Clinical trial results:
A multicentre randomized controlled trial evaluating the rate of sustained remission and the safety when stopping nucleos(t)ide analogue treatment in non-cirrhotic HBeAg-negative chronic Hepatitis B patients with long-term virologic response

Summary

EudraCT number	2013-004882-15
Trial protocol	DE
Global end of trial date	26 January 2022

Results information

Result version number	v1 (current)
This version publication date	20 April 2023
First version publication date	20 April 2023
Summary attachment (see zip file)	Ergebnisbericht (STOP-NUC_Ergebnisbericht_in_Arzneimittelpruefungen_final1.0_2023-01-17_publish.pdf)

Trial information

Trial identification

Sponsor protocol code	STOP-NUC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Deutsches Register für Klinische Studien: DRKS00006240

Notes:

Sponsors

Sponsor organisation name	Leipzig University
Sponsor organisation address	Ritterstr. 26, Leipzig, Germany,
Public contact	Florian van Bömmel, authorized representative of the sponsor, 49 34197 12200, Florian.vanBoemmel@medizin.uni-leipzig.de
Scientific contact	Florian van Bömmel, authorized representative of the sponsor, 49 34197 12200, Florian.vanBoemmel@medizin.uni-leipzig.de

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	17 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2022
Global end of trial reached?	Yes
Global end of trial date	26 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the STOP-NUC trial is to assess the potential of treatment cessation of nucleos(t)ide analogue treatment to induce complete and definitive remission in patients showing complete treatment response for at least 4 years. According to the EASL Clinical Practice Guidelines, sustained HBsAg loss will be used as marker for complete remission.
We hypothesize that after treatment discontinuation, the rate of complete remissions will be significantly higher than under continued nucleos(t)ide analogue treatment.

Protection of trial subjects:

not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 166
Worldwide total number of subjects	166
EEA total number of subjects	166

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)	150
From 65 to 84 years	16

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 2014-11-18 to 2018-01-11 a total of 201 patients were registered to the trial, from which 166 were randomised.
The first patient was randomised on 2014-11-27, the last patient on 2018-02-01

Pre-assignment

Screening details:

From 2014-11-18 to 2018-01-11 a total of 201 patients were registered to the trial, from which 166 were randomised.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Stop NUC therapy

Arm description: -

Arm type	experimental

No investigational medicinal product assigned in this arm

Arm title	NUC therapy

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Lamivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
100 mg per day

Investigational medicinal product name	Adefovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
10 mg per day

Investigational medicinal product name	Telbivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
600 mg per day

Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 0.5 mg per day	
Investigational medicinal product name	Tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 245 mg per day	

Number of subjects in period 1	Stop NUC therapy	NUC therapy
Started	83	83
Completed	79	79
Not completed	4	4
Consent withdrawn by subject	3	4
medical personnel	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Stop NUC therapy
Reporting group description: -	
Reporting group title	NUC therapy
Reporting group description: -	

Reporting group values	Stop NUC therapy	NUC therapy	Total
Number of subjects	83	83	166
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 Units: years			
arithmetic mean	51.6	52.0	
standard deviation	± 8.4	± 10.2	-
Gender categorical Units: Subjects			
Female	31	29	60
Male	52	54	106

End points

End points reporting groups

Reporting group title	Stop NUC therapy
Reporting group description: -	
Reporting group title	NUC therapy
Reporting group description: -	

Primary: sustained HBsAg loss up to week 96

End point title	sustained HBsAg loss up to week 96
End point description:	
HBsAg will be quantified in a central laboratory at every scheduled visit until week 96. HBsAg loss is defined as not detectable HBsAg in all subsequent assessments after HBsAg became undetectable for the first time. If at week 96, HBsAg is for the first time not detectable, a further measurement will be performed at week 108 in order to confirm the HBsAg loss.	
End point type	Primary
End point timeframe:	
96 weeks	

End point values	Stop NUC therapy	NUC therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[1]	79[2]		
Units: number	8	0		

Notes:

[1] - 4 drop-outs directly after randomisation are excluded

[2] - 4 drop-outs directly after randomisation are excluded

Statistical analyses

Statistical analysis title	HBsAg loss primary analysis

Statistical analysis description:

Fisher’s exact test will be used to compare the two treatment groups with respect to the primary endpoint. Wilson’s score interval method will be used to provide 95% confidence intervals for the efficacy rates and their difference.
Primary analysis will be based on the intent to treat principle (ITT).

Comparison groups	Stop NUC therapy v NUC therapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Fisher exact
Parameter estimate	rate difference
Point estimate	10.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	18

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 96 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Stop NUC therapy
Reporting group description: -	
Reporting group title	Continue NUC therapy
Reporting group description: -	

Serious adverse events	Stop NUC therapy	Continue NUC therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 79 (13.92%)	3 / 79 (3.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Schwannoma			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney rupture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Stent placement			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal			

conditions			
Abortion			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Panic attack			

subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Stop NUC therapy	Continue NUC therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 79 (68.35%)	48 / 79 (60.76%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 79 (11.39%)	9 / 79 (11.39%)	
occurrences (all)	10	11	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 79 (7.59%)	4 / 79 (5.06%)	
occurrences (all)	7	4	
Influenza like illness			
subjects affected / exposed	3 / 79 (3.80%)	9 / 79 (11.39%)	
occurrences (all)	6	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 79 (8.86%)	3 / 79 (3.80%)	
occurrences (all)	9	4	
Back pain			
subjects affected / exposed	5 / 79 (6.33%)	8 / 79 (10.13%)	
occurrences (all)	5	8	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed occurrences (all)	24 / 79 (30.38%) 29	15 / 79 (18.99%) 19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2015	Relevant changes at trial protocol with amendment01: Changes in different Inclusion criteria
23 March 2015	with amendment02: Change in one exclusion criterion
23 March 2020	with amendment03: Additional objectives of the prolonged observation period Further long-term endpoints Duration of Trial: prolonged observation period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported