Summary of the Trial Report
[Synopsis according to ICH E3]

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

A prospective, open, randomized, controlled multicentre trial

STOP-NUC

Name of Finished Product/Name of Active Substance:
not applicable

Indication/Diagnosis:
HBeAg negative chronic Hepatitis B virus (HBV) infection

EudraCT-Number:
2013-004882-15

Registration-Number:
DRKS00006240

Date of report: 17.01.2023
Version: final 1.0

Trial start: 27.11.2014
End of Trial: 26.01.2022

Coordinating Investigator

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Sponsor

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Signatures

The signing authors approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable statutory provisions.

Legal representative of the sponsor and coordinating investigator	[redacted]	17.01.2023 Date
Biometry		18.01.2023 Date
Further author		18.01.2023 Date

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1 Name of the Sponsor

Name of institution: Leipzig University

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04109 Leipzig

Representative of the Sponsor

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2 Name of Finished Product	3 Name of active Ingredient
Not applicable	Not applicable

Commercially available, approved medication has to be used during the treatment phase **prior to** inclusion in the study.
Due to the nature of the trial patients in the experimental arm **stop** taking any medication. In the control arm and in the case of treatment **re-initiation in the experimental arm** patients received standard therapy according to current guidelines.

4 Individual study table

Not applicable

5 Title of Study

A multicentre randomized controlled trial evaluating the rate of sustained remission and the safety when stopping nucleos(t)ide analogue (NUC) treatment in non-cirrhotic HBeAg-negative chronic Hepatitis B patients with long-term virologic response: final 5.0; 2020-06-23

including

- amendment 01; final 3.0 / 2015-03-30,
- amendment 02; final 4.0 / 2015-11-24
- amendment 03; final 5.0 / 2020-06-23

Relevant changes at trial protocol

- **with amendment01:**

Changes in different *Inclusion criteria*

- **with amendment02:**

Change in one exclusion criterion

Duration of Trial: prolongation of recruitment phase

- **with amendment03:**

Additional objectives of the prolonged observation period
→ Further long-term endpoints

Duration of Trial: prolonged observation period

6 Investigator	7 Study Centre(s)
see appendix	see appendix

8 Publications

Effect of cessation of nucleos(t)ide treatment in HBeAg-negative chronic hepatitis B on HBsAg loss: A randomized controlled multicenter trial
In press: JHEPAT-D-22-00440R2

9 Studied period (in years)

Date of first enrolment: 27.11.2014

Date of last completed: 26.01.2022

10 Phase of Development

not applicable

11 Objectives

Primary objective:

The primary objective of the STOP-NUC trial was 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 was used as marker for complete remission.
We hypothesized that after treatment discontinuation, the rate of complete remissions would be significantly higher than under continued nucleos(t)ide analogue treatment.

Secondary objectives:

Secondary objectives in terms of efficacy were

- to assess and compare virologic and biochemical response
- to evaluate if sustained HBsAg loss is followed by HBsAg seroconversion
- to describe the time course of HBsAg loss and HBsAg seroconversion
- to assess the effect of treatment cessation on liver stiffness (applicable only for trial sites where liver stiffness measurement is feasible).

In the experimental arm the number of patients fulfilling criteria for re-therapy as well as the respective time to re-therapy is of particular interest and was evaluated. For safety reasons, but also to better understand the underlying immune mechanisms, the number of ALT flares per patient are described.

Additional objectives of the prolonged observation period:
The time horizon of the original endpoints is 96 weeks after randomisation. The objective of the prolonged observation period is to provide further insights in the long-term course of patients, guided by the following questions:
In patients randomised to the experimental arm:

- Do further patients experience HBsAg loss resp. HBsAg seroconversion in years three to seven after stop of NUC-therapy?
- How long is the duration of the NUC-therapy free period, i.e. the time until NUC-therapy has to be resumed for medical reasons?
- How is the course of disease (in terms of response rates, duration until normalisation of liver parameters, resistance development) after re-initiation of NUC-therapy?

In patients randomised to the control arm:
What is the long-term rate of HBsAg loss under continuous NUC-therapy?

12 Methodology

STOP-NUC was a prospective, randomized (ratio 1:1), and controlled, open-label 2-armed trial.
Patients were randomized 1:1 either to the experimental arm, STOP-NUC, or the standard arm with NUC therapy. Randomisation of patients into both treatment arms was performed centrally by the ZKS Leipzig. The randomisation procedure was computer-assisted via internet, based on a minimisation algorithm as described in ZKS standard operating procedures for biometrical procedures.
Descriptive analyses concerning enrolment, trial conduct, protocol adherence and safety issues were regularly reviewed by a Data Monitoring and Safety Committee (DMSC). It recommended to the coordinating investigator and the sponsor whether to continue, modify, or stop the trial.

13 Number of patients (planned and analysed)

Planned number:	to be allocated to trial 160 (80 patients per treatment arm) to be analysed 144
Registered subjects:	201
Randomized subjects	166 (83 patients per treatment arm)
Analyzed patients:	158
Drop-outs:	8

For details see the CONSORT-flow diagram in appendix 21.2.

14 Diagnosis and main criteria for inclusion

Diagnosis	HBeAg negative chronic Hepatitis B virus (HBV) infection
Key inclusion criteria	1. HBeAg negative chronic hepatitis B **since** the begin of antiviral treatment and HBV-DNA >2000 IU/ml **at** the begin of treatment 2. HBsAg positive at screening 3. Age ≥ 18 years, male or female 4. Continuous nucleoside or nucleotide analogue therapy with either mono or combination therapy with adefovir dipivoxil (ADV), lamivudine (LMV), telbivudine (LdT), entecavir (ETV) or tenofovir disoproxil fumarate (TDF) for at least 4 years prior to screening. Of note, as in previous observation the rates of HBsAg loss in HBeAg negative patients were comparable during treatment with all the mentioned drugs (Figure 3) we anticipate that the different drug regimens do not represent a factor influencing the response rates after treatment cessation in this trial. However, randomisation will be stratified with respect to the kind of previous therapy 5. Documented **undetectable** HBV DNA level during treatment for at least 4 years prior to screening (quantification of HBV DNA must have been performed about every 4 to 8 months). **Please note: In terms of this trial, we define "undetectable" as below 1000 copies/mL (172 IU/mL).** This comparatively high upper limit of HBV DNA levels was chosen for the definition of response to take into account that assays for HBV DNA quantification with different sensitivity are used in the participating centres. 6. **Undetectable** HBV DNA level at screening (analysed by central laboratory, Limbach and partners, Heidelberg) 7. Normal serum ALT levels < ULN (upper limit of normal) according to the local laboratory 8. Written informed consent
Key exclusion criteria	1. Compensated or decompensated liver cirrhosis 2. History of decompensated liver disease 3. Advanced fibrosis - defined either histologically by Scheuer score ≥ stage 3 (within last year before screening) and/or liver stiffness ≥ 10 kPa by elastography (Fibroscan®) or ≥ 1.5 m/s by Acoustic Radiation Force Impulse (ARFI) (each within 6 months before screening) 4. Evidence of hepatocellular carcinoma (HCC) 5. HIV, HDV or HCV co-infection 6. Iatrogenic or disease-related immunosuppression (e.g. treatment with systemic glucocorticoids, TNFα-antibodies and other immunosuppressive drugs as well as chemotherapy or malignant disorders) 7. HBV associated extra hepatic manifestations (e.g. glomerulonephritis, panarteriitis nodosa, HBV-associated dermatosis)

	8. Patients with Gilbert-Meulengracht syndrome can be included in the study if other potentially underlying liver diseases causing bilirubin elevation or haemolysis can be ruled out. 9. Significant alcohol consumption (> 30 g/day for women and > 50 g/day for men) 10. Patients who work in the medical field and have patient contact 11. Pregnant or nursing women 12. Participation in any other interventional trial 13. Suspected lack of compliance 14. Fertile women (within two years of their last menstruation) without appropriate contraceptive measures (implanon, injections, oral contraceptives, intrauterine devices, partner with vasectomy) while participating in the trial (participants using a hormone-based method have to be informed of possible effects from the antiviral medication on contraception). 15. Patient is incapable to give informed consent

15 Information on the Test Product

Commercially available, approved nucleos(t)ide analogues (NUC) had to be used during the treatment phase **prior to** inclusion in the study.
Due to the nature of the trial patients in the experimental arm **stopped** taking any nucleos(t)ide analogues (NUC). In the case of treatment **re-initiation** in the experimental arm patients received standard nucleos(t)ide analogues (NUC) therapy according to current guidelines.

16 Duration of Intervention

- 96 weeks (resp. 108 weeks in the exceptional case that HBsAg loss is detected for the first time at the week 96 measurement) for the primary and key secondary endpoints
- Minimum of four and up to seven years after randomisation (for the first patients included) for the prolonged observation period

17 Reference Therapy

In the control arm patients received standard nucleos(t)ide analogues (NUC) therapy according to current guidelines.
This treatment may consist of monotherapy or a combined therapy with one or more of following drugs:

- Lamivudine
- Adefovir
- Telbivudine
- Entecavir
- Tenofovir

18 Criteria for Evaluation

18.1 Efficacy

Primary outcome measure was sustained HBsAg loss up to week 96.
HBsAg was 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 was for the first time not detectable, a further measurement was to be performed at week 108 in order to confirm the HBsAg loss.

Secondary efficacy endpoints were

- Sustained remission (i.e. HBV DNA < 2000 IU/mL and normal ALT levels, i.e. ALT < upper level normal) at week 96 in the non-treatment arm. Sustained remission is defined as HBV DNA < 2000 IU/mL and normal ALT levels in all subsequent assessments after the first occurrence of remission.
- HBsAg seroconversion status up to week 96 as a binary endpoint (anti-HBs detectable versus not detectable). HBsAg seroconversion is an event that follows HBsAg loss. Anti-HBs was measured regularly in patients with HBsAg loss in a central laboratory until week 96.
- Time to HBsAg loss, defined as time from randomisation to the first confirmed occurrence of HBsAg loss or to the last available measurement, if no HBsAg loss has been documented.
- Time to HBsAg seroconversion, defined as time from randomisation to the first time when anti-HBs are detectable or to the last available measurement, if no HBsAg seroconversion has been documented
- Virologic response at week 96 as a binary endpoint (HBV DNA > 20 IU/mL versus ≤ 20 IU/mL), measured at week 96 in the central laboratory.
- Biochemical response at week 96 as a binary endpoint (Alanine transaminase (ALT) > upper level normal (ULN) according to local laboratory versus ≤ ULN). ALT will be measured regularly in the local laboratory. Biochemical response refers to the upper level normal of the local laboratory.
- Optional: Liver stiffness in kPa by liver elastography (Fibroscan®) or by Acoustic Radiation Force Impulse (ARFI) in m/s at week 96
- Time to fulfilling criteria for re-therapy in the experimental (non-treatment) arm, defined as time from randomisation to the first time point when criteria for re-therapy are met or to the last visit, if the criteria have not been met.
- Number of ALT flares per patient, defined as ALT > 3x ULN after treatment discontinuation in the experimental (non-treatment) arm

18.2 Safety

The liver function (ALT, Bilirubin, PT or Quick or INR) as well as the virologic parameters, especially HBV DNA levels were regularly monitored. Patients fulfilling the criteria for severe hepatitis B reactivation or chronic hepatitis B reactivation in need for retreatment had to be immediately reported. In addition, adverse events were documented.

19 Statistical Methods/analysis procedures

A modified intention-to-treat (ITT) approach was applied for comparative analyses, including all randomized patients who had attended at least one regular trial visit. The primary endpoint was compared by Fisher's exact test. Wilson's score interval method was used to provide 95% confidence intervals for the efficacy rates and their difference. Secondary binary endpoints were analysed analogously to the primary endpoint. Time to event endpoints were described

with the Kaplan-Meier estimator. Changes in liver stiffness from baseline were analysed by ANCOVA. Exploratory subgroup analyses were predefined for the type of NUC before enrolment, and prior HBsAg levels.

20 Summary/Conclusion

20.1 Efficacy results

The primary endpoint is sustained HbsAg loss at week 96. A total of 8 / 79 patients in the experimental arm A (10.1%, 95% CI [4.8% - 19.5%]) and no patient in arm B (0%, 95% CI [0% - 5.8%]) experienced a sustained HBsAg loss (Fisher's exact test p=0.006).

Comparative secondary endpoints

HBsAg seroconversion (i.e. detectability of antiHBs) is an event that follows HBsAg loss. A total of 6 / 79 patients in the experimental arm A (7.6%, 95% CI [3.1% - 16.4%]) and no patient in arm B (0%, 95% CI [0% - 5.8%]) experienced HBsAg seroconversion (Fisher's exact test p=0.028).

The following Figures show time to HBsAg loss (Figure 1) and HBsAg seroconversion (Figure 2) by randomised arm.

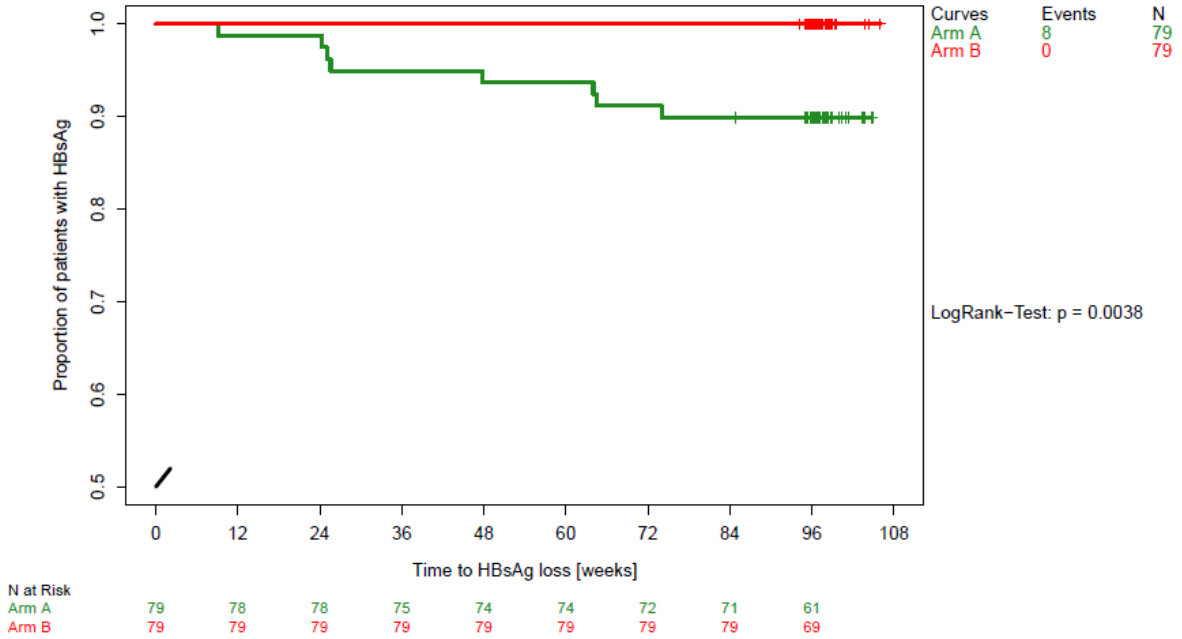

Figure 1: Time to HBsAg loss

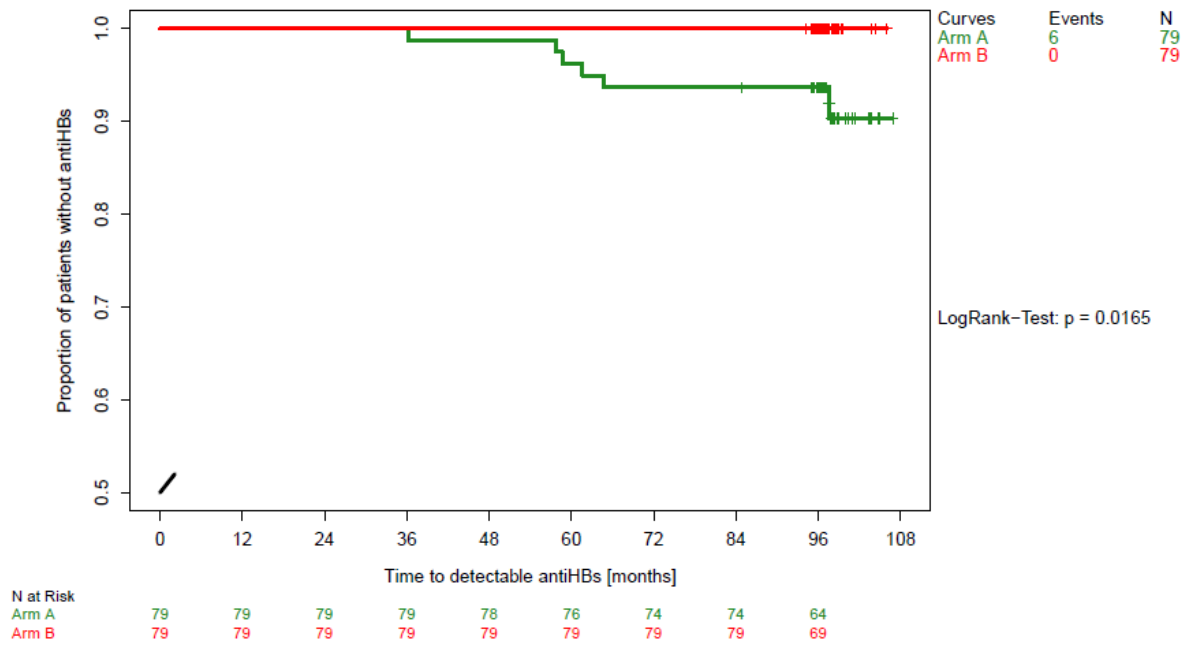

Figure 2: Time to HBsAg seroconversion

Liver stiffness measurements were scheduled at baseline and at visit 10. Both standard methods for measurement of liver stiffness (Fibroscan and ARFI) were allowed. However, trial sites were instructed to use the same method at baseline and at visit 10. Fibroscan results at baseline and visit 10 are available for 120 patients, and ARFI results for 19 patients, therefore only Fibroscan results are analysed. In Table 1 an analysis of covariance for the visit 10 result by randomisation arm is fitted, adjusting for the baseline result. The arm effect is not significant (p=0.329).

Covariates	Coefficient	Standard error	95% CI for the coefficient (lower limit)	95% CI for the coefficient (upper limit)	p value
(Intercept)	3.588	0.391	2.813	4.362	0.000
Fibroscan at baseline	0.326	0.062	0.203	0.450	0.000
Arm B - continue NUC-therapy	-0.246	0.251	-0.743	0.251	0.329

Table 1: Liver stiffness by Fibroscan – ANCOVA.

<u>Descriptive secondary endpoints in the experimental arm</u>

Virologic response at week 96 is claimed in case of HBV DNA ≤ 20 IU/ml. From the 79 patients in arm A, 11 had re-therapy and in one patient, central lab assessment is not available at week 96. In the remaining 67 patients in the experimental arm A without prior re-therapy and with central lab assessment at week 96, virologic response at week 96 was documented in14 patients (20.9%, 95% CI [12.3% - 32.9%]).

Biochemical response at week 96 is claimed in case of ALT ≤ ULN. In the 68 patients in the experimental arm A without prior re-therapy, biochemical response at week 96 was documented in 61 patients (89.7%, 95% CI [79.3% - 95.4%]).

According to the protocol, remission is defined as HBV DNA < 2000 IU/ml and normal ALT levels, i.e. ALT < upper level normal. Sustained remission is defined as HBV DNA < 2000 IU/ml and normal ALT levels in all subsequent assessments after the first occurrence of remission.

Sustained remission was achieved in 32 (47.8%, 95% CI [35.6% - 60.2%]) of 67 patients in in the experimental arm A without re-therapy and with central lab assessment at week 96.
ALT flares are defined as ALT > 3 ULN after treatment discontinuation. In total, 28 of the 79 patients in the experimental arm A (35.5%) experienced at least one ALT flare, with a mean of 0.37 ± 0.51 per patient.
Re-treatment with NUCs was initiated in 11 (13.9%) patients in the experimental arm A.

20.2 Safety results

In this study, 123 patients (66 in the experimental arm A, 57 in the control arm B) experienced a total of 441 adverse events (265 in arm A, 176 in arm B). The mean number of adverse events per patient was 2.8 ± 2.8 (3.4 ± 3.3 in arm A, 2.2 ± 2.1 in arm B). A total of 20 adverse events were classified as serious (17 in arm A, 3 in arm B). For more information on the serious adverse events, please see Table 2. None of the serious adverse events was related to NUC treatment, and none was related to discontinuation of NUC treatment.

Trial site	Patient	Randomised arm	AE (preferred term)	Severity	Relatedness (according to local assessment)	Outcome	Measures regarding study drug
Berlin (Checkpoint)	002-6	Arm A - stop NUC-therapy	Angina pectoris	Mild	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Tübingen	018-4	Arm A - stop NUC-therapy	Abortion	Severe	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Heidelberg	028-6	Arm A - stop NUC-therapy	Tibia fracture	Severe	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
			Joint injury	Severe	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
			Kidney rupture	Mild	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
			Rib fracture	Mild	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
			Splenic rupture	Mild	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Magdeburg	046-4	Arm A - stop NUC-therapy	Enteritis	Moderate	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Jena	078-5	Arm A - stop NUC-therapy	Influenza	Mild	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Aachen	097-6	Arm A - stop NUC-therapy	Ventricular tachycardia	Severe	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
			Atrial fibrillation	Severe	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Leipzig	118-5	Arm A - stop NUC-therapy	Acute myocardial infarction	Severe	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
			Stent placement	Severe	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Hamburg	135-0	Arm A - stop NUC-therapy	Inguinal hernia	Moderate	No reasonable possibility (during NUC-therapy)	Recovered	Dose not changed (Entecavir)
Magdeburg (Stein)	215-8	Arm A - stop NUC-therapy	Schwannoma	Moderate	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Jena	240-X	Arm A - stop NUC-therapy	Subileus	Severe	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Berlin (Checkpoint)	309-8	Arm A - stop NUC-therapy	Panic attack	Mild	No reasonable possibility (no NUC treatment)	Recovered	Not applicable
Hamburg	007-X	Arm B - continue NUC-therapy	Inflammation	Moderate	No reasonable possibility (during NUC-therapy)	Recovered	Dose not changed (Entecavir)
Leipzig	114-4	Arm B - continue NUC-therapy	Cerebrovascular accident	Life-Threatening	No reasonable possibility (during NUC-therapy)	Recovered	Dose not changed (Entecavir)
Stuttgart	150-0	Arm B - continue NUC-therapy	Gastritis	Severe	No reasonable possibility (during NUC-therapy)	Recovered	Dose not changed (Telbivudin)

Table 2 Serious adverse events

20.3 Conclusions

We observed an HBsAg loss rate, which is considered as functional cure in HBeAg-negative chronic Hepatitis B patients, of 10.1% at week 96 after NUC treatment, as compared to no patients who continued NUC therapy. Apart from HBsAg loss, a considerable proportion of patients achieved HBV DNA < 2,000 IU/mL and normal ALT values at the end of observation, and many patients were transferred into an inactive carrier state (40.5%) defined in our protocol as HBV DNA <2,000 IU/mL and normal ALT in all subsequent assessments after first occurrence. Importantly, only a minority of patients needed re-treatment (13.9%). Cessation of

NUC therapy in HBeAg-negative patients was effective in reaching treatment endpoints that cannot be achieved by long-term NUC treatment, and it therefore holds the potential to revolutionize the treatment for these patients. The powerful effect of NUC treatment cessation will need to be explored over longer time periods, but it may represent a step towards functional cure for many patients, especially those with low HBsAg levels, and it needs to be considered for novel treatment approaches (e.g., via ribonucleic acid interference mechanisms or immune stimulation) given in combination with NUCs for finite treatment durations.

21 Appendix

21.1 List of Investigators/Study Centres

Prof. Dr. Christoph Berg	**01 Tübingen** Uni. Klinik Tübingen Med. Klinik und Poliklinik Hep. Ambulanz 2 Otfried-Müller-Str. 10, 72076 Tübingen
Prof. Dr. Florian van Bömmel	**02 Leipzig** Universitätsklinikum Leipzig Sektion Hepatologie Klinik u. Poliklinik für Gastroenterologie u. Rheumatologie Liebigstraße 20, 04103 Leipzig
PD Dr. Matthias Dollinger	**03 Ulm** Universitätsklinikum Ulm Zentrum für Innere Medizin I, Hepatologie Albert-Einstein-Allee 23, 89070 Ulm
Prof. Dr. Guido Gerken	**04 Essen** Universitätsklinikum Essen (AöR) Medizinisches Zentrum Gastroenterologie und Hepatologie Hufelandstr. 55, 45147 Essen
Prof. Dr. Tobias Goeser	**05 Köln** Universitätsklinikum Köln (AöR) Klinik für Gastroenterologie und Hepatologie Kerpener Str. 62, 50937 Köln
Prof. Dr. Hans Bock	**06 Düsseldorf** Klinik für Gastroenterologie, Hepatologie und Infektiologie Leber- und Infektionszentrum, Geb. 13.57 Moorenstr. 5, 40225 Düsseldorf
Dr. Gisela Felten	**07 Gastroenterologische Gemeinschaftspraxis** Wiescherstr. 20, 44623 Herne
Prof. Dr. Marcin Krawczyk	**08 Homburg** Universitätsklinikum des Saarlandes Innere Medizin II, Gastroenterologie, Hepatologie, Endokrinologie Kirrbergerstraße 100, 66421 Homburg
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Prof. Dr. Jörg Petersen	**11 Leberzentrum Hamburg an der Asklepios Klinik St. Georg** Lohmühlenstraße 5, 20099 Hamburg
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PD Dr. Norbert Grüner	**13 LMU Klinikum Großhadern** Medizinischen Klinik und Poliklinik II Marchioninistraße 15, 81377 München
Prof. Dr. Stefan Zeuzem	**14 Frankfurt/Main** Klinikum der J.W. Goethe-Universität

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Prof. Dr. Birke Bausch	**17 Universitätsklinik Freiburg** Innere Medizin II Hugstetter Str. 55, 79106 Freiburg
Prof. Dr. Markus Cornberg	**19 Hannover** Medizinische Hochschule Hannover Klinik für Gastroenterologie, Hepatologie und Endokrinologie Carl-Neuberg-Str. 1, 30625 Hannover
PD Dr. Holger Hinrichsen	**20 Gastroenterologisch-Hepatologisches Zentrum Kiel** Goethestr. 11, 24116 Kiel
Prof. Dr. Andreas Stallmach	**21 Jena** Klinik für Innere Medizin KIM IV Am Klinikum 1, 07747 Jena
Dr. Andreas Trein	**22 Gemeinschaftspraxis** Schwabstrasse 59, 70197 Stuttgart
Prof. Dr. Tobias Müller	**23 Berlin (Virchow)** Charite Campus Virchow-Klinikum Medizinische Klinik m. S. Hepatologie und Gastroenterologie Augustenburger Platz 1, 13353 Berlin
Dr. Martin Sprinzl	**24 Mainz** Universitätsmedizin der Johannes-Gutenberg-Universität Mainz 1. Medizinische Klinik Langenbeckstr. 1, 55131 Mainz
Prof. Dr. Alexander Zipprich	**25 Halle** Klinik und Poliklinik für Innere Medizin I Universitätsklinikum Halle (Saale) Ernst-Grube-Str. 40 06120 Halle
Prof. Dr. Hartwig Klinker	**26 Würzburg** Universitätsklinikum Würzburg, Medizinische Klinik II, Oberdürrbacher Straße 6 97080 Würzburg
Dr. Kerstin Stein	**27 Magdeburg - Praxis** Breiter Weg 228m, 39104 Magdeburg
Dr. Karl-Georg Simon	**28 Leverkusen** MVZ Gastroenterologie Leverkusen, Franz-Kail-Str. 2, 51375 Leverkusen
Dr. Patrick Ingiliz	**29 Berlin** Zentrum für Infektiologie (zibp) Berlin, Driesener Str. 20, 10439 Berlin
Dr. Julian Schulze zur Wiesch	**30 Universitätsklinikum Hamburg-Eppendorf** I. Medizinische Klinik und Poliklinik, Martinistraße 52, 20246 Hamburg
Dr. Janina Trauth	**31 Universitätsklinikum Gießen** Medizinische Klinik II, Klinikstraße 33, 35385 Gießen

21.2 CONSORT Flow Diagram