INFORMATION SHEET AND CONSENT FORM FOR PARENT / GUARDIAN

Study title and number: 111442 (10PN-PD-DIT-043)

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.

Short title: FinIP vaccine trial

Person responsible for the study: MD Terhi Kilpi, Department of Vaccinations and Immune protection, National Institute for Health and Welfare (THL), Helsinki

Study sponsor: GlaxoSmithKline (GSK) Biologicals S.A.

STUDY SUMMARY

You are being asked to give your consent to your child's participation in a vaccine trial conducted by the National Institute for Health and Welfare (THL) in cooperation with the Finnish well-baby clinics.

Please take time to read the following information carefully before deciding if you want your child to take part in the study or not.

The effectiveness of a new pneumococcal vaccine is evaluated in the study.

In total around 91000 children less than two years of age are expected to participate in the study conducted in most of the municipalities in Finland. No additional visits to the well-baby clinic due to study participation are required as the study vaccines can be administered during the routine visits. Participation and vaccines given are free of charge. No samples are taken from your child in the study.

The pneumococcal vaccine used in the study is developed by GlaxoSmithKline Biologicals and it has been licensed by the European regulatory authorities.

The aim of the study is to evaluate the protection provided by the vaccine against diseases (pneumonia, meningitis, sepsis and middle ear infection) caused by the pneumococcus bacterium (*Streptococcus pneumoniae)* and haemophilus bacterium (*Haemophilus influenzae)*. Also the impact on tympanostomy tube placements and use of antibiotics due to ear infections and is assessed. Vaccination may benefit also the unvaccinated children, adults and elderly.

During the study the child is randomised to receive either the pneumococcal vaccine or a control vaccine: 2/3 of the study subjects receive the pneumococcal vaccine and 1/3 a control vaccine. The control vaccine is either a hepatitis A (Havrix™) or a hepatitis B (Engerix B™) vaccine depending on the age of the child at the time of study start. The study is blinded, meaning that neither you nor the well-baby clinic personnel will know during the study which vaccine the child receives.

Main criteria for study participation are:

- The child is 6 weeks – 18 months of age
- You have signed the informed consent form
- Well-baby clinic personnel has assessed the child to be healthy enough to be vaccinated
- The child has not already been vaccinated with pneumococcal, hepatitis A or hepatitis B vaccine

Study conduct:

- The number of vaccine doses (2-4) administered to your child will depend upon your child's age and place of residence
- The last vaccine dose is given 6 – 10 months after the first one
- The study includes long-term surveillance on vaccine effects which is based on national health register data

The study is described in more detail on next pages.

GIVING CONSENT

Your consent is asked for your child to voluntarily participate in the clinical trial described below. Before you decide if you allow your child to take part, please read this information carefully. The well-baby clinic nurse or physician will answer your questions and provide additional information on the study. If you want your child to participate in the study, please sign the actual informed consent form during the well-baby clinic visit.

AIM OF THE STUDY

The vaccine used in the study is a new pneumococcal conjugate vaccine (abbreviation PHiD-CV vaccine). The vaccine has been developed by GSK Biologicals to give protection against the diseases caused by the pneumococcus bacterium (*Streptococcus pneumoniae*) and haemophilus bacterium *(Haemophilus influenzae).*

Pneumococcus bacterium is one of the most common causes of otitis media. It is also a common cause of pneumonia, blood poisoning and meningitis. Annually it causes around 50 cases of meningitis, 700 cases of sepsis and over 10 000 cases of pneumonia in Finland. In addition it causes around 30 000 middle ear infections in children under two years of age.

Haemophilus bacterium is another common bacterium causing otitis media in children.

The aim of this study is to evaluate the benefits of children's pneumococcal vaccination programme on the population level, both directly on the vaccinated children but also indirectly on unvaccinated children, adults and elderly.

The study will evaluate vaccine efficacy in terms of protection against sepsis, meningitis and pneumonia when vaccine is administered according to different vaccination schedules. Also impact on number of tympanostomy tube placements and antibiotics prescription is assessed. This evaluation is made by comparing the number of disease cases reported in the group receiving the pneumococcal vaccine to the number of disease cases reported in the group receiving a control vaccine. The control vaccines used in the study are licensed hepatitis vaccines which have no effect on pneumococcal diseases. The control vaccine is administered in the same way as the pneumococcal vaccine.

Number of study subjects:

The study is conducted by the National Institute of Health and Welfare (THL) in cooperation with well-baby clinics in most municipalities in Finland. Approximately 91 000 children are expected to participate in the study: of these around 58 000 receives the first vaccine dose below seven months of age and around 33 000 children at the age of 7 – 18 months.

PARTICIPATION IN THE STUDY

Depending on the area of residence and well-baby clinic your child will receive either the PHiD-CV pneumococcal vaccine or the control vaccine during the study. The vaccine used in each area has been allocated by chance (randomised) and you can not choose the vaccine given to your child. Two out of three areas are using pneumococcal vaccine and one out of three the control vaccine during the study.

The study is double-blind. This means that neither you nor the well-baby clinic staff or study staff knows the vaccine used in your area. Later, when the unblinding is done (estimated in year 2011), you have a chance via the well-baby clinic to know which vaccine your child received.

Two control vaccines are used in the study depending on the age of the child:

- GSK Biologicals' hepatitis B vaccine (*Engerix B™*), if the child is below 12 months of age at time of first vaccination
- GSK Biologicals' hepatitis A vaccine (*Havrix™ 1440, 0,5 ml*), if the child is between 12 and 18 months of age at the time of first vaccination.

Your child can participate in this study if following criteria are met:

- Age between 6 weeks – 18 months.
- You have signed the informed consent form.

Your child can not take part in this study if any of the following apply:

- Your child has already been vaccinated with a pneumococcal, hepatitis A and/or hepatitis B vaccine or vaccination with any of these is planned outside of this study.
- Your child belongs to a high risk group for pneumococcal infections and according to instructions by the National Institute for Health and Welfare your child should be vaccinated with a pneumococcal vaccine.
- Your child has a history of allergic disease or reactions likely to be exacerbated by any component of the vaccines used in the study.

The number of vaccine doses administered to your child will depend upon your child's age at the time of the first vaccination (see table below). Additionally, half of the study areas use a 4-dose schedule and the other half use a 3-dose schedule of the study vaccines for children below seven months of age. This allows the most suitable dosing schedule for the vaccine to be assessed.

Age at first vaccination	**Vaccination schedule**
6 weeks - 6 months	• 3 primary doses at least 4 weeks apart OR 2 primary doses at least 8 weeks apart AND • 1 booster dose 6 months after the last primary dose (minimum 4 months) and the age of the child at least 11 months.
7 - 11 months	• 2 primary doses at least 4 weeks apart AND • 1 booster dose 6 months after the last primary dose (minimum 4 months)
12 - 18 months	• 2 doses at least 6 months apart

Study participation does not require any additional visits to the well-baby clinic as the vaccines can be administered during the routine visits. The children participating in the study will receive the normal childhood vaccination programme vaccines and the study vaccines can be administered at the same time.

IMPORTANT: If during the study there is a medical need to vaccinate your child with a hepatitis and/or pneumococcal vaccine or you move to a new well-baby clinic area, please contact your well-baby clinic nurse. The appropriate vaccines will be ordered and administered to your child in a blinded manner. In certain cases you can also be advised to get a prescription for the requested vaccine to be purchased at the pharmacy at your own cost.

The study vaccines are injected in the thigh muscle or the deltoid. If your child has a bleeding disorder, please inform the well-baby clinic nurse before vaccination.

No blood samples will be taken from your child during the study.

Information on your child (such as personal identity code, age, gender, area of residence, vaccinations) will be collected for study purposes at the well-baby clinic.

The study involves vaccine effect surveillance based on national health registers. THL retrieves registry data for example on occurrence of severe (invasive) diseases and pneumonia (THL Infectious Disease Register and Care Register), on number of tympanostomy tube placements and on antibiotics prescriptions (THL Care Register and the Social Insurance Institution of Finland Care Register for Social Welfare and Health Care) and on vaccine adverse effects (THL Vaccine Adverse Effects Register). Additional information is also collected from the medical records, including chest radiographies which can be collected and recorded. Also birth register

data (such as gestational age and birth weight, from THL Birth Register) and data from Population Register Centre can be collected if needed. THL will obtain permission from the Ministry of Social Affairs and Health, the Social Insurance Institution of Finland (KELA) and the Population Register Centre to retrieve this registry data. With your consent this registry data will be part of the information collected on your child for this study.

In case of severe diseases the aim is also to identify the bacterium causing the disease. This information will be obtained from any samples collected during routine treatment. No additional samples will be taken from your child for study purposes.

To retrieve essential study information, collection of registry data will last at least 22 months from study start. However, the registry follow-up period may be extended to evaluate long-term protective effects and/or adverse effects of the vaccines. Your consent to use the collected study data is valid also for the long-term register follow-up until your child is eight years old.

POSSIBLE BENEFITS FROM THE STUDY

Your child and also other children in the future may benefit from this trial.

Based on the vaccine (pneumococcal, hepatitis A or hepatitis B vaccine) administered in the study the benefits are:

- The opportunity to protect your child against diseases caused by pneumococcus and haemophilus bacteria. Also unvaccinated subjects living close to the vaccinated child may benefit through reduced transmission of the bacteria.

OR

- The opportunity to protect your child against hepatitis B (one of the most common viral infections of the liver). Chronic carriers of the hepatitis B virus have an increased risk of developing cirrhosis and liver cancer. Hepatitis B infection is rare among Finnish children, and the risk of getting the infection is low. However, vaccination is worldwide an important way to prevent hepatitis B infections.

OR

- The opportunity to protect your child against hepatitis A infection (a common infection of the liver in countries with lower level of hygiene). Vaccination against hepatitis A is commonly recommended when travelling outside the EU, USA and other high income countries.

At the time of study start the above mentioned pneumococcal, hepatitis A and hepatitis B vaccines have not been included in the Finnish national vaccination programme with the exception of vaccination of some risk groups. The pneumococcal vaccine has been recommended by the Finnish experts to be added into the programme. A vaccine against haemophilus bacterium type b is included in the national vaccination programme, but this vaccine do not give protection against other haemophilus bacteria types that are common causes of middle ear infections.

POSSIBLE RISKS OF THE STUDY

The vaccines used in this study can possibly induce similar adverse effects as those observed after administration of other childhood vaccines:

- As local reactions pain, redness, swelling and hardness at injection site
- As general reactions irritability, crying, loss of appetite, vomiting, diarrhoea, fever and sleepiness.

These symptoms are usually short-lived and self-limiting. If other or more serious symptoms occur after vaccination, please contact the well-baby clinic.

The vaccines used in this study may also cause some adverse effects that are not known at the present time. As with any vaccine, also unexpected serious adverse effects, for example hypersensitivity reactions (rash or allergy) to the vaccine, may occur.

As with any other vaccine, your child should be observed at the well-baby clinic for 30 minutes after vaccine administration to detect any acute adverse effects.

Vaccination with the PHiD-CV pneumococcal vaccine:

The regulatory authorities have recently granted marketing approval for the PHiD-CV pneumococcal vaccine in Europe.

In clinical trials conducted so far, more than 16 500 doses of the PHiD-CV vaccine have been administered. Some of these trials have been conducted in Finland. In addition, the target is to administer more than 55 000 doses of the vaccine in planned and ongoing trials. The PHiD-CV vaccine has been shown to be safe and it can not cause diseases induced by pneumococcal or haemophilus infections.

Following adverse effects have been reported in subjects who have received the PHiD-CV vaccine:

- as uncommon (in one of 100 doses of vaccine): hematoma, bleeding or lump at injection site, in premature babies (born before 28 weeks of pregnancy) temporary interruption of breathing.
- as rare (in one of 1000 doses of vaccine): febrile seizures, seizures without fever, rash, hives.

Vaccination with hepatitis A (Havrix™ 1440, 0.5 ml) and hepatitis B (Engerix B™) vaccine:

Hepatitis A and hepatitis B vaccines are generally well tolerated. Hepatitis A vaccine has been given to children for 16 years and hepatitis B vaccine for 22 years, in total millions of doses worldwide.

In subjects who received hepatitis A vaccine headache, malaise, nausea, rash and fatigue have been reported as adverse effects. Muscle and/or joint pain and convulsions have been very rare (in one of 10 000 doses of vaccine) side effects.

In subjects who received hepatitis B vaccine following rare adverse effects have been reported: rash, fatigue, malaise and muscle and/or joint pain. Seizures and low level of blood platelets were very rare.

In children below two years of age peripheral and central nervous system diseases (including infections and inflammations) have been reported after hepatitis B vaccination but the causal relationship to the vaccine has not been established.

ALTERNATIVES

For children under five years of age a pneumococcal conjugate vaccine containing seven pneumococcal types (7-valent) is available for protection against pneumococcal diseases. This Prevenar™ conjugate vaccine is manufactured by Wyeth Lederle. It has been shown to protect children against invasive pneumococcal diseases, pneumonia and otitis media. However, the vaccine does not protect against diseases caused by the haemophilus bacterium. The vaccine can be purchased on prescription at the pharmacy at own cost.

The diseases caused by the pneumococcal bacterium are treated with antibiotics. Despite treatment permanent damage or death may still occur.

Also the hepatitis A and B vaccines can be purchased on prescription at the pharmacy at own cost.

VOLUNTARY PARTICIPATION AND STUDY WITHDRAWAL

You have the right to stop your child's vaccination at any time without giving a reason. In this case administration of study vaccine ends but national health registry data follow-up continues.

If you want to stop utilisation of the data collected on your child from the health registers for study purposes, you should notify your well-baby clinic nurse or study staff about it. Withdrawal from the study does not impact in any way your child's medical care. Information that has been collected until time of withdrawal will not be removed from study data.

You will be notified as soon as possible if during the study any new information which might affect your willingness to let your child continue study participation becomes available.

INSURANCE

The child participating in the study has been insured in accordance with the patient insurance and the sponsor's pharmaceutical injuries insurance for the entire duration of the study. In case of pharmaceutical injury confirmed by the insurance company, GSK Biologicals will reimburse costs and losses of income if they remain below the minimum reimbursement level of the pharmaceutical injuries insurance.

CONFIDENTIALITY

Data from the national health registers is collected using the personal identity code. THL keeps the personal identity code confidential.

With your consent representatives of study sponsor, GSK Biologicals and national and foreign regulatory authorities responsible for control and safety of medicines are authorised to review the collected information and this way verify the accuracy of data and proper conduct of the study. All information is kept confidential.

Data collected in the study is transferred to GSK Biologicals. Before this your child's personal information is coded and does not include the personal identity code, name, initials, address or other direct identification data.

USE AND STORAGE OF STUDY DATA

With you consent you authorise THL and GSK Biologicals to use the data collected during the study in the coded format in the following ways:

- Data is stored and processed electronically for study purposes
- Regulatory authorities responsible for control and safety of medicines, or other groups can use the data to verify the accuracy of data and that the study is properly conducted. If information is sent to another country, it is protected as per legal requirements.
- Data can be used to publish study results. Your child can not be identified from these reports or publications. The results of the study are anticipated to benefit childhood vaccination programs in Finland and in other countries.

COMPENSATION

Study visits and administered vaccines are free of charge. No compensation for study participation is paid.

GSK Biologicals pays THL a fee covering costs resulting from conducting the study. THL compensates the extra work caused by the study to well-baby clinics to each participating health care centre.

ADDITIONAL INFORMATION

This study has been submitted for review to the National Agency for Medicines and the Coordinating ethics committee of Helsinki and Uusimaa hospital district (HUS) has given a favourable statement on the study.

If you have any questions related to study conduct, rights of the study subject, possible adverse effects of the vaccine, any possible injury due to the study or your child has a medical need to receive a pneumococcal, hepatitis A or B vaccine, please contact the well-baby clinic nurse or the responsible physician of the health care centre in your area.

Your questions are also answered by study contact persons at THL: *finip@thl.fi*

or 020 610 7940 (on Monday to Friday from 9 a.m. to 3 p.m.)

Additional information can also be found at the study website: www.finip.fi

After familiarizing yourself with this information sheet your consent is asked for your child's participation in the study. If you want your child to participate, please sign the consent form on the well-baby clinic visit.

CONSENT FORM

I, _____**FOR INORMATION ONLY, DO NOT FILL IN THIS PAGE**_____
(printed name of parent/guardian signing the form)

- confirm that I have read (or the information has been read to me) and understood the written informed consent form (version 3 –17.02.2009_FIN *or* version 3 –17.02.2009_SVE) for the parent/guardian for study 10PN-PD-DIT-043 (111442). Study conduct and purpose has been explained to me.
- confirm that I have been given enough of time to consider participation in the study, I have had the opportunity to ask questions and I have been provided with satisfactory answers.
- understand that I grant access to data about my child to authorised persons described in the information sheet.

By signing this consent form I voluntarily agree to that my child participates in the FinIP vaccine trial and will be vaccinated with either the pneumococcal (PHiD-CV), hepatitis A or hepatitis B vaccine and that information related to my child will be collected from national health registers during the study period and the long-term follow-up.

I understand that I can withdraw my consent at any time without having to give any reason. This will not have any impact on my child's right to receive the medical care he/she is entitled to.

Child's name: _____
(printed forename and surname)

Personal identity code |__|__|__|__|__|__|_A_|__|__|__|__|
d d m m y y

Street address: _____

Postal code and town: _____

Signature of parent/guardian: _____ Date:_____
Note: only the signature of a legal guardian is valid. *(dd/mm/yyyy)*

Person obtaining consent:

Name: _____
(forename and surname)

Job/position: *Well-baby clinic nurse* ☐ *physician* ☐

Well-baby clinic: _____

Signature: _____ Date: _____
(dd/mm/yyyy)

A copy of the signed consent form is given to the parent/guardian.

COMPLETED BY THE WELL-BABY CLINIC PERSONNEL:

Does the child meet all criteria for study participation?

☐ **Yes** →If yes, complete:

1) treatment code of the administered vaccine: |__|__|__|__|__|__|
2) and date of first vaccination (if different than consent date):_____
(dd/mm/yyyy)

☐ **No** → If no, record on next page those criteria that prevent the child from participation in the study.