SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study:

A phase II, open, single centre, exploratory study to evaluate the safety and immunogenicity of one booster dose of GSK Biologicals' HIV candidate vaccine (732461), administered intramuscularly, in conjunction with the administration of a single oral dose of chloroquine in healthy adults.

Principal investigator:

Prof. Dr. [redacted]

Study centre:

[redacted]
Belgium.

Publication (reference):

Not published as of 05 July 2011.

Study period:	**Clinical phase:** II
Study initiation date: 07 December 2009 Study completion date: 04 October 2010 Data lock point: 28 February 2011	

Objectives:

Co-primary:

- To evaluate the effect of chloroquine on a specific $CD8^+$ T-cell response to the F4co/$AS01_B$ candidate vaccine at Day 14.
- To evaluate the reactogenicity and safety of a booster dose of the investigational vaccine.

Secondary:

- To evaluate the $CD8^+$ T-cell immune response to the study vaccine with or without chloroquine, determined at Day 0, 7, 14, 30 and 180.
- To evaluate the $CD4^+$ T-cell immune response to the study vaccine with or without chloroquine, determined at Day 0, 7, 14, 30 and 180.
- To evaluate the serological response to the study vaccine with or without chloroquine, determined at Day 0, 7, 14, 30 and 180.

Study design:

Open-label, randomised study with 2 parallel treatment groups:

- The **group F4CQ** received a single dose of chloroquine, 2 days before 1 booster dose of the F4co/$AS01_B$ investigational vaccine.
- The **group F4** only received 1 booster dose of the F4co/$AS01_B$ investigational vaccine (control for group F4CQ).

Subjects were recruited amongst the $CD4^+$ T-cell responders who participated in the PRO-HIV-005 (108706) study, during which they received 2 doses of the F4co/$AS01_B$ investigational vaccine (10µg or 30µg/ vaccine dose) according to a 0, 1 month vaccination schedule.

Blood samples were taken at Screening and at Day 0, Day 7, Day 14, Day 30 and Day 180.

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Number of subjects:

- *Planned:* 44 subjects; 22 subjects per group.
- *Enrolled:* 34 subjects; 16 subjects per group and 2 subjects not randomized.
- *Completed*: 28 subjects; 13 in the group F4CQ and 15 in the group F4.
- *Safety:* Total Vaccinated cohort for safety; 13 in the group F4CQ and 15 in the group F4.
- *Immunogenicity:* According -To-Protocol (ATP) cohort for immunogenicity: 27 subjects; 13 in the group F4CQ and 14 in the group F4.

Diagnosis and criteria for inclusion:

Healthy adults from the 10µg or the 30µg groups of the PRO-HIV-005 (108706) study who were identified as $CD4^+$ T-cell responders, negative for anti-Hepatitis B core (HBc) and anti-Hepatitis C Virus (HCV) antibodies, who did not have ophthalmologic findings at screening (namely maculopathy, retinopathy, corneal opacities and cataracts) and who were willing to accept HIV test results.

Study vaccine, dose, mode of administration, lot no.:

Dosage and administration:
At Day 0, all subjects received 1 booster dose of the reconstituted F4co vaccine with $AS01_B$ as an intramuscular injection in the deltoid muscle of (preferably) the non-dominant arm.

Vaccine composition /dose /lot number:
The study vaccine consisted of 2 fractions to be used upon reconstitution prior to injection:

Synopsis Table 1: Study vaccine formulation and lot number

Vaccine name	Vaccine components	Formulation	Presentation	Volume	Lot number
F4co/$AS01_B$	F4co (p24-RT-Nef-p17)	10 µg of p24-RT-Nef-p17 20 mg sucrose 630 µg sodium sulfite	Lyophilized pellet in vial	N/A	DHIVA004A
	$AS01_B$	50 µg of MPL 50 µg QS21 in a suspension of liposomes in phosphate buffered saline per 0.5 mL	Liquid in monodose vial	0.5 mL	DA01A007A

N/A = not applicable

Study product, dose, mode of administration:

Dosage and administration:
At Day -2, subjects in the group F4CQ received 300 mg of chloroquine, orally (*i.e.* 3 tablets of Nivaquine® [Sanofi-Aventis, France]).

Product dose/ composition/ lot number:
Please refer to the patient leaflet for a description of Nivaquine®.
The Nivaquine® lot number was 638.

Duration of treatment:

Duration of the study was approximately 6 months for each subject (from Visit 1 to study conclusion).

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Criteria for evaluation:

Immunogenicity

Primary endpoint:

- Cellular immune response to components of the study vaccine at Day 14.

  Criteria for assessment:

  – $CD8^+$ T-cell responder rate identified as the number of subjects with frequencies of $CD8^+$ T-cells expressing at least 1 cytokine among IL-2, TNF-α and IFN-γ equal or above the cut-off to at least 1, 2, 3 antigens and to all 4 antigens at Day 14, as determined by Intracellular Cytokine Staining (ICS).

Secondary endpoint:

- Cellular and humoral immune response to components of the candidate vaccines at Days 0, 7, 14, 30 and 180 in all subjects.

  Criteria for assessment:

  – $CD8^+$ T-cell responder rate identified as the number of subjects with frequencies of $CD8^+$ T-cells expressing at least one cytokine among IL-2, TNF-α and IFN-γ equal or above the cut-off to at least 1, 2, 3 antigens and to all 4 antigens, as determined by ICS.

  – Magnitude of the $CD8^+$ T-cell response identified as the frequency of p17, p24, Nef, RT and F4co-specific $CD8^+$ T-cells expressing IL-2 and/or IFN-γ and/or TNF-α, as determined by ICS.

  – Cytokine/marker co-expression profile of the antigen-specific $CD8^+$ T-cells: Frequency p17, p24, Nef, RT and F4co-specific $CD8^+$ T-cells expressing IL-2 and/or TNF-α and/or IFN-γ and/or CD40L, as determined by ICS and analyzed by FlowJo software or equivalent.

  – $CD4^+$ T-cell responder rate identified as the number of subjects with frequencies of $CD4^+$ T-cells expressing at least 2 cytokines including IL-2 equal or above the cut-off to at least 1, 2, 3 antigens and to all 4 antigens, as determined by ICS.

  – Magnitude of the $CD4^+$ T-cell response identified as the frequency of p17, p24, Nef, RT and F4co-specific $CD4^+$ T-cells expressing at least 2 cytokines including IL-2, as determined by ICS.

  – Cytokine/marker co-expression profile of the antigen-specific $CD4^+$ T-cells: Frequency of p17, p24, Nef, RT and F4co-specific $CD4^+$ T-cells expressing CD40L and/or IL-2 and/or TNF-α and/or IFN-γ, as determined by ICS and analyzed by FlowJo software or equivalent.

  – Antibody concentrations and seropositivity rates to p17, p24, Nef, RT and F4co as measured by Enzyme-Linked Immunosorbent Assay (ELISA).

Safety /reactogenicity

Primary endpoints:

- Occurrence, intensity and relationship to vaccination of solicited local and general symptoms during a 7-day (Day 0 to Day 6) follow up period after vaccination.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms until Day 29 Post-Vaccination.

  Criteria for assessment:

  – Occurrence, intensity and relationship to vaccination of unsolicited symptoms during 32 days (Day -2 to Day 29) follow up period after chloroquine administration for F4CQ group or 30 days (Day 0 to Day 29) follow up period after vaccination for F4 group.

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Criteria for evaluation (cont'd):

Safety /reactogenicity
Primary endpoints (cont'd):

- Occurrence and relationship to vaccination of serious adverse events (SAEs) during the whole study period.
- Occurrence and relationship to vaccination of adverse events (AEs) of specific interest, including Immune-Mediated Disorders (IMDs) during the whole study period.
- Haematological and biochemical levels at Days 0, 7, 30 and 180 (visits 1, 2, 4 and 5) in all subjects.

Statistical methods:

The following cohorts were evaluated:

- *Immunogenicity*:
  - ATP cohort for immunogenicity: *primary analysis*.
  - ATP cohort for immunogenicity for 10µg primed subjects only (ATP10 cohort).
  - ATP cohort for immunogenicity for 10µg primed subjects only - Pooled groups (ATP10P cohort).
- *Safety*:
  - Total Vaccinated cohort for safety: *primary analysis*.
  - Total Vaccinated cohort for safety for 10µg primed subjects only - Pooled groups.

Analysis of demographics
Demographic characteristics, cohort description and withdrawal status were summarised by group using descriptive statistics.

Analysis of immunogenicity
Cell-mediated immune response

Within group assessment
For each treatment group, at each blood sampling time point for which results were available, descriptive statistics of the following parameters were tabulated:

For the $CD8^+$ T-cell response:

- The responder rate was defined as the number of $CD8^+$ T-cell responders identified with frequencies of $CD8^+$ T-cells expressing at least 1 cytokine among IL-2, TNF-α and IFN-γ equal or above the cut-off to at least 1, 2, 3 antigens and to all 4 antigens and to each individual antigen. The cut-off values for the specific $CD8^+$ T-cell responses were obtained based on the pre-booster responses to the different antigens/ the peptide pool spanning the complete recombinant F4 antigen.
- The magnitude was defined as the frequency of p17, p24, Nef, RT and F4co*-specific $CD8^+$ T-cells expressing at least 1 cytokine among IL-2, TNF-α and IFN-γ.
- The cytokine/marker co-expression profile was defined as the frequency of p17, p24, Nef, RT and F4co*-specific $CD8^+$ T-cells expressing IL-2 and/or TNF-α and/or IFN-γ and/or CD40L, as determined by ICS and analysed by FlowJo software or equivalent.

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Statistical methods (cont'd):

For $CD4^+$ T-cell response:

- The responder rate was defined as the number of $CD4^+$ T-cell responders identified with the frequency $CD4^+$ T-cells expressing at least 2 cytokines including IL-2 equal or above the cut-off value to at least 1, 2, 3 and to all 4 antigens and to each individual antigen. The cut-off values for the specific $CD4^+$ T-cell responses were determined as 300 (positive $CD4^+$ T-cells per million $CD4^+$ T-cells) in the PRO-HIV-005 study.
- The magnitude was defined as the frequency of p17, p24, Nef, RT and F4co*-specific $CD4^+$ T-cells expressing at least 2 cytokines including IL-2.
- The cytokine/marker co-expression profile was defined as the frequency of p17, p24, Nef, RT and F4co*-specific $CD4^+$ T-cells expressing CD40L and/or IL-2 and/or TNF-α and/or IFN-γ, as determined by ICS and analysed by FlowJo software or equivalent.

* The frequency of $CD4^+/CD8^+$ T-cells expressing cytokines in response to the fusion protein F4co was determined by 2 different methods: by stimulating with a peptide pool spanning the F4 antigen, or by adding the individual frequencies of the $CD4^+/CD8^+$ T-cell response to each of the 4 individual antigens (p17, p24, Nef and RT).

Between group assessment

To evaluate the primary endpoint, the proportion of subjects considered as $CD8^+$ T-cell responders, with T-cells expressing at least 1 cytokine among IL-2, TNF-α and IFN-γ equal or above the cut-off to at least 1, 2, 3 antigens and to all 4 antigens was compared using a test for proportions. The 2 study groups were considered to be significantly different if the standardised asymptotic 95% confidence interval (CI) for the difference in rates between the groups did not contain the value '0'.

Humoral immune response

For humoral immune response, the following parameters were tabulated by vaccine groups for each antigen (p17, p24, Nef, RT and F4co) at each blood sampling time point for which antibody concentrations were available:

- GMCs with 95% CIs.
- Seropositivity rates with exact 95% CIs.

Analysis of safety

Overall incidence of AEs (solicited and unsolicited)

The percentage of subjects with at least 1 local AE, with at least 1 general AE and with any AE during the solicited follow-up period (Day 0 to Day 6) was tabulated with exact 95% CI. The same tabulation was done for AEs related to vaccination, grade 3 symptoms and grade 3 symptoms related to vaccination.

Solicited symptoms

The number and percentage of subjects reporting each individual solicited local (any, grade 3) and general (any, grade 3, related, grade 3 and related) AEs during the solicited follow-up period was tabulated with exact 95% CI. The number and percentage of subjects reporting solicited AEs was also presented by duration (≤ 2 days or >2 days). For fever, maximum temperatures were also summarized in 0.5°C increments.

The number of days with solicited AEs (any), solicited general AEs with relationship to vaccination, grade 3 solicited AEs and of grade 3 solicited general AEs with relationship to vaccination during the solicited follow-up period was also presented.

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Statistical methods (cont'd):

Unsolicited symptoms

The proportion of subjects with at least 1 report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 30 days after vaccination was tabulated with exact 95% CI. The same tabulations were done for unsolicited AEs with relationship to vaccination, for unsolicited grade 3 AEs and for unsolicited grade 3 AE related to vaccination.

SAEs

SAEs and withdrawal due to AEs were to be described in detail.

AEs of specific interest

Occurrence and relationship to vaccination of AEs of specific interest, including IMDs, were to be described in detail.

Haematological and biochemical parameters

The frequency distribution of values below, within and above normal ranges was tabulated per treatment group at each scheduled time point. In addition, change from baseline was also tabulated.

Concomitant medication

The number and percentage of subjects with concomitant medication(s), with antipyretics, with antibiotics and with immunosuppressant within 30 days post-vaccination was tabulated with exact 95% CI. Concomitant medications were classified in antipyretics, antibiotics and immunosuppressant according to the World Health Organisation (WHO) drug dictionary.

Ophthalmologic examinations

An ophthalmologic examination including a slit lamp examination was performed at the Screening Visit and at the concluding visit (Visit 5). The information recorded in the ocular assessment form also contained the results of the ophthalmologic examination which consisted of visual acuity, reflexes, motility, intraocular pressure, Slit Lamp and fundus examination. All ophthalmologic results were tabulated for right and left eyes together, *e.g.* the type of examination was done and recorded at any eye.

Summary:

Demography:

ATP cohort for immunogenicity

The mean age at vaccination was 24.4 years (25.1 years in the group F4CQ and 23.9 years in the group F4). The majority of subjects were female (53.8% in the group F4CQ and 64.3% in the group F4). The population was predominantly White-Caucasian (100% in the group F4CQ and 85.7% in the group F4).

Total Vaccinated cohort

The mean age at vaccination was 24.6 years (25.1 years in the group F4CQ and 24.3 years in the group F4). The majority of subjects were female (53.8% in the group F4CQ and 66.7% in the group F4). The population was predominantly White-Caucasian (100% in the group F4CQ and 86.7% in the group F4).

Co-primary objectives:

Immunogenicity

Cellular immune response: $CD8^+$ T-cell response

Responder rate

Synopsis Table 2 relates to the primary immunogenicity objective. The data are not supportive of a difference in $CD8^+$ T-cell responder rate between the group F4CQ and the group F4. Please note that the planned number of 20 evaluable subjects/ group was not reached and there were only 13 evaluable subjects/ group.

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Summary (cont'd):

Synopsis Table 2: Difference between groups in percentage of responders to at least 1, 2, 3 and all 4 antigens: $CD8^+$ T-cells expressing at least 1 cytokine amongst IL-2, TNF-α and IFN-γ (ATP cohort for immunogenicity)

								Difference in percentage (F4CQ minus F4)		
		F4CQ			F4				95% CI	
Number of antigens	Timing	N	n	%	N	n	%	%	LL	UL
At least 1 antigen	PIII(D14)	13	1	7.69	13	3	23.08	-15.4	-45.1	15.39
At least 2 antigens	PIII(D14)	13	0	0.00	13	0	0.00	0.00	-23.5	23.51
At least 3 antigens	PIII(D14)	13	0	0.00	13	0	0.00	0.00	-23.5	23.51
All 4 antigens	PIII(D14)	13	0	0.00	13	0	0.00	0.00	-23.5	23.51

F4CQ = $F4co/AS01_B$ + chloroquine; F4 = $F4co/AS01_B$
N=number of subject with available results; n/%=number/percentage of responders
95%CI=standardised asymptotic 95% confidence interval, LL=Lower Limit, UL=Upper Limit
PIII(D14)=Day 14 Post Dose 3

Safety

Overall incidence of AEs (solicited and unsolicited)

All of the subjects in the group F4CQ and 93.3% (*i.e.* 14 out of 15 subjects) of the subjects in the group F4 reported at least 1 AE. 38.5% (*i.e.* 5 out of 13 subjects) of the subjects in the group F4CQ and 40% (*i.e.* 6 out of 15 subjects) of the subjects in the group F4 reported at least 1 grade 3 symptom considered by the investigator to be related to vaccination.

Solicited local AEs

Pain was the most frequent solicited local AE in both groups.
Grade 3 pain (in 7.7% or in 1 out of 13 of the subjects in the group F4CQ and in 13.3% or in 2 out of 15 subjects in the group F4), redness (in none of the subjects in the group F4CQ and in 6.7% or in 1 out of 15 subjects in the group F4) or swelling (in none of the subjects in the group F4CQ and in 13.3% or in 2 out of 13 subjects in the group F4) were reported for a maximum duration of 2 days.

Solicited general AEs

Fatigue and headache were the 2 most frequently reported solicited general AEs in both groups.
There was a trend for higher temperature in the group F4 with 40% (*i.e.* 6 out of 15 subjects) of the subjects in the group F4 showing a fever > 38.5°C within the 2 days after vaccination compared to 7.7% (*i.e.* 1 out of 13 subjects) of the subjects in the group F4CQ. This might reflect the chloroquine use in the latter group.
Grade 3 fatigue (in 23.1% or in 3 out of 13 subjects in the group F4CQ and in 20% or in 3 out of 15 subjects in the group F4), headache (in 23.1% or in 3 out of 13 subjects in the group F4CQ and in none of the subjects in the group F4), gastrointestinal symptoms (in 7.7% or in 1 out of 13 subjects in the group F4CQ and in none of the subjects in the group F4) or fever (in none of the subjects in the group F4CQ and in 6.7% or in 1 out of 15 subjects in the group F4) were reported with a maximum duration of 1 day.

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Summary (cont'd):

Unsolicited AEs

The unsolicited symptoms reported in 2 or more subjects in at least 1 of the groups were myalgia, influenza like illness, chills and headache.

Grade 3 unsolicited AEs were reported by 23.1% (*i.e.* 3 out of 13 subjects) of the subjects in the group F4CQ and by 13.3% (*i.e.* 2 out of 15 subjects) of the subjects in the group F4. Out of these cases, 4 cases were considered by the investigator to be causally related to vaccination: 1 case of influenza like illness and 1 case of myalgia in the group F4CQ and 1 case of chills and 1 case of insomnia in the group F4. All of the grade 3 unsolicited AEs were resolved without sequelae.

IMDs

No IMDs were reported.

SAEs and AEs leading to withdrawal

No subjects died, experienced an SAE, or withdrew due to an AE.

Pregnancies

There were no pregnancies reported.

Clinical laboratory evaluations

No clinically relevant changes from baseline in haematology or biochemistry parameters could be observed in any of the groups at any of the timepoints.

Ophthalmological examinations

None of the ophthalmologic observations was considered to be clinically relevant.

Secondary objective

Cellular immune response: $CD8^+$ T-cell response

Responder rate

In both groups, the specific $CD8^+$ T-cell responder rate was low. In the group F4CQ, 23.1% (*i.e.* 3 out of 13 subjects) responded to at least 1 antigen before administration of the booster dose, while there was 1 responder to at least 1 antigen, or no responders at all (30 days post-booster) at the post-booster timepoints. In the group F4, 21.4% (*i.e.* 3 out of 14 subjects) responded to at least 1 antigen before administration of the booster dose. In this group, 23.1% (*i.e.* 3 out of 13 subjects) responded to at least 1 antigen at Day 7 and Day 14 post-booster dose, while 1 subject responded at Day 30 and no subjects responded at Day 180 post-booster dose. None of the subjects in both groups responded to at least 3, or to all antigens at any of the post-booster timepoints.

Magnitude

In both groups, at all timepoints (pre- and post-booster dose), the median numbers of specific $CD8^+$ T-cells stayed below the pre-determined cut-off values.

Co-expression profile

No significant levels of polyfunctional $CD8^+$ T-cells could be detected before or after administration of the booster dose in both study groups.

Cellular immune response: $CD4^+$ T-cell response

Responder rate

In both groups, the specific $CD4^+$ T-cell responder rate was high. Before administration of the booster dose, 92.3% (*i.e.* 12 out of 13 subjects) of the subjects in the group F4CQ and 78.6% (*i.e.* 11 out of 14 subjects) of the subjects in the group F4 subjects responded to at least 1 antigen. At all post-booster timepoints, 63.6% to 83.3% of the subjects in the group F4CQ and 64.3% to 76.9% of the subjects in the group F4 responded to at least 3 antigens.

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Summary (cont'd)

Magnitude

In both groups, the median numbers of specific $CD4^+$ T-cells were above the pre-determined cut-off value before administration of the booster dose when stimulated with RT, p24 and with the peptide pool spanning the F4 antigen, and below the pre-determined cut-off value when stimulated with Nef and p17. In both groups, at all post-booster timepoints and for all stimulating antigens, an increase in the median numbers of specific $CD4^+$ T-cells could be observed, with a peak around Day 7- Day 14.

Co-expression profile

In both groups, polyfunctional $CD4^+$ T-cells were detected before administration of the booster dose and an increase in polyfunctional $CD4^+$ T-cells could be observed after booster dose vaccination with a peak around Day 7- Day 14 post-booster dose.

Humoral immune response

F4co fusion protein

All subjects in both groups were still seropositive for F4co fusion protein antibodies before administration of the booster dose and remained seropositive at all post-booster timepoints. In both groups, the booster dose elicited a robust increase in anti-F4co IgG antibodies with concentrations well above those observed after the primary vaccination course (PRO-HIV-005 study).

p17

None of the subjects in the group F4CQ and 1 of the subjects in the group F4 were seropositive for p17 antibodies before administration of the booster dose. In the group F4CQ, all subjects were seropositive for p17 from the Day 14 timepoint onwards. In the group F4, 78.6% (*i.e.* 11 out of 14 subjects) were seropositive at Day 14, and 57.1% (*i.e.* 8 out of 14 subjects) were seropositive at Day 180. In both groups, the booster dose elicited a robust increase in anti-p17 IgG antibodies with concentrations well above those observed after the primary vaccination course (PRO-HIV-005 study).

p24

All subjects in the group F4CQ and 85.7% (*i.e.* 12 out of 14 subjects) of the subjects in the group F4 were still seropositive for p24 antibodies before administration of the booster dose, and all subjects in both groups were seropositive for p24 as of the Day 7 timepoint. In both groups, the booster dose elicited a robust increase in anti-p24 IgG antibodies with concentrations well above those observed after the primary vaccination course (PRO-HIV-005 study).

Nef

76.9% (*i.e.* 10 out of 13 subjects) of the subjects in the group F4CQ and 78.6% (*i.e.* 11 out of 14 subjects) of the subjects in the group F4 were still seropositive for Nef antibodies before administration of the booster dose. All subjects in both groups were seropositive for Nef antibodies at all subsequent timepoints. In both groups, the booster dose elicited a robust increase in anti-Nef IgG antibodies with concentrations well above those observed after the primary vaccination course (PRO-HIV-005 study).

RT

61.5% (*i.e.* 8 out of 13 subjects) of the subjects in the group F4CQ and 64.3% (*i.e.* 9 out of 14 subjects) of the subjects in the group F4 were still seropositive for RT before administration of the booster dose. All subjects in both groups were seropositive for RT antibodies at all subsequent timepoints. In both groups, the booster dose elicited a robust increase in anti-RT IgG antibodies with concentrations well above those observed after the primary vaccination course (PRO-HIV-005 study).

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Summary (cont'd)

Immunogenicity additional exploratory analyses

Additional exploratory tables were generated to compare the magnitude of the specific $CD4^+$ T-cell response at pre-vaccination, post-dose 2, pre-booster and at post-booster timepoints. The booster dose vaccination induced a median frequency of specific $CD4^+$ T-cells with a peak around Day 7- Day 14 post-vaccination and with a magnitude that was comparable to the magnitude of the specific $CD4^+$ T-cell response after the primary vaccination course.

Overall Conclusions:

The study results are not supportive of a chloroquine effect on the specific $CD8^+$ T-cell response, on the specific $CD4^+$ T-cell response, or on the humoral immune response following administration of $F4co/AS01_B$ investigational vaccine.

The observed boostability of both the humoral immune response and the specific $CD4^+$ T-cells response to the $F4co/AS01_B$ investigational vaccine are supportive of the induction of a long lasting memory B-cell and memory $CD4^+$ T-cell response after the primary vaccination course.

The study results are supportive of an acceptable safety profile of the $F4co/AS01_B$ investigational vaccine with or without administration of chloroquine 2 days prior vaccination in the evaluated population.

Date of report: 05 July 2011

SYNOPSIS

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Study Numbers:

108706 (PRO HIV-005) and 113165 (EARLY-CLINRES-004)

Rationale for the annex report:

In this annex report, the results of additional exploratory laboratory assays which were not planned in the study protocols are presented. The aim of these analyses was to characterise more in detail the specific $CD4^+$ and $CD8^+$ T-cell responses to the F4co/$AS01_B$ candidate vaccine. More specifically, antigen-specific $CD4^+$ and $CD8^+$ T-cell proliferation was assessed by means of a 5,6-carboxyfluorescein diacetate succinimidyl ester (CFSE) lymphoproliferation assay, and the ability of proliferating $CD4^+$/$CD8^+$ T-cells to produce F4 antigen-specific cytokines was assessed by means of intracellular cytokine staining (ICS). Available blood samples from subjects who participated both in the study PRO HIV-005 (108706) and in the booster study EARLY-CLINRES-004 (113165) were used for the additional testing.

Titles of the studies:

PRO HIV-005 (108706): A phase I-II partially-blinded, randomised, dose- ranging study (10-30-90 µg) to compare the safety and immunogenicity of GSK Biologicals' candidate HIV vaccine F4co (p24-RT-Nef-p17), adjuvanted or not with $AS01_B$, administered intramuscularly according to a vaccination schedule of 0, 1 months to healthy adult HIV seronegative volunteers, aged 18 to 40 years.

EARLY-CLINRES-004 (113165): A phase II, open, single centre, exploratory study to evaluate the safety and immunogenicity of one booster dose of GSK Biologicals' HIV candidate vaccine (732461), administered intramuscularly, in conjunction with the administration of a single oral dose of chloroquine in healthy adults.

Principal investigator:

Prof. Dr. [redacted]

Study Centre:

[redacted]
Belgium

Publications (references):

PRO HIV-005 (108706):
Van Braeckel E, Bourguignon P, Koutsoukos M, *et al*. An adjuvanted polyprotein HIV-1 vaccine induces polyfunctional cross-reactive $CD4^+$ T cell responses in seronegative volunteers. *Clin Infect Dis.* 2011; 52: 522-31.

Van Braeckel E, Koutsoukos M, Bourguignon P, *et al*. Vaccine-induced HIV seropositivity: a problem on the rise. *J Clin Virol.* 2011; 50: 334-7.

EARLY-CLINRES-004 (113165):
Not published as of 12 March 2013.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)
Study periods: *PRO HIV-005 (108706):* **Study initiation date:** 20 February 2007 **Study completion date:** 13 June 2008 *EARLY-CLINRES-004 (113165):* **Study initiation date:** 07 December 2009 **Study completion date:** 04 October 2010 **Data lock point (Date of database freeze):** 23 October 2012		**Phase: I-II**
Indication: Immunisation against HIV in healthy HIV seronegative adults aged between 18-40 years old at first vaccination.		
Treatments: *PRO-HIV-005 (108706):* All subjects with blood samples analysed in this additional exploratory analysis received 2 doses of the F4co/ $AS01_B$ candidate vaccine (10µg or 30µg of F4 antigen/ vaccine dose), according to a 0, 1 month vaccination schedule. *EARLY-CLINRES-004 (113165):* All subjects received 1 booster dose of the F4co/ $AS01_B$ candidate vaccine (10µg of F4 antigen/ vaccine dose), approximately 3 years after vaccination in the study PRO HIV-005 (108706). This study included 2 groups: • Subjects in the group **F4CQ** received a single oral dose of chloroquine (300 mg), 2 days before the booster vaccine dose. • Subjects in the group **F4** only received the booster vaccine dose.		
Objectives: Refer to GlaxoSmithKline (GSK) Biologicals' Clinical Study Reports for the studies PRO HIV-005 (108706) and EARLY-CLINRES-004 (113165) for the objectives of the studies as per protocol. The objective of this additional exploratory analysis was to characterise the antigen-specific $CD4^+$ and $CD8^+$ T-cell responses to the F4co/$AS01_B$ candidate vaccine.		
108706 (PRO HIV-005) and 113165 (EARLY-CLINRES-004) Annex Report Synopsis page 2 of 11		

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Study designs:

The study *PRO HIV-005 (108706)* was a single-centre, dose-escalating, staggered, parallel-group study evaluating the safety and immunogenicity of several formulations of the F4co candidate vaccine, when administered according to a 0, 1 month schedule.

The study *EARLY-CLINRES-004 (113165)* was an open, randomised study with 2 parallel treatment groups evaluating the immunogenicity of a booster dose of the F4co candidate vaccine after administration of chloroquine. The subjects in the study EARLY-CLINRES-004 (113165) were recruited amongst the $CD4^+$ T-cell responders who participated in the study PRO-HIV-005 (108706) and who received 2 doses of the 10 µg or the 30 µg formulation of the F4co/ $AS01_B$ candidate vaccine in that study.

For the additional exploratory analysis described in this annex report, available blood samples from subjects who participated both in the study PRO HIV-005 (108706) and in the study EARLY-CLINRES-004 (113165) were used. The following timepoints were analysed:

- Study *PRO HIV-005 (108706)*: Day 0 (Pre Dose 1), Day 44 (Post Dose 2 Day 44) and Day 360 (Post Dose 2 Day 360).
- Study *EARLY-CLINRES-004 (113165)*: Day 0 (Pre Dose 3), Day 14 (Day 14 Post Dose 3) and Day 180 (Day 180 Post Dose 3).

Study vaccines, doses, mode of administration, lot no.:

Vaccination schedule/ doses /site

PRO HIV-005 (108706)

The subjects with blood samples analysed in this additional exploratory analysis received either the 10 µg or the 30 µg formulation of the F4co/ $AS01_B$ candidate vaccine as an intramuscular injection in the deltoid muscle of (preferably) the non-dominant arm at Day 0 and Day 30.

EARLY-CLINRES-004 (113165)

The subjects received 1 booster dose of the F4co/ $AS01_B$ candidate vaccine as an intramuscular injection in the deltoid muscle of (preferably) the non-dominant arm at Day 0.

Composition of vaccines /lot numbers

Refer to GSK Biologicals' Clinical Study Reports for the studies PRO HIV-005 (108706) and EARLY-CLINRES-004 (113165) for details on the composition of the vaccines and the lot numbers.

Reference vaccine/ Comparator, dose, mode of administration, lot no.:

PRO HIV-005 (108706):

No reference vaccine or comparator was used in the study PRO HIV-005 (108706). Refer to GSK Biologicals' Clinical Study Report for the study PRO HIV-005 (108706) for the description of the other F4co candidate vaccine formulations tested in this study.

EARLY-CLINRES-004 (*113165):*

No reference vaccine or comparator was used in the study EARLY-CLINRES-004 (113165). See below for a description of the study product administered in this study.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Study product, dose, mode of administration, lot no.:

EARLY-CLINRES-004(113165):

Dosage and administration

At Day -2, subjects in the group F4CQ received 300 mg of chloroquine, orally (*i.e.* 3 tablets of *Nivaquine* [Sanofi-Aventis, France]).

Product dose/ composition/ lot number

Please refer to the patient leaflet for a description of *Nivaquine*.
The *Nivaquine* lot number was 638.

Study Population:

Available blood samples of subjects who participated both in the study PRO HIV-005 (108706) and in the study EARLY-CLINRES-004 (113165) were used for this additional exploratory analysis. The subjects in the study EARLY-CLINRES-004 (113165) were recruited amongst the $CD4^+$ T-cell responders who participated in the study PRO-HIV-005 (108706) and who received 2 doses of the 10 µg or the 30 µg formulation of the F4co/ $AS01_B$ candidate vaccine in that study. In addition, subjects had to be negative for anti-Hepatitis B core and anti-Hepatitis C Virus antibodies, should not have ophthalmologic findings at screening (namely maculopathy, retinopathy, corneal opacities and cataracts) and had to be willing to accept HIV test results.

Duration of treatment:

PRO HIV-005 (108706):
The duration of the study was approximately 14 months for each subject.

EARLY-CLINRES-004 (113165):
The duration of the study was approximately 6 months for each subject.

Outcome/Efficacy Variables:

Refer to GSK Biologicals' Clinical Study Reports for the studies PRO HIV-005 (108706) and EARLY-CLINRES-004 (113165) for the complete lists of endpoints for these studies as per protocol.

The endpoints of this additional exploratory analysis were:

- Frequency (expressed as stimulation index) of F4-specific $CFSE^{low}$ $CD4^+$ T-cells, as measured by a CFSE lymphoproliferation assay.
- Frequency of F4-specific $CFSE^{low}$ $CD4^+$ T-cells expressing at least IL-2, at least TNF-α, at least IFN-γ and at least one cytokine (IL-2 and/ or TNF-α and/ or IFN-γ), as measured by ICS.
- Frequency (expressed as stimulation index) of F4-specific $CFSE^{low}$ $CD8^+$ T-cells, as measured by a CFSE lymphoproliferation assay.
- Frequency of F4-specific $CFSE^{low}$ $CD8^+$ T-cells expressing at least IL-2, at least TNF-α, at least IFN-γ and at least one cytokine (IL-2 and/ or TNF-α and/ or IFN-γ), as measured by ICS.

All endpoints were assessed at the following timepoints:

- Study *PRO HIV-005 (108706)*: Day 0 (pre Dose 1), Day 44 (Post Dose 2 Day 44) and Day 360 (Post Dose 2 Day 360).
- Study *EARLY-CLINRES-004 (113165)*: Day 0 (Pre Dose 3), Day 14 (Day 14 Post Dose 3) and Day 180 (Day 180 Post Dose 3).

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Laboratory assays:

CFSE lymphoproliferation assay

Peripheral Blood Mononuclear Cells (PBMCs) were labelled with the fluorescent dye CFSE and cultured for 5 days in medium containing a pool of peptides covering the sequence of F4 antigen, or in medium alone (F4 or MED, respectively). After 5 days of culture, all cells were re-stimulated in medium:

- not containing peptides (MED/ MED or F4/MED), or
- containing irrelevant peptides (F4/TRAP), or
- containing a pool of peptides covering the sequence of the F4 antigen (F4/F4).

Cells that proliferated showed a reduction in CFSE fluorescence intensity ($CFSE^{low}$ T-cells).

Intracellular cytokine staining (ICS)

Flow cytometry using ICS was performed to provide information on the type of cytokines produced by $CFSE^{low}$ T-cells.

Statistical methods:

All analyses were exploratory.

The analyses were performed on the according-to-protocol (ATP) cohort for immunogenicity. Refer to GSK Biologicals' Clinical Study Reports for the studies PRO HIV-005 (108706) and EARLY-CLINRES-004 (113165) for the definition of the ATP cohort for immunogenicity.

The analyses are presented both for the pooled groups (group Pooled) and per EARLY-CLINRES-004 (113165) study group (groups F4CQ and F4). As the study results of the study EARLY-CLINREs-004 (113165) were not supportive of a chloroquine effect on the specific $CD4^+$ or $CD8^+$ T-cell response, the Pooled group results are presented in the synopsis of this annex report.

CFSE lymphoproliferation assay

The lymphoproliferation results were expressed as stimulation index of the F4-specific $CFSE^{low}$ $CD4^+/CD8^+$ T-cells. This value was obtained by dividing the geometric mean (GM) of the percentage of F4-specific $CFSE^{low}$ $CD4^+/CD8^+$ T-cells among all $CD4^+/CD8^+$ T-cells (*i.e.* GM of the F4-stimulated results: F4/MED, F4/TRAP and F4/F4) by the GM of the background results (MED/MED).

At each blood sampling timepoint for which results were available, descriptive statistics (GM, number of subjects with available results [N], minimum, first quartile [Q1], median, third quartile [Q3], maximum) of the following parameters was tabulated overall (group Pooled) and by group (group F4CQ and group F4):

- Stimulation index of F4-specific $CFSE^{low}$ $CD4^+/CD8^+$ T-cells, by flow cytometry using CFSE.

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Statistical methods (cont'd):

Intracellular cytokine staining (ICS)

The ICS results were expressed as the percentage of $CFSE^{low}$ F4-specific $CD4^+/CD8^+$ T-cells expressing:

- at least IL-2
- at least TNF-α
- at least IFN-γ
- at least one cytokine (IL-2 and/ or TNF-α and/ or IFN-γ).

This value was obtained by calculating the difference between the response to stimulation with medium containing a pool of peptides covering the sequence of the F4 antigen (F4) and the response to stimulation with medium that did not contain peptides (MED) (*i.e.* F4/F4 minus F4/MED). As a control, the difference between the response to stimulation with medium containing irrelevant peptides (TRAP) and the response to stimulation with medium that did not contain peptides (MED) was used (*i.e.* F4/TRAP minus F4/MED). Resulting differences less than or equal to zero were set to 0.0001% for the purpose of GM calculation and graphical representation.

At each blood sampling timepoint for which results were available, descriptive statistics (GM, N, minimum, Q1, median, Q3, maximum) of the following parameters were tabulated overall (group Pooled) and by group (group F4CQ and group F4):

- Frequency of TRAP-specific (Irrelevant peptides) $CD4^+/CD8^+$ $CFSE^{low}$ T-cells expressing at least IL-2, at least TNF-α, at least IFN-γ and at least one cytokine (IL-2 and/ or TNF-α and/ or IFN-γ), by ICS.
- Frequency of F4-specific CD4+/CD8+ $CFSE^{low}$ T-cells expressing at least IL-2, at least TNF-α, at least IFN-γ and at least one cytokine (IL-2 and/ or TNF-α and/ or IFN-γ), by ICS.

Summary:

Distribution of subjects

Synopsis Table 1: Distribution of subjects with at least one result according to 10µg or 30 µg dosage group for F4co/ $AS01_B$ used in the primary study PRO HIV-005 (108706), for each timepoint and overall (ATP cohort for immunogenicity)

	Timepoint	PRE		PII(D44)		PII(D360)		PREIII		PIII(D14)		PIII(D180)		Overall	
	Study group in EARLY-CLINRES-004	F4CQ	F4	F4CQ	F4	F4CQ	F4	F4CQ	F4	F4CQ	F4	F4CQ	F4	F4CQ	F4
Study group in PRO HIV-005	10 µg	0	0	0	0	0	0	3	1	5	3	5	4	5	4
	30 µg	8	8	8	7	8	8	7	7	6	8	8	9	8	9

F4CQ = F4Co/$AS01_B$ + chloroquine; F4 = F4Co/$AS01_B$
Overall: Subjects who have contributed to at least one timepoint are counted
PRE = Pre Dose 1; PII(D44) = Post Dose 2 Day 44; PII(D360) = Post Dose 2 Day 360; PREIII = Pre Dose 3; PIII(D14) = Day 14 Post Dose 3; PIII(D180) = Day 180 Post Dose 3

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Summary (cont'd):

Stimulation index of F4-specific CFSE^{low} CD4^{+} T-cells

Synopsis Figure 1 shows a boxplot view of the stimulation index of F4-specific $CFSE^{low}$ $CD4^{+}$ T-cells at the different timepoints analysed.

Synopsis Figure 1: Individual results of the stimulation index of F4-specific $CD4^{+}$ $CFSE^{low}$ T-cells, by CFSE lymphoproliferation (ATP cohort for immunogenicity, Pooled groups)

Pooled = F4CQ and F4 Pooled groups
PRE = Pre Dose 1; PII(D44) = Post Dose 2 Day 44; PII(D360) = Post Dose 2 Day 360; PREIII = Pre Dose 3; PIII(D14) = Day 14 Post Dose 3; PIII(D180) = Day 180 Post Dose 3

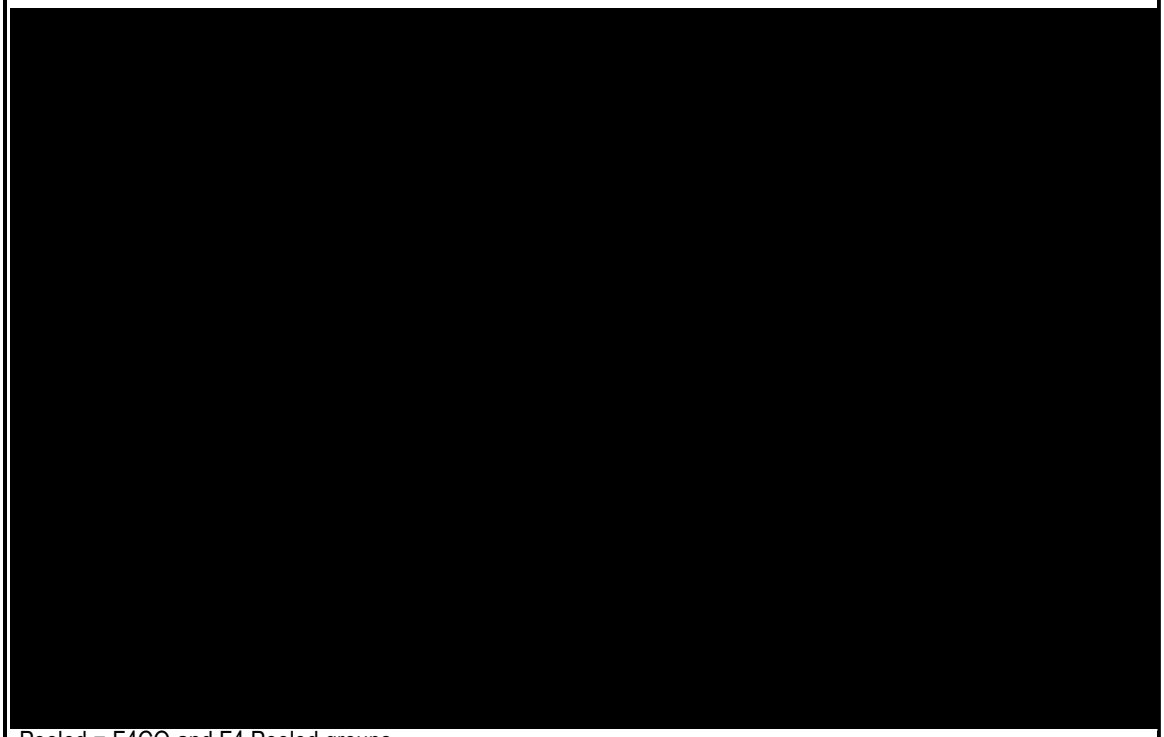
Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Summary (cont'd):

Stimulation index of F4-specific $CFSE^{low}$ $CD8^+$ T-cells

Synopsis Figure 2 shows a boxplot view of the frequency of F4-specific $CFSE^{low}$ $CD8^+$ T-cells at the different timepoints analysed.

Synopsis Figure 2: Individual results of the stimulation index of F4-specific $CD8^+$ $CFSE^{low}$ T-cells, by CFSE lymphoproliferation (ATP cohort for immunogenicity, Pooled groups)



Pooled = F4CQ and F4 Pooled groups
PRE = Pre Dose 1; PII(D44) = Post Dose 2 Day 44; PII(D360) = Post Dose 2 Day 360; PREIII = Pre Dose 3; PIII(D14) = Day 14 Post Dose 3; PIII(D180) = Day 180 Post Dose 3

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Summary (cont'd):

Frequency of F4-specific CFSE^{low} CD4^{+} T-cells expressing cytokines

Synopsis Figure 3 shows a boxplot view of the percentage of F4-specific $CFSE^{low}$ $CD4^{+}$ T-cells expressing at least one cytokine (IL-2 and/ or TNF-α and/ or IFN-γ) at the different timepoints analysed.

Synopsis Figure 3: Individual results of the frequency of Trap- and F4-specific CD4^{+} CFSE^{low} T-cells expressing at least one cytokine (IL2 and/ or TNFa and/ or IFNg) (in %), by ICS (ATP cohort for immunogenicity, Pooled groups)

[redacted]

Pooled = F4CQ and F4 Pooled groups
* = expressing at least one cytokine (IL2 and/ or TNFa and/ or IFNg)
PRE = Pre Dose 1; PII(D44) = Post Dose 2 Day 44; PII(D360) = Post Dose 2 Day 360; PREIII = Pre Dose 3; PIII(D14) = Day 14 Post Dose 3; PIII(D180) = Day 180 Post Dose 3

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Summary (cont'd):

Frequency of F4-specific CFSE^{low} CD8^{+} T-cells expressing cytokines

Synopsis Figure 4 shows a boxplot view of the percentage of F4-specific $CFSE^{low}$ $CD8^{+}$ T-cells expressing at least one cytokine (IL-2 and/ or TNF-α and/ or IFN-γ) at the different timepoints analysed.

Synopsis Figure 4: Individual results of the frequency of Trap- and F4-specific $CD8^{+}$ $CFSE^{low}$ T-cells expressing at least one cytokine (IL2 and/ or TNFa and/ or IFNg) (in %), by ICS (ATP cohort for immunogenicity, Pooled groups)

Pooled = F4CQ and F4 Pooled groups
* = expressing at least one cytokine (IL2 and/ or TNFa and/ or IFNg)
PRE = Pre Dose 1; PII(D44) = Post Dose 2 Day 44; PII(D360) = Post Dose 2 Day 360; PREIII = Pre Dose 3; PIII(D14) = Day 14 Post Dose 3; PIII(D180) = Day 180 Post Dose 3

Conclusions:

Refer to GSK Biologicals' Clinical Study Reports for the studies PRO HIV-005 (108706) and EARLY-CLINRES-004 (113165) for the main conclusions of both studies.

In the absence of pre-specified criteria, no formal conclusions can be drawn from this additional exploratory analysis.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** F4co (p24-RT-Nef-p17), $AS01_B$	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

References:

GSK Biologicals' Clinical Study Report 108706 (PRO HIV-005): A phase I-II partially-blinded, randomised, dose- ranging study (10-30-90 µg) to compare the safety and immunogenicity of GSK Biologicals' candidate HIV vaccine F4co (p24-RT-Nef-p17), adjuvanted or not with $AS01_B$, administered intramuscularly according to a vaccination schedule of 0, 1 months to healthy adult HIV seronegative volunteers, aged 18 to 40 years.

GSK Biologicals' Clinical Study Report 113165 (EARLY-CLINRES-004): A phase II, open, single centre, exploratory study to evaluate the safety and immunogenicity of one booster dose of GSK Biologicals' HIV candidate vaccine (732461), administered intramuscularly, in conjunction with the administration of a single oral dose of chloroquine in healthy adults.

Date of report: Final: 12 March 2013

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