The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 111149 (HAB-160 BST), 111572 (HAB-168 BST 160)

Title: A phase IV, open, multicentre, multicountry study to evaluate the immune response to a challenge dose of GSK Biologicals' *Twinrix*™ vaccine versus monovalent hepatitis A and B vaccines from different manufacturers in healthy and non-healthy adults aged > 41 years, approximately 48 months after primary vaccination in study 100382 (HAB-160).
Twinrix™ (HAB): GlaxoSmithKline (GSK) Biologicals' combined hepatitis A and hepatitis B vaccine.

Rationale: The aim of the study was to assess the immune response to a challenge dose of HAB vaccine versus monovalent hepatitis A and hepatitis B vaccines, *Engerix*™-B and *Havrix*™ as well as HB VAX PRO™ and *Vaqta*™, in subjects who had received the same vaccines in the primary study, HAB-160 (100382), 4 years ago.
Engerix™-B (HBV): GSK Biologicals' recombinant hepatitis B vaccine.
Havrix™ (HAV): GSK Biologicals' inactivated hepatitis A vaccine.
HB VAX PRO™ (HBVc): Sanofi Pasteur MSD's recombinant hepatitis B vaccine.
Vaqta™ (HAVc): Sanofi Pasteur MSD's inactivated hepatitis A vaccine.
Please refer to the CTRS on HAB-160 EXT Y1&Y2&Y3 for the results of primary study and follow-up.

Phase: IV

Study Period:
HAB-160 BST (111149): 14 January 2008 to 03 June 2008.
HAB-168 BST 160 (111572): 26 May 2008 to 03 November 2008.

Study Design: Open, multicentre, multi-country study with 3 parallel groups.

Centers: 9 study centers: 7 centers in Germany, 1 centre in Belgium and 1 centre in Czech Republic.

Indication: Vaccination against hepatitis A and hepatitis B diseases.

Treatment: The study groups were as follows:

- HAB Group: received a single challenge dose of combined HAB (720/20) vaccine.
- HBV + HAV Group: received separate administration of a single challenge dose of HBV (20 μg) vaccine and HAV (1440 EL.U) vaccine.
- HBVc + HAVc Group: received separate administration of a single challenge dose of HBVc (10 μg) vaccine and HAVc (50 IU) vaccine.

All vaccines were administered intramuscularly, HAB, HBV and HBVc vaccines in the left deltoid region and HAV and HAVc in the right deltoid region.

Objectives:
To evaluate the anti-HAV and anti-HBs immune memory (in terms of anti-HAV and anti-HBs immune response elicited by the challenge dose) in a population > 41 years of age (healthy and non-healthy), approximately 48 months after the first dose of the primary vaccination course.

Primary Outcome/Efficacy Variable:

- Anti-HAV anamnestic response to the challenge dose is defined as:
  - Anti-HAV antibody concentrations ≥ 15 mIU/mL at one month post-challenge dose in subjects seronegative at the pre-challenge time point.
  - At least a 2-fold increase in anti-HAV antibody concentration one month after the challenge dose, in subjects having anti-HAV antibody concentration ≥ 100 mIU/mL at the pre-challenge time point.
  - Or at least a 4-fold increase in anti-HAV antibody concentrations one month after the challenge dose, in seropositive subjects having anti-HAV antibody concentration < 100 mIU/mL at the pre-challenge time point.
- Anti-HBs anamnestic response to the challenge dose is defined as
  - Anti-HBs antibody concentration ≥ 10 mIU/mL, one month post-challenge dose in subjects seronegative at the pre-challenge time point.
  - At least a 4-fold increase in anti-HBs antibody concentration, one month post-challenge dose in subjects seropositive at the pre-challenge time point.

Secondary Outcome/Efficacy Variable(s):
Immunogenicity

- Anti-HAV seropositivity rates* and Geometric Mean Concentrations (GMCs), as well as anti-HBs seropositivity rates, seroprotection rates** and GMCs at Month 48.
- Percentage of subjects with anti-HAV antibody titers ≥ 15 mIU/mL and GMCs calculated on seropositive subjects,

two weeks and one month after the challenge dose.

- Percentage of subjects with anti-HBs antibody concentrations ≥ 3.3 mIU/mL, ≥ 10 mIU/mL, ≥ 100 mIU/mL and anti-HBs GMCs calculated on seropositive subjects, two weeks and one month after the challenge dose.

* Seropositivity rate was defined as the percentage of subjects with antibody concentrations greater than or equal to the cut-off value.

** Seroprotection rate for anti-HBs was defined as the percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/mL.

Safety

- Occurrence and intensity of solicited local symptoms in the 4-day (Day 0 to 3) follow-up period after the challenge dose.
- Occurrence, intensity and relationship of solicited general symptoms in the 4-day (Day 0 to 3) follow-up period after the challenge dose.
- Retrospective recording of all serious adverse events (SAEs) with causal relationship to vaccination or referring to hepatitis A or B infection that occurred since the last study visit of the HAB-160 long-term follow-up study.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms reported during the 31-day (Day 0 to 30) follow-up period after the challenge dose.
- Occurrence of all SAEs reported following the administration of the challenge dose.

Statistical Methods:

The analyses were performed on the Total Vaccinated Cohort and on the ATP cohort for analysis of immunogenicity and the Long Term (LT) ATP cohort for analysis of immunogenicity.

- The LT ATP cohort for analysis of immunogenicity included subjects who returned at the Month 48 time point who were included in the primary ATP immunogenicity analysis, who did not receive hepatitis A or hepatitis B vaccine not specified in the study protocol and who were not eliminated for abnormal increase† in antibody concentrations during LT follow-up period.
- The Total Vaccinated cohort included all subjects who received the challenge dose and for whom immunogenicity data were available.
- The ATP cohort for analysis of immunogenicity included all evaluable subjects who met all eligibility criteria, complied with the procedures and intervals defined in the protocol, had no elimination criteria during the study, who had received the challenge dose and for whom immunogenicity data for at least one antigen were available at the post-challenge dose time point.

† The criteria of antibody (anti-HAV or anti-HBs) concentrations abnormal increase depended on the magnitude of antibody level reached at first time point (i.e. the reference value). The case of an abnormal antibody concentrations increase was defined as a two-fold increase or more in antibody concentrations (when the antibody concentrations at the reference time point was ≥ 100 mIU/mL) or a four-fold increase or more in antibody concentrations (when the antibody concentrations at the reference time point was < 100 mIU/mL).

Analysis of immunogenicity:

The analysis was performed on the ATP cohort for analysis of immunogenicity and LT ATP cohort for analysis of immunogenicity.

For each vaccine group, at each time point the serological result was available, the percentage of subjects with anti-HAV and ant-HBs response to the challenge dose with exact 95% CIs and their GMCs with 95% CI were tabulated. The seroprotection rate, seropositivity rate and GMCs for anti-HBs antibodies and the seropositivity rate and GMCs for anti-HAV antibodies were tabulated with 95% CIs. For GMCs calculation, antibody concentrations below the assay cut-off were assigned an arbitrary value of half the cut-off.

Analysis of safety:

The analysis was performed on the Total Vaccinated Cohort.

The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Days 0–3) solicited follow-up period was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 symptoms and for general symptoms with relationship to vaccination. The proportion of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms , and reported up to 31 days (Day 0 -30) after vaccination was tabulated. The same tabulation was performed for Grade 3 unsolicited AEs and for unsolicited AEs with relationship to vaccination. The occurrence of SAEs after the last LTFU visit of the primary study HAB-160 until the end of the study (30 days post-challenge dose) was tabulated according to MedDRA preferred terms.

The occurrence of any SAE which the subject could have experienced since the last study visit of the HAB-160 long-

term follow-up was reported if the SAE was considered by the investigator to have a causal relationship to primary vaccination.

Study Population: Healthy and non-healthy male or female subject who had completed the primary vaccination phase of the HAB-160 study was included in the study. Women were to be of non-childbearing potential or if of childbearing potential, had to practice adequate contraception for 30 days prior to vaccination, to have a negative pregnancy test, and to continue such precautions for the duration of the study. Written informed consent was obtained prior to study entry.

Number of subjects	**HAB Group**	**HBV + HAV Group**	**HBVc + HAVc Group**
Planned, N	Not applicable	Not applicable	Not applicable
Randomized*, N (Total Vaccinated Cohort)	172	170	164
Completed, n (%)	169 (98.3)	170 (100)	164 (100)
Total Number Subjects Withdrawn, n (%)	3 (1.7)	0 (0.0)	0 (0.0)
Withdrawn due to Adverse Events, n (%)	1 (0.6)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	2 (1.2)	0 (0.0)	0 (0.0)
Demographics	**HAB Group**	**HBV + HAV Group**	**HBVc + HAVc Group**
N (Total Vaccinated Cohort)	172	170	164
Females: Males	85:87	83:87	85:79
Mean Age, years (SD)	58.4 (8.70)	59.5 (10.18)	59.1 (9.16)
White/Caucasian, n (%)	172 (100)	170 (100)	163 (99.4)

*Subjects were randomized at the beginning of the primary phase and kept their group assignment during the challenge dose vaccination phase

Primary Efficacy Results: Anamnestic response to the challenge dose for anti-HAV antibodies (ATP cohort for immunogenicity)

Group	**Pre-vaccination status**	**N**	**Immune response to the challenge dose**			
			n	**%**	**95% CI**	
					LL	**UL**
HAB	S-	5	4	80	28.4	99.5
	S+ (<100mIU/mL)	39	39	100	91.0	100
	S+ (≥100mIU/mL)	123	121	98.4	94.2	99.8
	Total	167	164	98.2	94.8	99.6
HBV + HAV	S-	11	10	90.9	58.7	99.8
	S+ (<100mIU/mL)	51	49	96.1	86.5	99.5
	S+ (≥100mIU/mL)	106	105	99.1	94.9	100
	Total	168	164	97.6	94.0	99.3
HBVc + HAVc	S-	5	4	80	28.4	99.5
	S+ (<100mIU/mL)	29	29	100	88.1	100
	S+ (≥100mIU/mL)	129	129	100	97.2	100
	Total	163	162	99.4	96.6	100

S- = seronegative subjects (antibody concentration < 15mIU/mL for anti-HAV) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 15mIU/mL for anti-HAV) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Anamnestic response defined as:

- for initially seronegative subjects, antibody concentration greater than or equal the cut-off (≥15mIU/mL)
- for initially seropositive subjects with pre-vaccination antibody concentration < 100mIU/mL: antibody concentration at least four times the pre-vaccination antibody concentration
- for initially seropositive subjects with pre-vaccination antibody concentration ≥100mIU/mL: antibody concentration at least two times the pre-vaccination antibody concentration

N = number of subjects with both pre- and post-vaccination results available
n (%) = number (percentage) of responders
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Primary Efficacy Results: Anamnestic response to the challenge dose for anti-HBs antibodies (ATP cohort for immunogenicity)

Group	**Pre-vaccination status**	**N**	**Booster response**

			n	%	95% CI	
					LL	UL
HAB	S-	39	32	82.1	66.5	92.5
	S+	128	124	96.9	92.2	99.1
	Total	167	156	93.4	88.5	96.7
HBV + HAV	S-	61	50	82	70.0	90.6
	S+	107	98	91.6	84.6	96.1
	Total	168	148	88.1	82.2	92.6
HBVc + HAVc	S-	73	53	72.6	60.9	82.4
	S+	90	83	92.2	84.6	96.8
	Total	163	136	83.4	76.8	88.8

S- = seronegative subjects (antibody concentration < 3.3 mIU/mL for HBV.S AB) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 3.3 mIU/mL for HBV.S AB) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Anamnestic response defined as :

- for initially seronegative subjects, antibody concentration ≥ 10 mIU/mL 30 days after challenge
- for initially seropositive subjects: antibody concentration at PI(D30) ≥ 4 fold the pre-vaccination antibody concentration

N = number of subjects with both pre- and post-vaccination results available
n (%) = number (percentage) of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): Seropositivity rates and geometric mean concentrations (GMC) calculated on seropositive subjects for Anti-HAV antibodies before and after the challenge dose (ATP immunogenicity cohort)

Group	Timing	N	≥ 15mIU/mL				GMC (mIU/mL)		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
HAB	Pre	167	162	97	93.2	99	212.2	177.5	253.7
	PI(D14)	167	166	99.4	96.7	100	2255.0	1928.5	2636.8
	PI(D30)	167	166	99.4	96.7	100	4062.0	3451.1	4781.0
HBV + HAV	Pre	168	157	93.5	88.6	96.7	175.4	147.3	208.9
	PI(D14)	168	167	99.4	96.7	100	1774.3	1493.5	2107.9
	PI(D30)	168	167	99.4	96.7	100	3124.1	2630.4	3710.5
HBVc + HAVc	Pre	163	158	96.9	93.0	99	308.4	255.6	372.1
	PI(D14)	163	162	99.4	96.6	100	2712.9	2290.4	3213.3
	PI(D30)	163	162	99.4	96.6	100	7481.6	6358.3	8803.3

N = number of subjects with available results
n (%) = number (percentage) of subjects with antibody concentrations above the specified cut-off
95% CI; LL, UL = exact 95% confidence interval; lower and upper limits
Pre = prior to administration of challenge dose
PI (D14) = two weeks after the administration of challenge dose
PI (D30) = one month after the administration of challenge dose

Secondary Outcome Variable(s): Seroprotection and seropositivity rates and geometric mean concentrations (GMC) calculated on seropositive subjects for anti-HBs antibodies before and after the challenge dose (ATP immunogenicity cohort)

Group	Timing	N	≥ 3.3mIU/mL				≥ 10 mIU/mL				≥ 100 mIU/mL				GMC (mIU/mL)		
			n	%	95% CI		n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL			LL	UL		LL	UL
HAB	Pre	167	128	76.6	69.5	82.8	93	55.7	47.8	63.4	35	21.0	15.1	27.9	40.3	30.0	54.2
	PI(D14)	167	162	97.0	93.2	99.0	160	95.8	91.6	98.3	153	91.6	86.3	95.3	8936.9	6071.1	13155.4
	PI(D30)	167	161	96.4	92.3	98.7	159	95.2	90.8	97.9	151	90.4	84.9	94.4	7233.7	4868.2	10748.7
HBV + HAV	Pre	168	107	63.7	55.9	71.0	72	42.9	35.3	50.7	19	11.3	6.9	17.1	26.7	19.6	36.3
	PI(D14)	168	160	95.2	90.8	97.9	150	89.3	83.6	93.5	137	81.5	74.8	87.1	1521.0	1012.5	2285.0
	PI(D30)	168	162	96.4	92.4	98.7	152	90.5	85.0	94.5	129	76.8	69.7	82.9	1242.5	823.5	1874.8
HBVc + HAVc	Pre	163	90	55.2	47.2	63.0	50	30.7	23.7	38.4	9	5.5	2.6	10.2	15.4	12.2	19.5
	PI(D14)	163	146	89.6	83.8	93.8	140	85.9	79.6	90.8	118	72.4	64.9	79.1	1222.4	821.3	1819.3

	PI(D30)	163	145	89.0	83.1	93.3	139	85.3	78.9	90.3	112	68.7	61.0	75.7	1075.1	717.2	1611.4

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with antibody concentrations above the specified cut-off
Pre= Prior to administration of challenge dose
PI (D14) =Two weeks after the administration of challenge dose
PI (D30) =One month after the administration of challenge dose
95% CI; LL, UL = exact 95% confidence interval; lower and upper limits

Secondary Outcome Variable(s): Seropositivity rates and GMCs (calculated on seropositive subjects) for Anti-HAV antibodies (LT ATP cohort for immunogenicity)

Group	Timing	N	S+				GMC		
			n	%	95% CI		value	95% CI	
					LL	UL		LL	UL
HAB	PIII(M7)	181	176	97.2	93.7	99.1	2746.5	2256.3	3343.2
	PIII(M12)	168	162	96.4	92.4	98.7	891.0	747.3	1062.2
	PIII(M24)	171	164	95.9	91.7	98.3	271.6	229.0	322.2
	PIII(M36)	163	158	96.9	93.0	99.0	216.9	182.6	257.6
	PIII(M48)	147	143	97.3	93.2	99.3	212.9	177.2	255.6
HBV + HAV	PII(M7)	182	180	98.9	96.1	99.9	1394.3	1159.8	1676.1
	PII(M12)	168	165	98.2	94.9	99.6	530.6	442.0	637.1
	PII(M24)	176	170	96.6	92.7	98.7	209.9	176.3	249.8
	PII(M36)	167	159	95.2	90.8	97.9	185.4	155.7	220.7
	PII(M48)	147	138	93.9	88.7	97.2	165.7	137.7	199.4
HBVc + HAVc	PII(M7)	176	174	98.9	96.0	99.9	3707.2	3081.4	4460.2
	PII(M12)	165	164	99.4	96.7	100	1200.5	999.3	1442.1
	PII(M24)	167	163	97.6	94.0	99.3	362.0	303.5	431.8
	PII(M36)	153	148	96.7	92.5	98.9	278.5	229.4	338.2
	PII(M48)	124	119	96.0	90.8	98.7	277.4	226.1	340.2

GMC = geometric mean antibody concentration calculated on subjects with concentration >= 15 mIU/mL
N = number of subjects with available results
Seropositivity: Subjects with anti-HAV antibody concentrations ≥ 15 mIU/mL
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(Mx) = Blood sampling after the third dose; x months after the first dose of primary vaccination course etc
PII(Mx) = Blood sampling after the second dose; x months after the first dose of primary vaccination course etc

Secondary Outcome Variable(s): Anti-HBs Seropositivity rates, proportion of subjects with antibody concentrations ≥ 10mIU/mL and GMCs (calculated on seropositive subjects) (LT ATP cohort for immunogenicity)

Group	Timing	N	S+				>= 10 mIU/mL				GMC		
			n	%	95% CI		n	%	95% CI		value	95% CI	
					LL	UL			LL	UL		LL	UL
HAB	PIII(M7)	181	168	92.8	88.0	96.1	166	91.7	86.7	95.3	1153.9	829.8	1604.7
	PIII(M12)	168	153	91.1	85.7	94.9	147	87.5	81.5	92.1	339.2	248.6	462.9
	PIII(M24)	171	136	79.5	72.7	85.3	127	74.3	67.0	80.6	113.2	83.9	152.8
	PIII(M24)*	169	137	81.1	74.3	86.7	125	74.0	66.7	80.4	99.3	75.4	130.7
	PIII(M36)	163	124	76.1	68.8	82.4	104	63.8	55.9	71.2	72.1	53.1	98.0
	PIII(M48)	147	113	76.9	69.2	83.4	84	57.1	48.7	65.3	42.3	31.3	57.3
HBV + HAV	PIII(M7)	182	152	83.5	77.3	88.6	145	79.7	73.1	85.3	491.2	342.3	704.9
	PIII(M12)	168	134	79.8	72.9	85.6	124	73.8	66.5	80.3	149.4	106.4	209.7
	PIII(M24)	176	123	69.9	62.5	76.6	88	50.0	42.4	57.6	46.5	33.0	65.4
	PIII(M24)*	175	129	73.7	66.5	80.1	99	56.6	48.9	64.0	40.8	30.4	54.9
	PIII(M36)	167	105	62.9	55.1	70.2	75	44.9	37.2	52.8	34.1	24.6	47.2
	PIII(M48)	147	91	61.9	53.5	69.8	59	40.1	32.1	48.5	23.6	17.5	31.8
HBVc + HAVc	PIII(M7)	176	137	77.8	71.0	83.7	125	71.0	63.7	77.6	179.1	128.5	249.7
	PIII(M12)	165	109	66.1	58.3	73.2	93	56.4	48.4	64.1	53.1	39.3	71.6

	PIII(M24)	167	74	44.3	36.6	52.2	50	29.9	23.1	37.5	21.3	15.5	29.4
	PIII(M24)*	165	76	46.1	38.3	54.0	56	33.9	26.8	41.7	22.3	16.9	29.4
	PIII(M36)	153	67	43.8	35.8	52.0	45	29.4	22.3	37.3	18.9	14.1	25.3
	PIII(M48)	124	64	51.6	42.5	60.7	33	26.6	19.1	35.3	13.7	10.6	17.7

GMC = geometric mean antibody concentration calculated on subjects with concentration >= 3.3 mIU/mL
N = number of subjects with available results
S+ : Seropositivity for anti-HBs antibodies defined as antibody concentrations ≥ 3.3 mIU/mL
Value = value of the considered parameter
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M7) to PIII(M24) = anti-HBs antibody concentrations tested with AUSAB ® EIA /Abbott assay with cut-off 3.3mIU/mL
PIII (M24)* was retested with in-house assay (bridging)
PIII(M24)* onwards = anti-HBs antibody concentrations tested with an in-house assay with cut-off 3.3mIU/mL
PIII(M48) = Blood sampling after the third dose; 48months after the first dose of primary vaccination course etc

Secondary Outcome Variable(s): Number/percentage of subjects reporting solicited local symptoms during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

Symptom	Intensity	HAB Group					HBV + HAV Group					HBVc + HAVc Group				
		N	n	%	95 % CI		N	n	%	95 % CI		N	n	%	95 % CI	
					LL	UL				LL	UL				LL	UL
Pain	Any	172	42	24.4	18.2	31.5	170	35	20.6	14.8	27.5	164	46	28.0	21.3	35.6
	Grade 3	172	0	0	0.0	2.1	170	0	0.0	0.0	2.1	164	1	0.6	0.0	3.4
Redness	Any	172	22	12.8	8.2	18.7	170	10	5.9	2.9	10.6	164	19	11.6	7.1	17.5
	≥ 50 mm	172	0	0	0.0	2.1	170	0	0.0	0.0	2.1	164	0	0.0	0.0	2.2
Swelling	Any	172	9	5.2	2.4	9.7	170	3	1.8	0.4	5.1	164	12	7.3	3.8	12.4
	≥ 50 mm	172	2	1.2	0.1	4.1	170	0	0	0.0	2.1	164	1	0.6	0.0	3.4

N = number of subjects with the documented dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
Grade 3 Pain: pain which prevented normal activity

Secondary Outcome Variable(s): Number/percentage of subjects reporting solicited general symptoms during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)

Symptom	Intensity/ relationship	HAB Group					HBV + HAV Group					HBVc + HAVc Group				
		N	n	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL				LL	UL
Fatigue	Any	172	29	16.9	11.6	23.3	170	24	14.1	9.3	20.3	164	28	17.1	11.7	23.7
	Grade 3	172	2	1.2	0.1	4.1	170	0	0.0	0.0	2.1	164	0	0.0	0.0	2.2
	Related	172	23	13.4	8.7	19.4	170	19	11.2	6.9	16.9	164	22	13.4	8.6	19.6
Gastrointestinal	Any	172	5	2.9	1.0	6.7	170	8	4.7	2.1	9.1	164	5	3.0	1.0	7.0
	Grade 3	172	2	1.2	0.1	4.1	170	0	0.0	0.0	2.1	164	0	0.0	0.0	2.2
	Related	172	1	0.6	0.0	3.2	170	6	3.5	1.3	7.5	164	4	2.4	0.7	6.1
Headache	Any	172	21	12.2	7.7	18.1	170	20	11.8	7.3	17.6	164	18	11.0	6.6	16.8
	Grade 3	172	1	0.6	0.0	3.2	170	0	0.0	0.0	2.1	164	0	0.0	0.0	2.2
	Related	172	15	8.7	5.0	14.0	170	16	9.4	5.5	14.8	164	14	8.5	4.7	13.9
Temperature (Axillary)	> 37.5°C	172	2	1.2	0.1	4.1	170	0	0.0	0.0	2.1	164	2	1.2	0.1	4.3
	> 39.5^0C	172	0	0.0	0.0	2.1	170	0	0.0	0.0	2.1	164	0	0.0	0.0	2.2
	Related	172	1	0.6	0.0	3.2	170	0	0.0	0.0	2.1	164	1	0.6	0.0	3.4

N = number of subjects with the documented dose
n (%)= number (percentage) of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Any = all reports of specified symptom irrespective of intensity grade and relationship to vaccination
Grade 3 Symptom = symptoms which prevented normal activity
Related = general symptom considered by the investigator to be causally related to the study vaccination.

Safety results: Number (%) of subjects with unsolicited AEs (Total Vaccinated Cohort)

Most frequent adverse events – On-Therapy (occurring within Day 0-30 following	**HAB Group N = 172**	**HBV + HAV Group**	**HBVc + HAVc Group N = 164**

vaccination)		N = 170	
Subjects with any AE(s), n (%)	28 (16.3)	10 (5.9)	21 (12.8)
Subjects with grade 3 AEs n (%)	4 (2.3)	2 (1.2)	1 (0.6)
Subjects with related AE, n (%)	4 (2.3)	1 (0.6)	-
Headache	2 (1.2)	2 (1.2)	2 (1.2)
Back pain	3 (1.7)	1 (0.6)	1 (0.6)
Nasopharyngitis	3 (1.7)	2 (1.2)	-
Bronchitis	2 (1.2)	-	1 (0.6)
Cystitis	1 (0.6)	-	1 (0.6)
Diarrhea	1 (0.6)	-	1 (0.6)
Fracture	-	1 (0.6)	1 (0.6)
Influenza	2 (1.2)	-	-
Lymphadenitis	1 (0.6)	-	1 (0.6)
Myalgia	1 (0.6)	-	1 (0.6)
Pharyngitis	-	-	2 (1.2)
Somnolence	-	1 (0.6)	1 (0.6)
Toothache	-	-	2 (1.2)
Upper respiratory tract infection	1 (0.6)	-	1 (0.6)
Abdominal pain upper	1 (0.6)	-	-
Arterial occlusive disease	-	1 (0.6)	-
Arthralgia	1 (0.6)	-	-
Arthropod bite	-	-	1 (0.6)
Asthma	1 (0.6)	-	-
Atrial fibrillation	1 (0.6)	-	-
Benign prostatic hyperplasia	-	-	1 (0.6)
Blood gonadotrophin decreased	1 (0.6)	-	-
Chills	1 (0.6)	-	-
Conjunctivitis	1 (0.6)	-	-
Contusion	-	-	1 (0.6)
Dermatitis atopic	-	-	1 (0.6)
Eczema	-	-	1 (0.6)
Enteritis	1 (0.6)	-	-
Fatigue	1 (0.6)	-	-
Gastroenteritis	1 (0.6)	-	-
Influenza like illness	-	1 (0.6)	-
Injection site haematoma	1 (0.6)	-	-
Injection site haemorrhage	1 (0.6)	-	-
Joint range of motion decreased	-	1 (0.6)	-
Nail bed infection fungal	1 (0.6)	-	-
Nephritis interstitial	1 (0.6)	-	-
Nephropathy	-	-	1 (0.6)
Nerve injury	1 (0.6)	-	-
Pain in extremity	-	1 (0.6)	-
Swelling face	1 (0.6)	-	-
Tonsillitis	-	-	1 (0.6)
Vertigo	-	-	1 (0.6)
Wound	1 (0.6)	-	-
- : Adverse event absent *Grade 3 AE: AE that prevented normal activity **Related AE: AE considered by the investigator to be causally related to the study vaccination			
Safety results: Number (%) of subjects with SAEs since the last study visit of the HAB-160 long-term follow-up study considered by the investigator to have a causal relationship to primary vaccination. (Total Vaccinated Cohort)			
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]			
All SAEs	**HAB Group (N = 172)**	**HBV + HAV Group (N = 170)**	**HBVc + HAVc Group (N = 164)**

Subjects with any SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	**HAB Group (N = 172)**	**HBV + HAV Group (N = 170)**	**HBVc + HAVc Group (N = 164)**
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Safety results: Number (%) of subjects with SAEs following the administration of the challenge dose (Total Vaccinated Cohort)			
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]			
All SAEs	**HAB Group (N = 172)**	**HBV + HAV Group (N = 170)**	**HBVc + HAVc Group (N = 164)**
Subjects with any SAE(s), n (%) [n related]	1 (0.6) [1]	2 (1.2) [0]	0 (0.0) [0]
Arterial occlusive disease	0 (0.0) [0]	1 (0.6) [0]	0 (0.0) [0]
Intervertebral disc protrusion	0 (0.0) [0]	1 (0.6) [0]	0 (0.0) [0]
Nephritis interstitial	1 (0.6) [1]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	**HAB Group (N = 172)**	**HBV + HAV Group (N = 170)**	**HBVc + HAVc Group (N = 164)**
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: One month after challenge dose administration, an anamnestic response for anti-HAV antibodies was observed in 98.2%, 97.6% and 99.4% of subjects in HAB, HBV + HAV and HBVc + HAVc groups, respectively. At the same time point, an anamnestic response for anti-HBV antibodies was observed in 93.4%, 88.1% and 83.4% of subjects in HAB, HBV + HAV and HBVc + HAVc groups, respectively.
At least one unsolicited symptom was reported by 28 (16.3%), 10 (5.9%) and 21 (12.8%) subjects in HAB, HBV + HAV and HBVc + HAVc groups, respectively, during the 31-day follow-up period after vaccination. No SAEs considered by the investigator as related to the primary vaccination were reported since the last visit of the HAB-160 long-term follow-up study. Three SAE s, 1 in the HAB Group and 2 in the HBV + HAV Group, were reported following the administration of the challenge dose; the SAE in the HAB Group (interstitial nephritis) was considered by the investigator to be possibly related to vaccination. No fatal SAEs were reported during the challenge dose study.
Please refer to the CTRS on HAB-160 EXT Y1&Y2&Y3 for the results of primary and long-term follow-up period.
Please also refer to the publication citation.

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