Clinical trial results:
Comparison of effectiveness of hepatitis B revaccination schemes in healthy non-responders

Summary

EudraCT number	2011-005627-40
Trial protocol	NL
Global end of trial date	31 January 2018

Results information

Result version number	v1 (current)
This version publication date	16 June 2023
First version publication date	16 June 2023

Trial information

Trial identification

Sponsor protocol code	P12.130

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trial register: NL3011

Notes:

Sponsors

Sponsor organisation name	LUMC
Sponsor organisation address	Albinusdreef 2, Leiden, Netherlands, 2333 ZA Leiden
Public contact	Department of infectious diseases, LUMC, Department of infectious diseases, LUMC, 0031 71 526 91 11, research@lumc.nl
Scientific contact	Department of infectious diseases, LUMC, Department of infectious diseases, LUMC, 0031 715262613, research@lumc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2018
Global end of trial reached?	Yes
Global end of trial date	31 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Study the efficacy of mounting a protective immunological response against hepatitis B infection in previous hepatitis B vaccine non-responders. In this trial 4 different Hepatitis B vaccines are investigated.

Protection of trial subjects:

Ethics Committee Opinion of the trial application was favourable.
Active safety follow up for 7 days post vaccination and passively for 30 days for any events post vaccination.

Background therapy:

Non-protective immunity after a hepatitis B vaccination series occurs in 5–30% of healthy adults, depending on age, and it has major implications for individuals at high risk of hepatitis B. We searched PubMed using the following keywords in different combinations: “vaccination”, “vaccine”, “recombinant vaccine”, “hepatitis b virus”, “HBV”, “hepatitis B infection”, “nonresponders”, “non-responders” and “non responders” for clinical trials comparing immunogenicity for hepatitis B vaccines in healthy non-responding adults between Jan 1, 1986, and May 1, 2018. We updated the search between May 1, 2018, and Oct 1, 2019; we can confirm that with these search items no similar study has been published in the past year. Previous clinical trials compared different administration routes, vaccines with different antigen doses or additional adjuvants, and additional doses given to non-responders after hepatitis B vaccination. However, these studies show great diversity; they had design limitations, and in general they had a small sample sizes that limited the evidence-based rationale for recommendations in guidelines regarding healthy non-responders

Evidence for comparator:

The exact immunological mechanisms of non-response have not yet been elucidated. Guidelines recommend revaccinating non-responders with additional vaccine doses. Dutch guidelines recommend three revaccinations of a standard vaccine administered at months 0, 1, and 2, which induces a seroconversion rate of 50–70%. In a proof-of-principle trial, increasing the cumulative antigen dose achieved by increasing the number of administered doses of a standard vaccine, all the participants eventually reached antibody concentrations greater than 10 IU/L.11
Additional strategies to increase the immune response in healthy non-responders are vaccination with higher doses of HBsAg, combining HBsAg with other antigens, and use of more potent adjuvants or alternative routes of administration. A meta-analysis comparing revaccination regimens by dosage and route of administration suggests a higher seroconversion rate after the first additional dose, regardless of the revaccination regimen chosen. This growing body of evidence strengthens the expectations that alternative vaccine schedules will overcome non-responsiveness. However, these trials generally had small sample sizes, deviating vaccine dosages or vaccination intervals or retrospective study designs, or both, and did not all report on antibody titres in non-responders. This is important as the nearly complete absence of an anti-HBs titre is associated with lower seroconversion rates after revaccination than an anti-HBs titre above the cutoff limit of detection. In some studies, the interval between final vaccine dose and anti-HBs testing was more than 6 months or unknown, the number of previous vaccinations was variable, or a vaccine had been used that was withdrawn from the market.5,18,19 We have done the current trial to overcome these limitations.

Actual start date of recruitment	01 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 480
Worldwide total number of subjects	480
EEA total number of subjects	480

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	454
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants were recruited between Nov 1, 2012, and Sept 1, 2017. Healthy adults (aged 18–80 years) from 16 Dutch centres (13 public health services, two university hospitals, and one travel clinic) were included in this multicentre, parallel group, randomised, controlled, superiority trial. The inclusion criterion was HBV vaccine non-response

Pre-assignment

Screening details:

Non-response was defined as an anti-HBs titre of less than 10 IU/L, measured in serum 4 weeks to 3 months after last vaccination and assessed according to the local laboratory serology. To rule out chronic or hidden HBV infection as a cause of vaccine non-response and to exclude people with a previous HBV infection, seropositivity for HBsAg.

Pre-assignment period milestones

Number of subjects started	640[1]
Number of subjects completed	480

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 160

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The participants were only screened for being eligible to participate in this study. We do not consider them as part of the included participants.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Investigator, Data analyst, Assessor[3]

Blinding implementation details:

After the participant's informed consent was obtained, a staff-member of that centre uploaded a limited patient-specific dataset in the randomisation programme that enabled the allocation to one of the vaccine groups. Participants and staff of the participating centres were unmasked to assignment after randomisation. The central laboratory staff (LUMC) who analysed the samples were masked to vaccine-group assignment. Investigators were masked to assignment for analysing data and assessing outcom

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: repeating initial series for the control group (HBVaxPro 10 µg or Engerix-B 20 µg),

Arm type	Active comparator
Investigational medicinal product name	Engerix / HBVaxPro-10
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

HBVaxPro 10 µg or Engerix-B 20 µg

Arm title	Twinrix

Arm description:

Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: a combined vaccine against hepatitis A and hepatitis B (Twinrix

Arm type	Experimental
Investigational medicinal product name	Twinrix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Twinrix 20 µg

Arm title	HBVaxPRO40

Arm description:

Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: or a vaccine with a higher antigen dose (HBVaxPro 40 µg).

Arm type	Experimental
Investigational medicinal product name	HBVaxPro 40
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

HBVaxPro 40 µg

Arm title	Fendrix

Arm description:

Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: r a vaccine with an AS04 adjuvant containing 3-deacylated monophosphoryl lipid A and aluminium salt (Fendrix 20 µg

Arm type	Experimental
Investigational medicinal product name	Fendrix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fendrix 20 µg

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: After the participant's informed consent was obtained, a staff-member of that centre uploaded a limited patient-specific dataset in the randomisation programme that enabled the allocation to one of the vaccine groups. Participants and staff of the participating centres were unmasked to assignment after randomisation. The central laboratory staff (LUMC) who analysed the samples were masked to vaccine-group assignment. Investigators were masked to assignment for analysing data and assessing outcom

[3] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: After the participant's informed consent was obtained, a staff-member of that centre uploaded a limited patient-specific dataset in the randomisation programme that enabled the allocation to one of the vaccine groups. Participants and staff of the participating centres were unmasked to assignment after randomisation. The central laboratory staff (LUMC) who analysed the samples were masked to vaccine-group assignment. Investigators were masked to assignment for analysing data and assessing outcom

Number of subjects in period 1	Control	Twinrix	HBVaxPRO40
Started	124	118	114
Completed	117	114	109
Not completed	7	4	5
Consent withdrawn by subject	5	3	5
inclusion criteria not met	2	-	-
Protocol deviation	-	1	-

Number of subjects in period 1	Fendrix
Started	124
Completed	119
Not completed	5
Consent withdrawn by subject	2
inclusion criteria not met	3
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: repeating initial series for the control group (HBVaxPro 10 µg or Engerix-B 20 µg),	
Reporting group title	Twinrix
Reporting group description:	
Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: a combined vaccine against hepatitis A and hepatitis B (Twinrix	
Reporting group title	HBVaxPRO40
Reporting group description:	
Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: or a vaccine with a higher antigen dose (HBVaxPro 40 µg).	
Reporting group title	Fendrix
Reporting group description:	
Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: r a vaccine with an AS04 adjuvant containing 3-deacylated monophosphoryl lipid A and aluminium salt (Fendrix 20 µg	

Reporting group values	Control	Twinrix	HBVaxPRO40
Number of subjects	124	118	114
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age in years at the start of the trial inclusion.			
Units: years			
arithmetic mean	45.3	44.8	46.1
standard deviation	± 14.4	± 14.2	± 15.9
Gender categorical			
Gender categories.			
Units: Subjects			
Female	48	62	43
Male	76	56	71
anti-HBs < 1 IU/l			
anti-HBs < 1 IU/l in the baseline sample (T=0)			
Units: Subjects			
anti-HBs < 1IU/l	54	53	50

anti-HBs 1 or >1 IU/l	70	65	64
active smoking			
active smoking was defined of smoking at least 5 or more cigarettes a day.			
Units: Subjects			
active smoking	31	40	31
non smoking	82	71	74
not recorded	11	7	9
Diabetes +			
Self reported diabetes type 1 and 2			
Units: Subjects			
diabetes	5	7	7
no diabetes	113	105	99
not recorded	6	6	8

Reporting group values	Fendrix	Total	
Number of subjects	124	480	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age in years at the start of the trial inclusion.			
Units: years			
arithmetic mean	45.6		
standard deviation	± 13.3	-	
Gender categorical			
Gender categories.			
Units: Subjects			
Female	59	212	
Male	65	268	
anti-HBs < 1 IU/l			
anti-HBs < 1 IU/l in the baseline sample (T=0)			
Units: Subjects			
anti-HBs < 1IU/l	62	219	
anti-HBs 1 or >1 IU/l	62	261	
active smoking			
active smoking was defined of smoking at least 5 or more cigarettes a day.			
Units: Subjects			
active smoking	30	132	
non smoking	88	315	
not recorded	6	33	
Diabetes +			
Self reported diabetes type 1 and 2			

Units: Subjects			
diabetes	8	27	
no diabetes	113	430	
not recorded	3	23	

Subject analysis sets	
Subject analysis set title	primary analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The primary analysis of this superiority trial was an intention-to-treat analysis with the last observation carried forward (LOCF) for participants with any missing anti-HBs titre measurements.

Reporting group values	primary analysis		
Number of subjects	480		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age in years at the start of the trial inclusion.			
Units: years			
arithmetic mean	45.3		
standard deviation	± 14.4		
Gender categorical			
Gender categories.			
Units: Subjects			
Female	212		
Male	268		
anti-HBs < 1 IU/l			
anti-HBs < 1 IU/l in the baseline sample (T=0)			
Units: Subjects			
anti-HBs < 1IU/l	219		
anti-HBs 1 or >1 IU/l	261		
active smoking			
active smoking was defined of smoking at least 5 or more cigarettes a day.			
Units: Subjects			
active smoking	132		
non smoking	315		
not recorded	33		
Diabetes +			
Self reported diabetes type 1 and 2			
Units: Subjects			

diabetes	27		
no diabetes	430		
not recorded	23		

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: repeating initial series for the control group (HBVaxPro 10 µg or Engerix-B 20 µg),	
Reporting group title	Twinrix
Reporting group description:	
Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: a combined vaccine against hepatitis A and hepatitis B (Twinrix	
Reporting group title	HBVaxPRO40
Reporting group description:	
Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: or a vaccine with a higher antigen dose (HBVaxPro 40 µg).	
Reporting group title	Fendrix
Reporting group description:	
Participants were individually randomly assigned in this open-label trial with an allocation ratio of 1:1:1:1 to one of the following groups: r a vaccine with an AS04 adjuvant containing 3-deacylated monophosphoryl lipid A and aluminium salt (Fendrix 20 µg	
Subject analysis set title	primary analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary analysis of this superiority trial was an intention-to-treat analysis with the last observation carried forward (LOCF) for participants with any missing anti-HBs titre measurements.	

Primary: percentage responders

End point title	percentage responders
End point description:	
As an anti-HBs titre of 10 IU/L or more is a correlate of protection against clinically relevant hepatitis B infections, our primary endpoint was the proportion of responders with an anti-HBs titre of 10 IU/L or more, 4 weeks to 3 months after completion of the revaccination series given at months 0, 1, and 2.	
End point type	Primary
End point timeframe:	
Between 1 Nov 2012, and 1 Sept 2017	

End point values	Control	Twinrix	HBVaxPRO40	Fendrix
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	118	114	124
Units: numbers				
percentage responders	83	94	95	108

End point values	primary analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	480			
Units: numbers				

percentage responders	380			

Attachments (see zip file)	reverse cumulative distribution curve/REVISIE ITV TIME 0-

Statistical analyses

Statistical analysis title	difference proportion

Statistical analysis description:

The proportion of responders (antiHBs ≥10 IU/L) in each vaccination group was calculated. The outcome variable (anti-HBs titre) was transformed to a log 10 variable to compute the geometric mean titre. Its sample mean per study group was back-transformed to express the geometric mean titre and 95% CI in terms of anti-HBs titres, which, at least in an approximate sense, refer to the median anti-HBs titres.

Comparison groups	Control v Twinrix v primary analysis
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	25
Confidence interval	
level	95 %
sides	2-sided
lower limit	13
upper limit	37

Statistical analysis title	difference proportion
Comparison groups	Control v HBVaxPRO40
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	21.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.4
upper limit	32.7

Statistical analysis title	difference proportion

Comparison groups	Control v Fendrix v primary analysis
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.4
upper limit	37.3

Primary: Difference proportion of responders

End point title	Difference proportion of responders[1]

End point description:

We used the permutation version of the test based on the so-called sum statistic to compare differences between vaccine groups regarding the proportion of responders and geometric mean titres. The sum statistic is equivalent to the Mantel–Haenszel test for a binary—our primary—outcome; it can be seen as a generalisation of Fisher's exact test for the situation in which the various pairs of samples come from different strata or blocks (the centres in our case) In the case of a continuous outcome (our secondary outcome), the sum statistic is the sum of the within-stratum differences between average responses in the two vaccine groups being compared. To estimate the p values we have used 1 million permutations. The Bonferroni method was used to correct for multiple testing separately for the two endpoints; in each case, the probability of at least one type 1 error among a set of three tests was kept at 0·05.

End point type	Primary

End point timeframe:

Between 1 Nov 2012, and 1 Sept 2017

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As the end point is a difference in proportion between the control group and one of the other arms the control group has been taken into account in this end point.

End point values	Twinrix	HBVaxPRO40	Fendrix	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118	114	124	
Units: percentage protection				
number (confidence interval 95%)				
difference in proportion responders	25 (13 to 37)	22 (10 to 33)	26 (15 to 37)	

Statistical analyses

Statistical analysis title	difference proportion 1
Comparison groups	Twinrix v HBVaxPRO40 v Fendrix

Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [2]
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[2] - The Bonferroni method was used to correct for multiple testing separately for the two endpoints; in each case, the probability of at least one
type 1 error among a set of three tests was kept at 0·05.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

7 days after vaccination, 30 days for SAE The participants classified the severity of the local and general reactions on a four-point scale (absent–mild–moderate–severe).

Assessment type	Systematic

Dictionary used

Dictionary name	self defined
Dictionary version	1

Reporting groups

Reporting group title	dose 1 all arms
Reporting group description: -	
Reporting group title	dose 2 all arms
Reporting group description: -	
Reporting group title	dose 3 all arms
Reporting group description: -	

Serious adverse events	dose 1 all arms	dose 2 all arms	dose 3 all arms
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 480 (0.00%)	1 / 480 (0.21%)	0 / 480 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
SAE	Additional description: herpes zoster ophtalmicus		
subjects affected / exposed	0 / 480 (0.00%)	1 / 480 (0.21%)	0 / 480 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	dose 1 all arms	dose 2 all arms	dose 3 all arms
Total subjects affected by non-serious adverse events			
subjects affected / exposed	222 / 480 (46.25%)	174 / 480 (36.25%)	145 / 480 (30.21%)
Investigations			
General symptom	Additional description: The diary card consisted of three items regarding a local reaction after vaccination (pain, erythema, and oedema), two items for systemic reactions (fever and myalgia), and free text fields for other possible reactions.		
subjects affected / exposed	222 / 480 (46.25%)	174 / 480 (36.25%)	145 / 480 (30.21%)
occurrences (all)	222	174	145

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31629649