model will include the group and the stratification factors as covariates. A potential signal will be identified as a 2-sided log-likelihood ratio p-value for the null hypothesis of no group difference < 5%. Adjustment for multiple comparisons will be based on a double ‘false discovery rate’ (FDR) [Mehrotra, 2004].

9.5.3. Analysis of effectiveness

9.5.3.1. Total effectiveness

The primary analysis of total effectiveness will be based on comparisons of numbers of vaccine-type IPD in the Infant Vaccinated cohort considering events occurring following administration of the first vaccine dose (total follow-up). Secondary analyses will be based on comparisons of numbers of vaccine-type IPD in the Total Vaccinated cohort (both infant and catch-up) during the total follow-up and in the Infant Vaccinated cohort or ATP cohort for analysis of effectiveness considering events occurring 2 weeks or more after completion of primary immunization (per protocol follow-up).

The number of subjects with vaccine-type IPD in each cluster will be compared between groups in a sequential manner. 10Pn_3+1 clusters will be first compared to the combined 3+1 and 2+1 control clusters in order to demonstrate positive vaccine effectiveness. If positive vaccine effectiveness was demonstrated in the 10Pn_3+1 clusters, 10Pn_2+1 clusters will be subsequently compared to the combined 3+1 and 2+1 control clusters in order to demonstrate positive vaccine effectiveness. These comparisons will be done using a Poisson regression model generalized to account for over-dispersion (i.e. negative binomial regression model fitted to the number of vaccine types IPD in clusters with log as link function and log of cohort sizes within clusters as offset term). The model will include the group and the stratification factors as covariates. Statistical difference between groups will be based on a 2-sided log-likelihood ratio p-value for the null hypothesis of no group difference < 5%.

This model will be applied to derive the VE, as 1 minus Relative Risk (RR).

In case the model cannot be adjusted due to the low number of events (convergence issue due to over-parametrisation), the analysis will be replaced by a comparison of the number of clusters with a least one event. Conditionally on the total number of clusters with at least one event, the number of treatment clusters with at least one event is binomially distributed and a 2-sided p-value for the null hypothesis of no group difference (= 2*min of one-sided test) < 5% will be used as criteria for statistical significance.

Secondary endpoints about ID will also be analysed in terms of comparisons of culture-confirmed ID or probable cases of ID in the Total Vaccinated cohort (infant and/or catch-up) or the ATP cohort for analysis of effectiveness (infant only).

Pneumonia, tympanostomy tube placements, outpatient antibiotic prescriptions ***and*** RTI, including AOM**,** will only be analysed in the Total vaccinated cohort. **(Amended 22 August 2011)**

9.5.3.2. Indirect effectiveness

For the primary analysis of indirect effectiveness, numbers of vaccine-type IPD in the Unvaccinated cohort occurred and diagnosed 6 months after study start will be compared between the treatment groups. For this evaluation, 10Pn_3+1 and 10Pn_2+1 clusters (total of 48 clusters) will be combined, and compared to 24 control clusters. The same model as for the analysis of total effectiveness (see section 9.5.3.1) will be applied for the primary indirect effectiveness analysis. For the analysis, vaccine-type IPD cases are placed in their appropriate clusters according to the place of residence at the time of the disease onset. For the offset term, the cohort size within each cluster is determined as the cluster's population size at the start of the study.

9.5.4. Planned interim analysis

No interim analysis is planned.

10. ADMINISTRATIVE MATTERS

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix A for details.

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Appendix A Administrative Matters

I. Responsibilities of the Investigator

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities and equipment which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae or Investigator Biography and other credentials (e.g., medical license number in the United States) to GSK and—where required—to relevant authorities. It is recommended that this documentation indicates any previous clinical research experience and history of training in GCP.
- To prepare and maintain adequate subject source data or raw data designed to record observations, and other data pertinent to the study.
- To conduct the study in compliance with the protocol any amendment and "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To permit drug regulatory agencies and GSK audits.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRBs/IECs for information only.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety

reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site preferably within 10 working days of becoming available. SAEs will be entered into a computer within 24 hours of the investigator becoming aware of the SAE. The site will be capable of modifying the data to assure accuracy with source documentation. New/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.

Specific instructions for use of RDE will be included in the training material provided to THL.

V. Monitoring by GSK Biologicals

To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place at THL early in the study, during the study at appropriate intervals and after the last subject has completed the study. Monitoring visits will be performed for a representative subset of subjects and well-baby clinics. It is anticipated that monitoring visits will occur at a frequency defined and communicated to the investigator before study start.

These visits are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study). Direct access to all study-related site and source data/ documents is mandatory for the purpose of monitoring review. The monitor will perform a CRF review and a Source Document verification (verifying database entries by comparing them with the source data/documents that will be made available by the investigator for this purpose: any data item for which the CRF will serve as the source must be identified, agreed and documented). Data to be recorded directly into database will be specified in writing preferably in the source documentation agreement form that is contained in both the

monitor's and investigator's study file. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits. Source data verification (SDV) must be conducted using a GSK standard SDV sampling strategy (as defined at the study start in the study specific monitoring guidelines) in which monitors will perform partial SDV for all subjects and full SDV for selected subjects.

VI. Archiving of Data

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit drug regulatory agencies and GSK audits, providing direct access to source data/ documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application, Biologics Licensing Application.

Having the highest quality data and studies are essential aspects of vaccine development. GSK has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that GSK Biologicals'

sponsored studies are in accordance with GCP and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. GSK's audits entail review of source documents supporting the adequacy and accuracy of eCRFs, review of documentation required to be maintained, and checks on vaccine accountability. GSK's audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- Study personnel
- Study file
- Safety reporting
- IRB/IEC and regulatory authority approvals
- Facilities
- monitoring
- Vaccine accountability
- Approved study protocol and amendments and investigator brochure
- Informed consent of the subjects (written consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of eCRF data
- Reports to the IRB/IEC and the sponsor
- Record retention.

GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 (twenty-one) days [or at least 15 (fifteen) working days for abstracts/posters/presentations]. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

Appendix B Overview of the Recruitment Plan

The study will be performed in 72 pre-defined Finnish clusters. In addition, some selected municipalities such as Espoo, Vantaa and surroundings municipalities and municipalities surrounding Oulu where vaccination is offered only in study 10PN-PD-DIT-053 are organised in 6 additional clusters according the same cluster randomization ratio (2:2:1:1). Therefore the total number of clusters is 78. The enrolled study population is estimated at approximately 91,000 subjects (± 58 000 subjects starting vaccination below or at 6 months of age and ± 33 000 subjects starting vaccination between 7 and 18 months of age). ***At the time of protocol amendment 2, the final enrolled study population in this trial included approximately 47 000 subjects (approximately 31 000 subjects starting vaccination below 7 months of age and approximately 16 000 subjects starting vaccination from 7 up to 18 months of age).***

(Amended 22 August 2011)

Monitoring of actual enrolment against target enrolment will be performed on a monthly basis; the frequency of monitoring visits will be adapted to the pace of enrolment.

The recruitment period will last approximately 14 months.

To encourage participation in the study and to achieve recruitment targets on time, various methods that are acceptable within local regulations will be used. All recruitment material intended for parents will be submitted for approval by the local ethics committee. Recruitment material may include, but it is not limited to, short information leaflets, information binders at well baby clinics, advertisements in news media, posters, open website with updated information. Additionally, telephone centre and e-mail contact for informing parents will be established. In big municipalities, public presentations of the study will be organized. To raise awareness of the study also press releases will be published and articles in different media will be promoted.

The specific terms for the achievement of recruitment targets and criteria for the termination of enrolment at a particular centre will be addressed in the investigator’s financial agreement.

Vaccinations are planned to take place in well-baby clinics.

Appendix C Vaccine supplies, packaging and accountability

1. Vaccine

GSK Biologicals will supply the following study vaccines, sufficient number of doses to administer to all subjects as described in the present protocol.

- 10Pn-PD-DiT vaccine in monodose vial or pre-filled syringe
- Havrix 720 Junior vaccine in monodose vial or pre-filled syringe
- Engerix B vaccine in monodose vial or pre-filled syringe

An appropriate amount of the study vaccines will be supplied for replacement in case of breakage, bad storage conditions or any other reason that would make the vaccine unusable (i.e. given by mistake to another subject).

All monodose vials or prefilled syringes must be accounted for on the form provided. Syringes or vials will be identified by a treatment number.

The investigator or pharmacist or delegate must sign a statement that he/she has received the clinical supplies for the study (vaccines and the study documentation).

It is NOT permitted to use any of the supplies provided by GSK Biologicals for purposes other than those specified in the protocol.

2. Vaccine packaging

The vaccines will be packed in labelled boxes. The box label will contain, as a minimum, the following information: study number, cluster treatment number, lot number (or numbers, when double-blind), instructions for vaccine administration and any other relevant regulatory requirements.

3. Vaccine shipment from GSK Biologicals Rixensart, Belgium to local warehouse, dispatching centres (i.e. hospital pharmacies and/or medical centre pharmacies) or health care centres and well-baby clinics.

Upon reception of the shipment, its content, quality and maintenance of the cold-chain must be checked.

The supplies receipt documents must then be returned to:

Attention of Clinical Trial Supplies Unit
GSK Biologicals Rixensart
Fax : +32 (0)2 656 75 17
E-mail: rix.ugCTSU@gskbio.com.

A specific temperature deviation management procedure will be set up and will be described in detail in a separate study-specific ***procedure manual (see latest version)***.
(Amended 22 August 2011)

4. Vaccine accountability

At all times the figures on supplied, used and remaining vaccine doses should match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. Monitoring visits to review the vaccine accountability records will be performed for a representative subset of subjects and well-baby clinics. Accountability and reconciliation for ***these*** subjects will be done based on completed documentation as described ***i***n ***the latest version of the*** study-specific ***procedure manual***. An explanation must be given of any discrepancies. **(Amended 22 August 2011)**

After approval from GSK Biologicals and in accordance with GSK ***SOP_54826***, used and unused vaccine vials should be destroyed at the study site using locally approved biosafety procedures and documentation unless otherwise described in the protocol. If no adequate biosafety procedures are available at the study site, the used and unused vaccine vials are to be returned to an appropriate GSK Biologicals site for destruction, also in accordance with current GSK ***SOP_54826***. **(Amended 22 August 2011)**

5. Transfers of clinical vaccines or products from warehouse to dispatch centres (i.e. hospital pharmacies and/or medical centre pharmacies) and from dispatch centres to health care centres and well-baby clinics

All transfers of clinical vaccines or products must be documented, storage temperatures must be maintained during transport and deviations must be reported to GSK for guidance as described ***i***n ***the latest version of the*** study-specific ***procedure manual***. **(Amended 22 August 2011)**

All packaging and shipment procedures for transfer of clinical vaccines or products are in accordance with the Medicine Act 1987/395, the Good Distribution Practice Regulations 4/2007 and Activities in Hospital Pharmacies and Medical Centre Pharmacies 7/2007 from the National Agency for Medicines (NAM).

Appendix D Medical request for additional vaccination

In case of a medical request for additional vaccination, blinded vaccine supplies will be provided according to the age at which vaccination was requested and the age at enrolment. Options for different orders of 1st, 2nd and 3rd request are described below:

- 1st request: the vaccine for which there is a medical need based on increased risk or susceptibility to complications.
- 2nd request: the vaccine for which there is a medical need in a subject for which 1st request vaccines have already been ordered.
- 3rd request: the vaccine for which there is a medical need in a subject for which both 1st and 2nd request vaccines have already been ordered.

1. Medical request for vaccination for children below 12 months of age

In case of a medical request for a child below 12 months of age, additional blinded vaccine supplies will be provided according to the age at enrolment, as described in Table 8 for children enrolled between 6 weeks and 6 months of age and in Table 9 for children enrolled between 7-11 months of age.

Table 8 Additional blinded study supplies and schedule recommended in case of medical request for vaccination for children below 12 months of age and enrolled between 6 weeks and 6 months of age

	1st request	2nd request	3rd request		1st request	2nd request	3rd request		1st request	2nd request	3rd request
Cluster [schedule]	**HBV**	**PCV**	**HAV**		**PCV**	**HBV**	**HAV**		**HAV**	**PCV**	**HBV**
10Pn_2+1 and 10Pn_3+1 [0-(1)-2-9 mo]	HBV [0-1-7 mo]	AP or 10Pn 1 dose^	open		HBV [0*-1-2-8 mo]	AP	open		HAV can not be requested for children below 12 months of age		
Control_2+1 and Control_3+1 [0-(1)-2-9 mo]	10Pn [0-1-7 mo]	AP or 10Pn 1 dose^	open		10Pn [0-1-2-8 mo]	AP	open				

option below for different order of 2nd and 3rd requests

	HBV	HAV	PCV		PCV	HAV	HBV		HAV	HBV	PCV
10Pn_2+1 and 10Pn_3+1 [0-(1)-2-9 mo]	HBV [0-1-7 mo]	open	AP or 10Pn 1 dose^		HBV [0*-1-2-8 mo]	open	AP		HAV can not be requested for children below 12 months of age		
Control_2+1 and Control_3+1 [0-(1)-2-9 mo]	10Pn [0-1-7 mo]	open	AP or 10Pn 1 dose^		10Pn [0-1-2-8 mo]	open	AP				

Note: schedule “0-1-2-8 mo” means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 2 months after Dose 1, Dose 4 – 8 months after Dose 1.
schedule “0-1-2-9 mo” means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 2 months after Dose 1, Dose 4 – 9 months after Dose 1.
schedule “0-1-7 mo” means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 7 months after Dose 1

^ In 2+1 clusters.

* In 10Pn_2+1 clusters, the first dose will be a 10Pn-PD-DiT vaccine dose to ensure optimal individual protection of children at high risk for pneumococcal infections.

Mo: months

Open: Commercial vaccines to be purchased on prescription at the pharmacy at subjects' parent(s)/guardians cost

AP: Already protected through earlier vaccinations

PCV: pneumococcal conjugate vaccine. HBV: GSK Biologicals’ Hepatitis B vaccine (Engerix B). HAV: GSK Biologicals’ Hepatitis A vaccine (Havrix 720 Junior).

10Pn: 10Pn-PD-DiT vaccine

Table 9 Additional blinded study supplies and schedule recommended in case of medical request for vaccination for children below 12 months of age and enrolled between 7-11 months of age

Cluster [schedule]	1st request	2nd request	3rd request	1st request	2nd request	3rd request	1st request	2nd request	3rd request
	HBV	**PCV**	**HAV**	**PCV**	**HBV**	**HAV**	**HAV**	**PCV**	**HBV**
10Pn_2+1 and 10Pn_3+1 [0-1-6 mo]	HBV [0-1-7 mo]	AP	open	HBV [0-1-7 mo]	AP	open	HAV can not be requested for children below 12 months of age		
Control_2+1 and Control_3+1 [0-1-6 mo]	10Pn [0-1-7 mo]	AP	open	10Pn [0-1-7 mo]	AP	open			

option below for different order of 2nd and 3rd requests

	HBV	**HAV**	**PCV**	**PCV**	**HAV**	**HBV**	**HAV**	**HBV**	**PCV**
10Pn_2+1 and 10Pn_3+1 [0-1-6 mo]	HBV [0-1-7 mo]	open	AP	HBV [0-1-7 mo]	open	AP	HAV can not be requested for children below 12 months of age		
Control_2+1 and Control_3+1 [0-1-6 mo]	10Pn [0-1-7 mo]	open	AP	10Pn [0-1-7 mo]	open	AP			

Note: schedule "0-1-6 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 6 months after Dose 1
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 7 months after Dose 1

Mo: months
Open: Commercial vaccines to be purchased on prescription at the pharmacy at subjects' parent(s)/guardians cost
AP: Already protected through earlier vaccinations
PCV: pneumococcal conjugate vaccine
HBV: GSK Biologicals' Hepatitis B vaccine (Engerix B)
HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 720 Junior)
10Pn: 10Pn-PD-DiT vaccine

2. Medical request for vaccination for children aged 12 months or above

In case of a medical request for a child aged 12 months or above, additional blinded vaccine supplies will be provided according to the age at enrolment, as described in Table 10 for children enrolled between 6 weeks and 6 months of age and in Table 11 for children enrolled between 7 -11 months of age and in Table 12 for children enrolled between 12-18 months of age.

Table 10 Additional blinded study supplies and schedule recommended in case of medical request for vaccination for children aged 12 months or above and enrolled between 6 weeks and 6 months of age

	1st request	2nd request	3rd request		1st request	2nd request	3rd request		1st request	2nd request	3rd request
Cluster [schedule]	**HBV**	**PCV**	**HAV**		**PCV**	**HBV**	**HAV**		**HAV**	**PCV**	**HBV**
10Pn_2+1 and 10PN_3+1 [0-(1)-2-9 mo]	HBV [0-1-7 mo]	HAV [0*-1-7 mo]	AP		HAV [0*-1-7 mo]	HBV [0-1-7 mo]	AP		open	HBV [0*-1-7 mo]	AP or HBV 1 dose^
Control_2+1 and Control_3+1 [0-(1)- 2-9 mo]	HAV [0-1-7 mo]	10Pn [0-1-7 mo]	AP		10Pn [0-1-7 mo]	HAV [0-1-7 mo]	AP		open	10Pn [0-1-7 mo]	AP
option below for different order of 2nd and 3rd requests											
	HBV	**HAV**	**PCV**		**PCV**	**HAV**	**HBV**		**HAV**	**HBV**	**PCV**
10Pn_2+1 and 10Pn_3+1 [0-(1)-2-9 mo]	HBV [0-1-7 mo]	HAV [0-1*-7 mo]	AP		HAV [0*-1-7 mo	HBV [0-1-7 mo]	AP		open	HBV [0-1-7 mo]	AP
Control_2+1 and Control_3+1 [0-(1)-2-9 mo]	HAV [0-1-7 mo]	10Pn [0-1-7 mo]	AP		10Pn [0-1-7 mo	HAV [0-1-7 mo]	AP		open	10Pn [0-1-7 mo]	AP

Note: schedule "0-1-2-9 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 2 months after Dose 1, Dose 4 – 9 months after Dose 1.
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 7 months after Dose 1
Request of HAB will be treated like HAV+HBV consecutive

^ In 2+1 clusters.

* In 10Pn_2+1 clusters, this dose will be a 10Pn-PD-DiT vaccine dose to ensure optimal individual protection of children at high risk for pneumococcal infections.

Mo: months

Open: Commercial vaccines to be purchased on prescription at the pharmacy at subjects' parent(s)/guardians cost

AP: Already protected through earlier vaccinations

PCV: pneumococcal conjugate vaccine

HBV: GSK Biologicals' Hepatitis B vaccine (Engerix B)

HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 720 Junior)

10Pn: 10Pn-PD-DiT vaccine

Table 11 Additional blinded study supplies and schedule recommended in case of medical request for vaccination for children aged 12 months or above and enrolled between 7-11 months of age

	1st request	2nd request	3rd request		1st request	2nd request	3rd request		1st request	2nd request	3rd request
Cluster [schedule]	**HBV**	**PCV**	**HAV**		**PCV**	**HBV**	**HAV**		**HAV**	**PCV**	HBV
10Pn_2+1 and 10Pn_3+1 [0-1-6 mo]	HBV [0-1-7 mo]	HAV [0-1-7 mo]	AP		HBV [0-1-7 mo]	AP	open		open	HBV [0-1-7 mo]	AP
Control_2+1 and Control_3+1 [0-1-6 mo]	HAV [0-1-7 mo]	10Pn [0-1-7 mo]	AP		10Pn [0-1-7 mo]	AP	open		open	10Pn [0-1-7 mo]	AP
option below for different order of 2nd and 3rd requests											
	HBV	**HAV**	**PCV**		**PCV**	**HAV**	**HBV**		**HAV**	**HBV**	**PCV**
10Pn_2+1 and 10Pn_3+1 [0-1-6 mo]	HBV [0-1-7 mo]	HAV [0-1-7 mo]	AP		HBV [0-1-7 mo]	open	AP		open	HBV [0-1-7 mo]	AP
Control_2+1 and Control_3+1 [0-1-6 mo]	HAV [0-1-7 mo]	10Pn [0-1-7 mo]	AP		10Pn [0-1-7 mo]	open	AP		open	10Pn [0-1-7 mo]	AP

Note: schedule "0-1-6 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 6 months after Dose 1.
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 7 months after Dose 1
Request of HAB will be treated like HAV+HBV consecutive
Request of PCV and HAV at the same time will be treated like PCV+HAV consecutive
Request of PCV and HBV at the same time will be treated like PCV+HBV consecutive

Mo: months
Open: Commercial vaccines to be purchased on prescription at the pharmacy at subjects' parent(s)/guardians cost
AP: Already protected through earlier vaccinations
PCV: pneumococcal conjugate vaccine
HBV: GSK Biologicals' Hepatitis B vaccine (Engerix B)
HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 720 Junior)
10Pn: 10Pn-PD-DiT vaccine

Table 12 Additional blinded study supplies and schedule recommended in case of medical request for vaccination for children aged 12 months or above and enrolled between 12-18 months of age

	1st request	2nd request	3rd request	1st request	2nd request	3rd request	1st request	2nd request	3rd request
Cluster [schedule]	**HBV**	**PCV**	**HAV**	**PCV**	**HBV**	**HAV**	**HAV**	**PCV**	**HBV**
10Pn_2+1 and 10Pn_3+1 [0-6 mo]	open	HAV [0*-1-7 mo]	AP	HAV [0*-1-7]	open	AP	HAV [0-1*-7 mo]	HBV [0-1-7 mo]	AP
Control_2+1 and Control_3+1 [0-6 mo]	open	10Pn [0-1-7 mo]	AP	10Pn [0-1-7 mo]	open	AP	HBV [0-1-7 mo]	10Pn [0-1-7 mo]	AP
option below for different order of 2nd and 3rd requests									
	HBV	**HAV**	**PCV**	**PCV**	**HAV**	**HBV**	**HAV**	**HBV**	**PCV**
10Pn_2+1 and 10Pn_3+1 [0-6 mo]	open	HAV [0-1*-7 mo]	AP	HAV [0*-1-7 mo]	AP	open	HAV [0-1*-7 mo]	HBV [0-1-7 mo]	AP
Control_2+1 and Control_3+1 [0-6 mo]	open	10Pn [0-1-7 mo]	AP	10Pn [0-1-7 mo]	AP	open	HBV [0-1-7 mo]	10Pn [0-1-7 mo]	AP

Note: schedule "0-6 mo" means : Dose 1 – at chosen date, Dose 2 – 6 months after Dose 1.
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month after Dose 1, Dose 3 – 7 months after Dose 1
Request of HAB will be treated like HBV+HAV consecutive
Request of PCV and HBV at the same time will be treated like PCV+HBV consecutive
Request of PCV and HAV at the same time will be treated like PCV+HAV consecutive

* This dose will be a 10Pn-PD-DiT vaccine dose to ensure optimal individual protection of children at high risk for pneumococcal infections.

Mo: months

Open: Commercial vaccines to be purchased on prescription at the pharmacy at subjects' parent(s)/guardians cost

AP: Already protected through earlier vaccinations

PCV: pneumococcal conjugate vaccine

HBV: GSK Biologicals' Hepatitis B vaccine (Engerix B)

HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 720 Junior)

10Pn: 10Pn-PD-DiT vaccine

Appendix E Serious adverse and/or unexpected reactions to be reported to the National Public Health Institute

The serious adverse and/or unexpected reactions to be reported by the health care personnel to the National Institute for Health and Welfare (THL) are described in the THL 'Vaccinator's Handbook' (*Rokottajan käsikirja*) 2005, section 5 / vaccine adverse reactions, updated in February 2008, available via the Internet:

http://www.thl.fi/portal/suomi/julkaisut/oppaat_ja_kirjat/rokottajan_kasikirja/taulukot/taulukko_20/

The concept of a vaccine adverse reaction always includes at least a suspicion that the adverse event has a causal relationship to the vaccine.

If a healthcare professional suspects or has found out that a vaccine has caused an adverse reaction, he/she must notify about it to the Vaccine Unit at THL. As defined by the Decree 421/2004 on vaccinations, at least serious or unexpected reactions caused by a vaccination must be reported. It is worthwhile also to report other significant events.

The list of vaccine adverse reactions to be notified to the Vaccine Unit at THL is provided in the table below:

Serious Adverse Reactions

Fatal
Life-threatening
Leading to hospitalisation or prolongation of hospitalisation
Leading to permanent or significant functional disability or incapacity

Unexpected Adverse Reactions

When the reaction differs in quality or intensity from the vaccine SPC

Other Adverse Reactions

Fever over +40°C
Intensive pain, swelling, warmth or induration (more than half of the limb)
Abscess
Extensive urticaria or other rash
Swelling at facial area
Breathing difficulties
Anaphylaxis
Convulsions
Symptoms of paralysis
Persistent, inconsolable crying lasting more than three hours
Impaired responsiveness

Appendix F Amendments and Administrative Changes to the Protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 1**	
eTrack study number and abbreviated title	111442 (10PN-PD-DIT-043)
EudraCT number	2008-005149-48
Title	Evaluation of effectiveness of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A against invasive disease.
Detailed Title:	A phase III/IV, cluster-randomized, controlled study to evaluate the effectiveness of GlaxoSmithKline Biologicals'10-valent pneumococcal and non-typeable *Haemophilus influenzae* protein D conjugate vaccine in reducing the incidence of invasive diseases.
Amendment number:	Amendment 1
Amendment date:	04 February 2009
Co-ordinating author:	Co-ordinating author name blinded

Rationale/background for changes:
Amendment 1 of the 10PN-PD-DIT-043 protocol was developed for the following reasons:
(1) Addition of collection of data on respiratory tract infections (RTIs), including acute otitis media (AOM) in a subset of subjects in Turku area.
(2) Addition of 6 clusters located in some selected municipalities where no collaboration with health care centres has been set up but where there is opportunity for parent(s) to let their child participate in study 10PN-PD-DIT-053 and receive the same vaccination as in the current study (i.e. Espoo, Vantaa and surroundings municipalities and municipalities surrounding Oulu).
(3) The National Public Health Institute (KTL) and the National Research and Development Centre for Welfare and Health (STAKES) have merged to the National Institute for Health and Welfare (THL).

Amended text has been included in *bold italics* in the following sections:

Throughout the document the following names were replaced:

- National Public Health Institute (KTL) was replaced with National Institute for Health and Welfare (THL)
- National Research and Development Centre for Welfare and Health (STAKES) was replaced with National Institute for Health and Welfare (THL)

Synopsis	
Rationale	See section 1.4 Rationale for the study
Objectives	See section 2 Objectives
Study design	See section 3.1 Study design
Secondary endpoints	See section 9.1.2 Secondary endpoints

List of abbreviation	
LRTI	***Lower respiratory tract infection***
NIP	***National Immunisation Programme***
RTI	***Respiratory tract infection***
~~**STAKES**~~	~~National Research and Development Centre for Welfare and Health, Finland (Sosiaali- ja terveysalan tutkimus- ja kehittämiskeskus)~~
THL	***National Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos), former National Public Health Institute (KTL), Finland***
URTI	***Upper respiratory tract infection***

Section 1 Introduction

In Finland, the incidence of invasive disease due to *S. pneumoniae* is monitored through the national infectious diseases surveillance system at the National ~~Public Health~~ Institute ***for Health and Welfare*** (~~KTL~~ ***THL***), ***former National Public Health Institute (KTL)***.

Section 1.3. Pneumococcal vaccine development

~~Furthermore, in order to optimise the immune response, GSK Biologicals developed other candidate vaccine formulations in which each pneumococcal polysaccharide was separately conjugated to either protein D (PD), diphtheria toxoid (DT) or tetanus toxoid (TT). A series of different vaccine formulations was tested in Phase II feasibility trials in order to evaluate the use of DT or TT as protein carriers for some of the serotypes and the impact of different dosages of polysaccharide for all serotypes. Results from these studies have led to the selection of the final 10-valent formulation (10Pn-PD-DiT) for further evaluation and licensure.~~

GSK Biologicals' 10-valent pneumococcal conjugate (10Pn-PD-DiT) vaccine is using the same protein D (PD) as carrier protein as the previous 11Pn-PD vaccine formulation for 8 of the 10 serotypes contained in the vaccine. In addition, the serotype 18C polysaccharide is conjugated to tetanus toxoid (TT) and serotype 19F polysaccharide is conjugated to diphtheria toxoid (DT).

To date, more than 16 500 doses of 10Pn-PD-DiT vaccine have been administered in completed clinical studies. The results of these studies showed that GSK Biologicals' 10Pn-PD-DiT vaccine is safe and well tolerated in infants and toddlers and a good immune response was demonstrated. In addition, more than 55 000 doses of the 10Pn-PD-DiT vaccine will be administered in planned and ongoing clinical trials.

Section 1.4. Rationale for the study

GSK Biologicals' 10-valent pneumococcal polysaccharide and non-typeable *H. influenzae* protein D conjugate vaccine (10Pn-PD-DiT) ***contains 10 serotypes of S. pneumoniae and uses Protein D derived from H. influenzae as carrier protein for eight of the ten serotype polysaccharides. It is therefore designed to protect against diseases caused by S. pneumoniae as well as diseases caused by non-typeable H. influenzae (NTHi). The vaccine is licensed in Canada and is marketed under the name Synflorix™. The vaccine is also submitted for licensure to be used throughout Europe and has received positive opinion from EU authorities.*** ~~has been submitted for licensure based on the WHO recommended immunological licensure criteria.~~ It is however desirable to assess vaccine effectiveness (VE) against invasive disease post-licensure. In addition, widespread implementation of immunization programs needs to be accompanied by an appropriate surveillance program, in order to identify epidemiological changes potentially related to vaccination, such as decrease in disease incidence due to vaccine serotypes in unvaccinated children (indirect effects also know as herd immunity), or emergence of disease due to pneumococcal serotypes not included in the vaccine, or other bacterial pathogens. In addition molecular typing and antimicrobial resistance patterns of *S. pneumoniae* and *H. influenzae* isolates from invasive disease cases will be evaluated.

This study is designed as a cluster-randomized, double-blind trial and will enable evaluation of the overall effectiveness of GSK Biologicals' 10Pn-PD-DiT vaccine against invasive disease caused by *S. pneumoniae* or *H. influenzae*, by measuring the effects both in vaccinated children (direct and indirect effects, i.e. total effects) and in unvaccinated population (indirect effects i.e. herd immunity). Effectiveness of immunization according to a 2-dose or 3-dose primary schedule, followed by a booster dose, will be assessed.

The study will also evaluate total and indirect vaccine impact on the incidence of hospital-diagnosed pneumonia, as well as the vaccine impact on tympanostomy tube placement and outpatient antimicrobial prescriptions.

In the Pneumococcal Otitis Efficacy Trial (POET study) conducted with an 11-valent pneumococcal protein D conjugate vaccine, a predecessor of GSK Biologicals' 10Pn-PD-DiT vaccine, a 33% reduction of any clinical AOM and a 42% reduction of any bacterial AOM were measured [Prymula, 2006]. The study demonstrated vaccine efficacy against AOM episodes caused by the serotypes of S. pneumoniae contained in the vaccine and in addition also a reduction of AOM episodes due to NTHi. This suggests that the 10Pn-PD-DiT vaccine could have a significant public health impact especially on non-invasive diseases such as AOM. Therefore, this study will also explore vaccine impact on occurrence of respiratory tract infections (RTIs), including AOM in a subset of subjects in Turku area.

In order to provide a benefit to the control group, two different control vaccines were selected for this study, depending on the age at the time of first vaccination:

- the licensed GSK Biologicals' Engerix B (HBV) vaccine for children < 12 months

of age at the time of first vaccination.

- the licensed GSK Biologicals' Havrix 720 Junior (HAV) vaccine for children ≥ 12 months of age at the time of first vaccination.

This study will also serve as basis for conducting a long-term evaluation of the impact of vaccination with GSK Biologicals' 10Pn-PD-DiT vaccine.

Approximately ~~4~~***7***000 subjects enrolled in study 10PN-PD-DIT-053 (112595) ~~according to the same cluster randomisation,~~ will contribute to the objectives of the current study. In addition, a detailed evaluation with regard to vaccination impact on carriage, ***AOM, RTI***, safety and immunogenicity (in a subset of subjects) will be performed in the study 10PN-PD-DIT-053.

Section 2.2. Secondary objectives

- ***To assess the impact of vaccination with the 10Pn-PD-DiT vaccine on the incidence of lower respiratory tract infections (LRTIs) in children starting vaccination below 18 months of age (in a subset of ± 1500 subjects in Turku area).***
- ***To assess the impact of vaccination with the 10Pn-PD-DiT vaccine on the incidence of upper respiratory tract infections (URTIs) including AOM in children starting vaccination below 18 months of age (in a subset of ± 1500 subjects in Turku area)***

Section 3.1 Study design

Note:

1. With the exception of hepatitis A, hepatitis B and/or pneumococcal vaccines, other licensed paediatric vaccines, ***including vaccinations of the National Immunisation Programme (NIP)*** may be administered or co-administered during the study period and will not be considered as study vaccines.

- Data source:

  The following national registers will be used to collect data on ~~health outcomes~~:

- ***Data on any RTI, including AOM will be collected in a subset of ±1500 subjects in Turku area, using a RTI/AOM diagnosis form. The evaluation of RTI in Turku population is conducted in a respiratory infection subcohort of study "Keys to a Good Childhood" lead by Turku Institute for Child and Youth research.***

Section 4.1. Number of subjects / centres

Approximately ~~4~~***7***000 subjects enrolled in study 10PN-PD-DIT-053 (112595)~~,~~ ~~following the same cluster randomisation,~~ will ~~thus~~ contribute to the objectives of the current study.

Section 4.2.1. Selection criteria for municipalities

Note:

2. In some selected municipalities where no collaboration with health care centres has been set up, there is opportunity for parent(s) to let their child participate in study 10PN-PD-DIT-053 and receive the same vaccination as in the current study (see section 6.4.1).

Section 5.1.2. Informed consent

A physician ***responsible for the study at each health care centre*** ~~should either be present at the well-baby clinics or he/she should be available by phone~~, ***can be contacted*** in case of ~~medical questions~~ ***any questions related to the study***.

5.2.2. Disease surveillance

5.2.2.1. Surveillance system *for invasive diseases, pneumonia, tympanostomy tube placement and outpatient antimicrobial prescriptions*

~~Health outcome~~ ~~d~~***D***ata ***on invasive disease, pneumonia, tympanostomy tube placement and outpatient antimicrobial prescriptions*** will be collected using 3 main national registers:

2. **The Finnish Care Registers for Social Welfare and Health Care**

To ascertain complete case finding of the invasive diseases the clinical syndromes compatible with invasive diseases will also be searched from the Finnish Care Registers for Social Welfare and Health Care ~~STAKES~~ ~~register~~ and combined with the NIDR data (see above).

5.2.2.2. *Surveillance system for RTI*

Surveillance of RTI, including AOM, will be done in a subset of ±1500 subjects in Turku area who also participate in a respiratory infection subcohort of study "Keys to a Good Childhood" lead by Turku Institute for Child and Youth research. Data will be collected using a RTI/AOM diagnosis form and will be recorded by the study staff in the study electronic case report form (eCRF).

The Finnish national consensus guidelines (Käypähoito suositus 2004) define the diagnostic criteria for acute otitis media (AOM) as presence of middle ear fluid and abnormal tympanic membrane finding together with a sign or signs of an acute infection (usually signs of concomitant respiratory infection). If tympanostomy tubes have been installed, an acute purulent discharge from ear(s) is also considered as AOM. The diagnosis is always confirmed by otoscopy done by a physician. Evaluation with tympanometer can provide supporting evidence for the presence or absence of AOM, but do not replace the otoscopy as the golden standard method. Otitis media with effusion (OME) is defined as presence of middle ear fluid and abnormal tympanic membrane without signs of an acute infection. While this is considered as part of the normal recovery process following AOM, the prolonged

presence of middle ear fluid (over 2 months) is considered as an indication for tympanic tube placement for chronic ear infection/inflammation.

Respiratory tract infections will be diagnosed using ICD-10 coding system.

5.2.2.3. Case definitions

Lower respiratory tract infection (LRTI)

LRTIs such as but not limited to bronchitis, obstructive bronchitis, bronchiolitis, pneumonia, bronchopneumonia, pleural effusion or empyema as diagnosed by a physician and documented in the medical file or other source document.

Upper respiratory tract infection (URTI)

URTIs such as but not limited to: rhinosinusitis, rhinorrhea, conjunctivitis, orbital celullitis, pharyngitis, laryngitis, tonsillitis, epiglottitis or sinusitis as diagnosed by a physician and documented in the medical file or other source document.

AOM

- ***Level 1 of diagnostic certainty: AOM episode defined as AOM event diagnosed by a physician according to the Finnish AOM management guidelines (confirmed cases) and documented in medical records or other source document (RTI/AOM diagnose form completed by diagnosing physician or copy of medical records available).***
- ***Level 2 of diagnostic certainty: AOM case reported with Level 1 of diagnostic certainty plus positive result of bacteria in middle ear fluid (after spontaneous perforation or tympanocentesis).***

Complicated AOM

A complicated AOM episode is defined an AOM episode associated with perforation, mastoiditis, labyrinthitis, Bell's palsy, petrositis, meningitis, epidural abscess, sepsis, cerebral vein thrombosis or any other complication with timely and causal relationship to the AOM as assessed by the investigator.

Section 5.2.3. Data collection and management

Data collected at ~~KTL~~ *THL*

In addition to data collected by qualified nurses/physicians at well-baby clinics, additional data will be collected at ***THL***:

- ~~health outcome~~ data ***on invasive disease, pneumonia, tympanostomy tube placement and outpatient antimicrobial prescriptions*** will be collected from the national health registers for the vaccinated and unvaccinated population, as described in section 5.2.2.1:

  For each ID case retrieved from registries and occurring in the vaccinated

population, hospital medical records will be reviewed retrospectively by the investigator or designated study staff for additional clinical information (focus of infection, ICU admission, duration of ICU treatment). For the other health outcome data in the vaccinated population and all health outcome data in the unvaccinated population, no further investigation in hospital medical records will be performed.

- demographic baseline data will be collected retrospectively from the Medical Birth Register ~~of the National Research and Development Centre for Welfare and Health~~ (maintained by ~~KTL~~ ***THL***) for the vaccinated and unvaccinated population.

Data collected at "Keys to a Good Childhood" study clinic

Data will be collected at "Keys to a Good Childhood" study clinic in Turku from the children whose parent/guardian has given consent to participate in "Keys to a Good Childhood" study. Data collected include personal identity code, clinical symptoms and otoscopy findings together with their severity, and viral/bacterial culture results from samples taken according to study protocol titled "Recurrent respiratory infections in children: viral-bacterial synergism, environmental factors, and genetic susceptibility".

Data from source documents (such as RTI/AOM diagnosis form) will be encoded by study staff into GSK Biologicals' RDE system using subject identification number without personal identity code.

Section 5.4. Outline of study procedures

During the study, there will be scheduled visits at well-baby clinics and, only in Turku area, unscheduled visits. Unscheduled visits will take place on an as needed basis, and will be reported in the RTI/AOM diagnosis form (see section 5.4.2).

Heading 5.4.1. (Scheduled visits and study procedures for all subjects) has been added

Title of Table 1 has been changed: List of study procedures ***applicable for all subjects***

Title of Table 2 has been changed: Intervals between study visits ***for all subjects***

Section 5.4.2. Unscheduled visits and study procedures applicable only for subjects in Turku area

Children who participate in study "Keys to a Good Childhood" and belong to the respiratory infection subcohort of that study are asked to contact "Keys to a Good Childhood" study clinic in Turku in case the child has symptoms of respiratory tract infection. In the study clinic, physical examination including otoscopy will be performed by study physician and data on clinical symptoms and otoscopy findings will be recorded on source documents (such as RTI/AOM diagnosis form) by nurses/physicians of "Keys to a Good Childhood" study. AOM will be diagnosed according to Finnish national consensus guidelines (Käypähoito suositus 2004).

Nasal swab will be taken for virology according to study protocol titled "Recurrent respiratory infections in children: viral-bacterial synergism, environmental factors, and genetic susceptibility". Similarly, a MEF sample for microbiological analysis will be collected in case of spontaneous perforation of tympanic membrane or excreting tympanic tube.

Section 5.5. Detailed description of *scheduled* study ~~stages/~~visits at well-baby clinics ***applicable for all subjects.***

The title of the section has been changed.

Section 6.4.1. Randomization of clusters

In addition, some selected municipalities such as Espoo, Vantaa and surroundings municipalities and municipalities surrounding Oulu where vaccination is offered only in study 10PN-PD-DIT-053 are organised in 6 additional clusters maintaining the cluster randomization ratio 2:2:1:1. Therefore the total number of clusters is 78.

Section 7.2.9. Regulatory reporting requirements for serious adverse events

In order to comply with local regulation, blinded summaries of invasive disease cases will be submitted to Competent Authorities every 6 months as of the time point when the data on ID cases are available to the Sponsor.

Section 9.1.2 Secondary endpoints

- ***Occurrence of LRTIs (in a subset of ±1500 subjects in Turku area).***
- ***Occurrence of URTIs, including AOM (in a subset of ±1500 subjects in Turku area).***

9.5.3.1. Total effectiveness

Pneumonia, tympanostomy tube placements, ~~and~~ outpatient antibiotic prescriptions, ***RTI, including AOM*** will only be analysed in the Total vaccinated cohort.

Appendix B Overview of the Recruitment Plan

In addition, some selected municipalities such as Espoo, Vantaa and surroundings municipalities and municipalities surrounding Oulu where vaccination is offered only in study 10PN-PD-DIT-053 are organised in 6 additional clusters according the same cluster randomization ratio (2:2:1:1). Therefore the total number of clusters is 78.

Appendix D Medical request for additional vaccination

Footnotes of Table 10:

Note: schedule "0-1-2-8 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – 2 months after Dose 1, Dose 4 – 8 months after Dose 1.
schedule "0-1-2-9 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – 2

months after Dose 1, Dose 4 – 9 months after Dose 1.
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – ~~6~~***7*** months after Dose 1
HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 72***0*** Junior).

Footnotes of Table 11:

Note: schedule "0-1-6 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – 6 months after Dose 1
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – ~~6~~***7*** months after Dose 1
HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 72***0*** Junior)

Footnotes of Table 12:

Note: schedule "0-1-2-9 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – 2 months after Dose 1, Dose 4 – 9 months after Dose 1.
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – ~~6~~***7*** months after Dose 1
HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 72***0*** Junior)

Footnotes of Table 13:

Note: schedule "0-1-6 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – 6 months after Dose 1.
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – ~~6~~***7*** months after Dose 1
HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 72***0*** Junior)

Footnotes of Table 14:

Note: schedule "0-6 mo" means : Dose 1 – at chosen date, Dose 2 – 6 months after Dose 1.
schedule "0-1-7 mo" means : Dose 1 – at chosen date, Dose 2 – 1 month~~s~~ after Dose 1, Dose 3 – ~~6~~***7*** months after Dose 1
HAV: GSK Biologicals' Hepatitis A vaccine (Havrix 72***0*** Junior)

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change 1

eTrack study number and Abbreviated Title(s)	111442 (10PN-PD-DIT-043)
Administrative change number:	Administrative change 1
Administrative change date:	06-JUL-2010
Co-ordinating author:	Co-ordinating authors' names blinded.

Rationale/background for changes:

The contact details for reporting of SAEs & the emergency code break have been clarified. As of now:

- Two fax numbers will be used as back-up for the safety contact for reporting SAEs
- New phone numbers (two for the US /Canada & two for the rest of the world) will be used for the safety contact for code break (emergency unblinding) depending on the region the study is conducted.

Amended text has been indicated in *bold italics* in the following sections:

Section 6.5.2 Breaking the study blind

GSK Biologicals ~~Clinical~~ *Central* Safety Physician
(Study Contact for Emergency Code Break)

~~Tel: +32 2 656 8850~~
~~Fax: +32 2 656 51 16 or +32 2 656 80 09~~
~~Mobile p~~***P***hones for 7/7 day availability:
+32 10 85 64 00 ~~+32 472/906 600~~ (~~Head Safety Evaluation and Risk Management Paediatric~~***GSK Biologicals Central Safety Physician on-call***)

Back-up ~~mobile~~ phone contact: ~~+32 474 53 48 68~~ ***+32 10 85 64 01***

Section 7.2.8 Completion and transmission of serious adverse event reports to GSK Biologicals

Back-up Study Contact for Reporting SAEs

GSK Biologicals Clinical Safety ~~Physician~~ *& Pharmacovigilance*
~~Tel: +32 2 656 8850~~
Fax: +32 2 656 51 16 or +32 2 656 80 09
~~Mobile phones for 7/7 day availability:~~
~~+32 472 906 600 (Head Safety Evaluation and Risk Management Paediatric)~~

~~Back-up mobile phone contact:~~
~~+32 474 53 48 68~~

24/24 hour and 7/7 day availability

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 2**	
eTrack study number and abbreviated title	111442 (10PN-PD-DIT-043)
EudraCT number	2008-005149-48
Title	Evaluation of effectiveness of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A against invasive disease.
Detailed Title:	A phase III/IV, cluster-randomized, controlled study to evaluate the effectiveness of GlaxoSmithKline Biologicals'10-valent pneumococcal and non-typeable *Haemophilus influenzae* protein D conjugate vaccine in reducing the incidence of invasive diseases.
Amendment number:	Amendment 2
Amendment date:	22 August 2011
Co-ordinating author:	Co-ordinating authors' names blinded.

Rationale/background for changes:

Amendment 2 was developed for the following reasons:

(1) The study enrolment reached only 50% of the initial recruitment plan; therefore, there has been a need to redefine the conditions for triggering IPD effectiveness analysis:

- The study follow-up period for primary analysis on invasive disease (ID) cases will end on 31 January 2012 (data lock point for ID cases), i.e. at least 30 months after study start. This allows inclusion of an age-related IPD peak at 11-19 months of age in the youngest enrolled subjects and an expected seasonal IPD peak in the fall of 2011 (J. Jokinen, oral communication), thereby increasing the potential to accrue additional IPD cases.
- Reaching a minimum number of 21 culture-confirmed vaccine-type IPD cases in the infant group will no longer be a condition for triggering IPD effectiveness analysis because that minimum number will most probably not be met due to the lower enrolment numbers.

The estimated target number of vaccine-type IPD cases was adjusted accordingly, based on an assumed vaccine efficacy estimate and the currently available information on the total number of IPD cases by age cohort.

Taking into account the lower than expected number of enrolled subjects, associated number of overall IPD cases reported so far and impact on power when considering 80% vaccine efficacy for the 2+1 vaccination schedule, it was decided to evaluate the effectiveness of the 10Pn-PD-DiT vaccine to prevent vaccine-type IPD in the infants assigned to a 2+1 vaccination course as a first secondary objective instead of the second primary objective (sequential) but to keep the pre-defined statistical criteria for success.

(2) Following IDMC recommendation, it was decided to have the chest X-rays from the hospital-diagnosed pneumonia cases in the vaccinated population evaluated by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005] for study purposes. The appropriate sections of the protocol were adjusted to reflect this.

(3) Minor corrections were done.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Title page

Co-ordinating author*s*
Co-ordinating authors' names blinded.
Contributing authors
Contributing authors' names blinded

Synopsis Rationale and Section 1.4 Rationale for the study

The vaccine is licensed in ***more than 100 countries worldwide, including*** Canada***, the European Union and Australia*** and is marketed under the name Synflorix™. ~~The vaccine is also submitted for licensure to be used throughout Europe and has received positive opinion from EU authorities.~~

Synopsis Objectives and Section 2.1 Primary Objective

Synopsis: ~~First p~~*P*rimary objective

Section 2.1 Primary Objectives~~: First primary objective:~~

To demonstrate the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in clusters assigned to a 3-dose primary vaccination course.

~~**Second primary objective (sequential):**~~

- ~~To demonstrate the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in clusters assigned to a 2-dose primary vaccination course.~~

Criteria for effectiveness:

*Effectiveness (VE) in preventing culture-confirmed IPD due to the 10 vaccine serotypes will be demonstrated if the 2-sided p-value calculated for the null hypothesis H0 = (**vaccine-type [VT]** IPD VE = 0%) is lower than 5%.*

~~Note: The second primary objective will be assessed sequentially: it will not be possible to conclude on the second primary objective if the first primary objective could not be demonstrated.~~

Synopsis Objectives and Section 2.2 Secondary Objectives

- ***To demonstrate the effectiveness of 10Pn-PD-DiT vaccine in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes in children vaccinated with at least one dose of 10Pn-PD-DiT within the first 7 months of life in***

clusters assigned to a 2-dose primary vaccination course.

Criteria for effectiveness:

Effectiveness (VE) in preventing culture-confirmed IPD due to the 10 vaccine serotypes will be demonstrated if the 2-sided p-value calculated for the null hypothesis H0 = (VT IPD VE = 0%) is lower than 5%.

- To assess the effectiveness of a 2- or 3-dose primary vaccination course with 10Pn-PD-DiT vaccine in preventing the culture-confirmed invasive disease caused by the bacterial pathogens listed above, in children starting vaccination within the first 7 months of life and having completed the age-appropriate vaccination schedule.
- ***To assess the effectiveness of the 10Pn-PD-DiT vaccine in reducing hospital-diagnosed pneumonia cases with abnormal pulmonary infiltrates on the chest X-ray (CXR pneumonia), hospital-diagnosed pneumonia cases with alveolar consolidation/pleural effusion on the chest X-ray (CXR-AC pneumonia), and hospital-diagnosed pneumonia cases without alveolar infiltrates or pleural effusion on the chest X-ray (CXR-NAC pneumonia), based on chest X-ray (CXR) reading according to WHO criteria, among children vaccinated with at least one dose of vaccine within the first 7 months of life and within or beyond the first 7 months of life.***

Synopsis Study design and Section 3 Study design Overview

- Experimental design: cluster-randomized, controlled study with four parallel groups of clusters:
  - **10Pn_3+1 group of clusters**: subjects enrolled in the 10Pn_3+1 clusters will receive 10Pn-PD-DiT vaccine (~~± 30 000~~ ***16 000*** subjects). Children enrolled in these clusters between 6 weeks and 6 months of age will receive a 3-dose primary vaccination schedule.
  - **10Pn_2+1 group of clusters**: subjects enrolled in the 10Pn_2+1 clusters will receive 10Pn-PD-DiT vaccine (~~±30 000~~ ***16 000*** subjects). Children enrolled in these clusters between 6 weeks and 6 months of age will receive a 2-dose primary vaccination schedule.
  - **Control_3+1 group of clusters**: subjects enrolled in the Control_3+1 clusters will receive Engerix B (HBV) vaccine if < 12 months of age at the time of first study vaccination, or Havrix 720 Junior (HAV) vaccine if ≥ 12 months of age at the time of first study vaccination (~~± 15 000~~ ***8000*** subjects). Children enrolled in these clusters within the first 7 months of life will receive a 3-dose primary vaccination schedule.
  - **Control_2+1 group of clusters**: subjects enrolled in the Control_2+1 clusters will receive Engerix B (HBV) vaccine if < 12 months of age at the time of first study vaccination, or Havrix 720 Junior (HAV) vaccine if ≥ 12 months of age at the time of first study vaccination (~~± 15 000~~ ***8000*** subjects). Children enrolled in these clusters within the first 7 months of life will receive a 2-dose primary vaccination schedule.

- Data source:

  The following national registers will be used to collect data on:

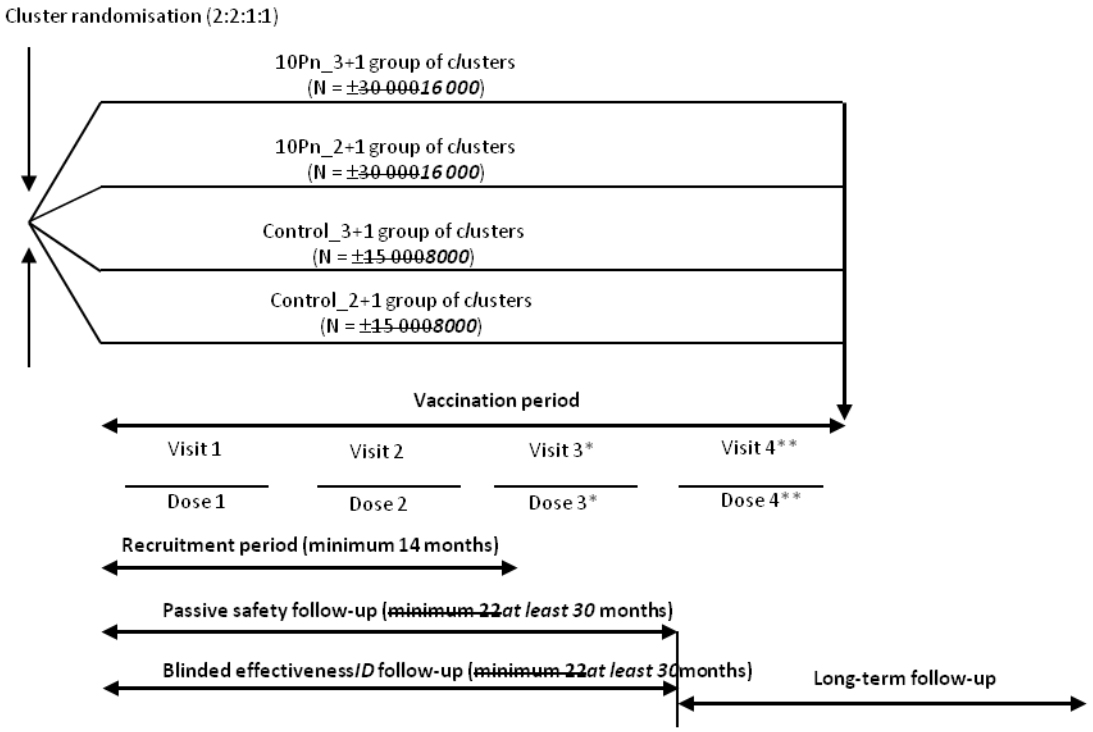
  – **Invasive disease**: National Infectious Disease Register (NIDR) of the Department of Infectious Diseases ~~Epidemiology~~ ***Surveillance and Control*** (~~INFE~~***TATO***) of the National Institute for Health and Welfare (THL).

- ***Chest X-rays (CXRs) from the hospital-diagnosed pneumonia cases in the vaccinated population will be collected and assessed by an independent review panel according to WHO guidelines* [*WHO, 2001; Cherian, 2005].***

- ~~Unblinding and IPD final total effectiveness analysis will be performed after at least 22~~***Blinded study follow-up for invasive disease will end on 31 January 2012, after at least 30*** months of follow-up from the study start ~~and when 21 culture-confirmed IPD cases due to vaccine serotypes reported in children vaccinated with at least one dose of study vaccines within the first 7 months of life in 10 different clusters will be reached~~. See section 9.2 for details.

- ~~Study vaccination will continue after unblinding for subjects who have not completed the vaccination schedule before unblinding.~~

In **Section 3 Study design Overview**, the following diagram was also amended:



(*)Vaccination visit 3 is only applicable for children that are less than 12 months of age when enrolled into the study (either for the 3rd primary dose for infants enrolled in their first 7 months of life in a 3+1 cluster, or for the booster dose in children enrolled in their first 7 months of life in a 2+1 cluster and children enrolled between 7 and 11 months of age).
(**)Vaccination visit 4 is only applicable for the booster dose in infants enrolled in their first 7 months of life in a 3+1 cluster.
N: number of subjects

Synopsis Number of subjects, Section 4.1. Number of subjects / centres and Appendix B Overview of the recruitment plan

At the time of protocol amendment 2, the final enrolled study population in this trial included approximately 47 000 subjects (approximately 31 000 subjects starting vaccination below 7 months of age and approximately 16 000 subjects starting vaccination from 7 up to 18 months of age).

Synopsis and Section 9.1.1. Primary endpoint

In children starting vaccination within the first 7 months of life *in clusters assigned to a 3-dose primary vaccination course*:

- Occurrence of culture-confirmed IPD due to any of the 10 pneumococcal vaccine serotypes.

Synopsis and Section 9.1.2. Secondary endpoints

In children starting vaccination within the first 7 months of life in clusters assigned to a 2-dose primary vaccination course):

- ***Occurrence of culture-confirmed IPD due to any of the 10 pneumococcal vaccine serotypes.***

In the vaccinated population:

- Occurrence of hospital-diagnosed pneumonia cases.
- ***Occurrence of hospital-diagnosed pneumonia cases with abnormal pulmonary infiltrates on the chest X-ray (CXR pneumonia) based on the CXR reading according to WHO criteria.***
- ***Occurrence of hospital-diagnosed pneumonia cases with alveolar consolidation/pleural effusion on the CXR (CXR-AC pneumonia) based on the CXR reading according to WHO criteria.***
- ***Occurrence of hospital-diagnosed pneumonia cases without alveolar infiltrates or pleural effusion on the CXR (CXR-NAC pneumonia) based on the CXR reading according to WHO criteria.***

A **List of Figures** was inserted because a new figure was introduced in this amendment:

LIST OF FIGURES

PAGE

List of Abbreviations

CXR	***Chest X-ray***
CXR pneumonia	***Pneumonia with abnormal pulmonary infiltrates on the chest X-ray***
CXR-AC pneumonia	***CXR pneumonia with alveolar consolidation/pleural effusion on the chest X-ray***

CXR-NAC pneumonia	***CXR pneumonia without alveolar infiltrates or pleural effusion on the chest X-ray***
~~**FRD**~~***FDR***	False Discovery Rate
KTL	National Public Health Institute (Kansanterveyslaitos), Finland***, now National Institute for Health and Welfare (THL), Finland***
~~**NDIR**~~***NIDR***	National Infectious Disease Register (Valtakunnallinen tartuntatautirekisteri)
Prevenar™	7-valent pneumococcal conjugate vaccine with diphtheria CRM_{197} as protein carrier. Serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F (***Pfizer*** ~~Wyeth~~), referred ***to*** throughout the document as Prevenar
TATO	***Department of Infectious Disease Surveillance and Control***
VT IPD	***Vaccine-Type Invasive Pneumococcal Disease***

Section 1.3. Pneumococcal vaccine development

To date, ~~one 7-valent pneumococcal conjugate vaccine has been licensed for use~~ ***three pneumococcal conjugate vaccines (Prevenar, Prevenar 13 and Synflorix) have a marketing authorisation*** in several parts of the world~~, under the trade name of Prevenar (or Prevnar)~~. Th***e***~~is~~ 7-valent pneumococcal conjugate vaccine***, Prevenar,*** comprises serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, each conjugated to CRM_{197}.

Following licensure of ***Pfizer's*** ~~Wyeth's~~ 7-valent pneumococcal conjugate vaccine (Prevenar) in the USA and in Europe, regulatory approval of new pneumococcal conjugate vaccines will be based on immunological criteria, in comparison to Prevenar.

To date, more than ***22 900*** ~~16 500~~ doses of 10Pn-PD-DiT vaccine have been administered in completed clinical studies. The results of these studies showed that GSK Biologicals' 10Pn-PD-DiT vaccine is safe and well tolerated in infants and toddlers and a good immune response was demonstrated. In addition, more than ~~55 000~~ ***219 000*** doses of the 10Pn-PD-DiT vaccine will be administered in planned and ongoing clinical trials.

Section 5.1.2 Informed consent

A copy of the signed and dated written informed consent form will be kept at well-baby clinics and the original will be sent to the investigator at ~~KTL~~ ***THL*** on a regular basis (i.e. at least every month but preferably weekly).

Section 5.2.2.1. Surveillance system for invasive diseases, pneumonia, tympanostomy tube placement and outpatient antimicrobial prescriptions

1. **The National Infectious Disease Register**

The National Infectious Disease Register (NIDR) will be used to capture cases of invasive disease. This register is maintained by the National Institute for Health and Welfare (THL) Department of Infectious Diseases ~~Epidemiology~~ ***Surveillance and Control*** (~~INFE~~***TATO***) and includes data on a variety of bacterial pathogens including, but not limited to the following

For the study purpose, ~~additional~~ serotyping using the Quellung method ***and/or PCR-based methodology***, antimicrobial sensitivity testing and molecular typing will be done to better characterise the isolates of *S. pneumoniae* and *H. influenzae.*

2. **The Finnish Care Registers for Social Welfare and Health Care**

For each identified pneumonia and/or TTP case at least the following information will be retrieved from the Finnish Care register: the current municipality of residence, hospital code, admission and discharge dates, medical specialty of the ward, need of care at discharge. ***CXRs from the hospital-diagnosed pneumonia cases in the vaccinated population will be collected and assessed by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005].*** No further investigation in hospital medical records will be performed.

Section 5.2.2.3 Case definitions

Pneumonia definitions

~~No verification of c~~**C**hest X-ray ~~results~~ ***images from the hospital-diagnosed pneumonia cases in the vaccinated population*** will be ~~performed to validate the diagnoses~~ ***evaluated by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005]*** for the study purpose. ***The 4 outcomes that could be attributed to the CXRs are (1) consolidation, (2) non-consolidation, (3) no pneumonia or (4) uninterpretable CXR. Based on the outcome attributed to the CXRs, the pneumonia cases will be classified for the purposes of this study based on the concepts and definitions mentioned hereunder.***

CXR pneumonia is defined as a pneumonia case with the presence of abnormal pulmonary infiltrates on the CXR as per the judgement of the independent review panel. These abnormal pulmonary infiltrates can be either with or without alveolar consolidation/pleural effusion.

- ***Pneumonia with alveolar consolidation or pleural effusion (CXR-AC pneumonia) is defined as CXR pneumonia with alveolar consolidation or pleural effusion on the CXR.***
- ***Non-consolidated pneumonia (CXR-NAC pneumonia) is defined as CXR pneumonia without alveolar consolidation (no alveolar infiltrates) or pleural effusion on the CXR.***

No pneumonia is defined as a CXR without abnormal pulmonary infiltrates.

Section 5.2.3. Data collection and management

Data collected at THL

For each ID case retrieved from registries and occurring in the vaccinated population, hospital medical records will be reviewed retrospectively by the investigator or designated study staff for additional clinical information (focus of infection, ICU admission, duration of ICU treatment). ***CXRs from the hospital-diagnosed pneumonia cases in the vaccinated population will be collected and assessed by an independent review panel according to WHO guidelines [WHO, 2001; Cherian, 2005].*** For the other health outcome data in the vaccinated population and all health outcome data in the unvaccinated population, no further investigation in hospital medical records will be performed.

Section 6.3 Storage

A specific temperature deviation management procedure will be set up and will be described in detail in a separate study-specific ~~guidance~~ ***procedure manual (see latest version)***.

This ~~guidance~~ ***study-specific procedure manual*** will also describe storage conditions for transport of the study vaccines from the warehouse to the dispatching centres (hospital pharmacies and/or medical centre pharmacies) or from dispatching centres to health care centres and well-baby clinics.

Section 7.1. Surveillance for adverse events following immunisation (AEFI) in Finland

A list of serious adverse and/or unexpected reactions to be reported by healthcare professionals to the Vaccine Safety Unit of the Department of Vaccines at ~~KTL~~ ***THL*** is provided in Appendix E.

Section 9.2.3. According-To-Protocol (ATP) cohort for analysis of effectiveness

Likewise an event beyond 20 months of age will be discarded in an infant who did not receive the booster dose before month 20 but any event occurring during the period between 2 weeks after dose 3 and ~~18~~***20*** months of age will be included.

Section 9.3.1. Primary *and first secondary* objectives - Total effect

The power of this study to reach ~~each of~~ the ~~sequential~~ primary objective~~s~~ ***or the first secondary objective*** is driven by the total number of IPD cases ***that will be reported during the ID follow-up (at least 30 months from study start)***. ***Based on the approximately 31 000 infants enrolled in this study and in the nested study 10PN-PD-DIT-053 (112595), and on revised assumptions of accrual of IPD cases, it is estimated that a total of 23 IPD cases could be collected in the infant cohort in all treatment groups by the end of January 2012 (see Figure 1). Assuming a proportion between 70 and 80% vaccine-serotypes (based on current observations), this translates into around 12 to 18 total VT IPD cases in the infant cohort at the end of the follow-up period.*** ~~The study is targeting to reach a total of 21 vaccine-type IPD cases in at least 10 different clusters (i.e. 15 in the control clusters + 3 in each of the 2-dose or 3-dose vaccine clusters, based on a 80% VE: see Table 6) in infants receiving their first dose within 7 months of life.~~

The effectiveness of 10Pn-PD-DiT to prevent vaccine-type IPD cases in subjects vaccinated with at least one dose of 10Pn-PD-DiT according to a ~~2~~***3***-dose ~~and/~~or ~~3~~***2***-dose primary vaccination course will be computed for each schedule tested in 24 clusters compared to the ***pooled*** 24 control clusters ~~(primary endpoints)~~.

Considering for both the ~~2~~***3***-dose or the ~~3~~***2***-dose primary vaccination course a 90%, 85% or 80% VE***,*** ~~and~~ a 0.12 or a 0.38 coefficient of variation between clusters~~, the target~~ ***and a*** number of ***10 to*** 15 vaccine-type IPD cases in the ***pooled*** control group***s, Table 5*** ~~will~~ provide***s*** the power ***to demonstrate vaccine efficacy in a 3-dose or 2-dose primary vaccination course*** ~~as shown in (Table 7)~~.

~~It is expected to reach this number of IPD cases through a 14 months enrolment period and an additional 8 months follow-up period; i.e. a total follow-up of 22 months from study start. The first 3 columns in Table 5 illustrate the total number of IPD cases occurring in the Infant cohort following administration of the first vaccine dose (total follow-up), assuming 100% coverage in Finland and no vaccine effectiveness. The last 3 columns illustrate the number of vaccine-type IPD cases (75% of the total number of IPD cases) expected in the control group (one third of the total number of IPD cases, occurring in the 24 control clusters), assuming that 90% of the Finnish birth cohort will be covered by the clusters to be randomized and that out of the eligible subjects, 80% of the infant cohort and 60% of the catch-up cohort will be enrolled. Considering a total number of 85 IPD cases in the infant cohort after 22 months of follow-up, we thus end up with a number of 15 vaccine-type IPD cases in the control clusters by multiplying 85 IPD cases with the proportions of cluster coverage (0.90), enrolment (0.80), treatment allocation (1/3) and vaccine types out of all IPD cases (0.75).~~

~~Table 6 provides the same information but considering only IPD cases occurring 2 weeks or more after completion of primary immunization (per protocol follow-up).~~

Table 5 and **Table 6** were deleted. The **List of Tables** was updated accordingly.

~~**Table 5 Number of IPD cases expected in study cohorts and in the control group: Total follow-up**~~

~~Total length of follow-up (months)~~	~~Total number of IPD cases in Finland assuming no vaccine effectivenes~~			~~Vaccine-type IPD cases in the control group (75% of IPD cases) for enrolled study subjects~~		
	~~< 7 months~~	~~7-11 months~~	~~12-18 months~~	~~<7 months~~	~~7-11 months~~	~~12-18 months~~
~~14~~	~~38.92~~	~~9.96~~	~~33.77~~	~~7.01~~	~~1.34~~	~~4.56~~
~~15~~	~~44.5~~	~~10.46~~	~~35.31~~	~~8.01~~	~~1.41~~	~~4.77~~
~~16~~	~~50.27~~	~~10.71~~	~~36.92~~	~~9.05~~	~~1.45~~	~~4.98~~
~~17~~	~~56.1~~	~~11.17~~	~~38.23~~	~~10.10~~	~~1.51~~	~~5.16~~
~~18~~	~~61.73~~	~~11.71~~	~~39.42~~	~~11.11~~	~~1.58~~	~~5.32~~
~~19~~	~~67.56~~	~~12.04~~	~~40.48~~	~~12.16~~	~~1.63~~	~~5.46~~
~~20~~	~~73.5~~	~~12.35~~	~~41.5~~	~~13.23~~	~~1.67~~	~~5.60~~
~~21~~	~~79.29~~	~~12.56~~	~~42.6~~	~~14.27~~	~~1.70~~	~~5.75~~
~~**22**~~	~~**84.98**~~	~~**12.73**~~	~~**43.69**~~	~~**15.30**~~	~~**1.72**~~	~~**5.90**~~
~~23~~	~~90.35~~	~~12.96~~	~~44.81~~	~~16.26~~	~~1.75~~	~~6.05~~
~~24~~	~~95.5~~	~~13.23~~	~~45.9~~	~~17.19~~	~~1.79~~	~~6.20~~
~~25~~	~~100.48~~	~~13.54~~	~~46.9~~	~~18.09~~	~~1.83~~	~~6.33~~

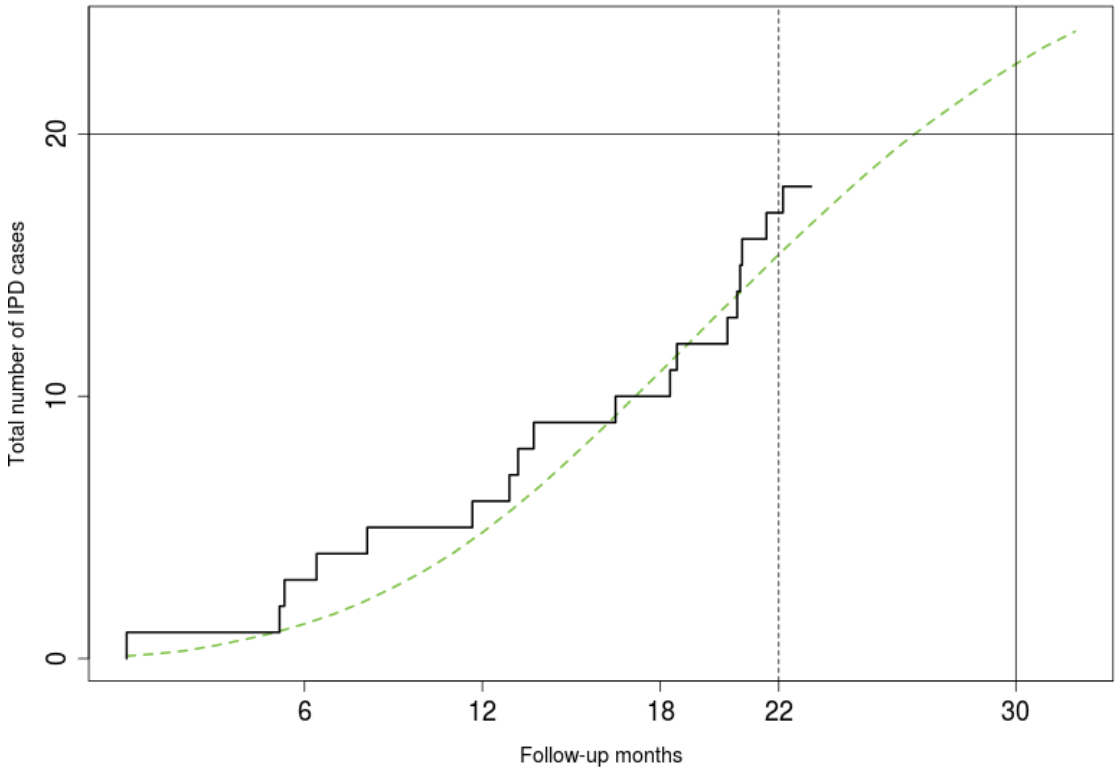
26	105.21	13.85	47.75	18.94	1.87	6.45
27	109.58	14.08	48.6	19.72	1.90	6.56
28	113.71	14.21	49.5	20.47	1.92	6.68
29	117.6	14.29	50.4	21.17	1.93	6.80
30	121.08	14.44	51.25	21.79	1.95	6.92
31	124.25	14.69	52.04	22.37	1.98	7.03
32	127	14.92	52.81	22.86	2.01	7.13
33	129.6	15.17	53.46	23.33	2.05	7.22
34	131.96	15.44	54	23.75	2.08	7.29

Table 6 Number of IPD cases expected in study cohorts and in the control group: Per protocol follow-up

Total length of follow-up (months)	Total number of IPD cases in Finland assuming no vaccine effectiveness			Vaccine-type IPD cases in the control group (75% of IPD cases) for enrolled study subjects		
	<7 months	7-11 months	12-18 months	<7 months	7-11 months	12-18 months
14	32.71	6.83	30.48	5.89	0.92	4.11
15	37.44	7.33	32.02	6.74	0.99	4.32
16	42.56	7.58	33.62	7.66	1.02	4.54
17	48	8.04	34.94	8.64	1.09	4.72
18	53.62	8.58	36.12	9.65	1.16	4.88
19	59.46	8.92	37.19	10.70	1.20	5.02
20	65.4	9.23	38.21	11.77	1.25	5.16
21	71.19	9.44	39.31	12.81	1.27	5.31
22	**76.88**	**9.6**	**40.4**	**13.84**	**1.30**	**5.45**
23	82.25	9.83	41.52	14.81	1.33	5.61
24	87.4	10.1	42.6	15.73	1.36	5.75
25	92.38	10.42	43.6	16.63	1.41	5.89
26	97.1	10.73	44.46	17.48	1.45	6.00
27	101.48	10.96	45.31	18.27	1.48	6.12
28	105.6	11.08	46.21	19.01	1.50	6.24
29	109.5	11.17	47.1	19.71	1.51	6.36
30	112.98	11.31	47.96	20.34	1.53	6.47
31	116.15	11.56	48.75	20.91	1.56	6.58
32	118.9	11.79	49.52	21.40	1.59	6.69
33	121.5	12.04	50.17	21.87	1.63	6.77
34	123.85	12.31	50.71	22.29	1.66	6.85

Figure 1 was added:

Figure 1 Estimated (dotted line) and actual (solid line) accrual of IPD cases in the infant cohort (all treatment groups, all serotypes) until May 2011.



Note: Assumptions were (i) VT proportion 80% of all IPD; (ii) Vaccine effectiveness 90% on VT IPD; (iii) baseline IPD incidence in Finland before the trial

The header row and the footnotes (and footnote numbering) of **Table 5** have been changed:

Table 5 Power to demonstrate a statistically significant effect of 10Pn-PD-DiT in preventing vaccine-type IPD cases in the Infant Vaccinated cohort: each of both schedules vs Control; 24:24 clusters allocation (2 sided type I error=5%) – Total follow-up

Expected number of cases in *pooled* control clusters	VE	Total Expected number of cases in *pooled* control & one of the two 10Pn group of clusters	Coefficient of variation between clusters	Power[21]

~~[1] Expected number of vaccine-type IPD cases in Infant Vaccinated cohort – Total follow-up.~~

[21] Power based on 1000 simulations using a negative binomial model with equal sized cluster and a log-likelihood ratio test (see analysis section for details).

[32] Estimate from negative binomial model, based on Infectious Disease Register data; IPD aggregated on a cluster level.

[43] Estimate from model for binomial proportions, based on Infectious Disease Register data; IPD aggregated on a hospital district level.

Section 9.5.3.1. Total effectiveness

Pneumonia, tympanostomy tube placements, outpatient antibiotic prescriptions~~,~~ ***and*** RTI, including AOM**,** will only be analysed in the Total vaccinated cohort.

Section 11. References

Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ. 2005; 83(5):353-359.

World Health Organization (WHO). Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children. WHO Pneumonia Vaccine Trial Investigator's Group. WHO/V&B/01.35. Geneva: WHO; 2001.

Appendix C Vaccine supplies, packaging and accountability

3. Vaccine shipment from GSK Biologicals Rixensart, Belgium to local warehouse, dispatching centres (i.e. hospital pharmacies and/or medical centre pharmacies) or health care centres and well-baby clinics.

A specific temperature deviation management procedure will be set up and will be described in detail in a separate study-specific ~~guidance~~ ***procedure manual (see latest version)***.

4. Vaccine accountability

Accountability and reconciliation for ~~all enrolled~~ ***these*** subjects will be done based on completed documentation as described ~~o~~***i***n ~~a~~ ***the latest version of the*** study-specific ~~guidance~~ ***procedure manual***.

After approval from GSK Biologicals and in accordance with GSK ~~SOP WWD-1100~~ ***SOP_54826***, used and unused vaccine vials should be destroyed at the study site using locally approved biosafety procedures and documentation unless otherwise described in the protocol. If no adequate biosafety procedures are available at the study site, the used and unused vaccine vials are to be returned to an appropriate GSK Biologicals site for destruction, also in accordance with current GSK ~~SOP WWD-1100~~ ***SOP_54826***.

5. Transfers of clinical vaccines or products from warehouse to dispatch centres (i.e. hospital pharmacies and/or medical centre pharmacies) and from dispatch centres to health care centres and well-baby clinics

All transfers of clinical vaccines or products must be documented, storage temperatures must be maintained during transport and deviations must be reported to GSK for guidance as described ~~o~~***i***n ~~a~~ ***the latest version of the*** study-specific ~~guidance~~ ***procedure manual***.