Clinical Study Report

for

"Induction of Fibrosis Regression regarding Chronic Hepatitis B Infection"

[INFIRE]

Investigational Product: Baraclude ®

Indication: Patients with chronic hepatitis B viral infection and relevant fibrosis (≥ F2)

Study type: Multicentre, prospective, uncontrolled phase IV study

Study initiation (first enrolment): 2010-03-24

Early study termination: 2013-11-30

Date of report: 2014-10-15

Version of report: Clinical Study Report v1.0

EudraCT-No.: 2010-019884-12

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The study was performed in compliance with Good Clinical Practices (GCP).

1. SYNOPSIS

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Title	Induction of Fibrosis Regression regarding Chronic Hepatitis B Infection
Short title	INFIRE
Sponsor Protocol Code	INFIRE-001
Information about study protocol version(s):	First submission: Study protocol version 1.0 of 30.09.2010 Subsequent substantial amendments: Substantial Amendment 1: Study protocol version 2.0 of 17.04.2012
EudraCT number	2010-019884-12
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Target population (or indication)	Patients with chronic hepatitis B viral (cHBV) infection and relevant fibrosis (histologically $\geq$ F2)
Study design	Multi-centre, prospective, uncontrolled phase IV study
Study objectives	<u>Primary objective</u> Prospective evaluation of fibrosis regression for therapy with entecavir (Baraclude®) in patients with cHBV infection by means of non-invasive markers (FibroScan®, hyaluronic acid value) after 12 months <u>Secondary objectives</u> Prospective evaluation of fibrosis regression by means of procollagen III N peptide, TIMP-1 and YKL-40 after 12 months Investigation of diagnostic accuracy (on the basis of sensitivity and specificity) of the non-invasive markers (FibroScan®, serum parameters) with liver biopsy as gold standard Evaluation of the proportional decrease in liver fibrosis after 6, 18, 24 and 36 months therapy with entecavir by means of FibroScan® and serum parameters Assessment of the anti-viral efficacy and safety of three years therapy with entecavir for fibrosis regression Investigation of the relationship between fibrosis regression and the efficacy and kinetics of viral suppression with entecavir (Baraclude®) therapy
Study endpoints (targets)	<u>Co-primary endpoints</u> Change in the liver stiffness measurement (LSM) value measured with the FibroScan and the hyaluronic acid value after 12 months therapy with entecavir (Baraclude)

	Secondary endpoints • Change in the serum parameters procollagen III N peptide, TIMP-1 and YKL-40 after 12 months • Sensitivity and specificity of the FibroScan and the serum parameters compared with baseline with the result of the liver biopsy as gold standard • Change in the LSM value (from the FibroScan®) values and the serum parameters 6, 18, 24 and 36 months • Reduction of HBV-DNA and the fraction of patients with non-detectable HBV-DNA at the different study visits (6, 12, 18, 24 and 36 months) • Fraction of patients with ALT normalisation at the different study visits (6, 12, 18, 24 and 36 months) • Fraction of patients with HBeAg loss, anti-HBe sero-conversion, HBsAg loss and anti-HBs sero-conversion at the different study visits 6, 12, 18, 24 and 36 months) Safety endpoint Frequency of adverse reactions
Number of patients	100 (in approx. 14 centres)
Time Schedule	With regard to the overall study Recruitment: approx. 3 years Total: approx. 6 years With regard to the patients Duration of treatment: 3 years
Inclusion criteria	• Patients aged 18 to 75 years at the time of inclusion in the study • Written informed consent of the patient • Chronic hepatitis B infection (cHBV) with detectable HBV-DNA at study start • Availability of results from a recent liver biopsy. The date of the liver biopsy may not be more than 6 months before the day of the screening visit. • Evidence for relevant liver fibrosis in the liver histology after percutaneous or laparoscopic puncture (histologically ≥ F2) according to the assessment of an experienced pathologist and sufficient evaluability of the biopsy material (as a rule, evaluation of at least eight portal fields) or clinical evidence of a liver cirrhosis (on the basis of unequivocal endoscopic or sonographic indications). The number of patients included with *clinical* evidence for a liver cirrhosis may not exceed 40%. After inclusion of 40 patients (= 40%) with *clinical* evidence for a liver cirrhosis all study centres will be notified not to include more patients from this subgroup • Therapy indication according to the current guidelines for the cHBV infection (i.e. every virus replication in patients with liver cirrhosis or detection of an HBV-DNA ≥ 2000 IU/ml and/or liver histology with inflammation ≥ degree 2/ fibrosis ≥ stage 2 and ALT < 5 x ULN) • Non-pregnant (verified by a negative pregnancy test) and non-breast

	feeding women fulfilling at least one of the following criteria: – post-menopausal (12 months natural amenorrhea or six months amenorrhea with serum FSH > 40mIU/ml) – 6 weeks after operative sterilisation by bilateral tubal ligation or bilateral ovarectomy with or without hysterectomy – Correct use of two methods for reliable contraception. This includes any combination of a hormonal contraceptive (pill, intra-uterine spiral, depot injection, hormone implant, hormone patch or vaginal ring) or an intra-uterine device with spermicidal barrier contraceptive agent (diaphragm, cervical cap, lea contraceptivum, femidom or condom) or a spermacide – Sexual abstinence from two weeks before the first administration of the investigational medicinal product (IMP), during the entire duration of the study, and 30 days following the study, covering the elimination of the IMP – Patients with only female sexual partners – Male partner of a patient who is sterile before inclusion of the female patient in the study and is the only sexual partner of the female patient
Exclusion criteria	• Anamnestically known hypersensitivity to Baraclude® or its components or to medication with a similar chemical structure • Participation of the patient in another clinical study within the last four weeks before inclusion or simultaneous participation in another clinical study • Anamnestically known addictive or other disorders, which do not allow the person to assess the nature, impact and possible consequences of the clinical study • Indications that the patient will probably not comply with the study protocol (e.g. lack of willingness to co-operate) • Anamnestically known co-infection with hepatitis C, hepatitis D or HIV • Evidence for a hepatocellular carcinoma • Severe chronic disease with an estimated survival prognosis of less than three years • Any previous therapy with lamivudine or telbivudine or previous therapy within the last six months before inclusion in the clinical study with another active anti-viral drug • Contra-indications for taking entecavir • Creatinine clearance < 50ml/min and/or need for haemodialysis • MELD Score > 15 points and/ or evidence for ascites
Progress of the study	Study visit 1 (screening visit, day – 42 to – 1) Study visit 2 (baseline visit, day 0) Study visit 3 (month 6 ± 10 days) Study visit 4 (month 12 ± 30 days) Study visit 5 (month 18 ± 30 days) Study visit 6 (month 24 ± 30 days) Study visit 7 (end of study visit, month 36 ± 30 days)

<table>
<tr><td>Investigational medicinal product</td><td>Trade name: Baraclude
Active substance: Entecavir
Manufacturer: Bristol-Myers Squibb</td></tr>
<tr><td>Treatment plan</td><td>IMP: Entecavir
Dose: 0.5 mg/day
Route of administration: oral
Frequency: 1-0-0
Duration of therapy: 3 years
(or until anti-HBs sero-conversion or at least 12 months after anti-HBe sero-conversion and HBeAg loss)</td></tr>
<tr><td>Statistical methods</td><td>For the primary analysis a two-factor ANCOVA with a two-sided type one error of 5% will be used. An adjustment of the type one error is not required, as both primary hypotheses must be rejected. For the LSM value the ANCOVA is used with the logarithmic data and for the hyaluronic acid value the untransformed values. In each case the target variable is the change in the value (at 12 months – baseline), the factors are the centre and cirrhosis yes/no, and the baseline values is taken as the co-variable.
The secondary endpoints are descriptively analysed with point and interval estimators.</td></tr>
<tr><td>Major protocol deviations in the conduct of the study</td><td>The study was stopped prematurely after 2.8 years due to a very weak recruitment. Only 10 (of 100 required) patients have been included until study termination as not enough patients with higher grades of fibrosis could be determined as initially expected.
Two patients were included to the study and received study medication even though two inclusion criteria were not fulfilled. The co-primary efficacy endpoint hyaluronic acid has not been measured for any of the patients and was not analysed. The primary analysis strategy (ANCOVA) was neither reasonable nor applicable in a setting with only 10 recruited patients. A paired t-test for logarithmic LSM was used instead.</td></tr>
<tr><td>Efficacy results</td><td>In the primary analysis the paired t-test revealed a significant result for fibrosis regression on therapy with entecavir (Baraclude ®) in patients with cHBV infection after 12 months. The back-transformed point estimate for the fold change from baseline is 0.78, that means LSM-values were significantly decreased by approx. 20-25% from baseline to 12 months:

<table>
<tr><th>Comparison</th><th>Mean fold change</th><th>lower limit 95% CI</th><th>upper limit 95% CI</th><th>p-value</th></tr>
<tr><td>12 months vs. baseline</td><td>0.78</td><td>0.61</td><td>0.99</td><td>0.040</td></tr>
</table>

A sensitivity analysis in the PP-population instead of the ITT-population supported these results. All analyses have been performed with SAS 9.3.</td></tr>
<tr><td>Safety results</td><td>A total of 26 adverse events occurred in 6 patients, that means 60% of the study population had at least one AE. One patient had 10 adverse events.</td></tr>
</table>

	3/26 adverse events (11.5%) were assessed to have a causal relationship to the study medication. All further AEs were assessed to have no causal relationship. A total of 2 serious adverse events occurred in 1 patient, that means 10% of the study population had SAEs. Both SAEs were gastrointestinal disorders and were assessed to have no causal relationship to the study treatment.
Conclusions	Treatment with Baraclude–® is safe and leads to fibrosis regression in patients with chronic HBV infection.

Name of active Substance

Medication: Entecavir
Chargennumber: C1302021
Dosage: 0,5 mg/Tag
Application: oral
Frequency: 1-0-0
Duration of therapy: 5 years
(or until seroconversion to anti-HBs respectively until 6-12 months after anti-HBe Serokonversion and loss of HBeAg)

Secondary objectives of the study

The secondary objectives of the study are:
a) the determination of fibrosis regression after 12 months, measured on the basis of procollagen III N peptide, TIMP-1 and YKL-40.
b) the investigation of diagnostic accuracy (on the basis of sensitivity and specificity) of the FibroScan and the serum parameters (hyaluronic acid, procollagen III N peptide, TIMP-1 and YKL-40) with liver biopsy as gold standard
c) the evaluation of fibrosis regression at the other study visits (6, 18, 24 and 36 months) by Fibroscan and the serum parameters. This can furnish the answer to the question of whether the liver fibrosis regresses continuously or exponentially.
d) the assessment of the anti-viral efficacy and safety of three years therapy with entecavir for the regression of fibrosis.
e) the investigation of the relationship between fibrosis regression and the efficacy and kinetics of viral suppression with entecavir (Baraclude) therapy.

EFFICACY EVALUATION

10.1 Data Sets Analysed

As defined in the study protocol, the primary analysis was performed on the **ITT population** including
all patients who have taken the trial medication at least once.
Secondary analyses were performed in a **PP population** (per-protocol) with all included patients having a measured value for the respective response variable at the respective time point. Patients with violated in- or exclusion criteria were nevertheless included to the PP population.
Safety analyses were performed on the ITT population (see above).
The study was stopped prematurely after 10 patients. Thus no extensive sensitivity analyses on different data sets have been done for the primary analysis. The primary analysis was only performed on the ITT and PP data set.

10.2 Descriptive Analysis

10.2.1 Demographics and Baseline Characteristics measured at Baseline only

Demographic Data			
		absolute	relative
Gender	female	2	20.0%
	male	8	80.0%
Ethnic origin	Caucasian	10	100.0%
Study site	Frankfurt/Main	2	20.0%
	Aachen	3	30.0%
	Bonn	2	20.0%
	Hamburg	1	10.0%
	Würzburg	2	20.0%
Age	N	10	
	MISSING	0	
	MEAN	37.50	
	STD	13.52	
	MIN	18	
	MEDIAN	39.50	
	MAX	56	
	95% CI MEAN	[27.83 ; 47.17]	

Liver biopsy was available for 8/10 patients (80%). Two patients were included without having an appropriate recent liver biopsy from the last 6 months.
Only one patient had liver cirrhosis (Pat-ID = 161). His MELD-Score was 11.

Liver biopsy			
		V1=Screening	
		absolute	relative
Staging	MISSING	2	
	2 - moderate fibrosis	4	50.0%
	3 - severe fibrosis	3	37.5%
	4 - cirrhosis	1	12.5%
Grading	MISSING	2	
	1 - minimal	4	50.0%
	2 - mild	2	25.0%
	3 - moderate	2	25.0%

HBV Serology			
		absolute	relative
anti-HBc	negative	1	10.0%
	positive	8	80.0%
	not done	1	10.0%
IgM-anti-HBc	negative	9	90.0%
	not done	1	10.0%
HBV-Genotype	A	2	20.0%
	D	6	60.0%
	E	1	10.0%
	Not done	1	10.0%

HCV, HDV, HIV - Serology			
		absolute	relative
Anti-HDV	negative	10	100.0%
Anti-HCV	negative	10	100.0%
Anti-HIV 1/2	Missing	1	
	negative	9	100.0%

Autoantibodies			
		absolute	relative
SMA	negative	5	50.0%
	positive	4	40.0%
	not done	1	10.0%
ANA	negative	6	60.0%
	positive	4	40.0%
AMA	negative	10	100.0%

		absolute	relative
Any comorbidity in medical history	no	4	40.0%
	yes	6	60.0%
Any concomitant medication	no	3	30.0%
	yes	7	70.0%

Comorbidities were existent in 6 patients (60%). A total number of 18 comorbidities were recorded. Seven patients (70%) had concomitant medication before and during the trial. A total of 46 concomitant medication was recorded. One patient had an exceptionally high intake of comedication with 17 items (Pat-ID = 182).
Frequency tables and full listings of all comorbidities and concomitant medication can be found in section 15. Please recognize that comorbidities were not MedDRA-coded in the dataset.
Comorbidities were neither combined for similar terms nor categorized in main- and sub-categories for the statistical analysis. The same applies to concomitant medication terms.

Number of comorbidities in medical history	Frequency of patients with comorbidities	
	absolute	relative
0	4	40.0%
1	2	20.0%
2	1	10.0%
3	1	10.0%
5	1	10.0%
6	1	10.0%

Number of concomitant medications	Frequency of patients with concomitant medications	
	absolute	relative
0	3	30.0%
1	3	30.0%
5	2	20.0%
7	1	10.0%
17	1	10.0%

Urine analysis			
		absolute	relative
protein	Missing	1	
	negative	7	77.8%
	positive	2	22.2%
bilirubin	Missing	1	
	negative	8	88.9%
	positive	1	11.1%
urobilinogen	Missing	1	
	negative	7	77.8%
	positive	2	22.2%
acetone	Missing	1	
	negative	5	55.6%
	not performed	4	44.4%
crystals	Missing	9	
	not performed	1	100.0%
cylinders	Missing	9	
	not present	1	100.0%
glucose	Missing	1	
	negative	8	88.9%
	positive	1	11.1%
nitrites	Missing	1	
	negative	9	100.0%
[illegible]	Missing	1	

Urine analysis			
		absolute	relative
	negative	8	88.9%
	positive	1	11.1%
leukocytes	Missing	9	
	present	1	100.0%
unrine	Missing	9	
	present	1	100.0%
bacteria	Missing	9	
	present	1	100.0%
Squamous cells	Missing	9	
	present	1	100.0%
Urine pH-value	N	9	
	MISSING	1	
	MEAN	6.22	
	STD	0.97	
	MIN	5	
	MEDIAN	6	
	MAX	8	
	95% CI MEAN	[5.48 ; 6.97]	

ECG			
		absolute	relative
ECG performed	No	4	40.0%
	Yes	6	60.0%
ECG result	MISSING	4	
	normal	5	83.3%
	pathological	1	16.7%
ECG pathology clin. relevant	Missing	9	
	No	1	100.0%

10.4 Efficacy Results and Tabulations of Individual Patient Data

10.4.1 Analysis of efficacy

Primary efficacy analysis

In the primary analysis the paired t-test revealed a significant result. The back-transformed point estimate for the fold change from baseline is 0.78, that means LSM-values were significantly decreased by approx. 20-25% from baseline to 12 months:

Comparison	Mean fold change	lower limit 95% CI	upper limit 95% CI	p-value
12 months vs. baseline	0.78	0.61	0.99	0.040

A sensitivity analysis in the PP-population instead of the ITT-population supports these results:

Comparison	Mean fold change	lower limit 95% CI	upper limit 95% CI	p-value
12 months vs. baseline	0.73	0.55	0.98	0.041

Secondary efficacy analyses

Not all of the pre-defined secondary objectives and secondary endpoints could be analyzed (see also section 10.2 Protocol Deviations).

a) ~~Determination of fibrosis regression after 12 months, measured on the basis of procollagen III N peptide, TIMP-1 and YKL-40.~~
   → endpoints not measured

b) Investigation of diagnostic accuracy (on the basis of sensitivity and specificity) of the FibroScan ~~and the serum parameters (hyaluronic acid, procollagen III N peptide, TIMP-1 and YKL-40)~~ with liver biopsy as gold standard.
   → endpoints not measured

c) Evaluation of fibrosis regression at the other study visits (6, 18, 24 ~~and 36~~ months) by Fibroscan ~~and the serum parameters~~. This can furnish the answer to the question of whether the liver fibrosis regresses continuously or exponentially.
   → 3 years not reached, endpoints not measured

d) ~~Assessment of the anti-viral efficacy and safety of three years therapy with entecavir for the regression of fibrosis.~~
   → 3 years therapy not reached

e) ~~Investigation of the relationship between fibrosis regression and the efficacy and kinetics of viral suppression with entecavir (Baraclude) therapy.~~
   → 3 years not reached, sample size too small

f) Reduction of HBV-DNA and the fraction of patients with non-detectable HBV-DNA at the different study visits (6, 12, 18, 24 ~~and 36~~ months)

g) Fraction of patients with ALT normalisation at the different study visits (6, 12, 18, 24 ~~and 36~~ months)

h) Fraction of patients with HBeAg loss, anti-HBe sero-conversion, HBsAg loss and anti-HBs sero-conversion at the different study visits 6, 12, 18, 24 ~~and 36~~ months)

b) Investigation of the diagnostic accuracy of FibroScan LSM-values:
The diagnostic test under evaluation is the Fibroscan LSM-median at baseline. It is compared to the diagnostic goldstandard liver biopsy.
LSM-median values are already established in the diagnosis and grading of fibrosis. The commonly used cutpoints for the different grades (Castera et al., 2008) were used in this analysis:

Fibrosis Grading in liver biopsy		LSM-cutpoints
F0-F1	none – mild	≤ 7
F2	moderate	(7, 9.5]
F3	severe	(9.5, 12.5]
F4	Cirrhosis	> 12.5

Diagnostic accuracy as determined by sensitivity and specificity was investigated for a cutoff between F2 and F3, i.e. for the diagnosis of "mild to moderate fibrosis" vs. "severe fibrosis or cirrhosis". Results for n=8 patients with an available goldstandard show a rather low agreement for the grading of fibrosis (only 3/8 correct classifications = 37.5%), but sensitivity and specificity are adequate with 75% each. No confidence limits are calculated due to the very small sample size in each group.

		Liver biopsy grading				
		F1	F2	F3	F4	total
LSM grading	F1	0	2	0	0	2
	F2	0	1	1	0	2
	F3	0	0	1	0	1
	F4	0	1	1	1	3
	total	0	4	3	1	8

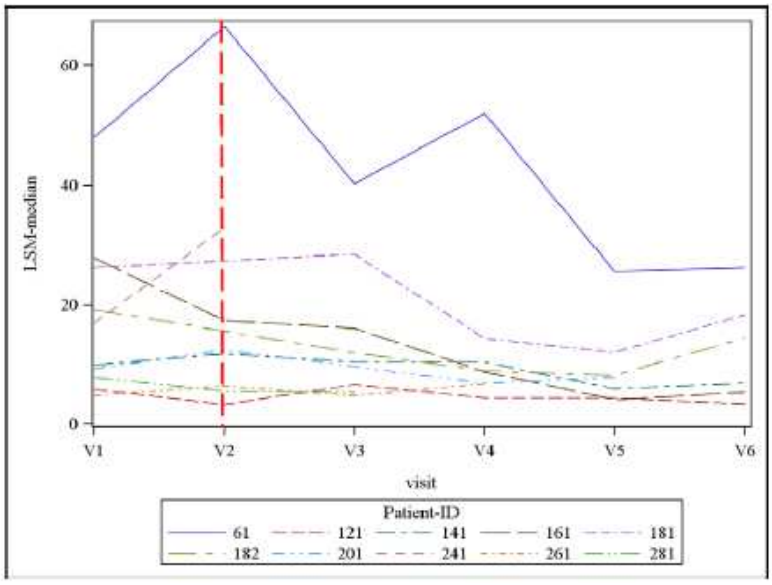
		Liver biopsy		
		F1/F2	F3/F4	Total
LSM	F1/F2	3 75.00%	1 25.00%	4
	F3/F4	1 25.00%	3 75.00%	4
	total	4	4	8

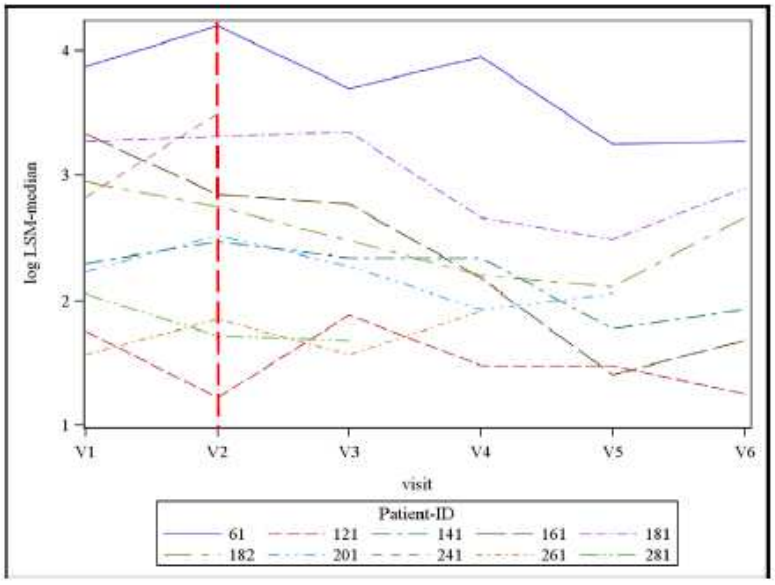
c) Evaluation of fibrosis regression at the other study visits (6, 18, 24 months) by Fibroscan to investigate if the liver fibrosis regresses continuously or exponentially:

Results of Fibroscan LSM-median values have been presented in section 11.2.2 for the untransformed, directly measured values. These results are repeated here and complemented by the descriptive measures per visit of the log-transformed LSM-medians.

Fibroscan							
		V1=Screening	V2=Baseline	V3=after 6 months	V4=after 12 months	V5=after 18 months	V6=after 24 months
LSM median	N	10	9	9	8	7	6
	MISSING	0	1	1	2	3	4
	MEAN	17.6	19.1	14.8	14.1	9.7	12.5
	STD	13.5	19.8	12.0	15.6	7.5	8.8
	MIN	4.8	3.4	4.8	4.4	4.1	3.5
	MEDIAN	13.4	12.4	10.4	8.9	7.8	10.7
	MAX	48.0	66.5	40.3	52.0	25.7	26.3
	95% CI MEAN	[7.9 ; 27.2]	[3.9 ; 34.4]	[5.6 ; 24.1]	[1.0 ; 27.1]	[2.8 ; 16.7]	[3.2 ; 21.7]
log LSM median	N	10	9	9	8	7	6
	MISSING	0	1	1	2	3	4
	MEAN	2.6	2.6	2.5	2.3	2.1	2.3
	STD	0.8	0.9	0.7	0.7	0.6	0.8
	MIN	1.6	1.2	1.6	1.5	1.4	1.3
	MEDIAN	2.6	2.5	2.3	2.2	2.1	2.3
	MAX	3.9	4.2	3.7	4.0	3.2	3.3
	95% CI MEAN	[2.1 ; 3.2]	[1.9 ; 3.3]	[1.9 ; 3.0]	[1.7 ; 2.9]	[1.5 ; 2.7]	[1.5 ; 3.1]

The results on a patient level are displayed in a spaghetti plot for the original as well as for the log-transformed LSM-medians. The red line depicts the treatment start with the study medication at baseline.





There seems to be a decline in liver fibrosis measured by LSM-median values, but the data base is too sparse to reliably detect any shape of the curve (e.g. linear, exponential, unstructured, etc.).
In further analyses, exploratory paired t-tests comparing baseline to the secondary follow-up visits were performed on the respective PP-population. Significant declines were observed for all time

points after 12 months. It has to be noticed that an increase in log-LSM values could be observed at 24 months compared to 18 months (4 patients increase again, 1 patient unchanged, 1 patient slightly decreased), but this result was not significant.

Comparison	Mean fold change	lower limit 95% CI	upper limit 95% CI	p-value
6 months (V3) vs. baseline	0.91	0.71	1.18	0.440
12 months (V4) vs. baseline	0.73	0.55	0.98	0.041
18 months (V5) vs. baseline	0.51	0.32	0.82	0.013
24 months (V6) vs. baseline	0.60	0.37	0.98	0.045
24 months vs. 18 months	1.23	0.91	1.65	0.143

f) Reduction of HBV-DNA and the fraction of patients with non-detectable HBV-DNA
HBV-DNA could be reduced considerably in the course of the study. The original data is displayed for each patient in the following table. There were different detection limits in the different study sites. Values of HBV-DNA under the respective detection limit are marked as bold and red in the table.

The fraction of patients with non-detectable HBV-DNA is 80% (8/10). The one patient lost-to-follow-up did not reach non-detectable HBV-DNA. The other patient with still detectable HBV-DNA had an extremely high starting value.

HBV-DNA						
Pat-ID	**V1=Screening**	**V2=Baseline**	**V3=after 6 months**	**V4=after 12 months**	**V5=after 18 months**	**V6=after 24 months**
61	29	118	34	115	10	0
121	7000	60000	100	20	10	10
141	35044139	11279964	17	.	0	9
161	15142	2447	14	.	9	9
181	4500000	1700000	12	6	6	6
182	6400	2600	6	6	6	6
201	294117	294117	10	10	0	.
241	200	34	.	.	.	.
261	170000000	170000000	694	80	64	.
281	4660	4780	20	20	.	.

g) Fraction of patients with ALT normalisation

ALT normalisation is defined as a reduction from above 45 to stable values below 45. In this study, 4 patients had constantly normal ALT (40%). Of the other 6 patients with increased ALT values at baseline, 4 patients (66.7%) reached ALT normalisation.

ALT						
Pat-ID	V1=Screening	V2=Baseline	V3=after 6 months	V4=after 12 months	V5=after 18 months	V6=after 24 months
61	72	65.0	53.0	54.0	31.0	33.0
121	25	21.0	30.0	16.0	16.0	20.0
141	105	103.0	32.0	36.0	45.0	67.0
161	38	25.0	21.0	28.0	33.0	37.0
181	100	123.5	34.8	27.7	27.2	30.3
182	146	182.0	160.8	116.2	100.4	36.0
201	46	41.0	38.0	35.0	39.0	.
241	32	37.0	.	.	.	.
261	46	.	29.0	19.0	21.0	.
281	34	.	19.0	20.0	.	.

h) Fraction of patients with HBeAg loss, anti-HBe sero-conversion, HBsAg loss and anti-HBs sero-conversion:

Descriptive results of these variables are shown in section 11.2.2 and can be summarized to the following.

Event	Freq.	Comment
HBeAG losses	0%	8 pat. always negative, 1 pat. always positive, 1 pat. unstable
anti-HBe seroconversion	0%	
HBsAG losses	0%	10 patients always positive
anti-HBs seroconversion	0%	

Observations for the unstable patient:

HBeAG						
Pat-ID	V1=Screening	V2=Baseline	V3=after 6 months	V4=after 12 months	V5=after 18 months	V6=after 24 months
181	negative	positive	negative	negative	positive	negative

10.4.7 Efficacy conclusions

In the primary analysis the paired t-test revealed a significant result for fibrosis regression on therapy with entecavir (Baraclude ®) in patients with cHBV infection after 12 months. The back-transformed point estimate for the fold change from baseline is 0.78, that means LSM-values were significantly decreased by approx. 20-25% from baseline to 12 months:

Comparison	Mean fold change	lower limit 95% CI	upper limit 95% CI	p-value
12 months vs. baseline	0.78	0.61	0.99	0.040

A sensitivity analysis in the PP-population instead of the ITT-population supported these results.

11 SAFETY EVALUATION

11.1 Extent of Exposure

All 10 included patients were exposed to the study medication. The patient lost-to-follow-up did not attend the first visit after treatment initiation (6-months after Baseline), but he returned medication and declared that he has taken the medication. Information about the administered doses for each patient and about the duration of exposure is presented in section 11.4.4.

11.2 Adverse Events (AEs)

Adverse events were not MedDRA-coded in the dataset. Adverse events were neither combined for similar terms nor categorized in main- and sub-categories for the statistical analysis. Thus, only rough frequency calculations have been performed,

11.2.1 Brief summary of adverse events

A total of 26 adverse events occurred in 6 patients, that means 60% of the study population had at least one AE. One patient (Pat-ID = 182) had 10 adverse events.

Total number of Adverse Events	26

	Frequency	
	absolute	relative
Number of patients	10	100.0%
Number of patients with at least one Adverse Event	6	60.0%

	Frequency of patients with adverse events	
Number of adverse events	**absolute**	**relative**
0	4	40.0%
2	1	10.0%
3	2	20.0%
4	2	20.0%
10	1	10.0%

11.2.2 Display of adverse events

	Frequency	
	absolute	**relative**
Antrumgastritis	1	10.0%
Blähungen	1	10.0%
Depression	1	10.0%
Durchblutungsstörung	1	10.0%
Dyspepsie	1	10.0%
Dyspnoe	1	10.0%
Gereiztheit	1	10.0%
Gliederschmerzen	1	10.0%
Helicobacter pylori positiv	1	10.0%
Hypercholesterinämie	1	10.0%
Hypothyreose	1	10.0%
kidney cyst	1	10.0%
Konzentrationsstörungen	1	10.0%
Kopfschmerzen	2	20.0%
muscular back pain	1	10.0%
Obstipation	1	10.0%
Oesophagal varicosal bleeding	1	10.0%
Pityriasis versicolor	1	10.0%
reduzierte Leistungsfähigkeit	1	10.0%
right chest pain	1	10.0%
Schlafstörungen	1	10.0%

Tendon injury (right DII)	1	10.0%
TIPS-Insertion because of fundus varicosis and prominent abdominal varicosis	1	10.0%
Vertigo	1	10.0%
weight loss	1	10.0%

Table 1: INFIRE- Listing of -all Adverse Events-

11.2.3 Analysis of adverse events

See section 12.2.1 and 12.2.2.

3/26 adverse events (11.5%) were assessed to have a causal relationship to the study medication. All further AEs were assessed to have no causal relationship. A complete listing of all AEs with their outcome, intensity and causality can be found in section 15.

Pat-ID	Adverse events	Outcome	Intensity	Causality to INFIRE regimen?
61	Obstipation	recovered	mild	yes
61	Dyspepsie	recovered	mild	yes
161	Kopfschmerzen	not recovered	moderate	yes

11.2.4 Listing of adverse events by patient

Listings are provided in section 15.

11.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

11.3.1 Listing of deaths, other serious adverse events, and other significant adverse events

Not applicable.

11.3.1.1 Deaths

No patient died within the study period.

11.3.1.2 Other Serious Adverse Events

A total of 2 serious adverse events occurred in 1 patient, that means 10% of the study population had SAEs. Both SAEs were gastrointestinal disorders and were assessed to have no causal relationship to the study treatment.

Total number of Serious Adverse Events	2	
	Frequency	
	absolute	relative
Number of patients	10	100.0%
Number of patients with at least one Serious Adverse Event	1	10.0%

SOC	Gastrointestinal disorders	2	20.0%
PT	Gastric varices	1	10.0%
	Oesophageal haemorrhage	1	10.0%

Table 2: INFIRE-Listing of all Serious Adverse Events

11.3.1.3 Other Significant Adverse Events

None.

11.3.2 Narratives of deaths, other serious adverse events, and certain other significant adverse events

Not applicable.

11.3.3 Analysis and discussion of deaths, other serious adverse events, and other significant adverse events

There were no deaths, no serious adverse events and no significant adverse events.

11.6 Safety Conclusions

A total of 26 adverse events occurred in 6 patients, that means 60% of the study population had at least one AE. One patient had 10 adverse events.
3/26 adverse events (11.5%) were assessed to have a causal relationship to the study medication. All further AEs were assessed to have no causal relationship.
A total of 2 serious adverse events occurred in 1 patient, that means 10% of the study population had SAEs. Both SAEs were gastrointestinal disorders and were assessed to have no causal relationship to the study treatment.

12 DISCUSSION AND OVERALL CONCLUSIONS

Treatment with Baraclude® is safe and leads to fibrosis regression in patients with chronic HBV infection. It should be noted that due to an early study termination, analysis and conclusions are only based on 10 patients.