EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human use (CHMP)

Assessment report

Synflorix

International non-proprietary name: PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE (ADSORBED)

Procedure No. EMEA/H/C/000973/II/0092

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Rapporteur(s) and type of application	
CHMP Rapporteur:	Kristina Dunder
This application is in the area of:	Clinical

Assessment Timetable / Steps taken for the assessment

Timetable	Dates
Start of procedure:	28 December 2014
CHMP Rapporteur Assessment Report	30 January 2015
CHMP comments	16 February 2015
Rapporteur Revised Assessment Report	23 February 2015
Request for Supplementary Information	26 February 2015
MAH submitted responses:	19 March 2015
CHMP Rapporteur Assessment Report	2 April 2015
CHMP comments	13 April 2015
Rapporteur Revised Assessment Report	17 April 2015
Opinion	23 April 2015

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1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Biologicals submitted to the European Medicines Agency on 26 November 2014 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of section 4.4 of the SmPC and corresponding section of the PL in order to reflect results from study 10PN-PD-DIT-050 which aimed to determine whether ibuprofen given prophylactically, significantly impacts the immune response in children receiving primary vaccination with Synflorix, co-administered with DTPa-combined vaccines, at 3, 4 and 5 months of age and a booster dose at 12-15 months of age. The impact of antipyretics on the incidence of febrile reactions and other safety and reactogenicity parameters was evaluated as well. This submission fulfils the obligations with regards to Article 46 of Regulation (EC) No 1901/2006.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

1.2. Rationale for the proposed change

The MAH has submitted a type II variation to update section 4.4 of the Synflorix Summary of Product Characteristics (SmPC) based on the results of the clinical study 10PN-PD-DIT-050 which aimed to determine whether ibuprofen or paracetamol given prophylactically in an immediate or delayed manner, significantly impacts the immune response in children receiving primary vaccination with Synflorix.

The present type II variation also aims to fulfil the following post-authorisation measure included in the Synflorix Risk Management Plan (RMP):

PAM	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
MEA 014	Study 10PN-PD-DIT-050 (112921): Impact of prophylactic and delayed administration of Ibuprofen on vaccine immunogenicity	Final clinical study report	30/11/2014

Additionally, the submission of the final report for study 10PN-PD-DIT-050 aims to fulfil the MAH's obligations with regards to Article 46 of Regulation (EC) No 1901/2006.

2. Overall conclusion and impact on the benefit/risk balance

In this study, there were no effects of prophylactic ibuprofen administration, either immediate or delayed, on the immune responses to Synflorix, or the routine childhood vaccines given concomitantly with Synflorix. The same conclusions can be drawn for both primary and booster vaccinations. In agreement with other studies, there was a reduction of immune responses, when prophylactic paracetamol, either immediate or delayed, was administered both with Synflorix and some concomitant vaccine antigens.

There were no beneficial effects of immediate administration of ibuprofen compared to no ibuprofen in terms of fever reduction, and a trend towards fever reduction in delayed ibuprofen administration. There were no new safety signals, and the overall safety profile was in agreement with previous studies.

The proposed updates of section 4.4 of the SmPC and corresponding changes to the PL are endorsed.

The benefit-risk balance of Synflorix remains positive. The following post approval commitment has been fulfilled with this variation - MEA 014.

Scientific Summary for the EPAR

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. Clinical data generated with ibuprofen suggest that its delayed use might reduce fever, while prophylactic use of ibuprofen showed a limited effect. Furthermore, the clinical data generated with paracetamol suggest that it might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of section 4.4 of the SmPC and corresponding section of the Package Leaflet with the information on effects of paracetamol and ibuprofen used prophylactically on fever and immune responses following primary vaccination and a booster dose of Synflorix. This submission fulfils the obligations with regards to Article 46 of Regulation (EC) No 1901/2006.

☒ is recommended for approval.

The requested group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet.

4. Scientific discussion

4.1. Introduction

Synflorix is a 10-valent pneumococcal conjugate vaccine containing polysaccharides of pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F conjugated individually to protein D (PD), a non-lipidated form of a highly conserved protein of non-typeable *Haemophilus influenzae* (NTHi), serotype 18C conjugated to

tetanus toxoid (TT) and serotype 19F conjugated to diphtheria (DT) toxoid. Synflorix was licensed by the European Commission (EC) on 30 March 2009.

To date, Synflorix is licensed for the active immunisation against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* (serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) in infants and children from 6 weeks up to 5 years of age.

The practice to give antipyretics prophylactically has been questioned due to some findings in clinical studies. The immune responses to Synflorix were found to decrease when paracetamol was given prophylactically, to decrease fever reactions. The same has been found for other vaccines. This application contains data from study 10PN-PD-DIT-050, where the aim was to study whether ibuprofen given prophylactically in an immediate or delayed manner, significantly impacts the immune response in children receiving primary vaccination with *Synflorix*, co-administered with DTPa-combined vaccines, at 3, 4 and 5 months of age and a booster dose at 12-15 months of age.

4.2. Clinical Efficacy aspects

Study 10PN-PD-DIT-050 was a phase IV randomised, open, controlled study to assess the effect of immediate or delayed prophylactic antipyretic treatment (ibuprofen or paracetamol) on the immunogenicity and safety following primary vaccination with Synflorix co-administered with DTPa-combined vaccines at 3, 4 and 5 months of age and booster vaccination at 12-15 months of age.

4.2.1. Methods – analysis of data submitted

Objectives

Primary:

- To show that GSK Biologicals' 10-valent pneumococcal conjugate vaccine administered as a three-dose primary vaccination course with immediate OR delayed prophylactic ibuprofen treatment is non-inferior to 10-valent pneumococcal conjugate vaccine without prophylactic ibuprofen treatment in terms of percentage of subjects with pneumococcal antibody concentrations ≥0.2 µg/mL, despite a statistically significant decrease in ELISA Geometric Mean Concentration (GMC).

Secondary:

- To determine the percentage reduction in febrile reactions (rectal temperature ≥38.0°C) when immediate or delayed prophylactic ibuprofen treatment is administered compared to no prophylactic ibuprofen treatment, after primary vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccines.
- To assess the impact of immediate or delayed prophylactic paracetamol treatment on the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccines as a three-dose primary vaccination course.
- To assess the impact of immediate or delayed prophylactic paracetamol treatment on the incidence of febrile reactions (rectal temperature ≥38.0°C) after primary vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccines.
- To assess the impact of immediate or delayed prophylactic ibuprofen treatment on the incidence of febrile reactions (rectal temperature ≥38.0 C) after booster vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccine.

- To assess the impact of immediate prophylactic paracetamol treatment on the incidence of febrile reactions (rectal temperature ≥38.0 C) after booster vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccine.
- To assess the impact of immediate or delayed prophylactic ibuprofen treatment on the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccines, when administered as a three-dose primary vaccination course or as a booster dose.
- To assess the impact of immediate or delayed prophylactic paracetamol treatment on the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccines, when administered as a three-dose primary vaccination course.
- To assess the impact of immediate prophylactic paracetamol treatment on the safety and reactogenicity of a booster dose of GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccine.
- To assess, prior to booster vaccination, the impact of immediate or delayed prophylactic ibuprofen treatment on the persistence of antibodies induced by GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccines given as primary vaccination course.
- To assess, prior to booster vaccination, the impact of immediate or delayed prophylactic paracetamol treatment on the persistence of antibodies induced by GSK Biologicals' 10-valent pneumococcal conjugate vaccine and DTPa-combined vaccines given as primary vaccination course.
- To assess the impact of immediate or delayed prophylactic ibuprofen treatment on the immunogenicity of a booster dose of GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccine.
- To assess the impact of immediate prophylactic paracetamol treatment on the immunogenicity of a booster dose of GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccine.

Treatment:

The study groups were as follows:

Primary vaccination:

IBU groups:

- **IIBU** group (Immediate ibuprofen group): subjects receiving immediate ibuprofen administration after each primary vaccine dose (N = 210).
- **DIBU** group (Delayed ibuprofen group): subjects receiving delayed ibuprofen administration after each primary vaccine dose (N = 210).
- **NIBU** group (No ibuprofen group): subjects receiving no prophylactic ibuprofen administration after each primary vaccine dose (N = 210).

PARA groups:

- **IPARA** group (Immediate paracetamol group): subjects receiving immediate paracetamol administration after each primary vaccine dose (N = 70).
- **DPARA** group (Delayed paracetamol group): subjects receiving delayed paracetamol administration after each primary vaccine dose (N = 70).

- **NPARA** group (No paracetamol group): subjects receiving no prophylactic paracetamol administration after each primary vaccine dose (N = 70).

Booster vaccination:

IBU groups:

- **IIBU-IIBU** group: 1/3 of the subjects from the primary IIBU group receiving immediate ibuprofen administration after booster vaccination (N = 70).
- **IIBU-DIBU** group: 1/3 of the subjects from the primary IIBU group receiving delayed ibuprofen administration after booster vaccination (N = 70).
- **IIBU-NIBU** group: 1/3 of the subjects from the primary IIBU group receiving no prophylactic ibuprofen administration after booster vaccination (N = 70).
- **DIBU-IIBU** group: 1/3 of the subjects from the primary DIBU group receiving immediate ibuprofen administration after booster vaccination (N = 70).
- **DIBU-DIBU** group: 1/3 of the subjects from the primary DIBU group receiving delayed ibuprofen administration after booster vaccination (N = 70).
- **DIBU-NIBU** group: 1/3 of the subjects from the primary DIBU group receiving no prophylactic ibuprofen administration after booster vaccination (N = 70).
- **NIBU-IIBU** group: 1/3 of the subjects from the primary NIBU group receiving immediate ibuprofen administration after booster vaccination (N = 70).
- **NIBU-DIBU** group: 1/3 of the subjects from the primary NIBU group receiving delayed ibuprofen administration after booster vaccination (N = 70).
- **NIBU-NIBU** group: 1/3 of the subjects from the primary NIBU group receiving no prophylactic ibuprofen administration after booster vaccination (N = 70).

PARA groups:

- **IPARA-NPARA** group: subjects from the primary IPARA group receiving no paracetamol administration after booster vaccination (N = 70).
- **DPARA-IPARA** group: subjects from the primary DPARA group receiving immediate paracetamol administration after booster vaccination (N = 70).
- **NPARA-IPARA** group: subjects from the primary NPARA group receiving immediate paracetamol administration after booster vaccination (N = 70).

Study Population:

Male or female infants between, and including, 12 and 16 weeks (84-118 days) of age at the time of the first vaccination, born after a gestation period of 36 to 42 weeks inclusive, free of obvious health problems as established by medical history and clinical examination before entering into the study and for whom the investigator believed that their parents/guardians could and would comply with the requirements of the protocol. Written informed consent was obtained from the parents/guardians of each subject.

Primary Outcome/Efficacy Variable:

- Evaluation of immune responses to components of the investigational vaccine one month after primary immunization.
    - Anti-pneumococcal antibody serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations ≥0.2 µg/mL.
    - Concentrations of antibodies against the 10 vaccine pneumococcal serotypes.
    - Concentrations of antibodies against protein D.

Secondary Outcome/Efficacy Variables:

Safety

- Occurrence of each solicited adverse event (AE) within 4 days (Days 0 to 3) after each primary vaccination dose and following booster vaccination.
    - Local (any, grade 3) AEs.
    - General (any, grade 3, related) AEs.
- Occurrence of unsolicited AEs within 31 days (Days 0 to 30) after each primary vaccination dose and following booster vaccination.
- Occurrence of serious adverse events (SAEs) during the entire study period.

Immunogenicity

- Evaluation of immune responses to components of the investigational vaccine for additional parameters, one month after primary immunization, prior to and one month after booster immunization:
    - Concentrations of antibodies against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F.
    - Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F.
    - Concentrations of antibodies against protein D.
- Evaluation of immune responses to components of the co-administered DTPa-HBV-IPV/Hib and DTPa-IPV/Hib vaccines, one month after primary immunization, prior to and one month after booster immunization:
    - Antibody concentrations against diphtheria toxoid, tetanus toxoid, pertussis toxoid, filamentous haemagglutinin, pertactin, hepatitis B surface antigen, polyribosylribitol phosphate.
    - Poliovirus types 1, 2 and 3 titres*.

**Note that the polio results were not included in the variation application.*

Statistical methods

Analysis of demographics

The analysis of demographics were performed separately for each epoch:

- Demographic characteristics (age in weeks at the time of each dose of primary vaccination and in months at the time of the booster dose, gender, weight, geographic ancestry) of each study cohort were tabulated.
- The mean age (plus range and standard deviation) of the enrolled subjects as a whole study population and per group was calculated.

Analysis of immunogenicity

The analysis of immunogenicity was performed separately for each epoch.

Within groups assessment

Where appropriate, for each group, at each timepoint that a blood sample result was available:

- Geometric Mean Concentrations/Titres (GMCs/GMTs) with 95% CIs were tabulated for each serotype/antigen.
- Seropositivity/seroprotection rates with exact 95% CIs were calculated for each appropriate serotype/antigen.
- Vaccine response rates one month post-dose III and one month post-booster dose with exact 95% CIs were calculated for each pertussis antigen.
- The distribution of antibody concentrations/titres for each appropriate serotype/antigen was displayed using tables and/or RCCs.

Between group assessment

Confirmatory inferential analysis

- Standardized asymptotic 98.25% CIs for the difference between groups (NIBU group minus IIBU group or NIBU group minus DIBU group), in terms of percentage of subjects with pneumococcal antibody concentrations ≥0.2 µg/mL one month post dose III, were computed using StatXact. The primary objective was demonstrated for one of the two pair-wise group comparisons if the UL of these two-sided 98.25% CIs was below 10% for seven out of the 10 vaccine pneumococcal serotypes.
- 99.8% CIs for the ELISA GMCs ratio (GMCs from the IIBU group over the GMCs from NIBU group OR GMCs from the DIBU group over the GMCs from NIBU group) one month post-dose III, was computed for each of the 10 conjugate vaccine pneumococcal serotypes and for protein D, using a one-sided ANOVA test on the logarithm10 transformation of the concentrations. A statistical significant difference in GMC was established if the UL of these two-sided 99.8% CIs was below 1 for at least one of the 10 vaccine pneumococcal serotypes or for protein D.

Analysis of safety

Analysis of safety relative to the primary epoch included analysis of safety data collected following administration of the three primary doses of study vaccine. Analysis of safety relative to the booster epoch included analysis of safety data collected following administration of the booster dose of study vaccine. At this second stage, in order to avoid missing SAEs that were reported, the SAE summary table included all events reported during the entire study period.

Within groups assessment

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 31-day (Day 0 - Day 30)

post-vaccination period was tabulated with exact 95% CI for each group, after each vaccine dose and overall primary doses. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE was tabulated for each group, over the full primary vaccination course, with exact 95% CI. The same calculations were performed for AEs rated as grade 3 and general AEs with causal relationship to vaccination.

- The percentage of subjects reporting each individual solicited local and general AE during the 4-day (Day 0 - Day 3) post-vaccination period was tabulated for each group, after each vaccine dose and overall primary doses, with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE was tabulated for each group, over the full primary vaccination course, with exact 95% CI. The same tabulation was performed for grade 3 solicited AEs and for solicited AEs with causal relationship to vaccination. For redness and swelling, grade 2 or 3 AEs were also tabulated. Occurrence of fever was reported per 0.5°C cumulative increments.
- The proportion of subjects/doses with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 30 days after primary or booster vaccination was tabulated with exact 95% CI for each group. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.
- The proportion of AEs resulting in a medically attended visit was also tabulated.
- The number and percentage of subjects who took concomitant antipyretic/medication at least once during the 4-day (Day 0 - Day 3) solicited follow-up period were tabulated for each group, after each vaccine dose and overall primary doses, with exact 95% CI. The number and percentage of doses for which the subjects took concomitant antipyretic/medication at least once during the 4-day (Day 0 - Day 3) solicited follow-up period were tabulated for each group, over the full primary vaccination course, with exact 95% CI.
- SAEs, large swelling reactions (after booster dose) and withdrawal(s) due to SAE(s) were described in detail.
- Dosage of antipyretics taken and the summary of time interval between study vaccination and antipyretics were described in the groups receiving ibuprofen or paracetamol.

Between group assessment

Confirmatory inferential analysis:

- Standardized asymptotic 97.5% CIs for the difference between groups (NIBU group minus IIBU group OR NIBU group minus DIBU group), in percentage of subjects reporting rectal temperature ≥38.0°C after at least one primary vaccination, were computed using StatXact.
- The first secondary objective was demonstrated if the primary objective was reached and if the LL of the 97.5% CI around the difference NIBU group minus IIBU group OR if the LL of the 97.5% CI around the difference NIBU group minus DIBU group was higher than 0%.

Conduct of the study

During the course of the study, the following issues with regard to the conduct of the study were identified, either via site monitoring activities or were brought to GSK Biologicals' attention by other mechanisms. These issues were investigated and corrective/preventive actions where possible were taken as described below:

Following a letter notifying GSK about potential improper study conduct at one study site, an assessment of this site was performed by the GSK's Global Quality Assurance group in March 2012. Following comparison of diaries from selected subjects, lack of confidence in the integrity of the data was noted. Additionally, there

were concerns that the conduct of the informed consent process and documentation practices at the site did not meet the ICH-GCP requirements. Therefore GSK Biologicals decided to terminate all study-related activities at this site. Ethics Committee and Regulatory authorities were informed. All subjects at this site, who had not completed the study when site activities were put on hold, were withdrawn from the study and offered continuation of vaccination outside the study. All 35 subjects enrolled at this site were eliminated from the Total Vaccinated Cohort. Their blood samples were used to assess the immune response to allow individual counselling of the impacted study subjects. The SAEs reported for the subjects enrolled at this centre are presented separately.

Assessor's comment: In addition to the above information, the study was inspected by the Romanian authority on October 7 and 10, 2014. The Company has received the preliminary inspection report and is preparing a response to the National Drug Agency and Medical Devices to address the observed findings. The Company does not consider that the preliminary findings of this inspection have an impact on the data quality or study conclusions presented in the present submission. An English summary of the inspection report should be provided before a conclusion regarding this variation can be drawn.

4.2.1. Results

Study population

This multicentre study was conducted in 23 centres in Romania, however all 35 subjects from one site were eliminated from the TVC (site closed after audit). Therefore the TVC included 812 subjects enrolled in 22 centres with a maximum of 210 subjects (25.9%) enrolled in a single study centre. A summary of study continuation for subjects initially vaccinated in the primary epoch is presented in Table 21.

Table 21. Summary of study continuation for subjects initially vaccinated in the primary epoch (Primary epoch) (Total vaccinated cohort)

	IIBU N = 198		DIBU N = 198		NIBU N = 199		IPARA N = 71		DPARA N = 72		NPARA N = 74		Total N = 812	
Categories	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Permanent discontinuation during primary epoch	4	2.0	3	1.5	3	1.5	2	2.8	1	1.4	7	9.5	20	2.5
Not willing to participate in booster epoch	6	3.0	6	3.0	6	3.0	2	2.8	3	4.2	0	0.0	23	2.8
Consent withdrawal / not willing to participate, not due to a (S)AE	5	2.5	3	1.5	2	1.0	0	0.0	2	2.8	0	0.0	12	1.5
Lost to follow-up	0	0.0	2	1.0	1	0.5	1	1.4	1	1.4	0	0.0	5	0.6
Migrated / moved from the study area	1	0.5	1	0.5	3	1.5	1	1.4	0	0.0	0	0.0	6	0.7
Participating in booster epoch	188	94.9	189	95.5	190	95.5	67	94.4	68	94.4	67	90.5	769	94.7

Out of the 812 subjects vaccinated in the primary epoch, 792 completed the primary vaccination phase and 20 subjects were withdrawn. Among those, one subject was withdrawn due to an SAE assessed by the investigator as not related to vaccination.

Out of the 792 subjects who completed the primary vaccination phase, 768 were vaccinated during the booster epoch (769 subjects participated in the booster epoch but one subject did not receive the booster dose). Among those, 751 subjects completed the study and 17 did not complete the booster phase (one subject was withdrawn because of an SAE assessed by the investigator as not related to vaccination).

Immunogenicity results

The primary confirmatory objective was to show that Synflorix administered as a three-dose primary vaccination course with immediate OR delayed prophylactic ibuprofen treatment was non-inferior to

10-valent pneumococcal conjugate vaccine without prophylactic ibuprofen treatment in terms of percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 µg/mL, despite a statistically significant decrease in ELISA GMC.

The results of the confirmatory analysis between groups are presented in the tables: 43-46.

Table 43. Difference between groups (NIBU minus IIBU) in percentage of subjects with pneumococcal antibody concentrations greater or equal to 0.2 µg/mL, one month after dose III, for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F (Primary epoch) (ATP cohort for immunogenicity)

					Difference in % ≥ 0.2 µg/mL (NIBU minus IIBU)		
	NIBU		IIBU			98.25 % CI	
Antibody	N	%	N	%	%	LL	UL
ANTI-1	161	99.4	144	100	-0.62	-4.52	3.17
ANTI-4	159	99.4	146	99.3	0.06	-3.94	4.38
ANTI-5	157	99.4	143	100	-0.64	-4.63	3.19
ANTI-6B	157	84.7	144	84.0	0.69	-9.40	10.99
ANTI-7F	164	100	154	99.4	0.65	-2.70	4.71
ANTI-9V	157	98.7	145	99.3	-0.58	-5.05	3.82
ANTI-14	155	99.4	144	100	-0.65	-4.68	3.15
ANTI-18C	157	98.7	144	99.3	-0.58	-5.04	3.85
ANTI-19F	158	99.4	145	100	-0.63	-4.60	3.14
ANTI-23F	162	92.0	148	91.9	0.08	-7.66	8.10

IIBU = Subjects who received immediate ibuprofen administration following each primary vaccine dose with 10Pn-PD-DiT + DTPa-(HBV)-IPV/Hib vaccines at 3, 4 and 5 months of age
NIBU = Subjects who received no ibuprofen administration following each primary vaccine dose with 10Pn-PD-DiT + DTPa-(HBV)-IPV/Hib vaccines at 3, 4 and 5 months of age

Table 44. Ratios of GMCs between IIBU over NIBU, for ANTI-1, ANTI-4, ANTI-5,ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F, ANTI-23F and anti-PD antibodies one month after dose III (Primary epoch) (ATP cohort for immunogenicity)

					GMC ratio (IIBU / NIBU)		
	IIBU		NIBU			99.8% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-1	144	1.82	161	1.90	0.96	0.71	1.29
ANTI-4	146	2.25	159	2.21	1.02	0.77	1.35
ANTI-5	143	2.93	157	2.77	1.06	0.80	1.41
ANTI-6B	144	0.67	157	0.60	1.12	0.72	1.74
ANTI-7F	154	2.87	164	2.77	1.04	0.79	1.35
ANTI-9V	145	2.10	157	2.18	0.96	0.70	1.31
ANTI-14	144	4.76	155	4.77	1.00	0.71	1.40
ANTI-18C	144	3.85	157	4.34	0.89	0.60	1.31
ANTI-19F	145	6.11	158	4.96	1.23	0.87	1.75
ANTI-23F	148	1.04	162	1.07	0.97	0.66	1.44
ANTI-PD	150	1461.28	164	1557.75	0.94	0.69	1.28

IIBU = Subjects who received immediate ibuprofen administration following each primary vaccine dose with 10Pn-PD-DiT + DTPa-(HBV)-IPV/Hib vaccines at 3, 4 and 5 months of age
NIBU = Subjects who received no ibuprofen administration following each primary vaccine dose with 10Pn-PD-DiT + DTPa-(HBV)-IPV/Hib vaccines at 3, 4 and 5 months of age

Table 45. Difference between groups (NIBU minus DIBU) in percentage of subjects with pneumococcal antibody concentrations greater or equal to 0.2 μg/mL, one month after dose III, for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F (Primary epoch) (ATP cohort for immunogenicity)

					Difference in % ≥ 0.2 µg/mL (NIBU minus DIBU)		
	NIBU		DIBU			98.25 % CI	
Antibody	N	%	N	%	%	LL	UL
ANTI-1	161	99.4	155	100	-0.62	-4.52	2.91
ANTI-4	159	99.4	155	100	-0.63	-4.57	2.91
ANTI-5	157	99.4	154	100	-0.64	-4.63	2.92
ANTI-6B	157	84.7	155	87.1	-2.38	-12.02	7.22
ANTI-7F	164	100	157	100	0.00	-3.34	3.48
ANTI-9V	157	98.7	153	100	-1.27	-5.66	2.32
ANTI-14	155	99.4	154	99.4	0.00	-4.08	4.12
ANTI-18C	157	98.7	154	99.4	-0.62	-5.08	3.54
ANTI-19F	158	99.4	154	98.7	0.67	-3.40	5.20
ANTI-23F	162	92.0	158	89.2	2.73	-5.30	11.04

DIBU = Subjects who received delayed ibuprofen administration following each primary vaccine dose with 10Pn-PD-DiT + DTPa-(HBV)-IPV/Hib vaccines at 3, 4 and 5 months of age
NIBU = Subjects who received no ibuprofen administration following each primary vaccine dose with 10Pn-PD-DiT + DTPa-(HBV)-IPV/Hib vaccines at 3, 4 and 5 months of age

Table 46. Ratios of GMCs between DIBU over NIBU, for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F, ANTI-23F and anti-PD antibodies one month after dose III (Primary epoch) (ATP cohort for immunogenicity)

					GMC ratio (DIBU / NIBU)		
	DIBU		NIBU			99.8% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-1	155	1.71	161	1.90	0.90	0.67	1.21
ANTI-4	155	2.21	159	2.21	1.00	0.76	1.32
ANTI-5	154	2.39	157	2.77	0.86	0.66	1.14
ANTI-6B	155	0.76	157	0.60	1.28	0.83	1.97
ANTI-7F	157	2.83	164	2.77	1.02	0.80	1.31
ANTI-9V	153	2.01	157	2.18	0.92	0.69	1.22
ANTI-14	154	4.52	155	4.77	0.95	0.68	1.32
ANTI-18C	154	3.80	157	4.34	0.88	0.60	1.27
ANTI-19F	154	5.04	158	4.96	1.02	0.72	1.44
ANTI-23F	158	0.92	162	1.07	0.86	0.58	1.27
ANTI-PD	158	1353.13	164	1557.75	0.87	0.64	1.17

DIBU = Subjects who received delayed ibuprofen administration following each primary vaccine dose with 10Pn-PD-DiT + DTPa-(HBV)-IPV/Hib vaccines at 3, 4 and 5 months of age
NIBU = Subjects who received no ibuprofen administration following each primary vaccine dose with 10Pn-PD-DiT + DTPa-(HBV)-IPV/Hib vaccines at 3, 4 and 5 months of age

Assessor's comment: There is no indication that either concomitant or delayed administration of ibuprofen causes diminished immune responses.

Within groups assessment

Immune response to the vaccine pneumococcal serotypes (Primary epoch)

The immune response to the vaccine pneumococcal serotypes as measured by 22F-inhibition ELISA is presented in the following table:

Table 47. Seropositivity rates and GMCs for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F antibodies (Primary epoch) (ATP cohort for immunogenicity)

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-1	IIBU	PRE	139	31	22.3	15.7	30.1	4	2.9	0.8	7.2	0.03	0.03	0.04
		PIII(M3)	144	144	100	97.5	100	144	100	97.5	100	1.82	1.59	2.09
		PIII(M9)	140	140	100	97.4	100	107	76.4	68.5	83.2	0.35	0.30	0.40
	DIBU	PRE	147	32	21.8	15.4	29.3	7	4.8	1.9	9.6	0.03	0.03	0.04
		PIII(M3)	155	155	100	97.6	100	155	100	97.6	100	1.71	1.49	1.95
		PIII(M9)	144	143	99.3	96.2	100	109	75.7	67.9	82.4	0.39	0.33	0.45
	NIBU	PRE	148	37	25.0	18.3	32.8	4	2.7	0.7	6.8	0.03	0.03	0.04
		PIII(M3)	161	161	100	97.7	100	160	99.4	96.6	100	1.90	1.67	2.17
		PIII(M9)	153	153	100	97.6	100	122	79.7	72.5	85.8	0.41	0.36	0.48
	IPARA	PRE	50	19	38.0	24.7	52.8	1	2.0	0.1	10.6	0.04	0.03	0.05
		PIII(M3)	54	54	100	93.4	100	52	96.3	87.3	99.5	1.32	1.04	1.67
		PIII(M9)	50	50	100	92.9	100	31	62.0	47.2	75.3	0.30	0.23	0.38
	DPARA	PRE	51	15	29.4	17.5	43.8	0	0.0	0.0	7.0	0.03	0.03	0.04
		PIII(M3)	51	51	100	93.0	100	50	98.0	89.6	100	1.38	1.09	1.74
		PIII(M9)	46	46	100	92.3	100	33	71.7	56.5	84.0	0.31	0.24	0.40
	NPARA	PRE	52	16	30.8	18.7	45.1	2	3.8	0.5	13.2	0.04	0.03	0.04
		PIII(M3)	55	55	100	93.5	100	55	100	93.5	100	1.95	1.64	2.32
		PIII(M9)	51	51	100	93.0	100	40	78.4	64.7	88.7	0.41	0.30	0.57
ANTI-4	IIBU	PRE	148	40	27.0	20.1	34.9	12	8.1	4.3	13.7	0.04	0.03	0.04
		PIII(M3)	146	146	100	97.5	100	145	99.3	96.2	100	2.25	1.97	2.57
		PIII(M9)	142	142	100	97.4	100	134	94.4	89.2	97.5	0.64	0.55	0.73
	DIBU	PRE	153	42	27.5	20.6	35.2	11	7.2	3.6	12.5	0.04	0.03	0.04
		PIII(M3)	155	155	100	97.6	100	155	100	97.6	100	2.21	1.95	2.51
		PIII(M9)	148	147	99.3	96.3	100	135	91.2	85.4	95.2	0.67	0.58	0.79
	NIBU	PRE	153	38	24.8	18.2	32.5	12	7.8	4.1	13.3	0.04	0.03	0.05
		PIII(M3)	159	159	100	97.7	100	158	99.4	96.5	100	2.21	1.96	2.50
		PIII(M9)	155	155	100	97.6	100	145	93.5	88.5	96.9	0.68	0.59	0.79
	IPARA	PRE	53	15	28.3	16.8	42.3	2	3.8	0.5	13.0	0.04	0.03	0.05
		PIII(M3)	55	55	100	93.5	100	53	96.4	87.5	99.6	1.57	1.21	2.04
		PIII(M9)	49	49	100	92.7	100	44	89.8	77.8	96.6	0.50	0.39	0.66
	DPARA	PRE	53	18	34.0	21.5	48.3	3	5.7	1.2	15.7	0.04	0.03	0.05
		PIII(M3)	51	51	100	93.0	100	51	100	93.0	100	1.95	1.63	2.32
		PIII(M9)	49	49	100	92.7	100	44	89.8	77.8	96.6	0.62	0.50	0.76
	NPARA	PRE	53	20	37.7	24.8	52.1	5	9.4	3.1	20.7	0.05	0.04	0.06
		PIII(M3)	56	56	100	93.6	100	56	100	93.6	100	2.59	2.07	3.24
		PIII(M9)	52	52	100	93.2	100	48	92.3	81.5	97.9	0.77	0.59	1.00

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-5	IIBU	PRE	132	38	28.8	21.2	37.3	8	6.1	2.7	11.6	0.04	0.04	0.05
		PIII(M3)	143	143	100	97.5	100	143	100	97.5	100	2.93	2.58	3.33
		PIII(M9)	141	141	100	97.4	100	137	97.2	92.9	99.2	0.85	0.73	0.97
	DIBU	PRE	144	52	36.1	28.3	44.5	13	9.0	4.9	14.9	0.04	0.04	0.05
		PIII(M3)	154	154	100	97.6	100	154	100	97.6	100	2.39	2.13	2.69
		PIII(M9)	146	146	100	97.5	100	138	94.5	89.5	97.6	0.76	0.67	0.88
	NIBU	PRE	146	53	36.3	28.5	44.7	10	6.8	3.3	12.2	0.04	0.04	0.05
		PIII(M3)	157	157	100	97.7	100	156	99.4	96.5	100	2.77	2.44	3.15
		PIII(M9)	153	153	100	97.6	100	152	99.3	96.4	100	0.86	0.76	0.98
	IPARA	PRE	48	19	39.6	25.8	54.7	3	6.3	1.3	17.2	0.05	0.04	0.06
		PIII(M3)	53	53	100	93.3	100	53	100	93.3	100	1.95	1.53	2.48
		PIII(M9)	48	48	100	92.6	100	46	95.8	85.7	99.5	0.58	0.45	0.75
	DPARA	PRE	51	17	33.3	20.8	47.9	1	2.0	0.0	10.4	0.04	0.03	0.05
		PIII(M3)	50	50	100	92.9	100	50	100	92.9	100	2.36	1.89	2.94
		PIII(M9)	50	50	100	92.9	100	46	92.0	80.8	97.8	0.74	0.59	0.93
	NPARA	PRE	48	24	50.0	35.2	64.8	6	12.5	4.7	25.2	0.06	0.04	0.08
		PIII(M3)	54	54	100	93.4	100	54	100	93.4	100	3.05	2.53	3.68
		PIII(M9)	51	51	100	93.0	100	44	86.3	73.7	94.3	0.76	0.57	1.02
ANTI-6B	IIBU	PRE	143	63	44.1	35.8	52.6	12	8.4	4.4	14.2	0.05	0.04	0.06
		PIII(M3)	144	138	95.8	91.2	98.5	121	84.0	77.0	89.6	0.67	0.55	0.81
		PIII(M9)	145	141	97.2	93.1	99.2	127	87.6	81.1	92.5	0.55	0.47	0.65
	DIBU	PRE	154	60	39.0	31.2	47.1	12	7.8	4.1	13.2	0.04	0.04	0.05
		PIII(M3)	155	150	96.8	92.6	98.9	135	87.1	80.8	91.9	0.76	0.63	0.92
		PIII(M9)	153	148	96.7	92.5	98.9	136	88.9	82.8	93.4	0.60	0.52	0.71
	NIBU	PRE	162	60	37.0	29.6	45.0	20	12.3	7.7	18.4	0.05	0.04	0.06
		PIII(M3)	157	151	96.2	91.9	98.6	133	84.7	78.1	90.0	0.60	0.49	0.72
		PIII(M9)	156	152	97.4	93.6	99.3	144	92.3	86.9	96.0	0.60	0.52	0.69
	IPARA	PRE	53	23	43.4	29.8	57.7	4	7.5	2.1	18.2	0.05	0.04	0.06
		PIII(M3)	53	50	94.3	84.3	98.8	42	79.2	65.9	89.2	0.49	0.34	0.69
		PIII(M9)	52	51	98.1	89.7	100	46	88.5	76.6	95.6	0.43	0.33	0.55
	DPARA	PRE	54	27	50.0	36.1	63.9	11	20.4	10.6	33.5	0.07	0.05	0.10
		PIII(M3)	51	46	90.2	78.6	96.7	37	72.5	58.3	84.1	0.42	0.28	0.62
		PIII(M9)	51	48	94.1	83.8	98.8	45	88.2	76.1	95.6	0.45	0.35	0.59
	NPARA	PRE	53	24	45.3	31.6	59.6	8	15.1	6.7	27.6	0.06	0.04	0.08
		PIII(M3)	55	52	94.5	84.9	98.9	48	87.3	75.5	94.7	0.72	0.51	1.02
		PIII(M9)	52	52	100	93.2	100	46	88.5	76.6	95.6	0.55	0.44	0.69
ANTI-7F	IIBU	PRE	135	66	48.9	40.2	57.6	18	13.3	8.1	20.3	0.06	0.05	0.07
		PIII(M3)	154	154	100	97.6	100	153	99.4	96.4	100	2.87	2.52	3.27
		PIII(M9)	141	141	100	97.4	100	141	100	97.4	100	1.07	0.95	1.21
	DIBU	PRE	144	76	52.8	44.3	61.1	24	16.7	11.0	23.8	0.06	0.05	0.08
		PIII(M3)	157	157	100	97.7	100	157	100	97.7	100	2.83	2.52	3.17
		PIII(M9)	147	147	100	97.5	100	144	98.0	94.2	99.6	1.11	0.97	1.27
	NIBU	PRE	152	73	48.0	39.9	56.3	23	15.1	9.8	21.8	0.06	0.05	0.07
		PIII(M3)	164	164	100	97.8	100	164	100	97.8	100	2.77	2.49	3.09
		PIII(M9)	153	153	100	97.6	100	151	98.7	95.4	99.8	1.13	1.00	1.29
	IPARA	PRE	50	23	46.0	31.8	60.7	10	20.0	10.0	33.7	0.06	0.04	0.08
		PIII(M3)	55	55	100	93.5	100	55	100	93.5	100	2.18	1.75	2.70
		PIII(M9)	51	51	100	93.0	100	50	98.0	89.6	100	0.84	0.67	1.05
	DPARA	PRE	50	27	54.0	39.3	68.2	8	16.0	7.2	29.1	0.06	0.05	0.08
		PIII(M3)	55	55	100	93.5	100	55	100	93.5	100	2.45	2.01	2.99
		PIII(M9)	48	48	100	92.6	100	47	97.9	88.9	99.9	1.00	0.82	1.22

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	NPARA	PRE	51	23	45.1	31.1	59.7	8	15.7	7.0	28.6	0.05	0.04	0.07
		PIII(M3)	56	56	100	93.6	100	56	100	93.6	100	2.95	2.37	3.69
		PIII(M9)	53	53	100	93.3	100	50	94.3	84.3	98.8	0.91	0.72	1.17
ANTI-9V	IIBU	PRE	136	55	40.4	32.1	49.2	18	13.2	8.0	20.1	0.05	0.04	0.06
		PIII(M3)	145	145	100	97.5	100	144	99.3	96.2	100	2.10	1.81	2.42
		PIII(M9)	145	145	100	97.5	100	142	97.9	94.1	99.6	0.92	0.81	1.05
	DIBU	PRE	151	64	42.4	34.4	50.7	16	10.6	6.2	16.6	0.05	0.04	0.06
		PIII(M3)	153	153	100	97.6	100	153	100	97.6	100	2.01	1.79	2.27
		PIII(M9)	149	149	100	97.6	100	146	98.0	94.2	99.6	1.01	0.88	1.15
	NIBU	PRE	148	62	41.9	33.8	50.3	20	13.5	8.5	20.1	0.05	0.05	0.06
		PIII(M3)	157	156	99.4	96.5	100	155	98.7	95.5	99.8	2.18	1.91	2.50
		PIII(M9)	156	155	99.4	96.5	100	153	98.1	94.5	99.6	1.05	0.91	1.22
	IPARA	PRE	51	26	51.0	36.6	65.2	9	17.6	8.4	30.9	0.06	0.05	0.09
		PIII(M3)	53	53	100	93.3	100	53	100	93.3	100	1.67	1.30	2.13
		PIII(M9)	52	52	100	93.2	100	51	98.1	89.7	100	0.72	0.57	0.92
	DPARA	PRE	51	27	52.9	38.5	67.1	3	5.9	1.2	16.2	0.05	0.04	0.07
		PIII(M3)	50	50	100	92.9	100	50	100	92.9	100	1.82	1.48	2.23
		PIII(M9)	51	51	100	93.0	100	51	100	93.0	100	0.95	0.79	1.16
	NPARA	PRE	51	28	54.9	40.3	68.9	4	7.8	2.2	18.9	0.06	0.04	0.07
		PIII(M3)	54	54	100	93.4	100	53	98.1	90.1	100	2.40	1.87	3.10
		PIII(M9)	55	55	100	93.5	100	52	94.5	84.9	98.9	0.92	0.70	1.19
ANTI-14	IIBU	PRE	133	119	89.5	83.0	94.1	78	58.6	49.8	67.1	0.29	0.23	0.37
		PIII(M3)	144	144	100	97.5	100	144	100	97.5	100	4.76	4.10	5.51
		PIII(M9)	142	141	99.3	96.1	100	136	95.8	91.0	98.4	1.52	1.25	1.85
	DIBU	PRE	148	134	90.5	84.6	94.7	88	59.5	51.1	67.4	0.28	0.23	0.36
		PIII(M3)	154	154	100	97.6	100	153	99.4	96.4	100	4.52	3.91	5.21
		PIII(M9)	148	146	98.6	95.2	99.8	143	96.6	92.3	98.9	1.58	1.32	1.90
	NIBU	PRE	147	140	95.2	90.4	98.1	96	65.3	57.0	73.0	0.42	0.33	0.52
		PIII(M3)	155	155	100	97.6	100	154	99.4	96.5	100	4.77	4.08	5.58
		PIII(M9)	156	154	98.7	95.4	99.8	149	95.5	91.0	98.2	1.75	1.44	2.14
	IPARA	PRE	49	47	95.9	86.0	99.5	30	61.2	46.2	74.8	0.26	0.20	0.35
		PIII(M3)	53	53	100	93.3	100	53	100	93.3	100	3.44	2.55	4.62
		PIII(M9)	51	51	100	93.0	100	49	96.1	86.5	99.5	1.15	0.84	1.59
	DPARA	PRE	50	49	98.0	89.4	99.9	40	80.0	66.3	90.0	0.48	0.34	0.68
		PIII(M3)	50	50	100	92.9	100	50	100	92.9	100	4.12	3.21	5.29
		PIII(M9)	49	49	100	92.7	100	48	98.0	89.1	99.9	1.56	1.14	2.12
	NPARA	PRE	49	42	85.7	72.8	94.1	36	73.5	58.9	85.1	0.44	0.27	0.74
		PIII(M3)	53	53	100	93.3	100	53	100	93.3	100	5.17	4.20	6.36
		PIII(M9)	53	53	100	93.3	100	51	96.2	87.0	99.5	1.76	1.33	2.35
ANTI-18C	IIBU	PRE	132	71	53.8	44.9	62.5	24	18.2	12.0	25.8	0.07	0.05	0.08
		PIII(M3)	144	143	99.3	96.2	100	143	99.3	96.2	100	3.85	3.23	4.60
		PIII(M9)	145	145	100	97.5	100	142	97.9	94.1	99.6	1.07	0.93	1.24
	DIBU	PRE	145	78	53.8	45.3	62.1	33	22.8	16.2	30.5	0.07	0.06	0.09
		PIII(M3)	154	153	99.4	96.4	100	153	99.4	96.4	100	3.80	3.24	4.46
		PIII(M9)	151	151	100	97.6	100	149	98.7	95.3	99.8	1.09	0.95	1.25
	NIBU	PRE	143	76	53.1	44.6	61.5	24	16.8	11.1	23.9	0.06	0.05	0.08
		PIII(M3)	157	156	99.4	96.5	100	155	98.7	95.5	99.8	4.34	3.65	5.15
		PIII(M9)	157	157	100	97.7	100	154	98.1	94.5	99.6	1.23	1.08	1.42
	IPARA	PRE	50	30	60.0	45.2	73.6	13	26.0	14.6	40.3	0.09	0.06	0.13
		PIII(M3)	53	53	100	93.3	100	52	98.1	89.9	100	3.08	2.29	4.15
		PIII(M9)	52	52	100	93.2	100	50	96.2	86.8	99.5	0.92	0.68	1.23

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	DPARA	PRE	49	29	59.2	44.2	73.0	10	20.4	10.2	34.3	0.08	0.05	0.10
		PIII(M3)	50	50	100	92.9	100	50	100	92.9	100	4.08	3.15	5.29
		PIII(M9)	51	51	100	93.0	100	51	100	93.0	100	1.10	0.89	1.36
	NPARA	PRE	48	31	64.6	49.5	77.8	13	27.1	15.3	41.8	0.08	0.06	0.11
		PIII(M3)	54	54	100	93.4	100	54	100	93.4	100	4.96	3.75	6.55
		PIII(M9)	54	54	100	93.4	100	53	98.1	90.1	100	1.26	0.97	1.63
ANTI-19F	IIBU	PRE	136	91	66.9	58.3	74.7	48	35.3	27.3	43.9	0.11	0.09	0.14
		PIII(M3)	145	145	100	97.5	100	145	100	97.5	100	6.11	5.26	7.10
		PIII(M9)	140	140	100	97.4	100	139	99.3	96.1	100	1.80	1.54	2.11
	DIBU	PRE	148	111	75.0	67.2	81.7	52	35.1	27.5	43.4	0.13	0.10	0.16
		PIII(M3)	154	154	100	97.6	100	152	98.7	95.4	99.8	5.04	4.35	5.86
		PIII(M9)	145	145	100	97.5	100	142	97.9	94.1	99.6	1.52	1.29	1.80
	NIBU	PRE	150	107	71.3	63.4	78.4	57	38.0	30.2	46.3	0.12	0.10	0.15
		PIII(M3)	158	157	99.4	96.5	100	157	99.4	96.5	100	4.96	4.22	5.83
		PIII(M9)	153	153	100	97.6	100	149	97.4	93.4	99.3	1.57	1.34	1.83
	IPARA	PRE	52	37	71.2	56.9	82.9	16	30.8	18.7	45.1	0.11	0.08	0.15
		PIII(M3)	53	53	100	93.3	100	53	100	93.3	100	4.95	3.74	6.54
		PIII(M9)	50	50	100	92.9	100	49	98.0	89.4	99.9	1.53	1.14	2.07
	DPARA	PRE	52	41	78.8	65.3	88.9	23	44.2	30.5	58.7	0.16	0.11	0.24
		PIII(M3)	50	50	100	92.9	100	50	100	92.9	100	5.20	3.94	6.85
		PIII(M9)	49	49	100	92.7	100	48	98.0	89.1	99.9	1.53	1.17	2.01
	NPARA	PRE	49	40	81.6	68.0	91.2	24	49.0	34.4	63.7	0.17	0.12	0.25
		PIII(M3)	54	54	100	93.4	100	54	100	93.4	100	6.98	5.48	8.88
		PIII(M9)	52	52	100	93.2	100	50	96.2	86.8	99.5	1.70	1.29	2.23
ANTI-23F	IIBU	PRE	134	55	41.0	32.6	49.9	24	17.9	11.8	25.5	0.06	0.05	0.07
		PIII(M3)	148	145	98.0	94.2	99.6	136	91.9	86.3	95.7	1.04	0.86	1.26
		PIII(M9)	142	137	96.5	92.0	98.8	127	89.4	83.2	94.0	0.56	0.47	0.67
	DIBU	PRE	148	62	41.9	33.8	50.3	15	10.1	5.8	16.2	0.05	0.04	0.06
		PIII(M3)	158	154	97.5	93.6	99.3	141	89.2	83.3	93.6	0.92	0.76	1.11
		PIII(M9)	147	142	96.6	92.2	98.9	126	85.7	79.0	90.9	0.58	0.48	0.69
	NIBU	PRE	149	55	36.9	29.2	45.2	17	11.4	6.8	17.6	0.05	0.04	0.06
		PIII(M3)	162	160	98.8	95.6	99.9	149	92.0	86.7	95.7	1.07	0.91	1.26
		PIII(M9)	155	151	97.4	93.5	99.3	136	87.7	81.5	92.5	0.62	0.52	0.73
	IPARA	PRE	51	20	39.2	25.8	53.9	5	9.8	3.3	21.4	0.05	0.04	0.06
		PIII(M3)	54	53	98.1	90.1	100	47	87.0	75.1	94.6	0.77	0.54	1.09
		PIII(M9)	51	50	98.0	89.6	100	43	84.3	71.4	93.0	0.47	0.35	0.65
	DPARA	PRE	50	18	36.0	22.9	50.8	7	14.0	5.8	26.7	0.05	0.04	0.07
		PIII(M3)	53	51	96.2	87.0	99.5	43	81.1	68.0	90.6	0.74	0.51	1.08
		PIII(M9)	49	46	93.9	83.1	98.7	40	81.6	68.0	91.2	0.45	0.32	0.63
	NPARA	PRE	49	23	46.9	32.5	61.7	8	16.3	7.3	29.7	0.06	0.05	0.09
		PIII(M3)	55	54	98.2	90.3	100	50	90.9	80.0	97.0	1.00	0.73	1.36
		PIII(M9)	53	50	94.3	84.3	98.8	45	84.9	72.4	93.3	0.51	0.37	0.70

Booster epoch

The immune response to the vaccine pneumococcal serotypes as measured by 22F-inhibition ELISA is presented in the following table:

Table 56. Seropositivity rates and GMCs for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F antibodies (Booster epoch) (ATP cohort for immunogenicity)

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-1	IIBU-IIBU	PRE	45	15	33.3	20.0	49.0	2	4.4	0.5	15.1	0.04	0.03	0.05
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	1.81	1.42	2.32
		PIII(M9)	46	46	100	92.3	100	37	80.4	66.1	90.6	0.41	0.31	0.54
		PIV(M10)	49	49	100	92.7	100	49	100	92.7	100	2.87	2.10	3.91
	IIBU-DIBU	PRE	42	5	11.9	4.0	25.6	1	2.4	0.1	12.6	0.03	0.03	0.03
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	1.96	1.52	2.51
		PIII(M9)	44	44	100	92.0	100	35	79.5	64.7	90.2	0.36	0.28	0.46
		PIV(M10)	46	46	100	92.3	100	44	95.7	85.2	99.5	2.23	1.57	3.17
	IIBU-NIBU	PRE	40	11	27.5	14.6	43.9	2	5.0	0.6	16.9	0.04	0.03	0.04
		PIII(M3)	39	39	100	91.0	100	39	100	91.0	100	1.66	1.28	2.16
		PIII(M9)	40	40	100	91.2	100	27	67.5	50.9	81.4	0.27	0.22	0.34
		PIV(M10)	36	36	100	90.3	100	35	97.2	85.5	99.9	2.39	1.68	3.41
	DIBU-IIBU	PRE	45	10	22.2	11.2	37.1	4	8.9	2.5	21.2	0.04	0.03	0.05
		PIII(M3)	45	45	100	92.1	100	45	100	92.1	100	1.70	1.27	2.28
		PIII(M9)	47	46	97.9	88.7	99.9	33	70.2	55.1	82.7	0.38	0.28	0.53
		PIV(M10)	44	44	100	92.0	100	44	100	92.0	100	2.69	1.99	3.63
	DIBU-DIBU	PRE	46	11	23.9	12.6	38.8	0	0.0	0.0	7.7	0.03	0.03	0.04
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	1.81	1.44	2.26
		PIII(M9)	44	44	100	92.0	100	36	81.8	67.3	91.8	0.42	0.31	0.57
		PIV(M10)	48	48	100	92.6	100	47	97.9	88.9	99.9	2.44	1.78	3.33
	DIBU-NIBU	PRE	43	10	23.3	11.8	38.6	4	9.3	2.6	22.1	0.04	0.03	0.05
		PIII(M3)	48	48	100	92.6	100	48	100	92.6	100	1.53	1.22	1.93
		PIII(M9)	44	44	100	92.0	100	33	75.0	59.7	86.8	0.34	0.27	0.42
		PIV(M10)	46	46	100	92.3	100	44	95.7	85.2	99.5	1.87	1.36	2.57
	NIBU-IIBU	PRE	40	10	25.0	12.7	41.2	1	2.5	0.1	13.2	0.03	0.03	0.04
		PIII(M3)	45	45	100	92.1	100	45	100	92.1	100	2.05	1.66	2.54
		PIII(M9)	46	46	100	92.3	100	38	82.6	68.6	92.2	0.44	0.34	0.58
		PIV(M10)	44	44	100	92.0	100	43	97.7	88.0	99.9	2.84	2.02	3.99
	NIBU-DIBU	PRE	43	10	23.3	11.8	38.6	1	2.3	0.1	12.3	0.03	0.03	0.04
		PIII(M3)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.58	1.22	2.04
		PIII(M9)	44	44	100	92.0	100	35	79.5	64.7	90.2	0.38	0.30	0.48
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	3.04	2.38	3.88
	NIBU-NIBU	PRE	40	11	27.5	14.6	43.9	2	5.0	0.6	16.9	0.04	0.03	0.05
		PIII(M3)	45	45	100	92.1	100	45	100	92.1	100	2.04	1.59	2.63
		PIII(M9)	45	45	100	92.1	100	36	80.0	65.4	90.4	0.43	0.32	0.58
		PIV(M10)	41	41	100	91.4	100	40	97.6	87.1	99.9	2.84	2.10	3.85
	IPARA-NPARA	PRE	47	18	38.3	24.5	53.6	1	2.1	0.1	11.3	0.04	0.03	0.05
		PIII(M3)	50	50	100	92.9	100	48	96.0	86.3	99.5	1.38	1.07	1.77
		PIII(M9)	48	48	100	92.6	100	30	62.5	47.4	76.0	0.31	0.24	0.40
		PIV(M10)	47	47	100	92.5	100	45	95.7	85.5	99.5	1.76	1.29	2.38
	DPARA-IPARA	PRE	45	14	31.1	18.2	46.6	0	0.0	0.0	7.9	0.03	0.03	0.04
		PIII(M3)	45	45	100	92.1	100	44	97.8	88.2	99.9	1.32	1.02	1.71
		PIII(M9)	41	41	100	91.4	100	30	73.2	57.1	85.8	0.30	0.23	0.40
		PIV(M10)	44	44	100	92.0	100	44	100	92.0	100	2.14	1.59	2.89

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	NPARA-IPARA	PRE	45	14	31.1	18.2	46.6	2	4.4	0.5	15.1	0.04	0.03	0.05
		PIII(M3)	48	48	100	92.6	100	48	100	92.6	100	1.91	1.59	2.31
		PIII(M9)	44	44	100	92.0	100	36	81.8	67.3	91.8	0.45	0.32	0.64
		PIV(M10)	47	47	100	92.5	100	46	97.9	88.7	99.9	2.84	2.06	3.89
ANTI-4	IIBU-IIBU	PRE	48	13	27.1	15.3	41.8	7	14.6	6.1	27.8	0.04	0.03	0.05
		PIII(M3)	49	49	100	92.7	100	48	98.0	89.1	99.9	2.13	1.67	2.71
		PIII(M9)	47	47	100	92.5	100	46	97.9	88.7	99.9	0.71	0.55	0.92
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	4.09	3.20	5.22
	IIBU-DIBU	PRE	46	15	32.6	19.5	48.0	4	8.7	2.4	20.8	0.04	0.03	0.06
		PIII(M3)	45	45	100	92.1	100	45	100	92.1	100	2.56	2.03	3.23
		PIII(M9)	45	45	100	92.1	100	42	93.3	81.7	98.6	0.63	0.50	0.80
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	3.65	2.76	4.84
	IIBU-NIBU	PRE	43	11	25.6	13.5	41.2	1	2.3	0.1	12.3	0.03	0.03	0.04
		PIII(M3)	38	38	100	90.7	100	38	100	90.7	100	2.02	1.55	2.61
		PIII(M9)	40	40	100	91.2	100	37	92.5	79.6	98.4	0.55	0.44	0.69
		PIV(M10)	36	36	100	90.3	100	36	100	90.3	100	3.22	2.36	4.39
	DIBU-IIBU	PRE	45	16	35.6	21.9	51.2	5	11.1	3.7	24.1	0.05	0.04	0.06
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	2.32	1.83	2.95
		PIII(M9)	47	46	97.9	88.7	99.9	43	91.5	79.6	97.6	0.63	0.47	0.85
		PIV(M10)	45	45	100	92.1	100	44	97.8	88.2	99.9	4.05	2.99	5.50
	DIBU-DIBU	PRE	49	9	18.4	8.8	32.0	1	2.0	0.1	10.9	0.03	0.03	0.04
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	2.28	1.85	2.82
		PIII(M9)	46	46	100	92.3	100	42	91.3	79.2	97.6	0.72	0.55	0.95
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	3.63	2.84	4.62
	DIBU-NIBU	PRE	45	14	31.1	18.2	46.6	4	8.9	2.5	21.2	0.04	0.03	0.05
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	2.02	1.56	2.61
		PIII(M9)	45	45	100	92.1	100	41	91.1	78.8	97.5	0.64	0.49	0.83
		PIV(M10)	46	46	100	92.3	100	46	100	92.3	100	3.41	2.46	4.71
	NIBU-IIBU	PRE	45	9	20.0	9.6	34.6	2	4.4	0.5	15.1	0.03	0.03	0.04
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	2.09	1.63	2.68
		PIII(M9)	46	46	100	92.3	100	44	95.7	85.2	99.5	0.72	0.55	0.93
		PIV(M10)	42	42	100	91.6	100	42	100	91.6	100	4.04	3.05	5.36
	NIBU-DIBU	PRE	41	15	36.6	22.1	53.1	7	17.1	7.2	32.1	0.05	0.04	0.07
		PIII(M3)	46	46	100	92.3	100	45	97.8	88.5	99.9	2.00	1.57	2.56
		PIII(M9)	46	46	100	92.3	100	43	93.5	82.1	98.6	0.73	0.55	0.98
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	4.08	3.11	5.36
	NIBU-NIBU	PRE	42	9	21.4	10.3	36.8	1	2.4	0.1	12.6	0.03	0.03	0.04
		PIII(M3)	45	45	100	92.1	100	45	100	92.1	100	2.46	1.98	3.05
		PIII(M9)	45	45	100	92.1	100	40	88.9	75.9	96.3	0.62	0.47	0.82
		PIV(M10)	41	41	100	91.4	100	41	100	91.4	100	4.07	3.09	5.35
	IPARA-NPARA	PRE	50	14	28.0	16.2	42.5	2	4.0	0.5	13.7	0.04	0.03	0.05
		PIII(M3)	51	51	100	93.0	100	49	96.1	86.5	99.5	1.58	1.20	2.08
		PIII(M9)	47	47	100	92.5	100	43	91.5	79.6	97.6	0.52	0.39	0.68
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	3.27	2.51	4.25
	DPARA-IPARA	PRE	47	15	31.9	19.1	47.1	2	4.3	0.5	14.5	0.04	0.03	0.05
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	1.84	1.52	2.23
		PIII(M9)	45	45	100	92.1	100	40	88.9	75.9	96.3	0.60	0.48	0.76
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	3.31	2.66	4.12
	NPARA-IPARA	PRE	46	19	41.3	27.0	56.8	5	10.9	3.6	23.6	0.05	0.04	0.06
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	2.42	1.90	3.09
		PIII(M9)	45	45	100	92.1	100	43	95.6	84.9	99.5	0.84	0.64	1.11
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	4.28	3.23	5.68

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-5	IIBU-IIBU	PRE	45	13	28.9	16.4	44.3	4	8.9	2.5	21.2	0.04	0.03	0.06
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	2.91	2.30	3.67
		PIII(M9)	46	46	100	92.3	100	46	100	92.3	100	0.98	0.74	1.29
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	4.50	3.45	5.88
	IIBU-DIBU	PRE	39	10	25.6	13.0	42.1	1	2.6	0.1	13.5	0.04	0.03	0.04
		PIII(M3)	43	43	100	91.8	100	43	100	91.8	100	3.30	2.64	4.13
		PIII(M9)	44	44	100	92.0	100	43	97.7	88.0	99.9	0.83	0.66	1.05
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	3.90	2.95	5.16
	IIBU-NIBU	PRE	37	12	32.4	18.0	49.8	3	8.1	1.7	21.9	0.05	0.03	0.07
		PIII(M3)	38	38	100	90.7	100	38	100	90.7	100	2.67	2.10	3.40
		PIII(M9)	41	41	100	91.4	100	39	95.1	83.5	99.4	0.76	0.59	0.98
		PIV(M10)	36	36	100	90.3	100	36	100	90.3	100	4.11	2.91	5.81
	DIBU-IIBU	PRE	44	14	31.8	18.6	47.6	3	6.8	1.4	18.7	0.04	0.03	0.05
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	2.66	2.18	3.23
		PIII(M9)	47	47	100	92.5	100	44	93.6	82.5	98.7	0.78	0.61	1.00
		PIV(M10)	44	44	100	92.0	100	44	100	92.0	100	3.42	2.62	4.46
	DIBU-DIBU	PRE	46	14	30.4	17.7	45.8	3	6.5	1.4	17.9	0.04	0.03	0.05
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	2.48	2.05	3.01
		PIII(M9)	45	45	100	92.1	100	43	95.6	84.9	99.5	0.76	0.58	0.99
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	3.33	2.56	4.33
	DIBU-NIBU	PRE	40	19	47.5	31.5	63.9	5	12.5	4.2	26.8	0.05	0.04	0.08
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	2.15	1.71	2.70
		PIII(M9)	44	44	100	92.0	100	42	95.5	84.5	99.4	0.70	0.57	0.86
		PIV(M10)	46	46	100	92.3	100	46	100	92.3	100	3.37	2.46	4.60
	NIBU-IIBU	PRE	41	16	39.0	24.2	55.5	3	7.3	1.5	19.9	0.05	0.03	0.06
		PIII(M3)	43	43	100	91.8	100	43	100	91.8	100	2.70	2.12	3.42
		PIII(M9)	46	46	100	92.3	100	46	100	92.3	100	0.83	0.66	1.05
		PIV(M10)	43	43	100	91.8	100	43	100	91.8	100	4.21	3.03	5.86
	NIBU-DIBU	PRE	39	14	35.9	21.2	52.8	1	2.6	0.1	13.5	0.04	0.03	0.05
		PIII(M3)	46	46	100	92.3	100	45	97.8	88.5	99.9	2.52	1.98	3.21
		PIII(M9)	45	45	100	92.1	100	45	100	92.1	100	0.84	0.67	1.04
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	3.92	3.06	5.01
	NIBU-NIBU	PRE	40	12	30.0	16.6	46.5	3	7.5	1.6	20.4	0.04	0.03	0.05
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	3.23	2.61	4.00
		PIII(M9)	45	45	100	92.1	100	45	100	92.1	100	0.96	0.76	1.23
		PIV(M10)	41	41	100	91.4	100	41	100	91.4	100	4.48	3.48	5.77
	IPARA-NPARA	PRE	45	17	37.8	23.8	53.5	2	4.4	0.5	15.1	0.05	0.03	0.06
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	2.02	1.57	2.60
		PIII(M9)	47	47	100	92.5	100	45	95.7	85.5	99.5	0.59	0.45	0.77
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	2.62	1.92	3.57
	DPARA-IPARA	PRE	45	13	28.9	16.4	44.3	1	2.2	0.1	11.8	0.04	0.03	0.05
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	2.24	1.76	2.86
		PIII(M9)	45	45	100	92.1	100	41	91.1	78.8	97.5	0.72	0.57	0.91
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	3.58	2.74	4.69
	NPARA-IPARA	PRE	41	20	48.8	32.9	64.9	6	14.6	5.6	29.2	0.06	0.04	0.08
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	2.99	2.43	3.67
		PIII(M9)	44	44	100	92.0	100	40	90.9	78.3	97.5	0.85	0.62	1.17
		PIV(M10)	47	47	100	92.5	100	46	97.9	88.7	99.9	4.33	3.26	5.76
ANTI-6B	IIBU-IIBU	PRE	49	25	51.0	36.3	65.6	7	14.3	5.9	27.2	0.06	0.05	0.09
		PIII(M3)	49	48	98.0	89.1	99.9	43	87.8	75.2	95.4	0.70	0.51	0.96
		PIII(M9)	49	49	100	92.7	100	43	87.8	75.2	95.4	0.63	0.48	0.82
		PIV(M10)	49	49	100	92.7	100	49	100	92.7	100	2.75	2.16	3.48

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	IIBU-DIBU	PRE	43	17	39.5	25.0	55.6	2	4.7	0.6	15.8	0.05	0.04	0.06
		PIII(M3)	45	42	93.3	81.7	98.6	35	77.8	62.9	88.8	0.64	0.42	0.97
		PIII(M9)	45	42	93.3	81.7	98.6	38	84.4	70.5	93.5	0.44	0.31	0.61
		PIV(M10)	45	44	97.8	88.2	99.9	44	97.8	88.2	99.9	1.97	1.41	2.74
	IIBU-NIBU	PRE	40	19	47.5	31.5	63.9	3	7.5	1.6	20.4	0.06	0.04	0.08
		PIII(M3)	38	36	94.7	82.3	99.4	31	81.6	65.7	92.3	0.59	0.40	0.87
		PIII(M9)	41	40	97.6	87.1	99.9	36	87.8	73.8	95.9	0.54	0.40	0.72
		PIV(M10)	36	36	100	90.3	100	36	100	90.3	100	2.43	1.85	3.19
	DIBU-IIBU	PRE	47	24	51.1	36.1	65.9	3	6.4	1.3	17.5	0.05	0.04	0.06
		PIII(M3)	46	45	97.8	88.5	99.9	42	91.3	79.2	97.6	0.79	0.57	1.08
		PIII(M9)	48	46	95.8	85.7	99.5	41	85.4	72.2	93.9	0.55	0.40	0.77
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	2.13	1.64	2.76
	DIBU-DIBU	PRE	48	19	39.6	25.8	54.7	3	6.3	1.3	17.2	0.05	0.04	0.06
		PIII(M3)	47	46	97.9	88.7	99.9	42	89.4	76.9	96.5	0.91	0.65	1.26
		PIII(M9)	48	47	97.9	88.9	99.9	44	91.7	80.0	97.7	0.62	0.48	0.80
		PIV(M10)	48	48	100	92.6	100	46	95.8	85.7	99.5	2.18	1.69	2.81
	DIBU-NIBU	PRE	46	17	37.0	23.2	52.5	5	10.9	3.6	23.6	0.04	0.03	0.06
		PIII(M3)	47	44	93.6	82.5	98.7	39	83.0	69.2	92.4	0.64	0.43	0.97
		PIII(M9)	47	45	95.7	85.5	99.5	42	89.4	76.9	96.5	0.60	0.45	0.80
		PIV(M10)	47	43	91.5	79.6	97.6	43	91.5	79.6	97.6	1.52	0.98	2.34
	NIBU-IIBU	PRE	45	16	35.6	21.9	51.2	6	13.3	5.1	26.8	0.05	0.04	0.06
		PIII(M3)	43	42	97.7	87.7	99.9	38	88.4	74.9	96.1	0.61	0.43	0.86
		PIII(M9)	46	44	95.7	85.2	99.5	40	87.0	73.7	95.1	0.56	0.42	0.75
		PIV(M10)	44	42	95.5	84.5	99.4	42	95.5	84.5	99.4	2.16	1.47	3.18
	NIBU-DIBU	PRE	46	19	41.3	27.0	56.8	7	15.2	6.3	28.9	0.06	0.04	0.08
		PIII(M3)	46	44	95.7	85.2	99.5	36	78.3	63.6	89.1	0.48	0.33	0.71
		PIII(M9)	46	44	95.7	85.2	99.5	42	91.3	79.2	97.6	0.58	0.43	0.78
		PIV(M10)	46	44	95.7	85.2	99.5	44	95.7	85.2	99.5	2.32	1.60	3.36
	NIBU-NIBU	PRE	45	13	28.9	16.4	44.3	3	6.7	1.4	18.3	0.04	0.03	0.05
		PIII(M3)	44	42	95.5	84.5	99.4	40	90.9	78.3	97.5	0.74	0.50	1.08
		PIII(M9)	45	45	100	92.1	100	43	95.6	84.9	99.5	0.67	0.51	0.87
		PIV(M10)	42	42	100	91.6	100	42	100	91.6	100	2.51	1.96	3.22
	IPARA-NPARA	PRE	49	21	42.9	28.8	57.8	4	8.2	2.3	19.6	0.05	0.04	0.07
		PIII(M3)	49	46	93.9	83.1	98.7	39	79.6	65.7	89.8	0.50	0.34	0.72
		PIII(M9)	50	49	98.0	89.4	99.9	44	88.0	75.7	95.5	0.43	0.33	0.56
		PIV(M10)	48	48	100	92.6	100	44	91.7	80.0	97.7	1.74	1.23	2.45
	DPARA-IPARA	PRE	48	24	50.0	35.2	64.8	9	18.8	8.9	32.6	0.07	0.05	0.10
		PIII(M3)	44	39	88.6	75.4	96.2	30	68.2	52.4	81.4	0.36	0.23	0.55
		PIII(M9)	47	44	93.6	82.5	98.7	41	87.2	74.3	95.2	0.43	0.33	0.57
		PIV(M10)	46	45	97.8	88.5	99.9	45	97.8	88.5	99.9	1.84	1.36	2.49
	NPARA-IPARA	PRE	46	18	39.1	25.1	54.6	7	15.2	6.3	28.9	0.05	0.04	0.07
		PIII(M3)	48	45	93.8	82.8	98.7	41	85.4	72.2	93.9	0.70	0.48	1.02
		PIII(M9)	45	45	100	92.1	100	42	93.3	81.7	98.6	0.61	0.49	0.76
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	2.29	1.79	2.91
ANTI-7F	IIBU-IIBU	PRE	47	22	46.8	32.1	61.9	7	14.9	6.2	28.3	0.06	0.04	0.08
		PIII(M3)	50	50	100	92.9	100	50	100	92.9	100	3.17	2.55	3.95
		PIII(M9)	47	47	100	92.5	100	47	100	92.5	100	1.33	1.07	1.64
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	5.75	4.59	7.21
	IIBU-DIBU	PRE	38	23	60.5	43.4	76.0	3	7.9	1.7	21.4	0.07	0.05	0.11
		PIII(M3)	46	46	100	92.3	100	45	97.8	88.5	99.9	2.68	2.01	3.57
		PIII(M9)	43	43	100	91.8	100	43	100	91.8	100	0.96	0.75	1.23
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	4.20	3.33	5.31

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	IIBU-NIBU	PRE	40	19	47.5	31.5	63.9	7	17.5	7.3	32.8	0.06	0.04	0.09
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	2.71	2.20	3.34
		PIII(M9)	41	41	100	91.4	100	41	100	91.4	100	0.89	0.74	1.07
		PIV(M10)	36	36	100	90.3	100	36	100	90.3	100	4.20	3.24	5.46
	DIBU-IIBU	PRE	46	28	60.9	45.4	74.9	10	21.7	10.9	36.4	0.08	0.06	0.11
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	2.77	2.20	3.49
		PIII(M9)	47	47	100	92.5	100	44	93.6	82.5	98.7	1.08	0.80	1.46
		PIV(M10)	44	44	100	92.0	100	44	100	92.0	100	4.96	3.77	6.54
	DIBU-DIBU	PRE	45	19	42.2	27.7	57.8	6	13.3	5.1	26.8	0.05	0.04	0.07
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	3.08	2.54	3.74
		PIII(M9)	46	46	100	92.3	100	46	100	92.3	100	1.10	0.90	1.35
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	4.36	3.35	5.66
	DIBU-NIBU	PRE	40	22	55.0	38.5	70.7	6	15.0	5.7	29.8	0.06	0.04	0.08
		PIII(M3)	48	48	100	92.6	100	48	100	92.6	100	2.73	2.21	3.37
		PIII(M9)	45	45	100	92.1	100	45	100	92.1	100	1.09	0.89	1.34
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	3.93	3.04	5.08
	NIBU-IIBU	PRE	42	22	52.4	36.4	68.0	4	9.5	2.7	22.6	0.05	0.04	0.07
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	2.53	2.09	3.07
		PIII(M9)	46	46	100	92.3	100	46	100	92.3	100	1.07	0.89	1.29
		PIV(M10)	42	42	100	91.6	100	42	100	91.6	100	5.43	4.13	7.14
	NIBU-DIBU	PRE	42	16	38.1	23.6	54.4	4	9.5	2.7	22.6	0.05	0.03	0.06
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	2.65	2.16	3.25
		PIII(M9)	45	45	100	92.1	100	45	100	92.1	100	1.31	1.02	1.67
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	5.55	4.38	7.04
	NIBU-NIBU	PRE	43	20	46.5	31.2	62.3	8	18.6	8.4	33.4	0.06	0.04	0.08
		PIII(M3)	45	45	100	92.1	100	45	100	92.1	100	3.03	2.40	3.82
		PIII(M9)	44	44	100	92.0	100	43	97.7	88.0	99.9	1.11	0.83	1.49
		PIV(M10)	41	41	100	91.4	100	41	100	91.4	100	4.93	3.64	6.69
	IPARA-NPARA	PRE	46	21	45.7	30.9	61.0	9	19.6	9.4	33.9	0.06	0.04	0.08
		PIII(M3)	51	51	100	93.0	100	51	100	93.0	100	2.21	1.77	2.77
		PIII(M9)	49	49	100	92.7	100	48	98.0	89.1	99.9	0.84	0.67	1.06
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	3.89	2.98	5.10
	DPARA-IPARA	PRE	44	24	54.5	38.8	69.6	8	18.2	8.2	32.7	0.07	0.05	0.09
		PIII(M3)	48	48	100	92.6	100	48	100	92.6	100	2.36	1.92	2.91
		PIII(M9)	43	43	100	91.8	100	42	97.7	87.7	99.9	0.98	0.79	1.22
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	4.63	3.56	6.04
	NPARA-IPARA	PRE	44	20	45.5	30.4	61.2	6	13.6	5.2	27.4	0.05	0.04	0.07
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	2.78	2.21	3.51
		PIII(M9)	46	46	100	92.3	100	44	95.7	85.2	99.5	0.97	0.76	1.24
		PIV(M10)	47	47	100	92.5	100	46	97.9	88.7	99.9	4.52	3.31	6.16
ANTI-9V	IIBU-IIBU	PRE	44	17	38.6	24.4	54.5	8	18.2	8.2	32.7	0.05	0.04	0.08
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	2.38	1.83	3.08
		PIII(M9)	48	48	100	92.6	100	47	97.9	88.9	99.9	1.07	0.82	1.39
		PIV(M10)	49	49	100	92.7	100	49	100	92.7	100	4.46	3.35	5.93
	IIBU-DIBU	PRE	41	17	41.5	26.3	57.9	4	9.8	2.7	23.1	0.05	0.04	0.07
		PIII(M3)	45	45	100	92.1	100	44	97.8	88.2	99.9	2.02	1.54	2.65
		PIII(M9)	45	45	100	92.1	100	44	97.8	88.2	99.9	0.83	0.67	1.02
		PIV(M10)	46	46	100	92.3	100	45	97.8	88.5	99.9	3.30	2.47	4.41
	IIBU-NIBU	PRE	40	19	47.5	31.5	63.9	6	15.0	5.7	29.8	0.06	0.04	0.08
		PIII(M3)	38	38	100	90.7	100	38	100	90.7	100	1.85	1.42	2.42
		PIII(M9)	42	42	100	91.6	100	42	100	91.6	100	0.83	0.67	1.03
		PIV(M10)	36	36	100	90.3	100	36	100	90.3	100	3.94	2.80	5.54

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	DIBU-IIBU	PRE	47	21	44.7	30.2	59.9	6	12.8	4.8	25.7	0.05	0.04	0.07
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	2.09	1.65	2.64
		PIII(M9)	47	47	100	92.5	100	44	93.6	82.5	98.7	1.03	0.79	1.36
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	3.47	2.76	4.36
	DIBU-DIBU	PRE	47	19	40.4	26.4	55.7	4	8.5	2.4	20.4	0.05	0.04	0.07
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	2.26	1.86	2.75
		PIII(M9)	47	47	100	92.5	100	47	100	92.5	100	1.03	0.81	1.30
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	3.16	2.39	4.17
	DIBU-NIBU	PRE	43	18	41.9	27.0	57.9	6	14.0	5.3	27.9	0.05	0.04	0.07
		PIII(M3)	45	45	100	92.1	100	45	100	92.1	100	1.78	1.43	2.21
		PIII(M9)	46	46	100	92.3	100	46	100	92.3	100	0.93	0.76	1.14
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	3.07	2.32	4.07
	NIBU-IIBU	PRE	40	16	40.0	24.9	56.7	5	12.5	4.2	26.8	0.05	0.04	0.08
		PIII(M3)	43	42	97.7	87.7	99.9	42	97.7	87.7	99.9	2.07	1.53	2.81
		PIII(M9)	46	45	97.8	88.5	99.9	45	97.8	88.5	99.9	1.09	0.83	1.44
		PIV(M10)	43	43	100	91.8	100	43	100	91.8	100	4.07	3.00	5.52
	NIBU-DIBU	PRE	39	14	35.9	21.2	52.8	5	12.8	4.3	27.4	0.05	0.04	0.07
		PIII(M3)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.90	1.50	2.39
		PIII(M9)	46	46	100	92.3	100	45	97.8	88.5	99.9	0.92	0.76	1.12
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	3.88	3.09	4.87
	NIBU-NIBU	PRE	43	20	46.5	31.2	62.3	5	11.6	3.9	25.1	0.05	0.04	0.07
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	2.62	2.07	3.30
		PIII(M9)	45	45	100	92.1	100	45	100	92.1	100	1.09	0.82	1.46
		PIV(M10)	42	42	100	91.6	100	42	100	91.6	100	4.05	3.18	5.15
	IPARA-NPARA	PRE	48	25	52.1	37.2	66.7	9	18.8	8.9	32.6	0.07	0.05	0.09
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	1.69	1.30	2.21
		PIII(M9)	50	50	100	92.9	100	49	98.0	89.4	99.9	0.74	0.58	0.95
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	3.11	2.36	4.09
	DPARA-IPARA	PRE	44	22	50.0	34.6	65.4	2	4.5	0.6	15.5	0.05	0.04	0.07
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	1.78	1.42	2.23
		PIII(M9)	47	47	100	92.5	100	47	100	92.5	100	0.93	0.76	1.14
		PIV(M10)	46	46	100	92.3	100	46	100	92.3	100	3.49	2.68	4.56
	NPARA-IPARA	PRE	44	26	59.1	43.2	73.7	4	9.1	2.5	21.7	0.06	0.05	0.08
		PIII(M3)	47	47	100	92.5	100	46	97.9	88.7	99.9	2.18	1.67	2.84
		PIII(M9)	48	48	100	92.6	100	46	95.8	85.7	99.5	0.97	0.73	1.28
		PIV(M10)	48	48	100	92.6	100	47	97.9	88.9	99.9	3.90	2.86	5.30
ANTI-14	IIBU-IIBU	PRE	45	40	88.9	75.9	96.3	31	68.9	53.4	81.8	0.37	0.23	0.58
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	4.87	3.83	6.19
		PIII(M9)	47	47	100	92.5	100	45	95.7	85.5	99.5	1.76	1.23	2.51
		PIV(M10)	49	49	100	92.7	100	49	100	92.7	100	6.02	4.47	8.12
	IIBU-DIBU	PRE	39	38	97.4	86.5	99.9	20	51.3	34.8	67.6	0.23	0.16	0.33
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	5.52	4.22	7.22
		PIII(M9)	44	44	100	92.0	100	44	100	92.0	100	1.74	1.25	2.41
		PIV(M10)	46	46	100	92.3	100	45	97.8	88.5	99.9	5.62	3.99	7.92
	IIBU-NIBU	PRE	37	30	81.1	64.8	92.0	19	51.4	34.4	68.1	0.28	0.16	0.49
		PIII(M3)	38	38	100	90.7	100	38	100	90.7	100	4.17	3.09	5.63
		PIII(M9)	41	40	97.6	87.1	99.9	37	90.2	76.9	97.3	1.06	0.71	1.57
		PIV(M10)	38	38	100	90.7	100	38	100	90.7	100	5.16	3.61	7.36
	DIBU-IIBU	PRE	45	40	88.9	75.9	96.3	23	51.1	35.8	66.3	0.25	0.16	0.40
		PIII(M3)	46	46	100	92.3	100	45	97.8	88.5	99.9	4.15	3.12	5.51
		PIII(M9)	47	47	100	92.5	100	45	95.7	85.5	99.5	1.31	0.99	1.74
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	4.54	3.45	5.98

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	DIBU-DIBU	PRE	47	43	91.5	79.6	97.6	31	66.0	50.7	79.1	0.32	0.21	0.49
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	4.44	3.44	5.71
		PIII(M9)	46	45	97.8	88.5	99.9	45	97.8	88.5	99.9	1.70	1.18	2.44
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	5.08	3.80	6.80
	DIBU-NIBU	PRE	41	37	90.2	76.9	97.3	24	58.5	42.1	73.7	0.26	0.17	0.40
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	4.91	3.86	6.24
		PIII(M9)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.73	1.29	2.33
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	4.61	3.37	6.30
	NIBU-IIBU	PRE	42	40	95.2	83.8	99.4	27	64.3	48.0	78.4	0.45	0.28	0.70
		PIII(M3)	42	42	100	91.6	100	42	100	91.6	100	4.73	3.64	6.15
		PIII(M9)	46	45	97.8	88.5	99.9	43	93.5	82.1	98.6	1.60	1.06	2.39
		PIV(M10)	44	44	100	92.0	100	44	100	92.0	100	6.03	4.18	8.70
	NIBU-DIBU	PRE	38	37	97.4	86.2	99.9	27	71.1	54.1	84.6	0.41	0.29	0.60
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	4.71	3.60	6.15
		PIII(M9)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.93	1.47	2.53
		PIV(M10)	46	46	100	92.3	100	46	100	92.3	100	6.56	5.06	8.51
	NIBU-NIBU	PRE	42	41	97.6	87.4	99.9	26	61.9	45.6	76.4	0.43	0.28	0.68
		PIII(M3)	44	44	100	92.0	100	43	97.7	88.0	99.9	4.44	3.06	6.43
		PIII(M9)	45	44	97.8	88.2	99.9	44	97.8	88.2	99.9	1.95	1.28	2.95
		PIV(M10)	43	43	100	91.8	100	43	100	91.8	100	6.30	4.45	8.92
	IPARA-NPARA	PRE	46	44	95.7	85.2	99.5	29	63.0	47.5	76.8	0.27	0.20	0.36
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	3.60	2.63	4.93
		PIII(M9)	49	49	100	92.7	100	47	95.9	86.0	99.5	1.18	0.85	1.64
		PIV(M10)	50	50	100	92.9	100	50	100	92.9	100	4.72	3.56	6.27
	DPARA-IPARA	PRE	43	42	97.7	87.7	99.9	35	81.4	66.6	91.6	0.47	0.33	0.67
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	3.93	2.98	5.19
		PIII(M9)	44	44	100	92.0	100	43	97.7	88.0	99.9	1.53	1.08	2.16
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	5.52	4.13	7.38
	NPARA-IPARA	PRE	42	36	85.7	71.5	94.6	31	73.8	58.0	86.1	0.42	0.24	0.71
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	5.22	4.22	6.45
		PIII(M9)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.86	1.38	2.52
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	5.62	4.23	7.48
ANTI-18C	IIBU-IIBU	PRE	46	27	58.7	43.2	73.0	12	26.1	14.3	41.1	0.08	0.05	0.12
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	4.31	3.19	5.83
		PIII(M9)	50	50	100	92.9	100	49	98.0	89.4	99.9	1.13	0.88	1.47
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	9.35	7.13	12.25
	IIBU-DIBU	PRE	38	17	44.7	28.6	61.7	6	15.8	6.0	31.3	0.06	0.04	0.08
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	4.04	3.10	5.28
		PIII(M9)	44	44	100	92.0	100	43	97.7	88.0	99.9	1.03	0.81	1.32
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	8.06	5.93	10.96
	IIBU-NIBU	PRE	37	24	64.9	47.5	79.8	6	16.2	6.2	32.0	0.08	0.05	0.11
		PIII(M3)	38	38	100	90.7	100	38	100	90.7	100	3.44	2.45	4.85
		PIII(M9)	41	41	100	91.4	100	41	100	91.4	100	0.96	0.73	1.26
		PIV(M10)	38	38	100	90.7	100	38	100	90.7	100	7.78	5.53	10.93
	DIBU-IIBU	PRE	45	22	48.9	33.7	64.2	10	22.2	11.2	37.1	0.07	0.05	0.10
		PIII(M3)	46	45	97.8	88.5	99.9	45	97.8	88.5	99.9	3.95	2.79	5.61
		PIII(M9)	47	47	100	92.5	100	45	95.7	85.5	99.5	1.08	0.82	1.41
		PIV(M10)	44	44	100	92.0	100	44	100	92.0	100	8.23	6.37	10.65
	DIBU-DIBU	PRE	45	23	51.1	35.8	66.3	12	26.7	14.6	41.9	0.07	0.05	0.10
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	4.39	3.43	5.62
		PIII(M9)	48	48	100	92.6	100	48	100	92.6	100	1.10	0.86	1.39
		PIV(M10)	48	48	100	92.6	100	48	100	92.6	100	7.16	5.41	9.46

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	DIBU-NIBU	PRE	40	26	65.0	48.3	79.4	9	22.5	10.8	38.5	0.08	0.06	0.12
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	3.24	2.40	4.38
		PIII(M9)	46	46	100	92.3	100	46	100	92.3	100	1.03	0.80	1.31
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	7.10	5.33	9.46
	NIBU-IIBU	PRE	41	23	56.1	39.7	71.5	4	9.8	2.7	23.1	0.06	0.04	0.08
		PIII(M3)	43	43	100	91.8	100	42	97.7	87.7	99.9	3.64	2.61	5.07
		PIII(M9)	46	46	100	92.3	100	46	100	92.3	100	1.12	0.87	1.43
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	7.15	5.13	9.96
	NIBU-DIBU	PRE	38	22	57.9	40.8	73.7	6	15.8	6.0	31.3	0.07	0.05	0.10
		PIII(M3)	46	45	97.8	88.5	99.9	45	97.8	88.5	99.9	4.38	3.08	6.22
		PIII(M9)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.39	1.08	1.79
		PIV(M10)	46	46	100	92.3	100	45	97.8	88.5	99.9	11.29	7.96	16.00
	NIBU-NIBU	PRE	40	20	50.0	33.8	66.2	8	20.0	9.1	35.6	0.06	0.04	0.08
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	4.60	3.47	6.09
		PIII(M9)	46	46	100	92.3	100	44	95.7	85.2	99.5	1.23	0.93	1.63
		PIV(M10)	42	42	100	91.6	100	42	100	91.6	100	8.68	6.41	11.75
	IPARA-NPARA	PRE	47	28	59.6	44.3	73.6	12	25.5	13.9	40.3	0.09	0.06	0.13
		PIII(M3)	49	49	100	92.7	100	48	98.0	89.1	99.9	3.17	2.31	4.34
		PIII(M9)	50	50	100	92.9	100	48	96.0	86.3	99.5	0.91	0.67	1.23
		PIV(M10)	49	49	100	92.7	100	49	100	92.7	100	6.18	4.65	8.20
	DPARA-IPARA	PRE	43	24	55.8	39.9	70.9	7	16.3	6.8	30.7	0.07	0.05	0.09
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	4.10	3.14	5.37
		PIII(M9)	47	47	100	92.5	100	47	100	92.5	100	1.14	0.92	1.41
		PIV(M10)	44	44	100	92.0	100	44	100	92.0	100	8.66	6.76	11.09
	NPARA-IPARA	PRE	41	25	61.0	44.5	75.8	12	29.3	16.1	45.5	0.08	0.06	0.11
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	4.48	3.31	6.06
		PIII(M9)	47	47	100	92.5	100	47	100	92.5	100	1.31	1.01	1.69
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	8.17	5.80	11.52
ANTI-19F	IIBU-IIBU	PRE	46	32	69.6	54.2	82.3	16	34.8	21.4	50.2	0.10	0.07	0.15
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	6.24	4.65	8.36
		PIII(M9)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.94	1.46	2.57
		PIV(M10)	49	49	100	92.7	100	49	100	92.7	100	6.90	4.89	9.72
	IIBU-DIBU	PRE	40	27	67.5	50.9	81.4	16	40.0	24.9	56.7	0.14	0.08	0.23
		PIII(M3)	45	45	100	92.1	100	45	100	92.1	100	5.57	4.29	7.23
		PIII(M9)	44	44	100	92.0	100	44	100	92.0	100	1.66	1.28	2.17
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	6.64	5.17	8.54
	IIBU-NIBU	PRE	38	24	63.2	46.0	78.2	16	42.1	26.3	59.2	0.12	0.07	0.19
		PIII(M3)	38	38	100	90.7	100	38	100	90.7	100	6.25	4.56	8.57
		PIII(M9)	40	40	100	91.2	100	40	100	91.2	100	1.72	1.23	2.39
		PIV(M10)	36	36	100	90.3	100	36	100	90.3	100	6.91	4.88	9.77
	DIBU-IIBU	PRE	45	33	73.3	58.1	85.4	16	35.6	21.9	51.2	0.13	0.09	0.21
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	5.02	3.82	6.59
		PIII(M9)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.58	1.14	2.19
		PIV(M10)	45	45	100	92.1	100	44	97.8	88.2	99.9	5.35	3.84	7.47
	DIBU-DIBU	PRE	46	34	73.9	58.9	85.7	19	41.3	27.0	56.8	0.13	0.09	0.20
		PIII(M3)	47	47	100	92.5	100	45	95.7	85.5	99.5	4.69	3.33	6.59
		PIII(M9)	46	46	100	92.3	100	44	95.7	85.2	99.5	1.54	1.09	2.19
		PIV(M10)	48	48	100	92.6	100	46	95.8	85.7	99.5	5.27	3.64	7.64
	DIBU-NIBU	PRE	43	31	72.1	56.3	84.7	12	27.9	15.3	43.7	0.12	0.08	0.18
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	5.25	4.16	6.64
		PIII(M9)	44	44	100	92.0	100	44	100	92.0	100	1.38	1.09	1.75
		PIV(M10)	46	46	100	92.3	100	46	100	92.3	100	5.57	4.14	7.51

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	NIBU-IIBU	PRE	43	31	72.1	56.3	84.7	23	53.5	37.7	68.8	0.15	0.10	0.22
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	4.76	3.53	6.42
		PIII(M9)	46	46	100	92.3	100	45	97.8	88.5	99.9	1.25	0.96	1.63
		PIV(M10)	44	44	100	92.0	100	43	97.7	88.0	99.9	5.24	3.66	7.49
	NIBU-DIBU	PRE	41	33	80.5	65.1	91.2	14	34.1	20.1	50.6	0.12	0.09	0.17
		PIII(M3)	46	46	100	92.3	100	46	100	92.3	100	5.42	4.18	7.04
		PIII(M9)	45	45	100	92.1	100	43	95.6	84.9	99.5	1.70	1.27	2.26
		PIV(M10)	45	45	100	92.1	100	45	100	92.1	100	7.26	5.28	9.97
	NIBU-NIBU	PRE	41	24	58.5	42.1	73.7	9	22.0	10.6	37.6	0.08	0.06	0.12
		PIII(M3)	44	43	97.7	88.0	99.9	43	97.7	88.0	99.9	4.80	3.35	6.89
		PIII(M9)	45	45	100	92.1	100	44	97.8	88.2	99.9	1.90	1.38	2.62
		PIV(M10)	41	41	100	91.4	100	41	100	91.4	100	7.34	5.55	9.73
	IPARA-NPARA	PRE	48	34	70.8	55.9	83.0	16	33.3	20.4	48.4	0.11	0.08	0.17
		PIII(M3)	49	49	100	92.7	100	49	100	92.7	100	5.03	3.73	6.79
		PIII(M9)	48	48	100	92.6	100	47	97.9	88.9	99.9	1.56	1.14	2.13
		PIV(M10)	47	47	100	92.5	100	47	100	92.5	100	5.94	4.43	7.97
	DPARA-IPARA	PRE	46	36	78.3	63.6	89.1	19	41.3	27.0	56.8	0.15	0.10	0.21
		PIII(M3)	44	44	100	92.0	100	44	100	92.0	100	5.16	3.86	6.89
		PIII(M9)	45	45	100	92.1	100	44	97.8	88.2	99.9	1.51	1.15	2.00
		PIV(M10)	44	44	100	92.0	100	43	97.7	88.0	99.9	5.54	3.88	7.93
	NPARA-IPARA	PRE	42	35	83.3	68.6	93.0	21	50.0	34.2	65.8	0.18	0.12	0.27
		PIII(M3)	47	47	100	92.5	100	47	100	92.5	100	6.87	5.35	8.82
		PIII(M9)	45	45	100	92.1	100	43	95.6	84.9	99.5	1.72	1.31	2.27
		PIV(M10)	47	47	100	92.5	100	46	97.9	88.7	99.9	6.66	4.92	9.01
ANTI-23F	IIBU-IIBU	PRE	45	24	53.3	37.9	68.3	10	22.2	11.2	37.1	0.07	0.05	0.10
		PIII(M3)	50	48	96.0	86.3	99.5	46	92.0	80.8	97.8	1.06	0.75	1.52
		PIII(M9)	48	46	95.8	85.7	99.5	41	85.4	72.2	93.9	0.65	0.45	0.94
		PIV(M10)	48	47	97.9	88.9	99.9	47	97.9	88.9	99.9	3.72	2.60	5.33
	IIBU-DIBU	PRE	40	13	32.5	18.6	49.1	5	12.5	4.2	26.8	0.04	0.03	0.06
		PIII(M3)	44	44	100	92.0	100	42	95.5	84.5	99.4	1.10	0.80	1.51
		PIII(M9)	43	43	100	91.8	100	42	97.7	87.7	99.9	0.64	0.52	0.79
		PIV(M10)	45	45	100	92.1	100	44	97.8	88.2	99.9	3.08	2.25	4.21
	IIBU-NIBU	PRE	38	16	42.1	26.3	59.2	9	23.7	11.4	40.2	0.06	0.04	0.09
		PIII(M3)	41	40	97.6	87.1	99.9	36	87.8	73.8	95.9	0.90	0.60	1.34
		PIII(M9)	41	38	92.7	80.1	98.5	34	82.9	67.9	92.8	0.41	0.28	0.58
		PIV(M10)	35	34	97.1	85.1	99.9	33	94.3	80.8	99.3	2.59	1.63	4.11
	DIBU-IIBU	PRE	45	18	40.0	25.7	55.7	3	6.7	1.4	18.3	0.05	0.03	0.06
		PIII(M3)	47	46	97.9	88.7	99.9	41	87.2	74.3	95.2	1.05	0.75	1.49
		PIII(M9)	47	45	95.7	85.5	99.5	39	83.0	69.2	92.4	0.55	0.39	0.77
		PIV(M10)	44	43	97.7	88.0	99.9	43	97.7	88.0	99.9	2.93	2.05	4.19
	DIBU-DIBU	PRE	46	21	45.7	30.9	61.0	6	13.0	4.9	26.3	0.06	0.04	0.08
		PIII(M3)	48	45	93.8	82.8	98.7	42	87.5	74.8	95.3	0.76	0.51	1.14
		PIII(M9)	46	43	93.5	82.1	98.6	39	84.8	71.1	93.7	0.50	0.34	0.72
		PIV(M10)	47	45	95.7	85.5	99.5	43	91.5	79.6	97.6	2.16	1.40	3.33
	DIBU-NIBU	PRE	42	14	33.3	19.6	49.5	4	9.5	2.7	22.6	0.05	0.03	0.07
		PIII(M3)	47	47	100	92.5	100	44	93.6	82.5	98.7	1.00	0.73	1.37
		PIII(M9)	45	45	100	92.1	100	41	91.1	78.8	97.5	0.65	0.50	0.84
		PIV(M10)	46	46	100	92.3	100	45	97.8	88.5	99.9	2.74	2.06	3.65
	NIBU-IIBU	PRE	42	14	33.3	19.6	49.5	6	14.3	5.4	28.5	0.05	0.03	0.08
		PIII(M3)	45	45	100	92.1	100	43	95.6	84.9	99.5	1.14	0.88	1.49
		PIII(M9)	46	45	97.8	88.5	99.9	40	87.0	73.7	95.1	0.61	0.45	0.81
		PIV(M10)	43	42	97.7	87.7	99.9	42	97.7	87.7	99.9	3.12	2.17	4.48

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
	NIBU-DIBU	PRE	41	15	36.6	22.1	53.1	1	2.4	0.1	12.9	0.04	0.03	0.05
		PIII(M3)	46	44	95.7	85.2	99.5	42	91.3	79.2	97.6	0.94	0.66	1.33
		PIII(M9)	46	45	97.8	88.5	99.9	43	93.5	82.1	98.6	0.69	0.51	0.92
		PIV(M10)	45	45	100	92.1	100	44	97.8	88.2	99.9	3.17	2.34	4.31
	NIBU-NIBU	PRE	41	13	31.7	18.1	48.1	4	9.8	2.7	23.1	0.04	0.03	0.06
		PIII(M3)	45	45	100	92.1	100	41	91.1	78.8	97.5	1.20	0.90	1.61
		PIII(M9)	45	44	97.8	88.2	99.9	38	84.4	70.5	93.5	0.58	0.43	0.79
		PIV(M10)	41	41	100	91.4	100	39	95.1	83.5	99.4	3.33	2.36	4.70
	IPARA-NPARA	PRE	48	18	37.5	24.0	52.6	4	8.3	2.3	20.0	0.05	0.03	0.06
		PIII(M3)	50	49	98.0	89.4	99.9	44	88.0	75.7	95.5	0.81	0.56	1.17
		PIII(M9)	49	48	98.0	89.1	99.9	41	83.7	70.3	92.7	0.47	0.34	0.65
		PIV(M10)	47	47	100	92.5	100	45	95.7	85.5	99.5	2.50	1.76	3.56
	DPARA-IPARA	PRE	44	15	34.1	20.5	49.9	4	9.1	2.5	21.7	0.04	0.03	0.06
		PIII(M3)	46	44	95.7	85.2	99.5	37	80.4	66.1	90.6	0.73	0.48	1.11
		PIII(M9)	45	42	93.3	81.7	98.6	36	80.0	65.4	90.4	0.43	0.30	0.62
		PIV(M10)	44	43	97.7	88.0	99.9	41	93.2	81.3	98.6	2.53	1.74	3.68
	NPARA-IPARA	PRE	42	19	45.2	29.8	61.3	7	16.7	7.0	31.4	0.06	0.04	0.09
		PIII(M3)	48	47	97.9	88.9	99.9	43	89.6	77.3	96.5	0.90	0.65	1.25
		PIII(M9)	46	43	93.5	82.1	98.6	40	87.0	73.7	95.1	0.52	0.37	0.74
		PIV(M10)	47	46	97.9	88.7	99.9	46	97.9	88.7	99.9	3.15	2.31	4.30

Immune response to the co-administered DTPa-combined vaccines Primary epoch

The results for the DTPa antigens are presented in tables 52, 53 and 55.

Table 52. Seroprotection rates and GMCs for ANTI-DIPHT and ANTI-TET antibodies (Primary epoch) (ATP cohort for immunogenicity)

				≥ 0.1 IU/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-DIPHT	IIBU	PRE	120	24	20.0	13.3	28.3	0.064	0.058	0.070
		PIII(M3)	137	137	100	97.3	100	3.326	2.970	3.725
		PIII(M9)	136	135	99.3	96.0	100	0.655	0.575	0.745
	DIBU	PRE	129	38	29.5	21.8	38.1	0.078	0.068	0.089
		PIII(M3)	150	150	100	97.6	100	2.938	2.651	3.257
		PIII(M9)	142	140	98.6	95.0	99.8	0.594	0.516	0.685
	NIBU	PRE	129	42	32.6	24.6	41.4	0.081	0.071	0.092
		PIII(M3)	153	153	100	97.6	100	3.132	2.801	3.503
		PIII(M9)	145	143	98.6	95.1	99.8	0.673	0.596	0.760
	IPARA	PRE	45	8	17.8	8.0	32.1	0.066	0.055	0.080
		PIII(M3)	50	50	100	92.9	100	3.062	2.565	3.655
		PIII(M9)	47	47	100	92.5	100	0.659	0.549	0.791
	DPARA	PRE	47	16	34.0	20.9	49.3	0.088	0.068	0.113
		PIII(M3)	49	49	100	92.7	100	2.891	2.324	3.597
		PIII(M9)	46	44	95.7	85.2	99.5	0.566	0.436	0.735
	NPARA	PRE	45	14	31.1	18.2	46.6	0.077	0.063	0.096
		PIII(M3)	53	53	100	93.3	100	3.457	2.907	4.109
		PIII(M9)	51	51	100	93.0	100	0.625	0.502	0.777
ANTI-TET	IIBU	PRE	119	85	71.4	62.4	79.3	0.315	0.234	0.425
		PIII(M3)	137	137	100	97.3	100	3.746	3.305	4.245
		PIII(M9)	133	132	99.2	95.9	100	0.755	0.662	0.861
	DIBU	PRE	129	97	75.2	66.8	82.4	0.327	0.248	0.432
		PIII(M3)	150	150	100	97.6	100	3.373	3.043	3.738
		PIII(M9)	142	141	99.3	96.1	100	0.753	0.657	0.863
	NIBU	PRE	129	99	76.7	68.5	83.7	0.326	0.250	0.426
		PIII(M3)	153	153	100	97.6	100	3.961	3.516	4.461
		PIII(M9)	145	143	98.6	95.1	99.8	0.861	0.755	0.983
	IPARA	PRE	45	31	68.9	53.4	81.8	0.347	0.202	0.599
		PIII(M3)	49	49	100	92.7	100	2.943	2.434	3.559
		PIII(M9)	47	46	97.9	88.7	99.9	0.679	0.534	0.863
	DPARA	PRE	47	37	78.7	64.3	89.3	0.350	0.227	0.540
		PIII(M3)	49	49	100	92.7	100	3.058	2.545	3.676
		PIII(M9)	45	44	97.8	88.2	99.9	0.666	0.524	0.846
	NPARA	PRE	45	34	75.6	60.5	87.1	0.355	0.223	0.565
		PIII(M3)	53	53	100	93.3	100	3.762	3.105	4.558
		PIII(M9)	51	51	100	93.0	100	0.908	0.729	1.131

Table 53. Seropositivity rates and GMCs for ANTI-PT, ANTI-FHA and ANTI-PRN antibodies (Primary epoch) (ATP cohort for immunogenicity)

				≥ 5 EL.U/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-PT	IIBU	PRE	108	21	19.4	12.5	28.2	3.1	2.8	3.5
		PIII(M3)	133	133	100	97.3	100	59.1	53.7	65.1
		PIII(M9)	130	123	94.6	89.2	97.8	12.4	11.1	13.9
	DIBU	PRE	118	19	16.1	10.0	24.0	3.1	2.8	3.5
		PIII(M3)	145	145	100	97.5	100	64.2	58.7	70.2
		PIII(M9)	139	132	95.0	89.9	98.0	14.2	12.5	16.2
	NIBU	PRE	123	16	13.0	7.6	20.3	3.0	2.7	3.2
		PIII(M3)	147	147	100	97.5	100	65.0	59.6	71.0
		PIII(M9)	143	130	90.9	85.0	95.1	13.5	11.9	15.4
	IPARA	PRE	44	10	22.7	11.5	37.8	3.3	2.8	3.9
		PIII(M3)	47	47	100	92.5	100	60.4	51.4	71.0
		PIII(M9)	46	43	93.5	82.1	98.6	13.0	10.6	16.0
	DPARA	PRE	43	6	14.0	5.3	27.9	3.4	2.5	4.7
		PIII(M3)	45	45	100	92.1	100	63.1	52.0	76.6
		PIII(M9)	43	37	86.0	72.1	94.7	10.7	8.6	13.3
	NPARA	PRE	45	6	13.3	5.1	26.8	3.0	2.6	3.4
		PIII(M3)	53	53	100	93.3	100	61.5	53.1	71.2
		PIII(M9)	50	44	88.0	75.7	95.5	13.4	10.2	17.6
ANTI-FHA	IIBU	PRE	110	82	74.5	65.4	82.4	7.9	6.7	9.2
		PIII(M3)	131	131	100	97.2	100	163.1	147.8	180.1
		PIII(M9)	130	130	100	97.2	100	43.7	38.6	49.4
	DIBU	PRE	113	84	74.3	65.3	82.1	9.5	7.8	11.4
		PIII(M3)	143	143	100	97.5	100	171.6	154.7	190.4
		PIII(M9)	135	135	100	97.3	100	56.6	48.2	66.4
	NIBU	PRE	119	87	73.1	64.2	80.8	8.4	7.1	9.8
		PIII(M3)	142	142	100	97.4	100	191.1	171.1	213.5
		PIII(M9)	141	141	100	97.4	100	53.4	46.6	61.3
	IPARA	PRE	41	30	73.2	57.1	85.8	8.1	6.1	10.9
		PIII(M3)	47	47	100	92.5	100	171.0	139.8	209.2
		PIII(M9)	46	46	100	92.3	100	49.6	41.0	60.0
	DPARA	PRE	43	33	76.7	61.4	88.2	9.5	7.2	12.7
		PIII(M3)	45	45	100	92.1	100	196.5	163.1	236.8
		PIII(M9)	43	43	100	91.8	100	47.5	39.1	57.8
	NPARA	PRE	43	31	72.1	56.3	84.7	8.4	6.3	11.2
		PIII(M3)	52	52	100	93.2	100	168.9	141.9	201.0
		PIII(M9)	49	49	100	92.7	100	53.1	40.4	69.8
ANTI-PRN	IIBU	PRE	119	12	10.1	5.3	17.0	2.9	2.7	3.1
		PIII(M3)	138	137	99.3	96.0	100	103.9	91.5	118.0
		PIII(M9)	137	127	92.7	87.0	96.4	17.0	14.7	19.8
	DIBU	PRE	128	25	19.5	13.1	27.5	3.4	3.0	3.8
		PIII(M3)	149	149	100	97.6	100	114.3	101.0	129.3
		PIII(M9)	143	134	93.7	88.4	97.1	21.6	18.2	25.6
	NIBU	PRE	129	25	19.4	13.0	27.3	3.4	3.0	3.9
		PIII(M3)	155	155	100	97.6	100	118.1	103.9	134.3
		PIII(M9)	151	142	94.0	89.0	97.2	21.8	18.5	25.6
	IPARA	PRE	45	10	22.2	11.2	37.1	3.4	2.8	4.1
		PIII(M3)	47	47	100	92.5	100	97.1	76.7	123.1
		PIII(M9)	50	49	98.0	89.4	99.9	19.9	14.6	27.1

				≥ 5 EL.U/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
	DPARA	PRE	48	9	18.8	8.9	32.6	3.3	2.8	4.0
		PIII(M3)	48	48	100	92.6	100	106.2	83.1	135.7
		PIII(M9)	47	45	95.7	85.5	99.5	18.6	14.0	24.6
	NPARA	PRE	45	8	17.8	8.0	32.1	3.2	2.7	3.8
		PIII(M3)	53	53	100	93.3	100	114.0	95.6	136.0
		PIII(M9)	51	46	90.2	78.6	96.7	18.6	13.4	25.8

Table 55. Seroprotection rates and GMCs for ANTI-PRP antibodies (Primary epoch) (ATP cohort for immunogenicity)

				≥ 0.15 µg/mL				≥ 1 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-PRP	IIBU	PRE	118	35	29.7	21.6	38.8	3	2.5	0.5	7.3	0.125	0.106	0.148
		PIII(M3)	136	136	100	97.3	100	124	91.2	85.1	95.4	3.994	3.268	4.882
		PIII(M9)	137	124	90.5	84.3	94.9	55	40.1	31.9	48.9	0.741	0.602	0.911
	DIBU	PRE	124	48	38.7	30.1	47.9	10	8.1	3.9	14.3	0.144	0.121	0.172
		PIII(M3)	147	146	99.3	96.3	100	135	91.8	86.2	95.7	3.660	3.073	4.359
		PIII(M9)	143	132	92.3	86.7	96.1	57	39.9	31.8	48.4	0.835	0.669	1.043
	NIBU	PRE	127	46	36.2	27.9	45.2	4	3.1	0.9	7.9	0.132	0.113	0.153
		PIII(M3)	150	150	100	97.6	100	136	90.7	84.8	94.8	4.510	3.753	5.419
		PIII(M9)	150	143	95.3	90.6	98.1	58	38.7	30.8	47.0	0.830	0.681	1.012
	IPARA	PRE	43	15	34.9	21.0	50.9	0	0.0	0.0	8.2	0.128	0.100	0.164
		PIII(M3)	52	52	100	93.2	100	42	80.8	67.5	90.4	3.290	2.362	4.583
		PIII(M9)	47	46	97.9	88.7	99.9	13	27.7	15.6	42.6	0.688	0.498	0.950
	DPARA	PRE	45	17	37.8	23.8	53.5	1	2.2	0.1	11.8	0.126	0.101	0.158
		PIII(M3)	47	47	100	92.5	100	41	87.2	74.3	95.2	4.230	3.025	5.914
		PIII(M9)	47	43	91.5	79.6	97.6	18	38.3	24.5	53.6	0.674	0.481	0.945
	NPARA	PRE	45	18	40.0	25.7	55.7	2	4.4	0.5	15.1	0.145	0.109	0.193
		PIII(M3)	53	53	100	93.3	100	48	90.6	79.3	96.9	5.007	3.690	6.793
		PIII(M9)	51	48	94.1	83.8	98.8	23	45.1	31.1	59.7	0.956	0.665	1.374

Booster responses to the co-administered antigens follow the same pattern as the primary responses.

Assessor's comment: As for the pneumococcal responses, no indication that ibuprophen diminishes the immune responses were seen. The responses in the paracetamol receiving groups were slightly lower compared to the control group.

4.2.2. Discussion

In this study, there were no effects of prophylactic ibuprofen administration, either delayed or immediate, on the immune responses to Synflorix. The same conclusions can be drawn for both primary and booster vaccinations. In agreement with other studies, there was a reduction of immune responses to Synflorix when prophylactic paracetamol was administered either immediately, or delayed.

4.3. Clinical Safety aspects

4.3.1. Results

Between groups assessment

The secondary confirmatory objective was to determine the percentage reduction in febrile reactions (rectal temperature ≥38.0°C) when immediate or delayed prophylactic ibuprofen treatment was administered compared to no prophylactic ibuprofen treatment, after primary vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine co-administered with DTPa-combined vaccines.

In order to control the type I error, the secondary objective was only assessable if the primary objective was met, which is the case.

The results for the confirmatory analysis between groups are presented in tables 112 and 113.

Table 112. Difference between groups (NIBU minus IIBU) in percentage of subjects reporting fever with rectal temperature ≥ 38.0°C during the 4-day (Days 0-3) after at least one primary vaccine dose (Primary epoch) (Total vaccinated cohort)

							Difference in % of subjects (NIBU minus IIBU)		
	NIBU			IIBU				97.5% CI	
Symptoms	N	n	%	N	n	%	%	LL	UL
Fever≥ 38.0°C (rectal)	199	122	61.3	197	121	61.4	-0.11	-11.04	10.82

Table 113. Difference between groups (NIBU minus DIBU) in percentage of subjects reporting fever with rectal temperature ≥ 38.0°C during the 4-day (Days 0-3) after at least one primary vaccine dose (Primary epoch) (Total vaccinated cohort)

							Difference in % of subjects (NIBU minus DIBU)		
	NIBU			DIBU				97.5% CI	
Symptoms	N	n	%	N	n	%	%	LL	UL
Fever≥ 38.0°C (rectal)	199	122	61.3	197	101	51.3	10.04	-1.15	20.98

Assessor's comment: There was no difference in fever in the no ibuprofen and immediate ibuprofen, while there was a tendency towards lower fever incidence in the delayed ibuprofen group.

Primary vaccination with 10Pn-PD-DiT vaccine and DTPa-(HBV)-IPV/Hib

- **Any symptom:** During the 31-day post-primary vaccination period, the overall/dose incidence of reported symptoms (solicited and/or unsolicited; local and/or general) ranged from 70.9% (DPARA group) to 85.2% (NPARA group).
- **Solicited local symptoms:** During the 4-day post-primary vaccination period, redness was the most frequently reported solicited local symptom (overall/dose incidence ranged from 29.5% [DIBU group] to 41.7% [NPARA group]), whatever the injection site, except for the DPARA group where the most frequently reported solicited local symptom was pain (overall/dose incidence was 33.3%). The overall/dose incidence of reported solicited grade 3 local symptom was not higher than 4.2% [pain in the NPARA group], whatever the injection site.

- **Solicited general symptoms:** During the 4-day post-primary vaccination period, irritability was the most frequently reported solicited general symptom (overall/dose incidence ranged from 35.6% [IPARA group] to 50.5% [NPARA group]), except for the IPARA group where the most frequently reported solicited general symptom was drowsiness (overall/dose incidence was 38.0%). The overall/dose incidence of grade 3 solicited general symptoms was not higher than 2.4% (irritability in the IPARA group). The incidence of solicited general symptoms with causal relationship to vaccination as assessed by the investigator ranged from 9.6% (loss of appetite in the IPARA group) to 33.4% (irritability in the NIBU group).
- **Unsolicited symptoms:** During the 31-day post-primary vaccination period, at least one unsolicited symptom was reported after a maximum of 9.5% of doses (NPARA group). One grade 3 unsolicited symptom was reported after 0.2% of doses in the DIBU and NIBU groups and after 0.5% of doses in the IPARA group. At least one unsolicited symptom with causal relationship to vaccination was reported after 0.3% of doses in the IIBU group, after 0.5% of doses in the DIBU group and after 1.0% of doses in the IPARA group.

Booster vaccination with 10Pn-PD-DiT vaccine and DTPa-HBV-IPV/Hib

- **Any symptom:** During the 31-day post-booster vaccination period, the incidence of reported symptom (solicited and/or unsolicited; local and/or general) ranged from 57.6% (IIBU-NIBU group) to 83.3% (NIBU-IIBU group).
- **Solicited local symptoms:** During the 4-day post-booster vaccination period, pain and redness were the most frequently reported solicited local symptoms (incidence of pain ranged from 25.4% [IIBU-NIBU group] to 50.8% [NIBU-DIBU group] and incidence of redness ranged from 24.6% [DIBU-DIBU group] to 42.9% [IIBU-IIBU group]), whatever the injection site. Solicited grade 3 local symptom were reported for a maximum of 7.9% of subjects [redness in the NIBU-DIBU group], whatever the injection site. A large swelling reaction was reported during the primary epoch for one subject from the NPARA-IPARA group one day after administration of the third dose of the 10Pn-PD-DiT vaccine.
- **Solicited general symptoms:** During the 4-day post-booster vaccination period, irritability was the most frequently reported solicited general symptom (incidence ranged from 32.8% [DPARAIPARA group] to 60.0% [NIBU-IIBU group]). Grade 3 solicited general symptoms were reported for a maximum of 5.1% of subjects (irritability in the IIBU-DIBU and DIBU-NIBU groups). The incidence of solicited general symptoms with causal relationship to vaccination as assessed by the investigator ranged from 6.8% (loss of appetite in the IIBU-NIBU group) to 45.0% (irritability in the NIBU-IIBU group).
- **Unsolicited symptoms:** During the 31-day post-booster vaccination period, at least one unsolicited symptom was reported for a maximum of 10.0% of subjects (IIBU-DIBU group). Two grade 3 unsolicited symptoms were reported: one for a subject (1.6%) in the IIBU-IIBU group and another for a subject (1.5%) in the IPARA-NPARA group. One unsolicited symptom with causal relationship to vaccination, which was of grade 3 intensity, was reported for a subject (1.6%) in the IIBU-IIBU group.
- **Serious adverse events: (Amended: 07 November 2014)**
    - One fatal SAE (craniocerebral injury) was reported for a subject from the Total enrolled cohort (DPARA group***;*** centre excluded from TVC) 132 days after the third dose and was considered by the investigator as not related to vaccination.
    - Among the subjects included in the TVC, at least one non-fatal SAE was reported for ten subjects during the primary epoch, for three subjects during the booster epoch and for two

subjects during the period between both epochs. All SAEs recovered/resolved and were assessed by the investigator as not related to vaccination.

- For subjects eliminated from the TVC from one centre, in addition to the fatal SAE, at least one non-fatal SAE was reported for three subjects during the period starting with the administration of study vaccine dose 1 up to the end of booster epoch. All SAEs recovered/resolved and were assessed by the investigator as not related to vaccination.

- **Withdrawals due to adverse events/serious adverse events:** Two subjects from the TVC were withdrawn due to an SAE during the study period. These events were considered as recovered/resolved and were assessed by the investigator as not related to vaccination.

4.3.2. Discussion

The primary safety outcome in this study was fever. There were no beneficial effects of immediate administration of ibuprofen compared to no ibuprofen in terms of fever reduction, and a trend towards fever reduction in delayed ibuprofen administration. There were no new safety signals, and the overall safety profile was in agreement with previous studies.

4.4. Changes to the Product Information

As a result of this variation section 4.4 of the SmPC is being updated.

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. ~~However,~~ ***Clinical*** data ***generated with paracetamol and ibuprofen*** suggest that the prophylactic use of paracetamol might reduce the immune response to Synflorix. The clinical relevance of this observation~~, as well as the impact of antipyretics other than paracetamol on the immune response to Synflorix~~ remains unknown.

The use of prophylactic antipyretic medicinal products is recommended:
- for all children receiving Synflorix simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions (see section 4.8).
- for children with seizure disorders or with a prior history of febrile seizures.
Antipyretic treatment should be initiated according to local treatment guidelines.

Assessor's comment: The proposed wording is not considered adequate, as it should also be mentioned that prophylactic ibuprofen had a limited capacity to reduce the fever rates. Otherwise caregivers and parents might preferentially use ibuprofen as prophylactic antipyretic, which may not be appropriate.

Proposed wording: Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. ~~However,~~ ***Clinical*** data ***generated with paracetamol and ibuprofen*** suggest that the prophylactic use of paracetamol might reduce ***the fever rate, while ibuprofen had a limited capacity to reduce fever rates. The same study*** suggests that paracetamol might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known.

Changes to the Package Leaflet:

Your doctor may ask you to give your child ***an antipyretic (such as*** paracetamol)~~ or other medicines that lower fever~~ before or immediately after Synflorix is given. This ~~will~~ can help to lower some of the side effects (febrile reactions) of Synflorix. However if your child has received paracetamol ***before or immediately after Synflorix is given***, their ~~protection~~ ***immune response (antibodies)*** against pneumococcal diseases may not be as good ~~(it is not known whether such an impact would be observed when medicines that lower fever, other than paracetamol, are given).~~

Assessor's comment: The proposed new wording is not fully endorsed, and an alternative suggestion is given below. The currently approved text in this section of the leaflet is given in plain language easily understandable to the general public in accordance with current guidance in the annotated QRD template and the Readability Guideline. New proposed words such as "antipyretic" and "immune response" are not considered as plain language. The following changes in the proposal are therefore suggested (new text in ***underlined bold italics*** and deleted text in ~~double strikethrough~~).

Proposed wording: Your doctor may ask you to give your child ***a medicine that lowers fever*** ~~an antipyretic~~ ***(such as*** paracetamol)~~ or other medicines that lower fever~~ before or immediately after Synflorix is given. This ~~will~~ can help to lower some of the side effects (febrile reactions) of Synflorix. However if your child has received paracetamol ***before or immediately after Synflorix is given***, their ***protection*** ~~protection~~ ~~immune response~~ (antibodies) against pneumococcal diseases may not be as good ~~(it is not known whether such an impact would be observed when medicines that lower fever, other than paracetamol, are given)~~.

5. Request for supplementary information

5.1. Other concerns

Clinical aspects

Question 1.

An English summary of the Romanian inspection report should be provided before a conclusion regarding this variation can be drawn.

Question 2.

A revised SmPC and package leaflet should be provided (suggestion given above)

6. Assessment of the responses to the request for supplementary information

6.1. Other concerns

Question 1. An English summary of the Romanian inspection report should be provided before a conclusion regarding this variation can be drawn.

MAH response:

A GCP inspection was held by the National Drug Agency and Medical Devices Agency -Pharmaceutical Inspection Department (NDAMD) of clinical study 112921 (10PN-PD-DIT-050). The inspection encompasses two entities:

- SS/001/14: GCP inspection at the GlaxoSmithKline Local Operating Company (LOC) in Romania: 7-8 October 2014.
- SI/001/14: GCP inspection at one investigational site: 9-10 October 2014.

Following the request from CHMP, GSK Biologicals s.a. provides an English summary of the findings listed in the above inspection reports and a summary of the responses. Initial responses to both the SS/001/14 and SI/001/14 inspections were provided in December 2014 by GSK Biologicals s.a., the GSK LOC in Romania and the investigational site. On January 16th 2015, NDAMD requested updated responses for some findings, and the point of view of the GSK LOC in Romania for the findings listed in the SI/001/14 inspection report. These responses were submitted on 16 February 2015. At this point in time the GSK LOC in Romania has not received any further feedback from NDAMD.

With respect to the GCP inspection at the investigational site (SI/001/14), it must be noted that all data from subjects enrolled at this centre were excluded from analyses. In addition, other subjects who were found non-eligible during the inspection of the GSK LOC in Romania (SS/001/14) were eliminated from the According to Protocol analysis. This has been described in the clinical study report (Report Amendment 1 dated 7 November 2014) submitted as part of this variation application.

Assessment re English summary of the Romanian inspection report SS/001/14: The MAH has concluded that the above findings do not influence the quality of the study. This is in principle agreed. The serological assay is stated to be fully validated, and considering that the same assay has been used for the clinical development program this is expected to be satisfactory. The traceability of investigational product should not be of major concern as the study was open label. The other points of concern do not seem to influence the final results of the study. **Issue resolved.**

Assessment re English summary of Romanian inspection report SI/001/14: Considering that the inspected site was excluded from the study, and the subjects were excluded from the final analysis. **Issue resolved.**

Question 2. A revised SmPC and package leaflet should be provided (suggestion given above)

Changes to the Product Information - section 4.4

Assessor's comment: The proposed wording is not considered adequate, as it should also be mentioned that prophylactic ibuprofen had a limited capacity to reduce the fever rates. Otherwise caregivers and parents might preferentially use ibuprofen as prophylactic antipyretic, which may not be appropriate.

Initial wording proposed by the Company:

"Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. ~~However,~~ ***Clinical*** data ***generated with paracetamol and ibuprofen*** suggest that the prophylactic use of paracetamol might reduce the immune response to Synflorix. The clinical relevance of this observation, ~~as well as the impact of antipyretics other than paracetamol on the immune response to Synflorix~~ remains unknown."

Assessor proposed wording:

"Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. ~~However,~~ ***Clinical*** data ***generated with paracetamol and ibuprofen*** suggest that the prophylactic use of paracetamol might reduce ***the fever rate, while ibuprofen had a limited capacity to reduce fever rates. The same study*** suggests that

paracetamol might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known."

MAH's response:

The MAH agrees to mention in the proposed wording that the prophylactic use of ibuprofen showed a limited effect in reducing fever rates.

The MAH would like to make some amendments to the wording proposed by the Assessor as shown in track changes below.

"Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. Clinical data generated with paracetamol and ibuprofen suggest that the prophylactic use of paracetamol might reduce ***the fever rate, while prophylactic use of ibuprofen ~~had~~ showed a limited ~~capacity~~ effect ~~to~~ in reducing~~e~~ fever rates~~.~~ The ~~same study~~ clinical data*** suggests that paracetamol might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known."

The MAH prefers the wording *"limited effect"* than "*limited capacity"* of ibuprofen to reduce fever rate as the sentence refers to the clinical data obtained and not to a general capacity of ibuprofen. With the addition in the sentence of *'prophylactic use'*, the Company would like to reiterate that this effect was observed when used prophylactically, without referring to any other use of ibuprofen.

The MAH would like to highlight that the effect of prophylactic use of paracetamol in reducing the immune response to Synflorix was not only observed in study 10PN-PD-DIT-050 but also, as discussed in the Clinical Overview, in previous studies 10PN-PD-DIT-010/014. For this reason, the Company proposes to change *'The same clinical study suggests that paracetamol might reduce the immune response to Synflorix."* into *"The clinical data suggest that paracetamol might reduce the immune response to Synflorix."*

Assessment: The MAH suggested changes to the SPC are considered acceptable. **Issue resolved.**

Changes to the Package Leaflet - section Other medicines and Synflorix

Assessor's comment: The proposed new wording is not fully endorsed, and an alternative suggestion is given below. The currently approved text in this section of the leaflet is given in plain language easily understandable to the general public in accordance with current guidance in the annotated QRD template and the Readability Guideline. New proposed words such as "antipyretic" and "immune response" are not considered as plain language. The following changes in the proposal are therefore suggested (new text in underlined bold italics and deleted text in double striketrough).

Assessor proposed wording:

Your doctor may ask you to give your child ***a medicine that lowers fever*** ~~an antipyretic~~ (***such as*** paracetamol) ~~or other medicines that lower fever~~ before or immediately after Synflorix is given. This~~ will~~ can help to lower some of the side effects (febrile reactions) of Synflorix. However if your child has received paracetamol ***before or immediately after Synflorix is given***, their ***protection*** ~~immune response~~ ***(antibodies)*** against pneumococcal diseases may not be as good ~~(it is not known whether such an impact would be observed when medicines that lower fever, other than paracetamol, are given)~~.

MAH's response:

The Company agrees to change the word "*an antipyretic*" into "*a medicine that lowers fever*" but suggest to keep the word "*immune response*" at the end of the paragraph.

The Company notes that in the current PIL section 'How Synflorix works', an explanation on the notion of 'antibodies' and 'immune system' is already provided ("Synflorix helps your body to make its own antibodies.

The antibodies form a part of the immune system that will protect your child against these diseases"). The Company also considers that the word "*protection*" could imply an effect on the efficacy of the vaccine while, as noted in section 4.4 of the SmPC, the clinical relevance of this finding is not known.

The revised wording proposed by the Company reads:

"Your doctor may ask you to give your child a medicine that lowers fever (such as paracetamol) before or immediately after Synflorix is given. This can help to lower some of the side effects (febrile reactions) of Synflorix. However if your child has received paracetamol before or immediately after Synflorix is given, their immune response (antibodies) against pneumococcal diseases may not be as good."

Assessment:

The further change to the PL suggested by the MAH is considered acceptable.

Furthermore, a comment from MS suggested that the two last sentences should be revised as follows, to better reflect that the clinical implication of reduced antibody levels after use of paracetamol is not known:

"However if your child has received paracetamol before or immediately after Synflorix is given, ***the*** ***obtained levels of antibodies may be slightly reduced*** ~~their immune response (antibodies) against pneumococcal diseases may not be as good.~~. ***However, whether the reduction in antibody levels has an impact on the protection against pneumococcal disease is not known.***

The Rapporteur acknowledges the MS comment and recommends revision of package leaflet text in accordance with this comment but with a minor rewording in the last sentence to use a direct language:

"***It is not known*** ~~However,~~ whether the reduction in antibody levels has an impact on the protection against pneumococcal disease~~ is not known~~.

Issue resolved.