Clinical trial results:
Norwegian Nucleoside Analogue Stop Study (Nuc-STOP) - A randomized open-label trial in HBeAg negative chronic hepatitis B, aiming at achieving a functional Cure

Summary

EudraCT number	2018-000724-34
Trial protocol	NO SE DK
Global end of trial date	31 January 2023

Results information

Result version number	v1 (current)
This version publication date	21 November 2024
First version publication date	21 November 2024
Summary attachment (see zip file)	Trial main article (Aliment Pharmacol Ther - 2024 - Johannessen - Clinical trial An openlabel randomised trial of different restart (1).pdf)

Trial information

Trial identification

Sponsor protocol code	Nuc-STOP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03681132
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oslo University Hospital
Sponsor organisation address	Kirkeveien 144, OSLO, Norway, 0424
Public contact	Asgeir Johannessen, Oslo University Hospital, 47 97983264 ,
Scientific contact	Asgeir Johannessen, Oslo University Hospital, 47 97983264 ,

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	26 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2022
Global end of trial reached?	Yes
Global end of trial date	31 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective:
To study whether stopping NA therapy – and delaying re-start - can trigger an immune response and set off a functional cure (i.e. HBsAg loss)

Protection of trial subjects:

This was a trial of stopping medical treatment and randomizing patients to two different re-treatment strategies.
Trial subjects were protected by:
Close monitoring after treatment cessation
Registration of all adverse events first three months
Registration of all severe or unexpected adverse events throughout the trial period.
All private data stored safely in approved online CRP according to national legislation and instruction of institutional data protection officer.
Study monitored according to national legislation and instruction of institutional data protection officer.
Special insurance of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2018
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	Ethiopia: 28
Country: Number of subjects enrolled	Norway: 75
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	Denmark: 6
Worldwide total number of subjects	127
EEA total number of subjects	99

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	126
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adults (18–70years) with HBeAg negative CHB were eligible for inclusion if they had been treated with tenofovir or entecavir uninterruptedly for 2years or more with full viral suppression and had liver fibrosis assessment performed within the past 12months not showing advanced fibrosis.

Pre-assignment

Screening details:

Adults (18–70years) with HBeAg negative CHB were eligible for inclusion if they had been treated with tenofovir or entecavir uninterruptedly for 2years or more with full viral suppression and had liver fibrosis assessment performed within the past 12months not showing advanced fibrosis.

Period 1

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

Blinding implementation details:

Randomized open label trial on two re-treatment strategies after stopping medication.

Arms

Are arms mutually exclusive?	Yes
Arm title	Low treshold

Arm description:

HBV DNA>2000IU/mL and ALT>80U/L at one assessment

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

Dosage and administration details:

Tenofovir disoproxilfumorat 245 mg OD
Tenofovir alafenamid 25 mg OD
Entecavir 0,5 mg OD

Arm title	High treshold

Arm description:

Alanine aminotransferase (ALT) >100U/L persisting for more than 4 months without any spontaneous decline toward normal, or ALT>400U/L persisting for more than 2months

Arm type	Experimental
Investigational medicinal product name	Tenofovir or entecavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tenofovir disoproxilfumorat 245 mg OD
Tenofovir alafenamid 25 mg OD
Entecavir 0,5 mg OD

Number of subjects in period 1	Low treshold	High treshold
Started	64	63
Completed	61	59
Not completed	3	4
Consent withdrawn by subject	1	2
Pregnancy	1	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Low treshold
Reporting group description:	
HBV DNA>2000IU/mL and ALT>80U/L at one assessment	
Reporting group title	High treshold
Reporting group description:	
Alanine aminotransferase (ALT) >100U/L persisting for more than 4 months without any spontaneous decline toward normal, or ALT>400U/L persisting for more than 2months	

Reporting group values	Low treshold	High treshold	Total
Number of subjects	64	63	127
Age categorical			
Units: Subjects			
Adults (18-64 years)	63	63	126
From 65-84 years	1	0	1
Age continuous			
Units: years			
arithmetic mean	45.7	42.7	
standard deviation	± 9.6	± 9.4	-
Gender categorical			
Units: Subjects			
Female	23	18	41
Male	41	45	86

End points

End points reporting groups

Reporting group title	Low treshold
Reporting group description:	
HBV DNA>2000IU/mL and ALT>80U/L at one assessment	
Reporting group title	High treshold
Reporting group description:	
Alanine aminotransferase (ALT) >100U/L persisting for more than 4 months without any spontaneous decline toward normal, or ALT>400U/L persisting for more than 2months	

Primary: HBsAg loss

End point title	HBsAg loss
End point description:	
End point type	Primary
End point timeframe:	
Inclusion through 36 months follow-up (End of Study)	

End point values	Low treshold	High treshold		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	63		
Units: Subjects	3	8		

Statistical analyses

Statistical analysis title	Primary outcome
Statistical analysis description:	
The effect measure was the difference between the probability of having HBsAg loss in the two groups using Agresti--Min exact unconditional 95% confidence interval (CI). The p--value was calculated with the Suissa--Shuster exact unconditional test.25 Missing data were imputed with the last observation carried forward (LOCF, worst--case scenario).	
Comparison groups	Low treshold v High treshold
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Risk difference (RD)
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	19.6

Notes:

[1] - The primary null hypothesis was that there was no difference in the proportion with HBsAg loss between the high--threshold and the low--threshold group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events, none-serious: Inclusion to 3 months
Serious adverse events: entire follow-up time, inclusion to 36 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Arm 1. Low-threshold
Reporting group description: -	
Reporting group title	Arm 2. High threshold

Reporting group description: -

Serious adverse events	Arm 1. Low-threshold	Arm 2. High threshold	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 64 (14.06%)	16 / 63 (25.40%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	7 / 64 (10.94%)	8 / 63 (12.70%)	
occurrences causally related to treatment / all	7 / 7	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Limb injury			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
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			
Pyrexia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Arm 1. Low-threshold	Arm 2. High threshold	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 64 (48.44%)	18 / 63 (28.57%)	
Vascular disorders			

Hypertension			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Surgical and medical procedures			
Gingival operation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 64 (3.13%)	2 / 63 (3.17%)	
occurrences (all)	2	2	
Chest discomfort			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	4 / 64 (6.25%)	3 / 63 (4.76%)	
occurrences (all)	4	3	
Influenza like illness			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	1	
Tenderness			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			

Haematospermia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Prostatomegaly			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 64 (6.25%)	0 / 63 (0.00%)	
occurrences (all)	4	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Sleep disorder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	1	
Blood glucose decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	

Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Migraine			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia macrocytic			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Abdominal pain			

subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Abdominal tenderness			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Haemorrhoid infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 64 (6.25%)	0 / 63 (0.00%)	
occurrences (all)	4	0	
Back pain			
subjects affected / exposed	1 / 64 (1.56%)	3 / 63 (4.76%)	
occurrences (all)	1	3	

Flank pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Rotator cuff syndrome			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	5 / 64 (7.81%)	2 / 63 (3.17%)	
occurrences (all)	5	2	
Epididymitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Fungal infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Nasopharyngitis			

subjects affected / exposed	7 / 64 (10.94%)	5 / 63 (7.94%)	
occurrences (all)	7	4	
Onychomycosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Syphilis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Blood creatinine increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	

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