

immunogenicity, with a booster response indicating the induction of an immunological memory and the involvement of T-helper cells.

Pharmacodynamics

- *Immunogenicity in rabbits*

Various studies were conducted in the rabbit to test the immunogenicity of a number of pneumococcal vaccine formulations, in addition to the 7-valent final formulations proposed for marketing. Some of these studies also contain data about systemic toxicity. The route of immunisation was via s.c., thus, not the intended clinical route. The clinical route of i.m. was used for immunogenicity analysis performed as part of the repeat dose toxicity study described below. ELISA was used in all studies to determine serum antibodies levels to each of the serotype.

- *Dose-IgG response relationship*

The ratio between pre and postvaccination titres (week 4) were calculated for each serotype following two immunisations with the conjugated 7-valent vaccine (adjuvant present) in the range 0.01-2 µg/dose or 0.02-4 µg/dose (for 6B). A dose-dependent increase in IgG level that significantly levelled off with increasing dose increment was demonstrated for most serotypes. A depression of response (-20-40%) at the top dose was determined for serotypes 6B, 19F and 23F. Similar high-dose effects were obtained in other experiments. Because the rabbit model may not be predictive of human response (see part II assessment) clinical data were used for the determination of the optimal vaccine dose. The order of response (ratio 4 week GMT/week 0 GMT) to each serotype in nine clinical lots (2 µg/dose or 4 µg/dose for 6B) was as follows: 18C (1387) > 4 (902) = 23F (939) > 9V (656) > 19F (353) > 6B (292) > 14 (168).

- *Demonstration of a booster response*

In an immunogenicity study, the antibody response to heptavalent PnC vaccine (same composition and dose level as Prevenar™) was evaluated in rabbits immunised at weeks 0 and 2. The results, showed that the antibody response is much more pronounced after the second immunisation (i.e. booster effect), for each of the 7 serotypes.

- *Comparison of immunogenicity of conjugated and unconjugated PnC vaccine*

Another immunogenicity study was conducted to evaluate the antibody response of rabbits to an heptavalent PnC conjugate vaccine, compared with a non-conjugate mixture of the 7 polysaccharides, either alone or with free CRM₁₉₇ (but non conjugated). The immunogenicity of the 23-valent licensed vaccine Pnu-Imune 23 was also tested. The composition and dose level of polysaccharides and adjuvant in the 7-valent vaccines used in this study were the same as in Prevenar™. Pnu-Imune 23 vaccine contained 10 µg of each polysaccharide serotype unconjugated and without adjuvant.

These results clearly demonstrate that the conjugation of the polysaccharides to the protein carrier CRM₁₉₇ strongly increased the antibody levels for each of the 7 serotypes.

- *Requirement for aluminium phosphate adjuvant*

The effect of aluminium phosphate as adjuvant on the antibody response of rabbits to 7 **monovalent** conjugate PnC vaccines (each containing 5 mcg of saccharide) was evaluated. The results showed an enhancing effect of the adjuvant on the antibody response to 6 of the 7 serotypes present in Prevenar™ (not for 9V), after both one or 2 doses of vaccine. It was thus decided to include aluminium phosphate as adjuvant in the Prevenar™ vaccine. The reasons for this enhancement of immunogenicity are not yet clear.

- *Functional antibody test*

Opsonic antibody testing (complement-mediated opsonisation of pneumococcus by human polymorphonuclear leukocytes) has been carried out with human antisera and is thus evaluated in the clinical part of the documentation. Regarding antisera from animals, the in vitro opsonophagocytic activity of antisera collected from immunised rabbits with antibodies directed against three (14, 19F and 23F) of the seven serotypes in Prevenar, was tested. The rabbit opsonic assay results demonstrated, for each of the three serotypes, for the week 7 post-immunization antisera a good

opsonisation activity (low colony growth) compared with the corresponding preimmune (control) serum. Since rabbit data may not be predictive of human response, testing was performed with clinical sera as reported in part IV.

- *Immunogenicity in mice*

Prevenar has not been tested in mice. Instead data on IgG titres following one and two vaccinations with a nona-valent pneumococcal vaccine (0.1-1 µg/dose or 0.2-2 µg/dose for 6B), including the seven serotypes in Prevenar, are presented. These data demonstrated clear increases in serotype-specific IgG titres following two injections compared with one injection. A clear positive adjuvant effect was also noted for all serotypes after the second injection. An apparent dose-related increase in response was observed for serotypes 4 and 14 but not for the other five serotypes. The order of serotype potency in the presence of adjuvant (0.1 µg/dose) was different from that obtained in rabbit; 9V > 6B (0.2 µg/dose) > 4 > 19F > 18C > 14 > 23F.

- *Pharmacodynamic drug interactions*

No specific data are presented in preclinical studies about the possible interactions between the PnC vaccine and other co-administered vaccines or medicinal products. Clinical findings are summarised in Part IV.

- *General and safety pharmacology programme*

No specific data about safety pharmacology has been provided. The lack of undesirable pharmacodynamic effects of the vaccine is considered as sufficiently demonstrated by data from toxicity studies, data from toxicity with related vaccines and the clinical safety data.

However, the possible induction of cross-reacting (auto-) antibodies by the PnC vaccine and the possible toxicity induced by the carrier protein CRM₁₉₇ have been considered and are detailed under "Toxicology".

Pharmacokinetics

The lack of pharmacokinetic studies has been justified on the basis of the CPMP Note for Guidance, and has not been submitted for the following reasons:

- the vaccine is intended for infrequent administration, at low dosage, over a short period of time
- the adjuvant used and the route of administration are not new

Toxicology

- *Single dose toxicity:*

No single dose toxicity study was conducted with the final product of Prevenar.

- *Repeat dose toxicity:*

No repeat dose toxicity study has been conducted with the final product of Prevenar.

However data from a 3-month repeat dose toxicity study in rabbits (5+5/dose) receiving a total of five intramuscular injections, given at three week intervals, of control vehicle (saline and aluminium phosphate/monophosphoryl lipid A, MPL, as adjuvant) or a CRM₁₉₇-conjugated 9-valent pneumococcal vaccine (+serotypes 1 and 5) at a single dose-level of 2 or 4 µg (6B) in the presence of aluminium phosphate (study SVT95-0001) were submitted. An additional four groups of rabbits were included in the study in order to investigate effects of adjuvant. Based on body weight, the margin of exposure at first injection, rabbit (at start 3-4 months old and weighed 2.2-2.3 kg) versus 6-week aged infant (body weight of approx. 4 kg) is only about 1-2x. In the in-life phase, clinical examination, temperature and body weight recording, urine collection and blood sampling at various time-points for clinical chemistry (including creatine kinase (CPK) analysis), hematology and ELISA IgG analysis were made (for IgG data see above). The pathology comprised of weighing and gross examination of spleen, kidney, liver, lung and heart, bone marrow histology and histopathology of injection site biopsies.

The rabbits (4-7 months of age) appeared to be immunologically mature (significant booster effect) in contrast to that expected in the proposed target group. According to the presently available data, besides events possibly related to injection-trauma (i.e. injection site blood and/or hematomas), possible treatment-related effects were; inflammation at the injection site (subcutaneous cellulitis and muscle myositis), similar incidence and total severity scoring between the vehicle adjuvant (Al and MPL) control group and the vaccine-test group.

An elevation in serum CPK was noted two days after the first injection compared with pre-immunisation levels in both the Al/MPL-vehicle ($365 \pm 94 \rightarrow 505 \pm 201$ IU/L) and the treatment-group ($391 \pm 153 \rightarrow 819 \pm 247$ IU/L). No elevation in CPK was observed at the next sampling occasion on day 7 or at any other time-point, including sampling two days after the last injection.

The study was stated to have not been conducted in strict accordance with GLP. The usefulness of this study is questionable since there are major deficiencies. However these deficiencies may be considered to be outweighed by the clinical experience gathered so far.

- ***Carcinogenicity and genotoxicity:***

No studies have been submitted for the following reasons:

- according to the vaccination schedule proposed for the product (a maximum of 4 administrations in young children), the exposure will be minimal in time;
- the components of the vaccine are naturally-occurring products of bacteria which may be carried in the human nasopharyngeal tract; no evidence for any mutagenic or carcinogenic effect has been reported after carriage or infection with the pneumococcal species;
- no evidence for any mutagenic or carcinogenic effect has never been reported after exposure to other approved related products (pneumococcal conjugated or not conjugated polysaccharide vaccines).

The justification provided by the applicant was considered to be acceptable. Moreover the CPMP Note for Guidance on vaccines states, « genotoxicity and carcinogenicity studies are normally not needed ».

- ***Reproduction Toxicity***

No specific study is presented in the file for the following reasons:

- the target population of the vaccine (children aged up to 2 years of age) does not include males or females of reproductive age;
- the vaccine contains non-living antigens, which will normally not pose any problem for the reproduction;
- there is considerable experience about the safety of other pneumococcal polysaccharide vaccines to support the tolerance of such preparations even in the age of sexual maturity.

- ***Local Tolerance:***

No tolerance data are presented with the intended product Prevenar™. The local tolerance of a 9-valent pneumococcal conjugate vaccine was evaluated in the same study as that presented for the repeated-dose toxicity.

The immunogenicity studies show that only reported injection site reaction was small nodules in 2 mice out of 950 mice observed. No adverse local reaction was reported during immunogenicity routine studies in rabbits, performed with the 7-valent PnC.

- ***Immunotoxicity studies:***

Induction of cross-reacting antibodies

The anti-nuclear antibody (ANA) IgG assay is routinely used to detect the presence of autoantibodies in the sera of patients. A study was conducted in 30 healthy adults (males and females; 18 to 60 years old) to compare Prevenar™ vaccine to Pnu-Imune® 23 for their ability to induce autoantibodies. Each adult received 0.5 ml of vaccine and blood samples were collected before and one month after the injection. The results of the ANA test showed that immunisation with Prevenar™ did not increase the

levels of antibodies reactive to the nuclei of human cells when tested 1 month after vaccine administration.

Potential toxicity of CRM₁₉₇

The CRM₁₉₇ protein used as carrier is derived from *C. diphtheriae* wild-type toxin by single point mutation. The reversion to wild type with production of active toxin during manufacture of CRM₁₉₇ is possible, in theory. Each batch of CRM₁₉₇ is monitored for the presence of active toxin by measuring the ADP-ribosyl transferase activity. Additionally, other tests (cytotoxicity in HeLa cells or Vero cells *in vitro*, lethality in guinea pigs *in vivo*, abnormal toxicity test) were used to demonstrate the non-toxicity of CRM₁₉₇ during the development of the production process, but these tests are considered to be less sensitive to detect the active toxin than the ADP-ribosyl transferase assay.

Published data have suggested that CRM₁₉₇ mutant has significantly greater specific nuclease activity *in vitro* than that of the wild-type molecule (Bruce et al, Proc Natl Acad Sci USA 87:2995:1990). The risk for the conjugated or the free CRM₁₉₇ protein to affect DNA integrity in cells likely to be relatively more exposed to the mutant protein (e.g. cells at the injection site and antigen-processing cells (APC, T and B cells)), has been considered. It is argued that endonucleases are present normally in the human body (with highest levels occurring in the pancreas, blood and platelets) and that low levels of endonuclease, if present in CRM₁₉₇ (finding disputed by others in the field), would not be expected to have any clinical effect. The human safety profiles of the licensed vaccines HibTITER, Meningitec and 7VPnC, all of which contain CRM₁₉₇ as a carrier protein, support the lack of toxicity of this protein.

Potential toxicity of process-derived residuals

Residual cyanide is expected to be present as sodium cyanide in the vaccine suspension. The residual specification of ≤ 5 ng cyanide per dose is 500,000 times lower than the ATSDR oral daily minimal risk level (MRL) value for sodium cyanide of 0.05 mg/kg/day (a factor of 100 to reproduction toxicity). The safety margin is considered to be comfortable. Great safety margins to LD₅₀ values in animals or LD_{L0} value in humans were also estimated. The applicant also refers to the clinical safety data for 7VPnC and HibTITER, which also has the same specification for cyanide.

DMSO is categorised by the ICH as a Class 3 solvent and has been administered orally, intravenously or topically for a wide range of medical medications. Category 3 solvents are recognised, as having low toxic potential, with daily exposure amounts of up to 50 mg considered acceptable without justification. The residual DMSO specification of <16 μ g/dose is many times lower than the limit for Class 3 solvents.

• ***Ecotoxicity/Environmental Risk Assessment:***

The applicant for the following reasons presents no specific study:

- the vaccine contains an established active ingredient (pneumococcal conjugated polysaccharides) with no known environmental implication ;
- the vaccine is proposed for administration at a very low dose level and at a small number of injections ;
- there is no evidence for elimination of the active ingredient from the body after injection ;
- the vaccine does not contain any live organisms or ingredients derived from recombinant DNA technology.

Discussion on toxico-pharmacological aspects

Sufficient data have been provided to demonstrate the safety of the product. The safety studies were not always strictly GLP compliant and were not always conducted with the final formulation, but the preparations used in these experiments were closely related to Prevenar™ formulation, so that they seem appropriate and relevant to evaluate the toxicity of the intended product and of all its components.

Several multidose studies have been conducted in rabbits and mice without any evidence of systemic or local toxic effects. The only observed effect was transient local irritation and inflammation at the injection site. The use of a closely related vaccine showed a good local tolerance.

The absence of reproductive toxicity, genotoxicity, and carcinogenicity studies is acceptable according to the CPMP guidelines on vaccines. Moreover, additional routine safety tests applied during development and production of the vaccine are provided and confirm the non-toxicity of the vaccine components.

The immunogenicity of the vaccine for each serotype has been also well demonstrated by a large number of studies, especially in rabbits. The enhancing role of the adjuvant has been shown. Protection against a challenge with the pathogen was not shown in animals as recommended in the CPMP guidelines, but the protection can be assumed from the in vitro opsonic activity of both rabbit and human antibodies.

No environmental risk is expected for this product.

3. Clinical aspects

The clinical development programme for the pneumococcal saccharide conjugated vaccine, adsorbed (7VPnC) included a dose finding study (D92-P5), a phase I study in adults (D118-P2) and 10 primary immunogenicity studies in children (US D118-P3, P7, P8, P12, P16 and EU D118-P6, P502, P501, P503, P809). The trials established vaccination schedules, but also evaluated concomitant administration of other routine paediatric vaccines, booster dose, consistency of manufacture and immunogenicity in older infants. In addition supportive data from several trials [D118-P9, D118-P12 (Amendments 2,4), D118-P15 (Amendment 1), D118-P16 and D118-P18] on the immunogenicity of the 7VPnC vaccine in older children were submitted.

The efficacy of the 7VPnC vaccine against invasive pneumococcal disease as well as against otitis media and pneumonia was assessed in a large-scale study (D118-P8), the Northern California Kaiser Permanente (NCKP) trial, which was performed between October 1995 and August 1998. A total of 37,868 infants were enrolled, whereof 18,297 received 7VPnC and 18,941 received an investigational meningococcal C conjugate vaccine (MenCC). A complete report on the efficacy trial (FinOM D118-P809) in Finnish children of 7VPnC for prevention of acute otitis media due to vaccine serotypes was provided during the evaluation procedure.

All study protocols were designed according to the GCP guidelines.

Complete reports of 12 clinical studies have been presented in this application.

D92-P5: a model and dose finding study in infants using pentavalent conjugate vaccine for primary vaccination and a plain polysaccharide vaccine as a booster to evaluate the induction of immune memory.

Phase I studies

D118-P2: a double-blind study in adults to compare the immunogenicity and acute safety of a single dose of 7VPnC vaccine with a licensed polysaccharide vaccine.

Phase II immunogenicity studies

D118-P3 and D118-P7: Two double-blind controlled studies of the safety and immunogenicity of the 7VPnC vaccine and a Meningococcal Group C conjugate vaccine given at 2, 4 and 6 months followed by a booster dose at 12-15 months.

D118-P12: a double-blind trial to compare the safety and immunogenicity of 3 pilot lots of 7VPnC vaccine given at 2, 4 and 6 months of age. A complementary report (Amendments 2, 4) evaluated the safety and immunogenicity of 7VPnC vaccine given at 7, 9 and 15-18 months.

D118-P16: a double-blind trial to compare the safety and immunogenicity of a full scale production lot of 7VPnC vaccine to a pilot lot of vaccine given at 2, 4 and 6 months of age.

Phase II immunogenicity studies in older children

D118-P9: a trial to evaluate the safety and immunogenicity of a single dose 7VPnC vaccine (2 lots administered on a double-blind randomised basis) given to 15 to 24 months old toddlers.

D118-P15: a double-blind study of the efficacy, immunogenicity, safety and tolerability of 7VPnC compared to MnCC vaccine in Navajo and Apache Indian infants (number planned=18,000). A report (Amendment 1) on a subset of children evaluated the immunogenicity of the 7VPnC vaccine and Meningococcal Group C conjugate vaccine given as 2 doses 2 months apart to children 12 to 24 months.

D118-P18: an open-label, non-controlled out-patient study of the safety, tolerability and immunogenicity of 7VPnC in children between 1 and 9 years of age. Children below 24 months received 2 doses 7VPnC with 2 months interval and those >24 months received one dose.

Immunogenicity phase II trials in Europe

D118-P6: an open label study to evaluate the safety and immunogenicity of the 7VPnC vaccine given at 2, 4 and 6 months followed by a booster of either the 7VPnC vaccine or a polysaccharide vaccine administered on a double-blind randomised basis.

D118-P501: a randomised trial controlled immunogenicity study performed in France. The study group received 7VPnC+DTP/IPV/Hib at 2, 3 and 4 months of age and the control group received DTP/IPV/Hib alone.

D118-P502: a single-blind controlled study to assess the safety and immunogenicity of the 7VPnC vaccine mixed immediately prior to injection with lyophilised Hib vaccine given at 2, 3 and 4 months.

D118-P503: an immunogenicity study performed in Germany of a DTPa-IPV/PRP-T combination administered alone or at the same time as the 7VPnC at 3, 4 and 5 months of age.

Phase III study

D118-P8, Northern California Kaiser Permanente trial: a double-blind controlled study of the safety, immunogenicity and efficacy of the 7VPnC vaccine and safety of a Meningococcal Group C conjugate vaccine in infants 2, 4 and 6 months with a booster at 12-15 months.

Supplementary phase II study

D118-P809, FinOM trial: a randomised double-blinded multicenter cohort study of Finnish children to evaluate the efficacy of 2 heptavalent pneumococcal conjugate vaccines (PncCRM and PncOMPC) in the prevention of acute otitis media due to the vaccine pneumococcal serotypes. Both vaccines were compared with the same control vaccine (HepB vaccine). Only the results evaluating the PncCRM were obtained.

The majority of submitted studies were performed in the USA. Altogether five trials were performed in Europe: 2 in Finland (D118-P6, D118-P809), 1 in UK (D118-P502), 1 in France (D118-P501) and 1 in Germany (D118-P503).

The vaccination schedules used were:

- Standard schedule: 2, 4, 6 months (US D118-P3, P7, P8, P12, P16 and EU D118-P6, P809)
- Accelerated schedule: 2, 3, 4 months (EU D118-P502, P501)
- Other schedule 3, 4, 5 months (EU D118-P503)
- Booster vaccination: 4th dose at 12-15 months of age (US D118-P3, P7, P8, EU D118-P6, P809)
- Schedule in older unvaccinated infants: (D118-P9, P12, P15, P16, P18)

- 7-11 month-old: 3 doses (1 month interval between first 2 doses and the 3rd dose after >2 months); 12-23 month-old: 2 doses (2 month interval); ≥24 month-old: 1 dose
- Compatibility with other childhood vaccines (D118-P3, P7, P12, P16, P502, P501, P503)

Overview of controlled trials

Controlled trials with reference therapy						
Study	Number enrolled	Schedule (months)	N of doses	Control	Blinding	Concomitant vaccines
D118-P2	30 adults	18-60 years	1	PNU-IMUNE®23	Double-blind	
D118-P3	Primary 212 Booster 122	2, 4, 6 12, 15	4	MnCC	Double-blind	DTP-HbOC, OPV, HbOC or MMR
D118-P7	Primary 302 Booster 211	2, 4, 6 12-15	4	MnCC	Double-blind	DTP-HbOC, OPV, HepB, DTaP + HbOC
D118-P8 (Kaiser efficacy trial)	37 868	2, 4, 6 12-15	4	MnCC	Double-blind	DTP-HbOC or DTaP + HbOC, OPV or IPV, HepB DTP-HbOC, DTaP+ HbOC, Varicella, OPV, MMR
D118-P502	360	2, 3, 4	3	DTPw/lyoHib	Single-blind	DTP, HbOC, OPV
D118-P15 Amendment I	204	12-17 18-23 ≥ 24	1 or 2 1 or 2 1	MnCC MnCC MnCC	Double-blind	DTaP, Hib, MMR, Varicella
D118-P501	160	2, 3, 4	3	DTP/IPV/Hib	Single-blind	DTP/IPV/Hib
D118-P503	200	3, 4, 5	3	DTaP/IPV/ Hib	Single-blind	DTaP/IPV/Hib
D118-P809	1662	2, 4, 6 12	3 1	HepB	Double-blind	DTP/Hib/IPV

Overview of non-controlled trials

Study	Number enrolled	Schedule (months)	N of doses	Control	Blinding	Concomitant vaccines
D92-P5 (SVPnC)	400	2, 4, 6	3	none	Double-blind	DTP-HbOC
	130	15-18	1	none	Open-label	DTP-HbOC
D118-P6	60	2, 4, 6	3	none	Open-label	DTP-HbOC, IPV,
	58	15	1	none	Double-blind	MMR
D118-P12 (lot-to-lot consistency)	342	2, 4, 6	3	none	Double-blind	DTaP + HbOC, OPV or IPV
D118-P16 (bridging pilot to manufacturing)	654	2, 4, 6	3	none	Double-blind	DTaP + HbOC, HepB, IPV
D118-P9	60	15-24	1	none	none	none
D118-P12 Amendments 2, 4	60	7, 9 15-18	2 or 3 2	none	none	none DTaP + HbOC or DTaP - HbOC
D118-P18	300	12-18	2	none	Single-blind	none
		18-24	2			
		>24 <36	1			
		>36 <60	1			
		>5 <10y	1			

Assays

The immunogenicity of the 7VPnC was evaluated by measuring the antibody response elicited by each vaccine pneumococcal serotype. The immune response to other concomitantly administered vaccines was assessed by quantitation of antibodies to each component; responses between vaccine groups that received 7VPnC, MnCC, or no investigational vaccine were compared. The evaluation of the immune

response of subjects immunised with the 7-valent pneumococcal conjugate vaccine used two methods: ELISA (enzyme linked immunosorbent assay) to measure the quantitative IgG levels to each serotype and OPA (opsonophagocytic assay) to estimate the functional activity of the antibodies. All serum samples for immunogenicity analyses were tested blinded.

The ELISA method developed by the company (WLV assay) is validated and standardised and has been shown to demonstrate specificity, linearity, precision and accuracy with infant sera. All serologic data were analysed in one Wyeth Lederle laboratory in Rochester, NY, except for samples from D118-P6, which were analysed by an ELISA (KTL assay) at the Finnish National Public Institute. The lower limit of the ELISA test (WLV assay) has been established at 0.01 µg/ml. The ELISA measured the IgG antibody of each individual subject to each of the seven serotypes contained in the vaccine. The antibody concentrations one month following the third dose and one month following the booster dose were presented as geometric mean concentration (GMCs), percentages of subjects who achieved antibody concentrations of at least 0.15-µg/ml and 0.50 µg/ml, and reverse cumulative distribution curves for each study by serotype. Geometric mean concentrations (GMCs) were obtained from computing the arithmetic mean of log-transformed (natural logarithm) antibody concentrations and then exponentiating this value, because historically antibody concentrations have followed a lognormal distribution.

For this application, the working definition of the protective antibody concentration was set at 0.15 µg/ml, based on the results obtained in the Kaiser efficacy trial. It was based on the estimate for vaccine serotype efficacy, the antibody concentrations reached and the reverse cumulative distribution curves showing the greatest difference between the vaccine and control group around the concentration of 0.15 µg/ml.

Discussion on ELISA methods and protective antibody levels:

Based on interlaboratory comparative studies of the ELISA, some differences in serotype-specific IgG assignments made by KTL and by WLV have been noted. However, there is general agreement in the assignment of antibody values in two Finnish trials (D118-P6; FinOM), with the exception of 6B. WLV assigns higher values to sera than KTL; the reasons for this are under active investigation. Because the Kaiser efficacy study has enabled Wyeth-Lederle to assign IgG concentrations that distinguish between protected and vulnerable populations, it is important that other laboratories can develop an equally sensitive ELISA. The company has committed to co-operate with other laboratories in Europe to work on the standardisation of the ELISA.

A significant antibody response was seen for all serotypes although GMCs varied among serotypes. The choice of the protective levels of IgG concentrations of 0.15 and 0.5 µg/ml has been explained but must be considered as an approximate. The minimum antibody concentration necessary for protection against invasive disease has not been determined for any serotype, which is clearly stated in the SPC.

The OPA is a functional assay and not a quantitative test. The test is designed to show the presence or absence of complement-dependent killing of each serotype strain of *S. Pneumoniae*. The test method has been evaluated for compliance with the ICH guidelines for assay validation. The assay includes the use of pooled polymorphonuclear leukocytes (PMNL) from multiple donors and the addition of exogenous complement with the inclusion of pre-colostral calf serum. The test is not precise; however the company has committed to standardise the OPA assay.

The evaluation of the immune response of subjects immunised with the routine paediatric vaccines used established methods i.e. standard EIAs for measuring antibodies to tetanus toxoid, diphtheria toxoid, H. influenzae type b polysaccharide, Hepatitis B, pertussis (pertactin, pertussis toxin, filamentous haemagglutinin, fimbrial proteins) and virus neutralisation assay for polio (1, 2, 3). The percent of subjects achieving defined antibody concentrations were calculated for each antigen. For the control MnCC vaccine, a standard EIA and a functional antibody assay, meningococcal group C serum bactericidal assay (SBA), were used.

Immunogenicity

Serum samples for measurement of antibodies following primary vaccination were obtained before the first dose and approximately one month after the last dose. In studies US D118-P3, P12, and EU D118-P6 additional samples were also obtained post dose 2 to investigate the kinetics of the antibody response. In the four studies of booster vaccination (4th dose at 12-15 months of age) serum samples were obtained before and 1 month following immunization. In some studies, follow-up samples were collected at 24 months of age.

D92-P5: Model and dose-finding study in infants

The safety and immunogenicity of 2 models (oligosaccharide and polysaccharide) of a pentavalent pneumococcal vaccine (5VPnC) including serotypes 6B, 14, 18C, 19F and 23F at 3 dose levels (5.0 µg, 2.0 µg and 0.5 µg) was evaluated in 400 infants immunized at 2, 4 and 6 months (6 treatment groups and a control group receiving DTP-HbOC only). There were no clinically significant differences between treatment groups in terms of local reactogenicity, and between treatment and control groups in terms of systemic symptoms. The polysaccharide formulations were more immunogenic than the oligosaccharide, and the 5.0 and 2.0 µg polysaccharide resulted in similar responses. Based on this data, the 2.0 µg polysaccharide formulation was used as the basis for the 7VPnC vaccine development. (For serotype 18C, due to manufacturing reasons, an oligosaccharide was used. For type 6B, the least immunogenic type, the dose was increased to 4µg).

In this study, a booster dose of plain 23-valent polysaccharide vaccine was administered at 15-18 months of age to all subjects, including the control group. All 5VPnC vaccine groups experienced a substantial increase in GMCs to all serotypes. The control group had virtually no immunologic response to the polysaccharide vaccine.

D118-P2: Adult phase I study

The acute safety and the immunogenicity of a single dose of 7VPnC vaccine was assessed in 30 healthy adults in a randomized double blind trial in comparison with the commercial polysaccharide. The 7VPnC vaccine resulted in post-immunization GMCs that were higher than the polysaccharide vaccine for all serotypes except for 9V. The rates of local and systemic reactions were quite high for both vaccines and somewhat higher, although not statistically significant, for the conjugate vaccine.

- Immunogenicity following primary immunisation

Studies US D118-P3, P7, P8, P12, P15 and EU D118-P6, P502 and supplementary data from D118-P501, D118-P503 and D118-P509

The immunogenicity of the 7VPnC vaccine was evaluated in 10 completed studies. Five of these studies were performed in the USA, and five in Europe. Seven studies evaluated the standard 2, 4 and 6 months schedule, two evaluated the accelerated 2, 3 and 4 month schedule (D118-P501 and P502) and one evaluated the 3, 4, 5 month schedule (D118-P503). Data were presented as GMCs post dose 3, as % of subjects with antibody concentrations equal or higher than 0.15 and 0.5 µg/ml and as reverse cumulative distribution curves for each serotype. The opsonophagocytic activity of antibodies generated by the candidate vaccine was studied in 48 children from study D118-P3 following primary immunization. The kinetics of antibody response after each dose of the primary vaccination series was evaluated in study D118-P6.

The following conclusions can be drawn from these studies:

- More than 90% of infants achieved antibody concentrations equal or higher than 0.15 µg/ml across all studies and serotypes. The immunogenicity differed between serotypes with the highest GMCs attained for serotype 14 and with the lowest for serotypes 4 and 9V. The kinetic antibody profiles were demonstrated to be serotype-specific but for most types the largest increase in antibody titer occurred following the second dose.
- The antibodies elicited by vaccination during the primary series had functional activity, as evaluated by the opsonophagocytic assay

- Other vaccines administered at the same time as the candidate vaccine varied among studies (acellular or whole cell pertussis, attenuated or inactivated polio, HBV, Hib). The distributions of antibody responses for each serotype were similar among studies, as shown by the reverse distribution curves. This suggests that other vaccines given concurrently did not have a significant impact on the immunological response to 7VPnC, except in association with the booster dose in study D118-P7 where concurrent DTaP and HbOC resulted in a lower response to all pneumococcal serotypes except for 18C. However, these differences were not statistically significant.
- The candidate vaccine administered at 2, 4 and 6 months resulted in levels of antibody that were associated with protective efficacy against invasive disease in the Kaiser efficacy trial. The results of the different studies were consistent.
- The immunogenicity of the 2, 3, 4-month schedule was documented in 2 studies (D118-P501 and D118-P502). The GMCs after the 3rd dose were satisfactory, (although lower for certain serotypes, see below) and comparable with those of the 2, 4, 6-month schedule in the Kaiser trial. The persistence of serotype-specific antibody response up to the age of 12 months (8 months after the 3rd dose) following the accelerated schedule has been documented in a total of 87 infants. The pre-challenge GMCs were lower than those attained with the standard immunisation schedule (6 months after the 3rd dose). No booster data on the 7VPnC vaccine after the accelerated schedule have yet been submitted. However, a booster dose with the polysaccharide vaccine resulted in an anamnestic response indicating an immunological memory.

Summary of salient findings

Of note is that the immunogenicity of the 7VPnC vaccine was never tested given alone in the primary series. In all studies different concurrent vaccines were administered. The overall results demonstrated that the primary schedule elicited a satisfactory and consistent antibody response.

Functional activity, as measured by OPA, was evaluated by WLV in a subset of immunized and control subjects after the primary series in one study (D118-P3). Additional data from immunized infants generated by KTL using a different OPA protocol were provided in the form of submitted and published papers. While the correlation of OPA titers to ELISA IgG concentrations varied by serotype and by method, the results show that the post-immunization sera were usually associated with functional activity. WLV has committed to standardize the OPA assay.

It is agreed that it is premature to interpret data that could estimate the avidity of antibodies due to the use of different and non-validated test methods as concluded by the investigators. The clinical significance of antibody avidity still needs to be demonstrated.

An important deficiency of the submitted documentation was the lack on data of vaccine immunogenicity and functional antibody activity in high-risk children. Only limited data in patients with sickle cell disease were provided which is stated as such in the SPC. The Company submitted additional information that briefly described the trials that have been completed in high-risk categories and those that are ongoing. The populations included are appropriate i.e. those of high-risk categories, but the numbers are insufficient for any conclusions to be drawn. In addition, certain risk groups such, as patients with nephrotic syndrome, congenital or acquired splenic dysfunction and malignancy were not included. The proposed revised SPC reflects the lack of data on groups with high risk of invasive pneumococcal disease.

Immunogenicity data on the 3, 5, 12 month schedule are not available.

- Immunogenicity following booster vaccination (4th dose administered 12-15 months of age)

Studies US D118-P3, P7, P8, and EU D118-P6 and supplementary data from D118-P503 and D118-P809:

The persistence of antibodies following the primary vaccination with 7VPnC vaccine and the immunogenicity of a booster administered at 12-15 months of age was evaluated in 4 trials (3 performed in the USA, 1 in Europe). In the 3 US trials, all children were boosted with the 7VPnC vaccine. In the European study (D118-P6), children were randomized to receive the 7VPnC vaccine or a polysaccharide vaccine as a booster. Data are presented as GMCs prior to and 1 month post booster dose, as % subjects with antibody concentrations equal or higher than 0.15 and 0.5 µg/ml and as reverse cumulative distribution curves for each serotype.

The following conclusions can be drawn from these studies:

- the antibody levels declined substantially during the period between the end of the primary vaccination series and the booster dose. In all studies there was a substantial increase in the antibody concentrations after the 4th dose.
- the priming effect of the primary vaccination which had been shown in study D95-P2 was confirmed in study D118-P6 in which children were randomized to receive the 7VPnC vaccine or a polysaccharide vaccine as a booster. The antibody response elicited by plain polysaccharide was either comparable or higher than that elicited by the 7VPnC vaccine.
- serotype 14 achieved the highest pre- and post-booster concentrations in most studies, and serotype 4 the lowest.

Summary of salient findings

The magnitude of the observed booster response of the 7VPnC suggests the induction of immunological memory. There were differences between serotypes regarding the booster response with type 4 being the least immunogenic. The highest rise in antibodies was observed for 6B. Of note is that there was a substantial decline in antibodies both at 6 to 8 months after the primary series and at 12 months after booster. Types 4, 9V and 18C exhibited the lowest levels before the 4th dose and also during follow-up at 24 months. The persistence of antibodies has only been followed up to 24 months and in a limited number of subjects. The rapid decline of antibody levels suggests that further booster doses might be needed.

The conjugate vaccine also showed a good priming capacity by a vigorous booster response to the 23-valent vaccines. However, according to a recent Finnish study the avidity of IgG pneumococcal antibodies after boosting with the polysaccharide vaccine seemed to be lower than after boosting with the conjugate vaccine. Due to the current lack of standardised methods to measure avidity or functional antibodies, no conclusion can be drawn regarding any differences in the qualitative antibody responses between the conjugated and unconjugated polysaccharide vaccines.

- Lot-to-lot consistency

Studies D118-P12 and P16:

The two efficacy studies (US D118-P8 and EU D118-P809) and most of the immunogenicity studies (US D118-P3, P7, P8 and EU D118-P6, P502, P501 and P503) were performed using pilot lots. The consistency of manufacture of 3 pilot lots was evaluated in study D118-P12. In this study children were randomized to receive 1 of 3 lots. There were no statistically significant differences in GMCs or percent subjects achieving antibody concentrations equal or higher than 0.15 and 0.5 µg/ml for any of the seven serotypes.

Study D118-P16 was designed to bridge between a pilot lot and manufacturing lots: 1 manufacturing lot using Lederle aluminium phosphate as the adjuvant (the formulation intended for marketing), and a manufacturing lot using another source of adjuvant. The immunogenicity of the manufacturing lot intended for marketing was comparable to the pilot lot used in the efficacy trial, although higher titres were observed for the pilot lot. Study D118-P16 was designed to test non-inferiority of the manufacturing and pilot lots. It is noteworthy that, with a response level of 0.15 µg/ml, all of the responses for the manufacturing lot were greater than 90% and, with a response level of 0.50 µg/ml, none of the estimated differences were greater than 10% for any antigen. It is considered unlikely that any of these differences has clinical relevance.

- Compatibility with other childhood vaccines

Studies US D118-P3, P7, P12, P16 and EU D118-P502 and supplementary data from D118-P501, 503:

The compatibility of administration of the candidate vaccine with other routine pediatric vaccines was assessed in 7 studies. Five of these studies (US D118-P12, P16 and EU D118-P502, P501 and P503) contained a control arm with routine pediatric vaccines only. In the others, the 7VPnC vaccine was compared with a meningococcal C conjugate vaccine in a randomized double blind manner. In study D118-P502, one group received the 7VPnC vaccine mixed with lyophilized Hib vaccine. In study D118-P7, children were randomized to receive the booster of the candidate vaccine either at the same time or at one-month distance of the DTP-HbOC booster. In the French study D118-P501 DTP/IPV/Hib was given concurrently and in study D118-P503, DTPa-IPV/PRP-T combination was administered alone or at the same time as the 7VPnC.

Primary immunisation:

The overall picture of interactions between 7VPnC and childhood vaccines, indicates that there is evidence for some interactions between 7VPnC and other vaccines; in particular, with acellular pertussis vaccines, that raises some concern. It should be noted that in Europe there is only one trial (D118 P503) in which acellular pertussis vaccine given concurrently with 7VPnC is evaluated. In this trial a significantly decreased response to pertactin post-dose 3 GMCs were found in the 7VPnC group. However, the response to pertactin was still of very high magnitude (28-fold) in the 7VPnC group. In the US study D118 P12 (DTaP) also an interaction with pertussis antigens FHA, pertactin and fimbriae was observed. Also a slight interference with the IPV (serotype I) was demonstrated in study D118-P16. The clinical relevance of these interactions is at present unknown. An amendment to the SPC has been made describing the occurrence of vaccine interactions regarding the pertussis, and polio components.

The enhanced response to HbOC and diphtheria observed in some studies might be influenced by the presence/immunogenicity of the carrier protein, which is contained in both the 7VPnC and HbOC vaccine. As all these antigens share a common protein, the diphtheria CRM₁₉₇ protein and immunisation with this carrier would increase the number and state of activation of diphtheria-specific memory T-cells. Upon subsequent exposure, these T-cells enhance the B-cell antibody response to both diphtheria and the conjugate polysaccharide. The mechanisms implicated however are complex. An amendment to the SPC has been made describing the occurrence of vaccine interactions regarding the diphtheria and Hib components.

The immunogenicity of the co-administered Hep B vaccine did not indicate a significant interaction. Few subjects were investigated for the MMR response and higher numbers of subjects needs to be studied to confirm the obtained results. A subset of samples was also investigated for diphtheria response by Vero cells to ascertain the validity of the ELISA results. These results were submitted post-authorisation and confirmed the consistency of both ELISA and Vero cell testing..

The compatibility of concurrent administration of 7VPnC with the new combined multicomponent vaccines childhood vaccines have not been performed which is clearly stated in the SPC.

Booster immunisation:

During booster vaccination statistically significant lower GMCs for diphtheria; HibPRP, PT and FHA were attained in the 7VPnC group compared with the control group. No differences between groups were detected for the percentage of subjects achieving defined antibody levels.

The studies suggest that there is some interference in antibody responses when 7VPnC is concurrently given with childhood vaccines, although the clinical relevance is difficult to evaluate. The negative interference of the 7VPnC on the booster responses to DTaP and HbOC has been included in the approved SPC.

- Immunogenicity in older children

Studies D118-P9, P12, P15 and supplementary data from D118 P18 and D118-P16: “Catch-up studies”

Schedules for the primary vaccination of children who are older than 7 months have been evaluated in so-called “Catch-up studies”. Five studies were performed, including subjects aged 7 to 35 months. Children were divided in 4 age groups for analysis: 7 to 11 months for whom a 2-dose and a 3-dose schedule were evaluated, 12-17 months and 18-24 months for whom a 1-dose and a 2-dose schedule were evaluated, and >24 months for whom a 1-dose schedule was evaluated. The schedule recommended by the manufacturer is the one for which the serological response exceeds the serological response of the subset of infants evaluated for immunogenicity in the D118-P8 Kaiser efficacy trial.

The data on the 7-11-month old group showed that the immune response after a 3-dose catch-up immunisation schedule was more optimal than after a 2-dose schedule. It was demonstrated that the GMCs after 3 doses were acceptable and similar to those achieved after the 2, 4, 6 month primary series of the efficacy trial, but documentation concerning the need for additional doses is lacking.

The 2-dose schedule in 11-23 month-old elicited a good response to each serotype and was assessed in more than 99 subjects.

Study D118-P18 investigated included subjects aged 12-17 months, 18-23 months, 24-35 months, 36-59 months, 5-9 years (mean 7.4 years). Although the number of analysed samples was limited, strong antibody responses and of an anamnestic character were demonstrated after most vaccine schedules. Almost all subjects had pre-dose serotype-specific antibody levels above the protective level of 0.50 µg/ml. However, in the age groups 24-35 month and 36-59 month olds, which included few subjects, a decreased antibody response to some of the serotypes following one vaccine dose was observed. It could be questioned whether two doses should be given to these age groups. A higher local reactogenicity of the vaccine was found in the older children as compared to infants. Due to the limited data on immunogenicity and safety in the older children the present indication has been restricted to children up to 2 years of age.

Data are lacking to support a booster recommendation after the first booster dose following the primary series or to assess the need for further vaccine doses in older children.

Clinical efficacy

Main study: Kaiser efficacy trial (Study D118-P8) (phase III, therapeutic confirmatory trial)

Description of the study

The efficacy of the heptavalent pneumococcal conjugate vaccine (7VPnC) was evaluated in one large randomised, double-blinded study in 2-month old infants. Subjects were equally randomised into one of four treatment groups (group A-D), such that two groups received the 7VPnC vaccine and two groups received the control, MnCC vaccine. The vaccines were given according to the standard schedule at 2, 4, 6 and 12-15 months, which was based on the recommended schedule for receiving of the childhood immunisations. Efficacy was assessed against culture proven invasive pneumococcal disease (IPD), clinical otitis media and clinical pneumonia. The rates of the diseases were compared between the 7VPnC and MnCC vaccine groups. A sequential design was used with an interim analysis to be performed when 17 cases of IPD due to vaccine serotypes had occurred (August 1998). The study was terminated at that date, but blinding was maintained so that vaccine efficacy on all cases of IPD could be assessed through the follow-up date of April 1999. For efficacy against otitis media and pneumonia, diagnosis was only considered until April 1998. For ruptured eardrums, the follow-up period was prolonged until November 1998.

Enrolment in the Kaiser study was terminated on 24 August 1998. At that time 37,868 infants had been randomised and received at least one immunisation, whereof 18,927 subjects had received the

7VPnC vaccine and 18,941 subjects the MnCC vaccine. The majority of children had received 3 doses of DTP-HbOC or DTaP vaccines concurrently by the age of 12 months, through August 24, 1998.

a) Efficacy measures for IPD

Primary efficacy endpoint:

The primary objective of the study was to determine the protective efficacy of the 7VPnC vaccine against IPD due to serotypes included in the vaccine during the per-protocol follow-up period

Secondary endpoints:

- To assess the safety and tolerability of the 7VPnC vaccine administered as a primary series in infants at 2, 4, 6 months of age with a booster at 12 and 15 months of age.
- To assess the safety and tolerability of meningococcal group C conjugate vaccine (MnCC) in infants immunised at 2, 4, 6 and 12 to 15 months of age
- To determine the protective efficacy of 7VPnC vaccine in an intention-to-treat analysis
- To evaluate the effectiveness of vaccination with 7VPnC on overall invasive pneumococcal disease in the PP and ITT populations
- To assess the effectiveness of vaccination on rates of acute otitis media and pneumonia in the study population as determined from computerised data sources
- To assess the immunogenicity of 7VPnC vaccine following a primary series and booster dose

Efficacy measures for otitis media

Primary outcome: Overall incidence of acute otitis media episodes (new visits) during per-protocol follow-up.

Secondary outcomes: Overall incidence of AOM (new visits) during the intention-to-treat follow-up period and risk of at least one episode, frequent otitis media episodes, tympanostomy tube placement, overall incidence of AOM (all visits) and spontaneously ruptured ear drums in all per-protocol vaccinated children during the per-protocol follow-up and in all randomised children during intention-to-treat follow-up.

Statistical analysis

Efficacy invasive disease/pneumonia

The protective efficacy of 7VPnC against IPD was estimated as 1– disease rate ratio. Exact binomial test was used to test the null hypothesis of no vaccine efficacy. Confidence interval for vaccine efficacy was determined using exact binomial distributions (Clopper-Pearson method). The trial incorporated a group sequential design with one interim analysis at 17 cases of primary endpoint-invasive pneumococcal disease due to vaccine serotypes during per-protocol follow-up period in immunocompetent children and the final analysis at 26 cases. The acceptance criteria set for the primary analysis had a type 1 error of 0.0024 and ensured that the overall type 1 error α for the group sequential design was below 0.05.

Effectiveness of otitis media

Andersen-Gill formulation of proportional hazard method was used to analyse recurrent event data including the primary otitis media endpoint-overall incidence of all otitis media episodes during per-protocol follow-up. Robust variance estimates were used. The Cox proportional hazard model was used to analyse single event data including risk of first episode, frequent otitis media, and tympanostomy tube replacement. The exact binomial test was used to analyse the cases of ruptured eardrum due to vaccine types. Secondary analyses included the evaluation of frequent otitis media, tympanostomy tube placement and ruptured eardrums due to pneumococcal infections.

Efficacy results

Efficacy against invasive pneumococcal disease.

Of the randomised 37,868 subjects (ITT population), 27,118 infants were included in the Per-protocol (PP) population (13,549 in 7VPnC and 13,569 in MnCC group).

Analysis of vaccine efficacy against invasive pneumococcal disease

Cases October 1995 through August 20, 1998						
Invasive pneumococcal disease	Number of cases		p-value* between vaccine groups	Vaccine Efficacy Estimate(VE)	95% confidence limits of VE	
	7VPnC	MnCC			Two-sided limits	One-sided limit
Vaccine serotypes						
PP analysis	0	17	<0.0001	100%	(75.4%, 100%)	80.5%
ITT analysis	0	22	<0.0001	100%	(81.7%, 100%)	85.4%
All serotypes						
PP analysis	2	20	0.0001	90.0%	(58.3%, 98.9%)	64.5%
ITT analysis	3	27	<0.0001	88.9%	(63.8%, 97.9%)	68.6%
Cases October 1995 through April, 20 1999						
Vaccine serotypes						
PP analysis	1	39	<0.0001	97.4%	(84.8%, 99.9%)	87.2%
ITT analysis	3	49	<0.0001	93.9%	(81.0%, 98.8%)	83.4%
All serotypes						
PP analysis	3	42	<0.0001	92.9%	(77.6%, 98.6%)	80.5%
ITT analysis	6	55	<0.0001	89.1%	(74.7%, 96.2%)	77.3%

*Two-sided P-values and confidence limits were based on exact binomial distributions

At the time of interim analysis (August 20, 1998) all 17 cases of IPD had occurred in the MnCC group. Fourteen of the 17 cases had a diagnosis of bacteremia (including 2 with AOM, 1 with cellulitis and 1 with febrile seizure), whereas 2 had septicaemia and 1 had pneumonia. The most common serotype was 19F (n=7, 35%) followed by 18C (n=4), two of each of 6B and 9V and one each of type 14 and 23F. There was no invasive disease due to serotype 4 observed during the study.

ITT analysis confirmed the VE demonstrated in the PP analysis (0 vs 22 cases). The estimated incidence of vaccine-serotype disease in children vaccinated with 7VPnC was 0 versus 82.0 cases per 100,000 child-years in the MnCC recipients.

Exploratory analysis of vaccine efficacy against vaccine-serotype by dose was 100% regardless of the number of doses. Due to the limited follow-up and number of IPD cases, the point efficacy estimate in children who received 2 doses or less was uncertain (p=0.063).

Explorative analysis of vaccine efficacy against **all** IPD accrued through April 1999 revealed that further 30 IPD cases were identified. The estimated efficacy against IPD due to **all pneumococcal serotypes** was 85.7% in children who received 2 doses or less (p=0.070). In the ITT population for **all**

serotypes a total of 61 cases were recorded with 6 cases in the 7VPnC and 55 in the MnCC group. The corresponding figures for **vaccine** serotypes were 3 and 49 cases, respectively. The three IPD cases in the 7VPnC group included one immunocompromised child with AML (type 19F) and two immunocompetent subjects, whereof one was pneumonia (type 19F) after receipt of 4 doses and one was bacteremia (type 6B) after receipt of only one dose.

The distribution of vaccine serotypes among the 49 IPD cases in MnCC group (ITT analysis) was 19F (n=13), 14 (n=11), 18C (n=9), 6B (n=7), 23F (n=6), 9V (n=3) and 4 (n=0). IPD cases caused by non-vaccine serotypes (3 in the 7VPnC and 6 in the MnCC group) were scattered among several different types without any specific pattern. An analysis of serotype-specific efficacy for all per-protocol vaccine serotype cases revealed statistically significant differences between treatment groups for serotypes 19F, 14, and 18C. In the ITT analysis significant differences were detected for serotypes 19F, 14, 18C, 6B and 23F. Significance level was not reached for 6B. Of all IPD cases, 92.9% were caused by vaccine serotypes.

Efficacy against bacteremic pneumonia due to vaccine serotypes of *S. Pneumoniae* was 87% (7,99-95%CI)

Effectiveness (no microbiological confirmation of diagnosis was performed) against clinical pneumonia was also assessed. The estimated risk reduction for clinical pneumonia with abnormal X-ray (primary outcome) was 33% (6,52- 95% CI) and for clinical pneumonia with consolidation 73% (36,90- 95% CI).

Efficacy against clinical otitis media

Summary of vaccine effect on acute otitis media

Acute otitis media outcome	Per-protocol analysis		Intention-to-treat analysis	
	Estimated risk reduction (95% CI)	p-value	Estimated risk reduction (95% CI)	p-value
All AOM episodes	7.0% (4.1%, 9.7%)	<0.0001	6.4% (3.9%, 8.7%)	<0.0001
First AOM episode	5.4% (2.3%, 8.4%)	0.0008	4.9% (2.3%, 7.5%)	0.0003
Frequent AOM	9.5% (3.2%, 15.3%)	0.0035	9.2% (4.3%, 13.9%)	0.0004
Tympanostomy tube placement	20.3% (1.8%, 35.4%)	0.0335	20.6% (4.0%, 34.3%)	0.0171
All AOM visits	8.9% (5.8%, 11.8%)	<0.0001	7.8% (5.2%, 10.2%)	<0.0001
Ruptured ear drum with vaccine serotypes	55.6% (-5.3%, 90.0%)	0.267	57.1% (-18.7%, 86.5%)	0.115

The primary analysis was the overall incidence of AOM episodes (new visits) during the per protocol follow-up. From the beginning of the study Oct 1995 through the end of April 1998 a total of 16,124 AOM episodes were identified in 11,849 7VPnC children versus 17,405 AOM episodes in 11,897 MnCC subjects. The overall incidence of AOM episodes was reduced from 1.72 episodes per child year in MnCC recipients to 1,60 episodes per child-year in the 7VPnC recipients, a 7.0% reduction, which represents a prevention of 12 episodes per 100 child-year. The incidence of AOM decreased over time in both vaccine groups reflecting the increasing age of the subjects. A lower incidence was seen in the 7VPnC group for all but one time point throughout the follow-up period. Secondary outcomes are shown in the above table. A total of 157 children in the 7VPnC group had tympanostomy tubes placed versus 198 in the MnCC group, which equaled a 20% reduction in risk of tube replacement.

Supplementary phase III study: Finnish Acute Otitis Media (AOM) trial (D118-P809):

This was a randomised double-blinded multicenter cohort study that estimated the protective efficacy of 7VPnC against bacteriologic proven acute otitis media in 1,662 Finnish children. Altogether 831 children were assigned to receive PncCRM and 831 HepB vaccines. Vaccines were administered at 2, 4 and 6 months, and a 4th dose was given at 12 months. The vaccinees were further randomised to receive concomitantly DTPw-HbOC or DTPw-PRP-T in the other thigh. The surveillance for otitis media was carried out at study clinics. AOM was defined as having at least one symptom suggesting AOM and abnormal tympanic membrane at pneumatic otoscopy suggesting middle ear fluid. If AOM

was diagnosed, myringotomy with fluid aspiration for bacterial culture was performed. Immunogenicity of the vaccine was also evaluated by measuring serotype-specific antibody levels prior to vaccination, 1 month post-dose 3 and post-dose 4. Systemic and local reactogenicity of 7VPnC was recorded.

The following table summarizes the results:

	7VPnC group	Control (Hepatitis B Vaccine) group	Total
Clinical OM with MEF sample obtained	1177	1267	2444
Pneumococcal otitis media	271	414	685
Vaccine serotype pneumococcal otitis media	107	250	357

The point estimate for the efficacy of the 7VPnC vaccine is 57% against vaccine serotype otitis media, 34% against all pneumococcal otitis media and 6% against all episodes of otitis media with MEF taken. The data reported from the control group indicate that *Streptococcus pneumoniae* accounted for 33% (414/1267) of the episodes of otitis media and that vaccine serotypes accounted for 66% (250/414) of the episodes caused by *Streptococcus pneumoniae*. This percentage is in the range expected from background epidemiological information.

In the FinOM trial significant efficacy was demonstrated against serotypes 6B, 14, 23F and for related serotype 6A with efficacy estimates of 57-85%. The point estimate for vaccine efficacy was highest for serotype 6B (84%). However, for serotype 19F low efficacy was shown (25%) and also against the related serotype 19A (34%). Also in the Kaiser efficacy trial cultures from draining ears suggested low protection against 19F. Despite the low efficacy, the serological response to 19F was excellent in the Finnish children.

It can not be denied that the 7VPnC vaccine has efficacy against otitis media caused by the vaccine serotypes of pneumococci, but to a lower extent than against invasive infections. Moreover the overall impact of the vaccine on total number of otitis media episodes is small, approximately 6%. Even if otitis media is a very common disease in children this extent of vaccine efficacy does not support an indication. The protection afforded by the vaccine against otitis is an add-on beneficial effect, and is only described in the section 5.1 of the SPC.

In the FinOM Trial, pneumococcal nasopharyngeal carriage was measured at 12 and 18 months of age, as present or absent. At 12 months, when the booster dose was administered, no significant impact on pneumococcal nasopharyngeal carriage was evidenced. At 18 months, a statistically significant decrease in the percentage of vaccine serotypes carried, 16.2% versus 9.5% (difference: 6.7%; 95%CI 3.3-10.1; p<0.01) was observed indicating that the 7VPnC vaccine reduces vaccine serotype carriage. Meanwhile, a higher proportion of serotypes other than vaccine and vaccine-related serotypes (11.2% versus 7.7%) (Difference: 3.5%; 95%CI -6.5,-0.5; p=0.02) was found among 7VPnC recipients, indicating that replacement by other serotypes had occurred.

During a follow-up period comparable to the Kaiser Efficacy Trial, the FinOM Trial has shown an increase in AOM due to other than vaccine and vaccine-related serotypes among 7VPnC recipients, with a rate of 10.69 versus 7.96 per 100-person year, indicating that replacing serotypes may cause AOM. However significant overall vaccine efficacy against all pneumococcal AOM, a 34 % reduction (21-45, 95% CI), was still demonstrated.

Summary of salient findings

In the Kaiser efficacy trial, the 7-valent vaccine was shown to be highly efficacious against invasive pneumococcal disease caused by the serotypes contained in the vaccine. There was no indication of decreasing efficacy during the follow-up period. Due to the limited number of cases of IPD, serotype-specific efficacy could not be demonstrated for types 6B, 9V and 4.

The power to assess efficacy in partially immunised children was limited by the short follow-up period between dose 1, 2 and 3 allowing for accrual of 8 IPD cases due to any pneumococcal serotype only. Therefore, in spite of high point estimate of efficacy in partially immunised children, no definitive conclusion can be drawn about VE for those that received ≤ 2 doses. Twelve of the 22 vaccine-serotype IPD cases accrued up to August 20, 1998 occurred in children less than 12 months of age but the amount of follow-up was highest in the age group of 6.5 months to 12 months old.

In the Kaiser efficacy study, there was no evidence of increase of disease due to non-vaccine serotypes. However, post-vaccination epidemiologic studies of serotypes causing both colonisation and invasion will be important to determine if serotypes not covered in the vaccine will become more prevalent.

The effectiveness of 7VPnC against otitis media was demonstrated in this trial across all endpoints except ruptured ear drums. The overall risk reduction (7% PP, 6.4% ITT) of the primary outcome measure was low, representing prevention of 12 episodes per 100 child-years. Efficacy was more promising in the group with recurrent and potentially more serious otitis (tube placement) (20.3%). Most likely the vaccine should be targeted at this group with more serious and recurrent AOM. However, the otitis part of the Kaiser trial suffers from important limitations, since there were no pre-specified criteria for the diagnosis and no bacteriologic confirmation. The results of the FinOM vaccine trial (overall efficacy 6%) were very similar to that obtained in the Kaiser trial (overall efficacy 6.4%).

The 7VPnC vaccine was demonstrated to be efficacious against clinical pneumonia with abnormal X-ray and consolidation, i.e. those pneumonia cases with the most probable bacterial diagnosis. The effect was more pronounced in the ITT population for unknown reasons.

The modest efficacy of 7VPnC in relation to the observed side effects does not support otitis and non-bacteraemic pneumonia as separate indications.

In conclusion

The efficacy of the candidate vaccine against invasive pneumococcal disease caused by vaccine serotypes has been established in a large scale field trial performed in the USA (the Kaiser Permanent trial). In this study, vaccine serotypes caused >90% of the invasive diseases. In the same study, there was some evidence that the vaccine reduced the risk of clinical pneumonia with consolidation on chest X-ray, and had an impact on the occurrence of otitis media.

In the FinOM vaccine trial the efficacy against otitis media has been presented. The efficacy against vaccine serotype otitis media (57%) was lower than that reported for invasive infections in the Kaiser Permanent trial (97%). Vaccine serotypes caused only 66% of the pneumococcal otitis media in this trial, and *S. pneumoniae* caused 33% of the otitis media with MEF sample obtained. As a consequence, the vaccine had only a modest impact on the total number of acute otitis media episodes with MEF obtained regardless of etiology (6% reduction).

During a follow-up period comparable to the Kaiser Efficacy Trial, the FinOM Trial has shown an increase in AOM due to other than vaccine and vaccine-related serotypes among 7VPnC recipients, with a rate of 10.69 versus 7.96 per 100-person year, indicating that replacing serotypes may cause AOM. Importantly, the overall vaccine efficacy against all pneumococcal AOM was significant, with a 34 % reduction (21-45, 95% CI).

As to whether serotype replacement really occurred, or whether previously co-colonising serotypes have actually increased in density with the absence of dominant serotypes is not clear. If serotype

replacement does occur, the propensity of these strains to cause IPD is not known. However, the relatively limited number of serotypes associated with invasive diseases in children suggests that only a small number of them are intrinsically virulent. Furthermore, antibiotic resistance today is associated with a few serotypes 6B, 9V, 14, 19F and 23F, that are well represented in the 7VPnC vaccine. Replacement strains are likely to be susceptible to most commonly used antibiotics, at least initially.

In conclusion, although replacing serotypes have been associated with AOM in the FinOM Trial, it is reassuring that the most recent available data on IPD from the Kaiser Efficacy Trial do not support a possible increase in IPD caused by non-vaccine serotypes.

Clinical safety

Patient exposure

In the immunogenicity trials no deaths occurred except for 3.5 month-old male infant in trial D 18-P16 who died of SIDS 47 days following 7VPnC immunisation. During the Kaiser efficacy trial 18 deaths were reported through April 30, 1998 and an additional 12 deaths during May 1 and December 1998. Of these 30 deaths, 10 occurred in the 7VPnC and 20 in the MnCC group. None of the deaths were considered related to vaccination. The most prevalent diagnosis was SIDS (n=13, 4 7VPnC, 9 MnCC) and only three occurred in relatively close temporal relation to immunisation (5, 6 and 7 days following the vaccine dose). Other deaths were due to events such as accidents, drowning, congenital diseases and homicide.

Local and systemic reactions

• Local reactions

Primary immunisation:

The local reactions recorded after each dose were erythema, induration and tenderness. Significant reactions were defined as erythema and induration >2.4 cm or tenderness that interfered with leg movement. The local reactogenicity of concurrent immunisations in the opposite leg of the same subjects was also assessed for comparison. If two injections were given in the same limb at separate sites and reactions occurred at both sites the most severe reaction was recorded. For studies D118-P3, P12, and P16, acute reactions were assessed for 3 days, whereas for D118-P7 and P8 reactions were assessed for two time periods following each immunisation: first 2 days and 3-14 days.

Across all studies rates of erythema were 12.1%, 14%, and 15.2% after doses 1, 2 and 3, respectively. Induration occurred in 10.7%, 12.4% and 12.1% of subjects and tenderness in 25.2%, 22.9% and 22.3% of subjects after dose 1, 2 and 3, respectively. For erythema a modest increase upon repeated doses was observed in the majority of trials, which was not the case for other local reactions. Significant reactions for erythema (>2.4 cm) in 0.6% to 3.8% of immunised subjects, for induration (>2.4 cm) in less than 3% and for tenderness (interference with leg movement) in 1.8% to 7.9% of subjects. 7VPnC vaccine was in general less reactogenic than DTP-HbOC, whereas the opposite was demonstrated in comparison with DTaP injection site.

In the Finnish trial (D118-P6) a much higher rate of local reactions was reported and, in particular for tenderness, than in the US trial. Up to 23.7% (mean 17.2%) of the 59 Finnish infants who received 7VPnC experienced significant tenderness with interference of movement compared with 6.9% of the US infants. Also, regarding erythema and induration high rates of around 26% were observed. In the UK trial (accelerated schedule) the local reactogenicity was also higher than that reported in the US. The rates of swelling, induration and tenderness were 25.2%, 20.7 % and 23.5%, respectively. However frequencies of significant reactions did not differ. Increased reactogenicity was observed when 7VPnC was mixed with IyoHib, with rates of tenderness of up to 31.1%. Subjects receiving DTwP suffered from local reactions nearly twice as often as the ones receiving 7VPnC.

In older children the safety profile was different regarding local reactogenicity compared with that in infants. In study D118-P9, enrolling subjects 15-24 months of age, a higher rate (46.7% to 48.3%) of local reactions were reported compared with other catch-up trials in this age group (13-16.7%). The results in older children >24 months of age and in particular, in those >36 months of age indicated an

unusually high rate of local reactogenicity. Especially the rates for tenderness were very high, 58%-82%, and those of significant grade interfering with leg movements (21%-39%).

Table: Summary of local reactions within 3 days of immunisation (% of subjects)

Protocol Age group	Sample size	Erythema	Significant erythema	Induration	Significant induration	Tenderness	Significant tenderness
D118-P12 7-11 months 3 doses	Dose 1 54	16.7	1.9	16.7	3.7	13.0	1.9
	Dose 2 51	11.8	0	11.8	0	11.8	2.0
	Dose 3 24	20.8	0	8.3	0	12.5	4.2
D118-P16 7-11 months 3 doses	Dose 1 81	7.4	0	7.4	0	8.6	1.2
	Dose 2 76	7.9	0	3.9	0	10.5	1.3
	Dose 3 50	14.0	0	10.0	0	12.0	0
D118-P9 12-23 months	Dose 1 60	48.3	6.7	48.3	3.3	46.7	3.3
D118-P18 12-23 months	Dose 1 114	10.5	1.8	8.8	0.9	25.7	6.2
	Dose 2 117	9.4	1.7	6.0	0.9	26.5	8.5
24-35 months	Dose 1 46	6.5	0	10.9	2.2	41.3	13.0
36-59 months	Dose 1 48	29.2	8.3	22.9	6.5	58.3	20.8
5-9 years	Dose 1 49	24.2	7.1	22.5	9.3	82.8	39.4

Booster immunisation:

The local reactogenicity of the 4th dose did not reveal any increased rate of erythema and swelling. However, for significant tenderness as many as 13.5% of the children receiving DTP-HbOC had significant tenderness that interfered with leg movement, which is much higher than that during the primary series (7.9%). Similar to the primary series, reactogenicity was lower for DTaP than for 7VPnC. Compared with the polysaccharide vaccine (PNU-IMUNE) administered as a booster in D118-P6, the 7VPnC subjects experienced more local reactions, although not statistically significantly higher. The Finnish children again had a very high frequency of local reactions following the booster dose.

- Systemic reactions

Primary immunisation:

Systemic events were assessed for 2 or 3 days following each dose by diary cards and telephone interviews. Rates of fever, fussiness, drowsiness and decreased appetite were recorded in all studies as well as gastrointestinal symptoms, rash/hives and sleep disturbances in most studies. Prompted systemic events were recorded in up to 9,191 doses of 7VPnC+DTP-HbOC, 3,848 doses of 7VPnC+DTaP and HbOC and 538 doses of DTaP and HbOC alone.

The rates of systemic events in the US trials have been presented. Compared to the MnCC vaccine, the 7VPnC vaccine was more reactogenic with regard to fever $\geq 38^{\circ}\text{C}$, with frequencies ranging from 15.1% to 40.6% (fever $\geq 39^{\circ}\text{C}$ 0% to 5.3%). Across all studies the concurrently given DTP-HbOC was more reactogenic regarding fever, decreased appetite, fussiness than the DTaP and HbOC. Fever also tended to increase with increasing number of doses, possibly due to the whole-cell pertussis vaccine. When 7VPnC recipients were compared with controls receiving DTaP and HbOC alone, higher rates of fever $\geq 38^{\circ}\text{C}$ were observed (15.7% vs 9.5%). Overall fussiness was the most prevalent reaction with the highest rate (71.3%) in study D118-P8 (DTP-HbOC). In the FinOM trial the fever rate $\geq 38^{\circ}\text{C}$ following any one of the 3 primary series doses in the 7VPnC group (41.2%) exceeded statistically significantly ($p < 0.001$) the fever rate in the control group (27.9%). The reactions were transient, of limited duration and fever $> 39^{\circ}\text{C}$ was reported in 3.3% (vs 1.2%) ($p = 0.007$) of children. These results are consistent with what was observed in the Kaiser Trial and other US studies where DTP was

concomitantly administered. In the UK trial, lower than expected temperatures were observed, possibly due to auxiliary temperatures being used. A recommendation for the use of prophylactic antipyretic has been mentioned in section 4.4 of the SPC.

In the older age groups receiving primary immunisation there was no consistent increase in systemic reactogenicity. In study D118-P9 the highest rates of reactions were observed with fever $\geq 38^{\circ}\text{C}$ in 36.7% and fussiness in 40% of the subjects.

Booster immunisation:

The incidence of systemic events associated with a booster of 7VPnC was similar to that of the primary series. The incidence was highest in infants receiving the whole-cell pertussis vaccine concurrently and considerably lower in the ones receiving 7VPnC alone (n=727). In the Finnish trial the polysaccharide booster elicited more reactions except for fever.

Adverse events and serious adverse event/deaths

In the non-Kaiser US trials (D118-P3, P12) a total of 20.4% of 362 subjects reported AEs compared with 17.4% of 86 controls. The most common event was upper respiratory infections such as otitis media (4.7%), bronchitis (3.3%) and viral infections (3.3%). From the listing, the following events were notable: apnoea (n=1), abnormal crying (n=4), HHE episode (n=1) and convulsions (n=2). It is noted that these infants were concurrently given pertussis vaccines. One case of seizure occurred 4 days after the first dose of 7VPnC and was judged possibly related to immunisation.

In the Kaiser trials (D118-P7, P8 and P16) a total of 17,806 infants that received the 7VPnC vaccine were monitored. The vaccine studies were combined together across all doses and regardless of concurrent vaccinations. A summary of the most frequent reasons for hospitalisation within 60 days is presented. The most common reason was bronchiolitis (3.5%). Of note is that 16 children (1.87 per 1000 person-years) had febrile seizures, whereof one case was considered related to immunisation? Emergency room visits within 30 days revealed that infectious diseases were the most prevalent diagnosis such as otitis media (1.3%). Fourteen children sought the ER due to seizures. Twenty-six AEs were considered possibly related to immunisation; febrile illness (n=17), irritable child (n=4), febrile seizure (n=2), and one each of HHE, sepsis and upper respiratory infection.

Seizures: In comparison with the control vaccine MnCC, there were some events that occurred in statistically higher frequencies in the 7VPnC group, the most important being febrile seizures. Since both vaccine groups received the same concurrent vaccinations the whole-cell pertussis vaccine may not be the sole cause for the difference in rates. Seizures were pre-specified events of particular concern during the Kaiser trial and the occurrence of these events was followed very carefully. In total, 32 children (out of 17,066 7VPnC vaccinated) experienced an acute seizure within 30 days after immunisation, whereof 8 within 3 days. Out of the 8 febrile seizures in the 7VPnC recipients, 4 children had other possible causes of febrile seizures. Six out of 8 received whole-cell DTP; 2 DTaP concomitantly. In the MnCC group 4 cases with febrile seizures within 3 days of vaccination were identified. The true incidence of febrile seizures in relation to 7VPnC is difficult to estimate, due to the concomitant pertussis vaccines. A causal relationship of 7VPnC with the HHE episode and the eight cases with unusual crying is also difficult to establish. All these events will be subject to particular attention during post-marketing surveillance undertaken by the company.

In the FinOM trial 12 febrile seizures were observed in the 7VPnC group. None of them occurred within 3 days after vaccination. The earliest febrile seizure was experienced 28 days after vaccination and none of them was considered vaccine related by the investigator. The overall incidence of febrile seizures was not different from the one in the control group (N = 14). There were no febrile seizures in the French (D118 P501) and the UK (D118 P502) trials.

In conclusion

The 7VPnC vaccine was shown to be quite reactogenic in combination with the whole-cell pertussis vaccine. Significantly higher rates of fever $>38^{\circ}\text{C}$ (41 vs 28% and of high fever $>39^{\circ}\text{C}$ (3.3 vs 1.2%) occurred when the 7VPnC vaccine was given concomitantly with DTP, as was also the case for seizures, the majority of febrile origin. The SPC section 4.4 have been amended accordingly i.e. a

recommendation to use prophylactic antipyretic medication when 7VPnC is used concurrently with whole-cell DTP or when administered to children with seizure disorders. The rate of seizures occurring in the Kaiser trial was lower than that found in another referenced study with DTP immunisations.

Discontinuation due to adverse events

Of the approximately 18,000 subjects receiving pneumococcal conjugate vaccine, 71 subjects were withdrawn from the study due to adverse events, whereof 43 due to seizure activity. Sixteen AEs were considered temporally related to vaccination, of which 8 due to unusual crying, 3 due to HHE, 2 due to rash/hives and 4 due to febrile convulsion.

Laboratory findings

The limited data submitted on laboratory measurements did not allow any conclusions. In the Kaiser trial medical records of children were reviewed for haematological and other diagnosis throughout the length of the study. The incidence of other conditions such as aplastic anemia, autoimmune disease, diabetes mellitus and neutropenia did not exceed those of historical controls. Ten cases of thrombocytopenia were reported, which should be viewed in relation to 22 expected cases on historical rates.

Discussion on clinical safety

One important deficiency of the submitted documentation is that in no infant study was the 7VPnC vaccine given alone. It could be argued that the 7VPnC vaccine would probably always be used concurrently with other childhood vaccines, but nevertheless a study evaluating the safety of 7VPnC alone is considered appropriate. The exact contribution to systemic reactogenicity of the 7VPnC was difficult to determine due to the concurrently given vaccines.

Local tolerance of the 7VPnC vaccine assessed at two primary schedules was acceptable, except for that reported in the Finnish trial (D118-P6). The rate of 23.7% (n=59) for significant tenderness following the primary series that was reported in this trial is not acceptable. However, in the larger FinOM trial D118-P809 (n=822) such high rates of local reactions were not recorded, which is reassuring. The unusually high rates of local reactions observed in study D118-P9 remain unexplained, but might be due to normal variability, since the larger trial (D118-P18) did not confirm these findings. The second dose at 12-23 months did not result in increased frequency of local reactions. However, the results in older children >24 months of age and in particular, in those >36 months of age indicate an unusually high rate of local reactogenicity. Especially the rates for tenderness were very high, 58%-82%, and those of significant grade interfering with leg movements (21%-39%). Although the numbers are small, the high frequencies of local reactions were confirmed in two trials. This finding is important and might indicate that the vaccine should not be used in older children. The indication as stated in the SPC has been modified and is limited to children up to 2 years of age.

Except for erythema, no tendency of increased reactogenicity with subsequent doses was noted.

In association with the booster dose a high rate of significant tenderness (18.5%) was reported. This was documented in the largest study including 599 infants and, thus, it seems that reactogenicity might be increased following the 4th dose.

The 7VPnC vaccine in general was less reactogenic than DTP-HbOC but more reactogenic compared with DTaP.

Systemic reactogenicity data revealed that the 7VPnC elicited higher rates of fever compared with the control groups (MnCC and DTaP alone). An unknown factor in this context is the extent of antipyretic use and any differences that might be present between groups. In most trials it seems that the 7VPnC group used more antipyretics, which could have resulted in an underestimation of fever reactions. The very high rates of fever that was reported in the Finnish trial D118-P6 (61% after dose 3) may indicate a higher actual incidence, although the fever (>38°C) rate following dose 3 in the larger Finnish trial D118-P809 (n=813) was 26%. Study D118 P3 showed that the use of antipyretics was significantly higher in the 7VPnC group (75%) compared with the MnCC control group (58%) (p=0.013), whereas

the rate of fever was similar in both groups. These data demonstrate the higher systemic reactogenicity following administration of the 7VPnC vaccine. A general statement on antipyretics was included in the SPC.

The whole cell pertussis vaccine and concurrently administered 7VPnC were associated with high reactogenicity, in particular with regard to fever (33%) and fussiness (71%).

4. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Viral Safety and Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

The currently available information demonstrates a sufficiently consistent production of Prevenar and a well-defined quality, suitable for human use. The company has undertaken to provide all the outstanding data, which remain as follow-up measures.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that Prevenar is immunogenic in rabbits and mice.

The lack of carcinogenicity and reproductive toxicity studies has been justified. Overall, no major objections were identified in the toxicology programme performed.

Safety and efficacy

The outstanding issues presented by the company during an oral explanation before the CPMP in their meeting in September 2000 are summarised below.

The serotype epidemiology in Europe differs from that in the US and the coverage of vaccine strains is generally lower in Europe (55-85%). The coverage is less in the Nordic countries, but is high in some countries such as the UK, France, Belgium and Spain (80%). The Company has revised the SPC with amendments to section 5.1 regarding the serotype epidemiology within Europe, the vaccine coverage in Europe compared to the US.

An age dependent coverage of the vaccine serotypes was demonstrated with reduced coverage in children >2 years. Of all IPD cases 25% occur in the age group 2-5 years. It is estimated that this will correspond to 434 preventable IPD cases per year in Europe. In addition, data from clinical studies suggest a contribution of herd immunity with reduction of the carriage of vaccine serotypes in siblings. These facts might support an extension of the indication up to the age of 5 years. However, at the time of the initial approval there were only limited data available on safety and immunogenicity of Prevenar in the age groups above 2 years. The decreased antibody response to some of the serotypes in the 24-35 month old group following one dose of Prevenar raises the question whether two doses should be given. The high reactogenicity observed in older children was also taken into consideration in the risk/benefit balance.

Due to the limited data on immunogenicity and safety in the older children the indication was restricted to children up to 2 years of age at the time of the initial granting of the marketing authorisation.

The Prevenar vaccine has efficacy against otitis media caused by the vaccine serotypes of pneumococci, but to a lower extent than the efficacy against invasive infections. Moreover the overall impact of the vaccine on total number of otitis media episodes is small, approximately 6%. Even if

otitis media is a very common disease in children this extent of vaccine efficacy does not support an indication. The protection afforded by the vaccine against otitis is an add-on beneficial effect, and has only been described in the section 5.1.

The updated report from the Kaiser trial (February 2000) has not revealed an increase in cases with IPD caused by non-vaccine serotypes, whereas the FinOM trial showed an increase in AOM due to non-vaccine serotypes among the 7VPnC recipients. Monitoring of pneumococcal nasopharyngeal carriage in the FinOM study at 18 months after immunisation revealed a limited decrease in the carriage of vaccine serotype pneumococci, but a decrease of non vaccine-associated serotypes among the vaccinated subjects compared with the control group. Also in South Africa similar shifts in carriage of serotypes were observed. These findings are early warnings and suggest that the non-vaccine serotypes could increase, replace the vaccine serotypes and cause disease leading to a reduction in vaccine efficacy. The virulence/susceptibility to penicillin of the non-vaccine strains might change/increase in this scenario.

The validity of the assumption that the 7VPnC would also cover vaccine-related serotypes is strengthened by the submitted documentation, including preclinical data. The efficacy data in the FinOM trial supports the concept of cross-protection against related serotypes. It is reasonable to believe that this is also the case for invasive pneumococcal disease. The serogroup estimations could thus be considered justified. However, regarding vaccine serotype 19F and the related type 19A, preclinical data suggest poor cross-protection.

Additional issues have been addressed in a number of postmarketing surveillance programs and post marketing studies that have been undertaken by the company.

Post marketing data

Since the Marketing Authorisation was granted, new data have been received which led to changes in the prescribing and patient information. These data concerned the occurrence of febrile seizures and post-marketing information in relation to serious and severe hypersensitivity reactions, skin and subcutaneous tissue disorders (angioneurotic oedema and erythema multiforme), general disorders and administration site conditions. New safety information on lymphadenopathy and on overdose cases was also introduced. Moreover, changes have been introduced to reflect available data on concomitant administration with meningococcal C conjugate vaccines as well as with hexavalent vaccines.

As a condition for licensing, the MAH committed to further evaluate the safety and immunogenicity of Prevenar in previously unvaccinated older children aged 24-36 months (study 0887X-100961). In addition, the MAH committed to submit the final study report from a phase IV observational safety trial in older US children, involving four different paediatric age groups: 7 to 11 months, 12 to 23 months, 2 to 5 years and 5 to 9 years (study 0887X -100175). These two studies have now been submitted and constitute the basis for a variation application to extend the maximum age of vaccination from 2 years to 5 years of age.

Although the rate of local reactions following a Prevenar injection in the older children was remarkably high in these studies, this must be weighed against the seriousness of the invasive pneumococcal disease. However, the incidence rates of IPD and its occurrence in different age groups as well as the distribution of serotypes vary by age and by geographic region both on a global basis and within the European community. Based on contemporary surveillance data from the countries of Europe, the serotype-specific vaccine coverage of Prevenar for older children (from 2 to 5 years, or from 2 to 6 years) is about 50 to 75%. In general the incidence rates of invasive pneumococcal disease are much lower in children above 2 years of age than in the younger infants, but still some 25% of IPD occur in children 2 to 5 years of age. The incidence of invasive disease varies also greatly by geographic region. In addition, there is an age-dependent difference in vaccine coverage, being less in older children. However, the increasing incidence of drug-resistant pneumococcal strains is problematic and more so in certain regions, such as in South and Eastern Europe. Also, the seriousness of IPD, as shown by data on mortality rates and rates of sequelae, is notable also in older children and this supports the requested extension of indication. In conclusion, the benefit/risk ratio differs between

countries and the use of the vaccine in general and in the older children, in particular, must be determined on the basis of official recommendations, as already stated in the current SPC.

The local reactogenicity of the vaccine in children >2 years of age is troublesome, but it was demonstrated that these reactions were transient and self-limited. Moreover, only a single injection is required in these age groups. The safety data do not seem to raise any major concerns, with the exception of those for children with symptomatic HIV infection. Additional data are needed to clarify the benefit/risk ratio in this risk group.

The overall benefit/risk relationship of Prevenar in older children from 2 to 5 years of age was considered favourable and this variation (II-0018) received a positive opinion of the CHMP in June 2004 and a positive Commission Decision in August 2004.

Benefit/risk assessment

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk profile of Prevenar was favourable in the following indication:

Active immunisation against invasive disease (including sepsis, meningitis, bacteraemic pneumonia, bacteraemia) caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in:

- infants and young children from 2 months of age to 2 years of age

- previously unvaccinated children aged 2 years to 5 years