# 1. NIS INFORMATION

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| **Title** | Real Life, Long-term Effectiveness and Safety of Zutectra® Self-Administration for HBV Re-Infection Prophylaxis after Liver Transplantation in France and Spain |
| **NIS-Number:** | Zutectra NIS-14 |
| **Version identifier of the final study report** | Final 1.0 |
| **Date of last version of the final study report** | 17-June-2021 |
| **ENCEPP register number** | 8116 |
| **Active substance** | 1 mL Zutectra® contains:<br>Human protein 150 mg of which at least 96 % is IgG, with a content of antibodies to hepatitis B virus surface antigen (HBs) of 500 IU.<br>(ATC code: J06BB04) |
| **Medicinal product** | Zutectra® |
| **Product reference** | EU/1/09/600/001 |
| **Marketing authorisation holder(s)** | Biotest Pharma GmbH<br>Landsteinerstrasse 5<br>D-63303 Dreieich, Germany<br>Phone: +49 6103 801-0 |
| **Research question and objectives** | Prospective documentation of long-term effectiveness, safety, convenience and patient adherence to Zutectra® subcutaneous self-administration for protection from HBV-recurrence after liver transplantation (LT) aiming at confirmation of existing data under real life conditions. |
| **Country(-ies) of study** | France, Spain |
| **Author(s)** | [redacted]<br>Senior Director Corp. Medical Affairs<br>Biotest AG<br>Landsteinerstraße 5<br>63303 Dreieich, Germany<br>[redacted]<br>Steinbeis Beratungszentrum<br>medACT − Analysis of Clinical Trials<br>Hermann-von-Vicari-Straße 37<br>78464 Konstanz, Germany |

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# 3. ABSTRACT


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| **Title** | Real Life, Long-term Effectiveness and Safety of Zutectra® Self-Administration for HBV Re-Infection Prophylaxis after Liver Transplantation in France and Spain |
| **Keywords** | Hepatitis B immunoglobulin (HBIg), hepatitis B virus (HBV), HBV-induced hepatocellular carcinoma (HBV-HCC), HBV recurrence, nucleos(t)ide analogue (NUC), liver transplantation (LT) |
| **Rationale and Background** | Data from clinical trials have demonstrated that prevention of HBV recurrence after LT by subcutaneous self-administration of HBIg in combination with NUC(s) is effective and safe. Clinical results and compliance with self-treatment under home care conditions have been confirmed by one non-interventional post-approval safety study (NIS-PASS) in Germany in 61 patients (median treatment duration: 18 weeks). The current study was performed to increase the volume of data in an international setting and to extend the documented treatment period to two years. In addition, patient adherence to Zutectra® treatment, patient satisfaction, and quality of life were included as secondary objectives. |
| **Research question and objectives** | Prospective documentation of long-term effectiveness, safety, convenience and patient adherence to Zutectra® subcutaneous self-administration for protection from HBV-recurrence after LT aiming at confirmation of the existing dataset under real-life conditions in France and Spain. |
| **Study design** | This was a non-interventional, prospective, single-arm, multicentre, international post-approval study.<br>HBV treatment-related information were to be collected under routine treatment conditions. Patients should have been documented from treatment start over a period of two years. All baseline data and the first planned Zutectra® treatment were to be documented at the baseline visit (BL). Data were then to be collected at all subsequent clinic visits that occurred as per normal practice. Visits relevant for analysis were the follow-up visits after 3 months (3-month FU) and after two years (2-year FU). In addition, a last available visit value analysis was done (FU last). |
| **Setting** | Clinical centres performing LT: 19 hospitals in France and Spain. |
| **Subjects and Study Size** | It was planned to include 200 patients. Patients were eligible for documentation if they met all of the following criteria:<br>• Patients 18 years or older.<br>• Patients with LT for fulminant hepatitis B, hepatitis B–cirrhosis, or HBV-induced HBV-HCC, or with liver re-transplantation except due to HBV recurrence.<br>• Subjects under Zutectra® treatment without or with a virostatic (NUC) treatment.<br>• Written informed consent to allow data collection and data transfer to third party. |

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| | In total, 202 patients signed the informed consent form and were included in the full data set (FDS). The full analysis set (FAS = patients treated with Zutectra® and eligible by inclusion criteria) comprised 195 patients (96.5% of 202 patients). Two subgroups were analysed based on the FAS: patients with HBV-HCC as main reason for LT (n=83) and patients with hepatitis D virus (HDV) co-infection (n=43 patients). |
| **Variables and data sources** | Primary variables:<br>• Proportion of patients with/without HBV recurrence after LT;<br>• Incidence rate per year of HBV recurrence after LT;<br>• Time to HBV recurrence after LT;<br>• Proportion and type of adverse events (AEs) including seriousness and relatedness.<br>Secondary variables:<br>• Serum trough levels of anti-HBs;<br>• Proportion of patients with anti-HBs < or ≥ 100 IU/mL;<br>• Proportion of subjects with recurrence of HBV-HCC after LT;<br>• Incidence rate/year of HBV-HCC recurrence after LT;<br>• Time to HBV-HCC recurrence after LT.<br>• Proportion of subjects with occurrence of new cancer(s) other than HCC after LT;<br>• Incidence rate/year of new cancer(s) other than HCC after LT;<br>• Time to occurrence of new cancer(s) other than HCC after LT.<br>• Time to start with Zutectra® after LT;<br>• Frequency of Zutectra® administration;<br>• Dose of Zutectra® applied;<br>• Number of self-administrations performed;<br>• Number of treatments at home and at the clinic;<br>• Immunosuppressive treatment;<br>• Viral status (serum level of HBsAg, HBeAg, HBV DNA);<br>• Laboratory parameters (liver and kidney function);<br>• Quality of life (EuroQol EQ-5D questionnaire);<br>• Subject satisfaction (TSQM-11 questionnaire).<br>Additional variables:<br>• Acute rejection episode;<br>• Chronic rejection episodes and other complications;<br>• Overall and disease-free survival.<br>Study-relevant data were collected prospectively at patient visits and could be extracted from source documents which may have included clinical records, patient files, laboratory reports, and treatment diaries. |
| **Results** | All descriptive and main results summarised below refer to the total FAS (n=195; male: 82.1%; mean age: 58.4 ± 10.5 years), except if otherwise stated. Results of subgroup analyses are presented only for primary variables. |

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| | *Medical history*<br>The most frequent HBV-related main reason for the last LT was HBV-induced liver cirrhosis (n=100, 51.3%), followed by HBV-HCC (n=83, 42.6%), and HBV-induced fulminant hepatitis (n=12, 6.2%). The status of liver disease at the time of LT was 'compensated' in 89 patients (45.6%) and 'decompensated' in 106 patients (54.4%).<br>*Immunosuppressive treatment after LT*<br>Immunosuppressives were received after LT by ≥ 99% of the patients at each documentation time point. Most common were calcineurin inhibitors (e.g. 79.5% at the 2-year FU) and mycophenolated mofetil (63.7% at the 2-year FU.<br>*Concomitant antiviral treatment*<br>At least one concomitant antiviral medication was documented in 162 patients (83.1%). NUCs were the most frequent concomitant antivirals (n=159, 98.2% of 162 patients) with tenofovir disoproxil (n=63, 38.9%), entecavir (n=59, 36.4%), and lamivudine (n=39, 24.1%) being the most common individual drugs. Concomitant treatment with HBIgs were reported in 18 patients (11.1%).<br>*Exposure to Zutectra®*<br>The median duration of treatment was 23.8 months and the median average monthly dose was 1087.1 IU. The most frequent dosing interval was biweekly (n=134, 68.7%), followed by weekly (n=108, 55.4%), every 4 weeks/monthly (n=73, 37.4%), and every 3 weeks (n=66, 33.8%); other dosing intervals were reported in 12 patients (6.2%). Dosing intervals could have changed during the study period. At least one change in treatment was documented in 111 patients (56.9%). Zutectra® was mainly self-administered (71.6% of 9021 administrations) at home (94.4% of 9021 administrations).<br>*HBV recurrence after LT*<br>HBV recurrence was not documented or observed based on non-detectability of serum HBsAg and/or HBV DNA in 188 patients (96.4%) and was detected in 7 patients (3.6%). The incidence rate of HBV recurrence per year was 2.01%. The median time to HBV recurrence was 18.5 months (range: 13.1 to 34.6 months). HBV recurrence based on HBV DNA detectability alone was seen in only 1 patient (0.5%) with an incidence rate per year of 0.29%.<br>Subgroup analysis: All 7 patients with HBV recurrence belonged into the HBV-HCC subgroup (8.4% of 83 patients). The incidence rate of HBV recurrence in the HBV-HCC subgroup was 5.05%. Three patients with HBV recurrence additionally suffered from HDV co-infection (7.0% of 43 patients). The incidence rate of HBV recurrence in the HDV co-infection subgroup was 4.12% and the mean time to HBV recurrence was 17.2 ± 5.5 months.<br>*Safety*<br>*(Adverse events [AEs], serious AEs [SAEs], related AEs/adverse drug reactions [ADRs], and serious ADRs [SADRs])* |

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| | AEs were reported in 111 patients (56.9%; number of AEs: 342); SAEs were observed in 52 patients (26.7%; number of SAEs: 133). Six patients (3.1%) died during the study period; none of the fatal SAEs were related to treatment with Zutectra®. ADRs were reported in 16 patients (8.2%; number of ADRs: 29). SADRs were observed in 5 patients (2.6%; number of SADRs: 12).<br>The most frequently reported ADRs were asthenia (n=3, 1.5%), back pain (n=2, 1.0%), headache (n=2, 1.0%), nausea (n=2, 1.0%), pyrexia (n=2, 1.0%), and rash pruritic (n=2, 1.0%).<br>Subgroup analysis: In the HBV-HCC subgroup, 55 patients (66.3% of 83 patients) had 171 AEs; 27 patients (32.5%) were reported with a total of 60 SAEs. Two SAEs in 2 patients (2.4%) were fatal. Eight patients (9.6%) were reported with a total of 12 ADRs; 3 patients (3.6%) had 6 SADRs.<br><br>*Positive anti-HBs tests and serum levels ≥ 100 IU/L after LT*<br>At each post-baseline time point, > 90% of the patients had a positive anti-HBs test: 170 patients (98.8% of 172 patients) at the 3 month-FU, 113 patients (95.8% of 118 patients) at the 2-year FU, and 184 patients (94.8% of 184 patients) at FU last. There was only 1 patient at each post-baseline time point without detectable anti-HBs. Serum anti-HBs trough levels were ≥ 100 IU/L in 146 patients (85.4% of 171 patients) at the 3-month FU, in 84 patients (74.3% of 113 patients) at the 2-year FU, and in 139 patients (71.6% of 194 patients) at FU last.<br><br>*HBV-HCC recurrence after LT*<br>HBV-HCC recurrence was seen in 4 patients (2.1%; incidence rate per year: 1.15%). The median time to recurrence of HBV-HCC was 17.5 months. HBV-HCC had been the main reason for LT in all 4 patients with HBV-HCC recurrence. Three of the 4 patients also developed HBV recurrence during the observation period.<br><br>*Occurrence of any new cancer(s) other than HCC after LT*<br>Occurrence of new cancer(s) other than HCC was observed in 4 patients (2.1%; incidence rate per year: 1.15%). The median time to occurrence of any new cancer(s) was 211.6 months. HBV-HCC had been the main reason for LT in 1 of the 4 patients with new cancer other than HCC after LT.<br><br>*Safety Laboratory Parameters of Liver and Kidney Function*<br>Safety laboratory parameters changed between baseline (here: last measurement before LT) and all documentation time points during the observation period. Median changes at FU last were: -22.0 IU/L (n=175; ALT), -33.0 IU/L (n=176; AST), -28.5 IU/L (n=164; GGT), -17.3 µmol/L (n=174; total bilirubin), 8.0 g/L (n=98; albumin), 13.1 µmol/L (n=170; serum creatinine), and -17.9 mL/min/1.73m$^2$ (n=170, eGFR, MDRD formula).<br>In contrast, median and mean values of all documented safety laboratory parameters remained stable during the entire observation period, i.e. under treatment with Zutectra®. |

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Patient satisfaction (TSQM-11 questionnaire)<br>
The median scores for the following 3 dimensions were:
<table>
<tr><th></th><th>Effectiveness</th><th>Convenience</th><th>Overall satisfaction</th></tr>
<tr><td>Baseline</td><td>66.7 (n=135)</td><td>66.7 (n=139)</td><td>66.7 (n=137)</td></tr>
<tr><td>3-month FU</td><td>66.7 (n=145)</td><td>72.2 (n=149)</td><td>75.0 (n=146)</td></tr>
<tr><td>2-year FU</td><td>83.3 (n=81)</td><td>77.8 (n=89)</td><td>83.3 (n=86)</td></tr>
<tr><td>FU last</td><td>70.8 (n=156)</td><td>72.2 (n=166)</td><td>75.0 (n=161)</td></tr>
</table>
Statistical significance ($p<0.05$) for improvement vs. baseline was reached for the ‘effectiveness’ dimension score only at the 2-year FU, and for the dimensions ‘convenience’ and ‘overall satisfaction’ at all post-baseline time points.<br>
Quality of life (EQ-5D questionnaire)<br>
Self-assessed overall quality of life was relatively high over the entire course of the observation period. The median total score was 0.80 (n=170) at baseline and 0.81 at all post-baseline time points (n=163 at FU last). Likewise, the patients’ self-assessed health state remained stable with a median VAS score of 80.0 at baseline and all post-baseline time points.
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<tr><td>Conclusions</td><td>
In this NIS performed in France and Spain, a low rate of HBV recurrence (3.6%) was observed over a 2-year period in patients treated with Zutectra® after LT (mostly in combination with NUC therapy) for HBV-induced liver diseases. All 7 HBV recurrent patients had received NUC therapy at the time of recurrence and had at least one risk factor for graft re-infection (all had undergone LT for HBV-HCC, 3 patients had HDV co-infection, and 1 patient had positive HBV DNA at LT). Under Zutectra®, which was mostly self-administered at home, anti-HBs levels were adequately high for protection against HBV recurrence in more than 70% of the patients at all documentation time points.<br>
Zutectra® was well tolerated and no new safety signal was observed in this study.<br>
Patient satisfaction as measured with the TSQM-11 was good throughout the observation period with significant improvements vs. baseline regarding convenience and overall satisfaction already after 3 months of Zutectra® treatment. The high level of self-assessed quality of life established around the time of therapy start was maintained until the end of the observation period.<br>
Overall, the results of this NIS support the evidence that Zutectra® in combination with NUC therapy is efficacious in the long-term prophylaxis of HBV recurrence in liver transplant patients under real-life conditions and is well tolerated and accepted by the patients.
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<tr><td>Marketing Authorisation Holder</td><td>Biotest Pharma GmbH,<br>Landsteinerstrasse 5, D-63303 Dreieich</td></tr>
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# 4. LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| Anti-HBc | Antibodies against hepatitis B core antigen |
| Anti-HBs | Antibodies against hepatitis B surface antigen |
| AST | Aspartate aminotransferase |
| BL | Baseline |
| BMI | Body mass index |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CMV | Cytomegalovirus |
| CNI | Calcineurin inhibitor |
| CRF | Case report form |
| CRO | Contract research organisation |
| DNA | Desoxyribonucleic acid |
| eCRF | Electronic case report form |
| EDC | Electronic Data Capture |
| e.g. | For example |
| eGFR | Estimated glomerular filtration rate |
| ETV | Entecavir |
| EU | European Union |
| FAS | Full analysis set |
| FDS | Full data set |
| GGT | Gamma glutamyl transferase |
| HBeAg | Hepatitis B envelope antigen |
| HBIg | Human hepatitis B immunoglobulin |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HBV-HCC | Hepatitis B virus induced hepatocellular carcinoma |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HDV | Hepatitis D virus |

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| HIV | Human immunodeficiency virus antibody |
| i.e. | That is |
| IEC/IRB | Independent ethics committee/institutional review board |
| i.m. | intramuscular |
| i.v. | intravenous |
| LAM | Lamivudine |
| LT | Liver transplantation |
| MAH | Marketing authorisation holder |
| Max | Maximum |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MELD | The Model for End-Stage Liver Disease |
| Min, min | Minimum, minute |
| N, n | Number (of patients) |
| n.a. | Not applicable |
| NIS | Non-interventional study |
| NIS-PASS | Non-interventional post-approval safety study |
| NUC | Nucleos(t)id analogue |
| RNA | Ribonucleic acid |
| SADR | Serious adverse drug reaction |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| s.c. HBIg | subcutaneous self-administration of human hepatitis B immunoglobulin |
| SD | Standard deviation |
| TDV | Tenofovir |
| TSQM-11 | Treatment Satisfaction Questionnaire for Medication (11 items) |
| VAS | Visual analogue scale |
| vs. | Versus |
| WHO | World Health Organization |

# 5. PHYSICIANS / HEALTH CARE PROFESSIONALS

A list of the participating physicians for each country is kept as a stand-alone document and is listed in Appendix 1 (Section 16.1, stand-alone document 1.6).

# 6. MILESTONES

| Milestone | Planned date | Actual date | Comments |
|---|---|---|---|
| Start of data collection | Q3 2015 | 15-Jul-2015 (date of first informed consent) | |
| End of data collection | Q2 2019 | 03-Mar-2021 (last changes in database after receipt of final query answers) | Study completion was delayed due to slow recruitment and CRO replacement due to insolvency of the responsible CRO. |
| Final report of study results | Q4 2019 | 17-Jun-2021 | |

# 7. RATIONALE AND BACKGROUND

## 7.1 Background

Worldwide about 15-30% of the more than 300 million chronic carriers of the hepatitis B virus (HBV) are at risk of developing end-stage liver disease [1]. Today, liver transplantation (LT) is generally accepted as the most reliable medical intervention to rescue patients suffering from life-threatening decompensated liver disease due to chronic HBV as well as HBV-induced hepatocellular carcinoma (HBV-HCC).

The prerequisite for that successful intervention was the introduction of hepatitis B immunoglobulin (HBIg) fractionated from human plasma which reduced the rate of HBV re-infection of the transplanted liver from > 80% if no prophylaxis was performed to 20-30% [2, 3, 4, 5]. The next significant improvement was the introduction of lamivudine (LAM) combined with HBIg. The combination treatment quickly turned out to be the worldwide "gold-standard" for HBV re-infection prophylaxis by reducing the risk of HBV re-infection to less than 10% as long as no HBV resistance to LAM pre-existed in the patient [5, 6, 7, 8]. The disadvantage of LAM as mono-prophylaxis was the high risk of generating escape mutants of the YMDD motif (10% after 12 months; 22-50% after 36 months) [9, 10, 11, 12, 13]. The availability of the high genetic barrier nucleos(t)ide analogues (NUCs), entecavir (ETV) and tenofovir (TDV), succeeded in further reduction of the HBV re-infection rate below 4% if combined with HBIg (ETV+HBIg: 3/197; TDV+HBIg 0/106) [28]. However, the use of ETV is not recommended for those patients having shown resistance to LAM

treatment before switch to ETV because of a significant increase of HBV-escape mutations to ETV (40-50%) within 5 years of mono-virostatic treatment [15]. Mono-virostatic maintenance HBV re-infection prophylaxis using ETV, TDV, TDV+LAM and TDV+emtricitabine after cessation of combination prophylaxis with HBIg showed HBV recurrence in 5 of 103 patients [16]. Currently it is too early to calculate a reliable statistical significance due to the low number of patients treated with HBIg in combination with NUCs during the maintenance phase after LT. Today the chance to protect the allograft from being re-infected with HBV is higher than it has ever been before.

New strategies for HBV re-infection prophylaxis focus on patient individualised treatment regimens at which patients are classified according to risk criteria for HBV-recurrence. Those criteria are the HBV load at time of transplantation [17], co-infection with other viruses, e.g. hepatitis D virus (HDV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) [18], HCC (outside or inside the Milan criteria) and in particular for mono-virostatic prophylaxis, the patients' adherence to the treatment recommendations of their physicians. In addition, increasing financial pressure in almost all national health systems result in strenuous efforts for cost reduction. Thus, a fixed dosage regimen will rather be converted to an individualised regimen considering the patient's individual situation as a basis [19]. However, even after more than 20 years of steadily improving HBV re-infection prophylaxis there is still no consensus on the optimal treatment and dosage regimen in particular for HBIg.

## 7.2 Rationale for the Study

Data from clinical trials have demonstrated that prevention of HBV recurrence after LT by subcutaneous self-administration of human hepatitis B immunoglobulin (s.c. HBIg) in combination with NUCs is effective and safe. Several clinical studies have been conducted by the MAH for central registration of Zutectra® in the EU [20, 21, 22, 23, 24].

This and compliance with self-treatment under home care conditions has been confirmed by one non-interventional post-approval safety study (NIS-PASS) in Germany with 61 patients and a median treatment duration of 18 weeks.

To further increase the volume of data in an international setting, the observation of treatment under real-life conditions was extended to other countries (France and Spain) with a considerable number of HBV-induced LTs. In the current study the documented treatment period was additionally extended to two years. It was assumed that a documentation period of two years fulfilled the requirements of a long-term treatment. In addition, patient adherence to the subcutaneous treatment with Zutectra® and patient satisfaction including quality of life were included as secondary objectives.

# 8. RESEARCH QUESTION AND OBJECTIVES

The objective of this observational, non-interventional study (NIS) was the prospective documentation of long-term effectiveness, safety, convenience, and patient adherence to Zutectra® s.c. self-administration for protection from HBV recurrence after LT, aiming at confirmation of the existing clinical data under real life conditions in France and Spain.

## 8.1 Primary Objectives

### Effectiveness

Patients without and with at least one HBV related recurrence after LT determined by:

- Detection of hepatitis B surface antigen (HBsAg), and/or
- Detection of HBV DNA in patients' serum.

### Safety

The number and nature of adverse events (AEs) including physician's assessment of causal relationship to Zutectra® was to be documented. AEs were documented by the physician during regular patient visits including review of the patient diary (routine diaries kept by the patients, no study-specific diaries were used in this study).

## 8.2 Secondary Objectives

### Effectiveness

The achieved mean serum HBIg trough levels under Zutectra® treatment as determined at clinical visits.

### Safety

The following laboratory parameters for liver and kidney function were measured: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), albumin, total bilirubin, and serum creatinine. The derived (estimated) glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas.

### Compliance: Adherence to the s.c. Treatment with Zutectra®

The following data on Zutectra® treatment were to be documented:

- Frequency and dosage of Zutectra® administered;
- Place of administration and whether the patient him/herself or a caretaker performed the administration.

In addition, the following laboratory values were determined at patient clinical visits:

- Trough levels of serum anti-HBs concentrations.

### Patient Satisfaction and Quality of Life

Patient satisfaction was evaluated by using the Treatment Satisfaction Questionnaire for Medication (TSQM-11).

Quality of life was assessed by using the EuroQol EQ-5 questionnaire.

The questionnaires were to be applied before first treatment with Zutectra®, three months after start of treatment, and at the end of documentation.

# 9. AMENDMENTS AND UPDATES

There was one updated version to the observation plan (final version 2.0, dated 17 August 2015; listed as stand-alone document in Section 16.1, Appendix 1) and one country-specific amendment (version 3.0) valid for Spain only.

# 10. RESEARCH METHODS

## 10.1 Study Design

### 10.1.1 Overall Design

This was a non-interventional, prospective, single-arm, multi-centre, international, post-approval study. The aim was to collect long-term data on the treatment of subjects with LT for HBV-related liver diseases under routine treatment conditions in two different countries, i.e. France and Spain. The decision on details of Zutectra® treatment was at the discretion of the physicians, reflecting their standard practice, and was based purely on medical need.

An inclusion period of one year was planned. Individual patients were to be documented over a period of two years after treatment start. The end of the study was defined as the last documentation performed after a 2-year treatment in 200 patients.

### 10.1.2 Data Documentation

Documentation of patients being treated after LT with Zutectra® with or without a combination of a NUC was to begin immediately after start of Zutectra® treatment and was to be continued over a period of two years. Study-related data recorded by the treating physician during patient visits within the observational period and from laboratory investigations were to be documented in a standardised (electronic) case report form (CRF) and were included in the evaluation.

All baseline data and the first planned Zutectra® treatment were to be documented at the baseline visit (BL). Data were then to be collected at all subsequent clinic visits that occurred as per normal practice.

#### *10.1.2.1 Baseline Documentation*

The following data were recorded at the baseline visit:

- Demographic characteristics (gender, year of birth, height, current body weight, ethnicity);
- Current professional activities;
- Medical history:
    - LT (date, MELD score*);
    - Another LT previous to current one (date, MELD score);

- HBV based main reason for the last LT (HBV-induced liver cirrhosis, HBV-induced fulminant hepatitis, HBV-HCC);
- Histopathological determination of HBV-HCC in the explant;
- Viral co-infection (HDV, HCV, HIV, not applicable);
- Status of liver diseases at time of LT;
- Concomitant liver disease at time of LT;
- Concomitant non-hepatic disease at time of LT (kidney disease, diabetes, arterial hypertension, allergy, cancer);

*The Model for End-Stage Liver Disease (MELD) is a scoring system for assessing the severity of chronic liver disease [25]. The MELD score is calculated by using the patient's serum bilirubin and creatinine values, and the patient's international normalised ratio (INR) for prothrombin time.

- Viral status before LT, i.e. last measurement before LT (date, serum trough levels of Anti-HBs, HBsAg, and HBeAg, HBV DNA, assay system used, detection limit);
- Liver and kidney function before LT, i.e. last measurement before LT (date, levels of ALT, AST, GGT, total bilirubin, albumin, and serum creatinine);
- Previous immunosuppressive treatment (start/change/stop date, drug class, daily dose and unit, frequency);
- Previous antiviral treatment (drug name, daily dose and unit, route, frequency, start/end date);
- Treatment of HCC before LT:
  - Types of bridging therapies;
  - Downstaging of HCC before LT to be within the Milan criteria;
  - Characteristics of tumour size at LT according to radiology and histopathology report (number of nodules, total size of tumour nodules, TNM staging, i.e. T = primary tumour size, N = involvement of regional lymph nodes, M = distant metastasis);
- Donor organ:
  - Characteristics of the transplanted allograft (whole liver, liver and kidney co-transplant, split liver - deceased donor liver transplant, living donor liver transplant);
  - Age of donor;
  - Markers of virus infection of the donor (HBsAg, anti-HBs, anti-HBc, anti-HCV, anti-HIV1+2, HIVAg, CMV IgG, CMV IgM);
- Quality of life questionnaire EQ-5D (mobility, self-care, usual activities, pain/discomfort, anxiety/depression);
- Treatment satisfaction questionnaire TSQM-11.

#### *10.1.2.2 Follow-up Documentation*

The following data were recorded at the regular patient visits:

- Date of follow-up;
- Follow-up status:
  - Regular follow-up after three months treatment,
  - Regular follow-up after two years;
  - Intermediate follow-up;
  - Early discontinuation (if yes: reason of discontinuation);
  - Patients diseased (if yes: cause of death);
- Current professional activities (only to be documented at the regular follow-up visits);
- Viral status: all measurements of anti-HBs, HBsAg, HBeAg, and HBV DNA performed during the study period had to be documented at routine visits;
- Immunosuppressive treatment;
- Treatment with Zutectra® (treatment changes since last visit, dosage, interval, self-administration, home administration);
- Current liver and kidney function (differences in laboratory values since last visit);
- HBV recurrence since last visit (yes/no, if yes: specification of clinical signs); all clinical signs related to HBV recurrence observed and considered by the investigator had to be documented;
- Recurrence of HBV-HCC since last visit (yes/no, if yes: diagnosis based on clinical diagnosis or histopathology, date of diagnosis, manifestation of recurrent HCC, tumour size after HCC recurrence, number of nodules, TNM staging);
- Occurrence of new cancer(s) other than HCC since last visit (yes/no, if yes: specification of cancer, date of diagnosis);
- Acute rejection episode since last visit (yes/no, if yes: date of diagnosis, characteristics of the reaction, i.e. lymphocyte infiltrate in liver, bile duct damage, cholestasis, hepatocyte swelling, apoptotic bodies in lobules, and/or endothelitis);
- Chronic rejection diagnosed since last visit (yes/no, if yes: date of diagnosis, kind of reaction, characteristics of the reaction, i.e. presents > 6-12 months post-transplant, bile duct loss in at least 50% of portal tract, centrilobular cholestasis, and/or scattered apoptotic bodies present);
- Other complications since last visit (yes/no);
- Concomitant antiviral/HBV-related medication after LT (treatment changed since last visit, drug name, dose and unit, route, frequency, start/end date);
- Quality of life questionnaire EQ-5D – only to be completed at the regular follow-up visits performed three months and two years after start of treatment with Zutectra®;
- Treatment satisfaction questionnaire TSQM-11 – only to be completed at the regular follow-up visits performed three months and two years after start of treatment with Zutectra®;
- Adverse events (AEs)/adverse drug reactions (ADRs)* (start/end date and time, ongoing event, administration date and time of last Zutectra® administration before start of the event, batch number, causality, seriousness, serious criteria, intensity,

outcome, action taken, liver and kidney function values regarding the AE/ADR, if available).

*HBV recurrence, recurrence of HBV-HCC, occurrence of new cancer(s), acute rejection episode, chronic rejection, and any other complication were to be documented also in the AE/ADR section of the CRF.

#### *10.1.2.3 Documentation and Reporting of Adverse Events (AEs) /Adverse Drug Reactions (ADRs)*

Definitions of AE, ADR and SAE

**An AE** was any unfavourable or unintended sign, symptom, or disease that appeared or worsened in a study patient during the period of observation. The AE may have been any of the following:

- A new illness;
- An exacerbation of a sign or symptom or the underlying condition under treatment or of a concomitant disease (including symptoms of HBV recurrence and clinically relevant changes in laboratory values);
- Unrelated to participation in the study or an effect of the study medication or comparator drug;
- A combination of one or more of the above factors.

No causal relationship with the study medication under investigation was implied by using the term 'AE' (see causality criteria below).

**An ADR** was defined as an AE considered by the treating physician as being related to the treatment with Zutectra®.

**A serious AE (SAE)** was any untoward medical occurrence or effect that at any dose:

- Resulted in death:
  - Death was an outcome of an AE and not an AE itself (all deaths of study patients, regardless of cause or relationship had to be reported);
- Was life threatening:
  - i.e. the patient was at immediate risk of death from the event as it occurred;
- Required hospitalisation or prolongation of existing hospitalisation:
  - Complications that occurred during hospitalisations were counted as AEs, but if a complication prolonged hospitalisation or required new hospitalisation, it was counted as SAE (in-patient hospitalisation meant the patient had been formally admitted to a hospital for medical reasons and for any length of time which may or may not have been overnight; hospitalisation did not include presentation to and care within an emergency department);
  - An AE that was experienced by a patient during dosing was not to be considered an SAE, even if the patient remained in hospital until the symptoms resolved, unless the investigator found that this event would have required hospitalisation;
- Resulted in persistent or significant disability or incapacity;
- Was a congenital anomaly or birth defect, or

- Was another medically important condition:
    - An important medical event that was not immediately life threatening or resulted in death or hospitalisation, but which may have jeopardised the patient or may have required medical intervention to prevent one of the outcomes listed above, was to be reported as 'serious'.

Documentation of AEs

In this study all AEs independent of their relatedness to the study medication were to be recorded in the CRF. The investigator had to assess whether the AE was serious or non-serious (see definitions above). Furthermore, the investigator had to assess the severity of the AE, i.e. the extent to which the AE affected the patient's daily activities, and the causality, i.e. whether the AE was related or not related to the treatment with Zutectra®. If AEs were reported in a regular treatment diary of a patient they were to be transferred to the study data base by an authorised person at the study centre.

The following criteria were used for the assessments of causality and severity:

- Related AE (i.e. adverse drug reaction, ADR):
    - A reasonably possible clinical and/or pharmacological relationship between a suspected medical product and an AE was implied.
- Not related:
    - A reasonable explanation for an alternative cause was considered plausible, e.g. no drug taken, plausible clinical alternative like accidental injury, expected progression of underlying or concomitant disease, pharmacologically incompatible temporal relationship (intercurrent illness was not to be documented);
- AE severity (i.e. 'intensity' of the event):
    - Mild (the AE did not interfere with the patient's routine activities;
    - Moderate (the AE interfered with the patient's daily routine, but usual routine activities could still be carried out);
    - Severe (the AE resulted in the inability to perform routine activities).

The highest severity grade attained was to be reported for AEs with divergent severities.

Reporting of AEs

All AEs were forwarded electronically to the Safety department of Biotest for assessment by the MAH and for further processing of the individual cases as outlined in the standard operating procedures of Biotest.

### 10.1.3 Ethics

This study was performed in accordance with the observation plan (listed as stand-alone document in Section 16.1, Appendix 1) which had been submitted to a properly constituted independent ethics committee (IEC)/institutional review board (IRB) and/or regulatory authorities, in agreement with applicable regulatory requirements, for formal approval before start of the documentation (if required by law). Copies of these approvals (if applicable) had to be submitted to the contract research organisation (CRO) executing the study before initiation of the NIS and each site had to keep a copy of these documents.

Only pseudonymised data were stored and forwarded to the CRO for analysis. All patients had to sign an agreement to give their consent to use their medical data relevant for this

study (see below). The informed consent form was included in the documents submitted to the respective competent EC prior to the start of the study.

#### 10.1.4 Patient Information and Consent

Patients eligible for documentation were informed about the study according to the legal requirements. The patient had to provide written consent to allow the documentation and analysis of study-relevant medical data by signing and personally dating an informed consent form before the start of the documentation. A duplicate of the signed and dated written informed consent form had to be handed over to the patient. Informed consent documentation had to be kept at the centre to not disclose the patients' identity to the sponsor or contract research organisation (CRO).

### 10.2 Setting

It was planned to include 200 patients from approximately 20 study centres. As a similar number of LTs is performed in both Spain and France, it was planned to include an equal number of patients (i.e. 100 patients) from each country. Patients treated with Zutectra® at the clinic or at home for prophylaxis of HBV recurrence after LT were considered for inclusion in the study.

Zutectra® is authorised in France and Spain for the prevention of HBV reinfections. The marketed medication used in this study was prescribed as per the usual local prescription handling process. Patients were treated with commercially available Zutectra®. Participation in this study was not to influence the prescription of Zutectra® or any other drug. In case Zutectra® was used this had to be the result of the physician's independent decision, based purely on medical need. All other details of treatment were also determined by the physician.

The decision for Zutectra® treatment (in accordance with the specifications given in the current Summary of Product Characteristics) had to be made before inclusion of the patient into the study at the discretion of the treating physician (investigator).

### 10.3 Subjects

#### 10.3.1 Inclusion Criteria

Only patients meeting all of the following inclusion criteria were enrolled into this NIS:

1. Patients 18 years or older.
2. Patients with LT for fulminant hepatitis B, hepatitis B–cirrhosis, or HBV-induced HBV-HCC, or with liver re-transplantation except due to HBV recurrence.
3. Subjects under Zutectra® treatment without or with a virostatic (NUC) treatment.
4. Written informed consent to allow data collection and data transfer to third party.

#### 10.3.2 Discontinuation Criteria

There were no formal discontinuation criteria. Patients who discontinued the treatment with Zutectra® before the end of the 2-year period were not replaced.

## 10.4 Variables

All analysis variables were specified in the statistical analysis plan (SAP, final version 2.0, dated 16 February 2021) which is appended to this report as a stand-alone document (see Section 16.1, Appendix 1).

### 10.4.1 Primary Variables of Effectiveness and Safety

Hepatitis B virus:

- Proportion of subjects with and without HBV recurrence after LT;
- Incidence rate per year of HBV recurrence after LT;
- Time to HBV recurrence after LT.

AEs/ADRs:

- Proportion and type of AEs including seriousness and relatedness;
    - AEs/ADRs;
    - Serious AEs (SAEs)/serious ADRs (SADRs).

### 10.4.2 Secondary Variables

Anti-HBs:

- Serum (trough) levels of anti-HBs;
- Proportion of subjects with anti-HBs < or ≥ 100 IU/L;

Recurrence of HBV-HCC after LT:

- Proportion of subjects with recurrence of HBV-HCC after LT;
- Incidence rate per year of HBV-HCC recurrence after LT;
- Time to HBV-HCC recurrence after LT.

Occurrence of new cancer(s) other than HCC after LT:

- Proportion of subjects with occurrence of new cancer(s) other than HCC after LT;
- Incidence rate per year of new cancer(s) other than HCC after LT;
- Time to occurrence of new cancer(s) other than HCC after LT.

Exposure, treatment adherence and immunosuppressive treatment:

Adherence to treatment was assessed using patient diaries (documentation of Zutectra® treatment) and the documentation of trough levels of serum anti-HBs concentration.

- Time to start with Zutectra® after LT;
- Frequency of Zutectra® administration;
- Dose of Zutectra® applied;
- Number of self-administrations performed (person performing the administration);
- Number of treatments at home and at the clinic;
- Immunosuppressive treatment (mycophenolate mofetil [MMF], corticosteroids, calcineurin inhibitor, mTor inhibitor, azathioprine, anti-IL-2-receptor antibody).

Safety:

- Viral status: serum (trough) levels of HBsAg, HBeAg, HBV DNA)[1].
- Laboratory parameters:
  - Liver function (ALT, AST, GGT, total bilirubin, albumin);
  - Kidney function (serum creatinine, eGFR).

Quality of life and patient satisfaction:

- Quality of life (EuroQol EQ-5D questionnaire):
  - Level of perceived problems;
  - EQ-5D score;
  - VAS score.
- Subject satisfaction (TSQM-11 questionnaire, TSQM measures 4 dimensions)[2]:
  - Effectiveness;
  - Side effects;
  - Convenience (user-friendliness);
  - Overall satisfaction;

### 10.4.3 Additional Variables

Recurrence of HBV-HCC:

- Manifestation of recurrent HCC (liver, extrahepatic dissemination, etc.);
- Tumour size after HCC recurrence:
  - Number of nodules;
  - Total size of tumour nodules;
  - TNM staging (primary tumour, regional lymph nodes, distant metastasis).

Acute rejection episodes:

- Time to acute rejection;
- Lymphocytic infiltrate in bile duct;
- Bile duct damage;
- Cholestasis;
- Hepatocyte swelling;
- Apoptotic bodies in lobules;
- Endothelitis.

Chronic rejection episodes and other complications:

- Time to chronic rejection;

[1] In the SAP, final version 2.0, dated 16 February 2021, anti-HBs was also listed as a safety variable; in the objectives described in the final observation plan, version 2.0, dated 17 August 2015, serum trough levels of anti-HBs were determined as a measure of effectiveness and adherence to treatment; thus, anti-HBs is not mentioned here as a safety variable, but under a separate secondary variable ‘anti-HBs’.
[2] Note: The analysis of the TSQM-11 was changed from the procedure described in the SAP, final version 2.0, dated 16 February 2021. The calculation of the 4 dimension scores was corrected and a total score was not computed.

- Presents > 6-12 months post-transplant;
- Bile duct loss in at least 50% of portal tract;
- Centrilobular cholestasis;
- Scattered apoptotic bodies present;
- Date of other complications than rejections diagnosis.

Overall and disease-free survival:

- Overall survival time (months);
- Disease-free survival time (months).

### 10.4.4 Derived Variables

Derived variables were specified in the SAP (stand-alone document, see Section 16.1).

- Age = year of informed consent – year of birth;
- Average daily dosage = dosage per interval/interval days;[3]
- Average daily dose summarised per month = ~ 30.4375 average daily doses per complete month and patient;
- Average daily dose over documented period = sum of all average daily doses/duration of exposure [days];
- Average monthly dose over documented period = average daily dose over documented period x 30.4375
- BMI [kg/m$^2$] = weight [kg] / height [m];
- Duration of exposure [days] = ((stop date of treatment administration [TA] – start date of TA) + 1);
- Duration of exposure [month] = ((stop date of TA – start date of TA + 1) / 30.4375);
- Time to HBV recurrence after LT [months]= ((date of HBV recurrence – date of LT) + 1) / 30.4375;
- Time to HBV-HCC recurrence after LT [months] = ((date of HBV-HCC recurrence – date of LT) + 1) / 30.4375;
- Time to occurrence of new cancer other than HBV-HCC after LT [months] = ((date of new cancer other than HBV-HCC after LT - date of LT) +1) / 30.4375;
- Time of first treatment with Zutectra® after LT = (start date of treatment – date of LT + 1);
- Proportion of patients with HBV recurrence after LT (patients with at least one dose of Zutectra®):
  HBV recurrence [%] = (number of patients with at least one HBV recurrence after LT divided by number of patients treated with Zutectra®) x 100;

  [For a definition of HBV recurrence see Section 10.8.3.]

[3] The definition of ‘average daily dosage’ described here was used in the analysis instead of the definition given in the SAP, final version 2.0, dated 16 February 2021. In addition, three further ‘average daily dose’ variables were defined and analysed, which were not described in the SAP.

- Proportion of patients free of HBV recurrence after LT (patients with at least one dose of Zutectra®):
  HBV recurrence free [%] = (number of patients free of HBV recurrence after LT divided by number of patients treated with Zutectra®) x 100;
- Proportion of patients with HBV-HCC recurrence after LT (patients with at least one dose of Zutectra®):
  HBV-HCC recurrence [%] = (number of patients with HBV-HCC recurrence after LT divided by number of patients treated with Zutectra®) x 100;
- Proportion of patients with development of any new cancer(s) after LT (patients with at least one dose of Zutectra®):
  New cancer(s) [%] = (number of patients with any new cancer(s) after LT divided by number of patients treated with Zutectra®) x 100;
- Incidence rate (in general):
  Rate = number of new cases of disease during a defined period divided by the person-years-at-risk.
  Person-years-at-risk was defined as follows: estimation of the actual time-at-risk in years: sum of all days from informed consent to last visit date for all patients, divided by 365.25;
- Incidence rate per year of HBV recurrence after LT [%]:
  $Rate_{HBVr}$ = (number of HBV recurrences after LT/person-years-at-risk) x 100;
- Incidence rate per year of HBV-HCC recurrence after LT [%]:
  $Rate_{HCCr}$ = (number of HCC recurrences after LT/person-years-at-risk) x 100;
- Incidence rate per year of occurrence of any new cancer(s) after LT [%]:
  $Rate_{NC}$ = (number of occurrences of any new cancer(s) after LT/person-years-at-risk) x 100.

Definition of visits:

- Baseline visit (BL):
  Last measurement before treatment start.
  Exception: for serum levels of anti-HBs, HBsAg, HBeAg, HBV-DNA, and safety laboratory parameters the test results before LT (last measurements prior to LT) were used as baseline in the analysis.
- 3 months visit (3-month follow-up [FU]):
  First follow-up after three months of treatment duration (after 91 days). A visit window of [71,181 days] was accepted to identify the 3-month FU, except for questionnaires and professional status (investigator's classifications were used for these variables).
- 2 years visit (2-year FU):
  First follow-up after two years of treatment duration (after 730 days). A visit window of [640 days, no border] was accepted to identify the 2-year FU, except for questionnaires and professional status (investigator's classifications were used for these variables).
- Last follow-up visit (FU last):
  Last available follow-up visit value for a subject which was not missing for the respective parameter (not applicable for single questions of the questionnaires).

Visits that had taken place more than 62 days after the last Zutectra® intake were not considered for the analysis. The same applies for AEs which occurred more than 62 days after last Zutectra® intake and any medication (immunosuppressive and concomitant antiviral medication) which had been started more 62 days after last Zutectra® intake. These data were only listed.

## 10.5 Data Sources and Measurements

### 10.5.1 Data Sources

Data were obtained from clinical hepatic centres performing LT in France and Spain.

Source data were all information in original records and certified copies of original records of medical findings, observations, or other activities in a NIS necessary for the reconstruction and evaluation of the NIS. Source data could be extracted from source documents which comprised clinical documentation, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments).

The investigator was asked to keep a confidential list of the names of all patients participating in the NIS, giving reference to the patients' records.

If the patient routinely kept a treatment-related patient diary, the diary may have been used by the investigator to ascertain the occurrence of adverse events.

### 10.5.2 Measurements

This was an observational, non-interventional study, i.e. normal clinical practice was not modified. Only those treatments and data were recorded which would have been obtained regardless of whether the investigator participated in the study or not. There was no intervention by the investigator or sponsor.

Quality of questionnaire (EQ-5D)

Quality of life was measured with the EuroQol EQ-5D questionnaire at the patient visits. The EQ-5D questionnaire consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) plus a visual analogue scale (VAS) for evaluating the quality-of-life state ranging from 0 (= worst quality of life state) to 100 (= best quality of life state). Each dimension was assessed according to a 3-point scale (dimension scores): level 1 (no problems), level 2 (some problems), level 3 (extreme problems).

The combination of levels from each of the five dimensions resulted in a health state code, e.g. 11111 (indicating a perfect health state).

The EQ-5D total score was calculated by converting the health state code into a score as follows:

1. Start with score 1.000 = (11111) (perfect health state).
2. Subtract 0.081 (constant) for any other state.
3. Subtract nothing for level 1 on any dimension.
4. Subtract appropriate level 2 or level 3 value for each dimension (see table below).

5. Subtract 0.269 (N3 factor) if any dimension has a level 3 problem.

The following coefficients were used:

| Dimension | Level 2 | Level 3 |
|---|---|---|
| Mobility | 0.069 | 0.314 |
| Self-care | 0.104 | 0.214 |
| Usual activity | 0.036 | 0.094 |
| Pain / discomfort | 0.123 | 0.386 |
| Anxiety / depression | 0.071 | 0.236 |
| | Constant = 0.081 | N3 = 0.269 |

If any dimension score was missing, the total score was set to missing.

Treatment satisfaction questionnaire for medication (TSQM-11)[4]

Patient satisfaction with treatment was determined with the TSQM-11 questionnaire at the study visits. The TSQM-11 score consists of 11 questions (items) measuring four dimensions of treatment satisfaction: effectiveness, side effects, convenience, and overall satisfaction. Each item is assessed by the patient on a 7-point Likert scale (items 1, 2, and 7-11) or on a 5-point Likert scale (items 4-6):

1= extremely dissatisfied, 2 = very dissatisfied, 3 = dissatisfied, 4 = somewhat satisfied (5-point scale: somewhat dissatisfied), 5 = satisfied (5-point scale: not at all dissatisfied), 6 = very satisfied, 7 = extremely satisfied.

Item 3 is answered on a 2-point scale (‘yes’ or ‘no’).

The results of the Likert scales were then linearised to four dimension scores ranging from 0 (extremely dissatisfied) to 100 (extremely satisfied) as follows:

- Effectiveness score:
  ([(Item 1 + Item 2) − 2] divided by (12) × 100;
- Side effect score:
  ([Sum of Item 4 to Item 6) − 3] divided by 12) × 100;
  if one item was missing: ([(Sum of the two completed items) − 2] divided by (8) × 100;
- Convenience score:
  ([Sum of Item 7 to Item 9) − 3] divided by 18) × 100;
  If one item is missing: ([Sum of the two completed items) − 2] divided by 12) × 100;
- Overall satisfaction score:
  ([Sum of Item 10 to Item 11) − 2] divided by 12) × 100.

## 10.6 Bias

Compared to clinical studies, NIS are more vulnerable to confounding and other forms of bias, e.g. recall or selection bias. High rates of dropouts or missing data, which are often a problem in observational/non-interventional studies may lead to certain biases, if these dropouts are not random. For possible bias and limitations of this NIS see Section 12.2.

[4] Note: the analysis of the TSQM-11 was performed as described in this report. The analysis was changed from the procedure described in the SAP, final version 2.0, dated 16 February 2021. The calculation of the 4 dimension scores was corrected and a total score was not computed.

## 10.7 Study Size

The sample size was not based on power calculations but based on the number of available centres performing LT in France and Spain.

Of approximately 18 centres performing LT in France, 12 centres were planned to participate in this study, representing two thirds of all centres. In these 12 centres about 600 patients receive maintenance treatment with HBIg after LT. Inclusion of 100 patients into the study within one year represents about 17% of all treated patients in these 12 centres. As the number of performed LTs is similar between Spain and France, another 100 patients were planned to be enrolled in Spain.

With the documentation of 200 patients and an expected recurrence rate of 5%, the 95% confidence interval was calculated to be between 2.4% and 9.0%.

## 10.8 Data Transformation, Missing Values, and other Analysis Rules

### 10.8.1 Data Transformation

All data were analysed as they appeared in the data base. In addition, the following rules were implemented in derived datasets:

- If date of prior LT > date of LT, the value was to be set to missing;
- If anti-HBs < 10 IU/L, the value was to be set to missing;
- If HBsAg < 10 IU/mL, the value was to be set to missing;
- If HBeAg < 10 IU/mL, the value was to be set to missing;
- If HBV DNA [IU/ml] < detection limit of the assay [IU/ml], the respective value for HBV DNA was to be set to missing;
- If for any reference range, the ‘to’ value was smaller than the ‘from’ value, values were changed (from=to and vice versa);
- If for any laboratory value a value and a ‘less than’ was specified, the value was to be used;
- In case one of the laboratory reference values was missing, only the none-missing one was used to flag a value above (or below respectively).

### 10.8.2 Missing Data

Missing data were displayed in patient data listings and were indicated in analysis tables as appropriate. In frequency tables of categorical data, a category ‘missing data’ was added to any parameter for which information was not available for any patient and included in all calculations [%]. For analysis, the following rules were implemented in case of missing data:

- TSQM-11: Answers to questions regarding side effects (questions 4 to 6) might be missing if no adverse events occurred during the study period in a patient; the side effects score was calculated only if the patient experienced side effects, i.e. item 3 was answered with ‘yes’.[5]

[5] Note: The analysis of the TSQM-11 was changed from the procedure described in the SAP, final version 2.0, dated 16 February 2021. The calculation of the 4 dimension scores was corrected and a total score was not computed. The rules regarding missing values were adapted respectively.

- If any EQ-5D dimension score was missing, the total EQ-5D score was set to missing.
- AEs/ADRs with unknown onset date/time were counted as treatment emergent AEs/ADRs.
- AEs/ADRs with unknown end date/time were counted as ongoing AEs/ADRs.
- AEs/ADRs with unknown causality to Zutectra® were counted as Zutectra®-related AEs/ADRs.
- AEs/ADRs with unknown seriousness were counted as serious AEs/ADRs.
- AEs/ADRs with missing severity were counted as 'severe'.

### 10.8.3 Analysis Rules for HBV Recurrence

HBV recurrence was defined as positivation of HBsAg and/or HBV DNA at any time point after the respective negative value was determined and Zutectra® treatment had been started. If only a single measurement during the follow up was positive and not confirmed thereafter by a second measurement, the patient was not counted as 'HBV recurrent'. This did not apply for positive test results that were the last documented results of a patient during the observation period. In such a case, the patient was counted as 'HBV recurrent' (exceptions: the patient was not counted as 'HBV recurrent' if treatment with Zutectra® had stopped before the last measurement or if a query at the centre confirmed that the last documented result could not be confirmed afterwards).

### 10.8.4 Analysis Rules for Laboratory Test Results (Serum Markers of HBV, Liver and Kidney Function Tests)

Frequencies of the parameters of viral status (anti-HBs, HBsAg, HBeAg, and HBV DNA) were provided by visit and by the following categories: not available, not detectable, positive. If there were several tests available per visit, the patient was counted in the category 'positive' in case at least one measurement for the respective marker was positive. If no measurement was documented as 'positive' and at least one measurement was 'not detectable', the patient was counted in this category. Otherwise, the patient was counted in the category 'not available'. If several positive test results were available, the results closest to the respective visit date were used in the summary analysis.

The serum values of HBV markers and the values of clinical laboratory parameters for liver and kidney function before LT were used as baseline values in the analyses of serum trough levels and clinical laboratory tests. If several values of a parameter were available, the results closest to the respective visit date were used for the calculations.

## 10.9 Statistical Methods

Data analysis was performed as specified in the final SAP (listed as stand-alone document in Section 16.1, Appendix 1).

All data processing, summarisation, and analyses were performed using the statistical software package SAS® version 9.4.

Previous and concomitant antiviral medications were coded according to the World Health Organization (WHO) Drug List and summarised by international nonproprietary names (INN). Subjects taking the same medication multiple times were counted once per

medication. Medications with doses taken both before and after start of treatment with Zutectra® were considered as both previous and concomitant to the study treatment.

The Medical Dictionary for Regulatory Activities (MedDRA v. 23.1) was used for coding of adverse events and adverse drug reactions. The drug safety department of Biotest provided MedDRA coding after the final AE reconciliation.

### 10.9.1 Analysis Sets and Subgroups

The following analysis sets were defined:

- Full data set (FDS): all subjects with any data captured within this prospective study.
- Full analysis set (FAS): all subjects according to the inclusion criteria and included all subjects who had received at least one dose of Zutectra® treatment.

All analyses of demographic and baseline characteristics as well as all effectiveness and safety variables were based on the FAS. The FDS was used for selected summaries (subject disposition) and data listings (subject disposition, eligibility criteria) only.

The following subgroups were defined:

- Subgroup HBV-HCC: all FAS patients with HBV-HCC as main reason for LT.
- Subgroup HBV/HDV co-infection at LT: all FAS patients with HDV co-infection at the time of LT.

All analyses performed on the FAS were repeated on the subgroup of patients with HBV-HCC as main reason for LT (indicated in the in-text tables as ‘Sub HBV-HCC’).

The subgroup of patients with HDV co-infection (indicated in the in-text tables as ‘Sub Co-HDV) was used to provide tables 14.7.1, 14.8.1.1, 14.8.1.2 and 14.8.2.

Analyses by country (France and Spain) were performed on all described variables. All subject data listings were sorted first by country and second by subject ID.

### 10.9.2 Main Summary Measures

In general, all patient data collected in the CRF were listed, sorted by country and patient ID, and, if appropriate, by visit.

All analyses were performed in an exploratory sense. Since there were no confirmatory analyses planned, hypotheses were not formulated. Data were analysed using descriptive statistics. All summary tables were presented by country and total, and, if appropriate by visit.

Summary statistics including mean, standard deviation (SD), minimum, maximum, median, 25% (Q1) and 75% (Q3) percentiles were provided for continuous variables. Frequencies and percentages in each category were provided for categorical data.

AEs, SAEs, ADRs and SADRs were summarised by MedDRA System Organ Class (SOC) and Preferred Term (PT). SOCs were presented alphabetically, and PTs were also sorted alphabetically within each SOC.

### 10.9.3 Main Statistical Methods

Two-sided 95% confidence intervals, based on the exact binomial distribution according to Clopper-Pearson method, were presented together with number and percentage for the following primary and secondary effectiveness variables: subjects with and without HBV

recurrence after LT, HBV-HCC recurrence after LT, subjects with occurrence of new cancers other than HCC after LT.

Pre-/post comparisons were performed for patient satisfaction scores (TSQM-11), quality of life scores (EQ-5D), HBV-related serum levels (anti-HBs, HBsAg, HBeAg, and HBV DNA), and laboratory variables for liver and kidney function. Changes from baseline were tested by using the two-sided nonparametric Wilcoxon signed rank test at the 5% level of significance.

Kaplan-Meier survival plots for time to HBV recurrence after LT, time to HBV-HCC recurrence after LT, and time to occurrence of new cancer other than HCC after LT were presented.[6]

The Kaplan-Meier method was also used for an additional analysis of the time to overall survival and disease-free survival. This analysis included the number of subjects at risk for the incidents HBV recurrence after LT, HBV-HCC recurrence after LT, and occurrence of new cancer other than HCC after LT. Overall survival was defined as the time from LT until death from any cause during the 2-year observation period. Death was treated as an event. Patients who discontinued or were lost to follow-up, and patients with a 'last known alive date' greater than two years after the LT date were censored. Disease-free survival was defined as the time from LT until first recurrence of HBV, cancer, or death from any cause during the 2-year observation period. For patients not known to have died and who did not have cancer (HCC or new cancer other than HCC), disease-free survival was censored at the last assessment date or cut-off date if the last assessment date was greater than two years.[7]

#### 10.9.4 Sensitivity and/or Interim Analyses

A sensitivity analysis was neither planned nor performed.

According to the observation plan, an interim analysis was considered only in case it would have taken more time to complete the study in Spain than in France. An interim analysis was not planned in the SAP and was not performed.

### 10.10 Quality Control

#### 10.10.1 Electronic Data Capture (EDC)

All study-relevant data which had to be recorded according to this documentation plan had to be documented in the electronic CRF (eCRF, layout, dated 14 October 2016).

Prior to the start of the documentation, investigators had been instructed on the usage of the eCRF for data entry. Entries in the eCRF were only to be made by the investigator or persons authorised by the investigator. The personnel responsible for data entry, controlling, and specific data handling procedures had to be defined upfront.

The investigator had to verify that all data entries in the eCRF were accurate and correct. Data entries were checked by automatic and manual queries according to the data validation plan. Any correction had to be entered into the eCRF at the study centre.

[6] In addition to the Kaplan-Meier plots for time to 'event' after LT, as describe above and in the SAP, final version 2.0, dated 16 February 2021, similar plots for time to HBV recurrence, HBV-HCC recurrence, and occurrence of any new cancer(s) other than HCC after Zutectra® start were also prepared (see stand-alone document 1.4)

[7] In addition to the Kaplan-Meier plots for overall survival and disease-free survival, as describe above and in the SAP, final version 2.0, dated 16 February 2021, similar plots for overall survival and disease-free survival after Zutectra® start were also prepared (see stand-alone document 1.4).

Due to a replacement of the responsible CRO, the EDC system was no longer available from July 2020.[8] Thus, all subsequently gathered study data were collected and approved via paper CRF (CRF layout was based on EDC screenshots, paper CRF versions, dated 08 and 21 October 2020, and paper queries). After double data entry and reconciliation, all data derived from paper CRFs were transferred together with the EDC data as final raw data to the SAS-system for subsequent data analyses in accordance with the SAP.

### 10.10.2 Data Quality Assurance and Audits

A combination of central and on-site visits was applied to assure data quality in this NIS. The monitor was responsible for checking the quality of the data by source data verification and for checking the adherence to the NIS documentation plan as well as to legal and ethical requirements according to local laws. The extent and nature of data quality assurance visits was described in detail in the monitoring plan. For this NIS, one to two quality assurance visits per site were performed to check the data entered. In addition, regular phone contacts were planned to resolve questions regarding data entry in the eCRF. NIS source data verification was an essential part of the quality assurance process and the investigator had to grant direct access to the NIS patients' source data.

The investigator was also to permit study-related data quality assurance visits, audits, and reviews by the IEC/IRB and/or Regulatory Authorities and was to allow direct access to source data and source documents for data quality assurance visits, audits, and inspections.

### 10.10.3 Archiving

After evaluation and reporting of the data, all documents relating to the NIS were to be kept in the archives of the CRO or sponsor for at least 10 years according to national and European law. Study-relevant documents were to be kept at the clinical site(s) according to applicable local regulatory requirements.

[8] After the insolvency of the responsible CRO Navitas Life Sciences GmbH, the proprietary EDC System was not adopted by the Indian parent company or any other prospective client and was therefore no longer maintained.

# 11. RESULTS

The results for the total FAS and the results of the subgroup analyses are summarised in the sections below. Complete analysis results, including the presentation of the results by country, can be found in a separate document appended to this report (end-of-text Tables, stand-alone document 1.3; see list of stand-alone documents in Appendix 1, Section 16.1). Figures on time courses (Zutectra® dosing, mean serum anti-HBs levels) and Kaplan-Meier plots are appended in stand-alone document 1.4. Stand-alone document 1.5 contains all subject data listings (Listing 16.2.1 to Listing 16.2.9.2) of this study.

## 11.1 Participants

This study was conducted at 11 centres in France and at 8 centres in Spain (centres that enrolled patients). The first baseline visit of a patient was performed on 15 July 2015 (also earliest date of signed informed consent) and the last follow-up (FU) visit of a patient was performed on 25 June 2020. Last changes to the database were made on 03 March 2021 following the receipt of last data query answers (last documentation of patient data). Visit dates, FU status, and date of informed consent are listed by patient in Listing 16.2.2.1.

In total, 202 patients signed the informed consent form and were included in the full data set (FDS): 76 patients in Spain and 126 patients in France (Table 1 and end-of-text Table 14.1.1). Two of these patients did not meet all required inclusion criteria. Patient #20103 was not under HBIg treatment and patient #20303 had undergone LT due to hepatitis C virus infection (Listings 16.2.2.1.and 16.2.1). Thus, 200 patients were eligible according to the inclusion criteria.

Overall, 6 patients in the FDS did not receive Zutectra® treatment (Table 1): 1 non-eligible patient and 5 eligible patients according to the inclusion criteria. The full analysis set (FAS) thus comprised 195 patients (96.5% of 202 patients): 73 patients in Spain and 122 patients in France. Listing 16.2.1 presents for each documented patient whether the patient was included in the FAS and the patient's possible assignment to one or both FAS subgroups. Two subgroups were analysed based on the FAS: the subgroup of patients with HBV-HCC as main reason for LT comprised 83 patients and the subgroup of patients with HDV co-infection comprised 43 patients.

**Table 1 Subject disposition**

| Characteristic [n (%)][a] | Category | FDS (N=202) |
|---|---|---|
| Patients who signed informed consent | | 202 |
| Patients eligible by inclusion criteria | Yes | 200 (99.0%) |
| | No | 2 (1.0%) |
| Patients enrolled but not treated with Zutectra® | | 6 (3.0%) |
| Patients treated with Zutectra® and eligible by inclusion criteria (FAS) | | 195 (96.5%) |
| FAS patients with HBV-HCC as main reason for LT | Sub HBV-HCC | 83 (41.1%) |
| FAS patients with HDV co-infection at the time of LT | Sub Co-HDV | 43 (21.3%) |

[a] Percentages are based on the total number of patients in the full data set (FDS = all patients with any data captured within this prospective study).
**Data source:** end-of-text Table 14.1.1 (stand-alone document 1.3, Appendix 1, Section 16.1).

As shown in Table 2, 181 patients (92.8% of 195 patients) had a documented follow-up visit three months after start of Zutectra® treatment and 147 patients (75.4%) had a 2-year FU visit. Four of the patients with a documented 2-year FU did not have a documented 3-month FU (Listing 16.2.2.1).

The mean time between the baseline visit and the last documented FU visit, calculated for all 195 FAS patients, was 21.4 ± 7.3 months (median: 24.0 months) with a range between 1.0 and 31.5 months.

On average, patients had a total of 4.2 ± 2.7 (median: 4.0) documented intermediate visits between baseline and 3-month FU/early discontinuation and/or between 3-month FU and 2-year FU/early discontinuation. The number of intermediate visits ranged between 0 and 10 visits.

In the FAS, 39 patients (20% of 195 patients) discontinued the study prematurely. The percentage of patients with early discontinuation was higher in Spain (n=18, 24.7% of 73 patients) than in France (n=21, 17.2% of 122 patients; see end-of-text Table 14.1.2, stand-alone document 1.3). In addition to the 39 patients with documented early discontinuation visits, there were 3 patients who at some time after the 3-month FU stopped Zutectra® treatment but were followed for up to approximately 20 months without a documented early discontinuation visit (the last relevant study visit was the 3-month visit in these patients; Listing 16.2.2.1).

**Table 2 Study completion and early discontinuation**

| Characteristic | Statistics/ Category | **FAS (N=195)** |
|---|---|---|
| Follow-up status (documented visits) [n (%)][a] | 3-month FU | 181 (92.8%) |
| | 2-year FU | 147 (75.4%) |
| | FU last | 195 (100.0%) |
| Time between baseline and FU last [months] | n | 195 |
| | Mean (SD) | 21.4 (7.3) |
| | Median (Min, Max) | 24.0 (1.0, 31.5) |
| Number of intermediate visits per patient | n | 195 |
| | Mean (SD) | 4.2 (2.7) |
| | Median (Min, Max) | 4.0 (0, 10) |
| Patients who discontinued the study early [n (%)][a] | | 39 (20.0%) |
| Reason for early discontinuation [n (%)][b,c] | Patient ended Zutectra® treatment | 25 (64.1%) |
| | AE/ADR | 9 (23.1%) |
| | Withdrawal of informed consent | 3 (7.7%) |
| | Patient lost to follow-up | 1 (2.6%) |
| | Other | 7 (17.9%) |
| Deaths [n (%)][a] | | 6 (3.1%) |

[a] Percentages are based on the total number of patients in the FAS.
[b] Percentages are based on the number of patients who discontinued early.
[c] More than one reason for early discontinuation was possible per patient.
**Data source:** end-of-text Table 14.1.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

As presented in Table 2, the most frequent reason for early discontinuation was ‘stop of Zutectra® treatment by the patient’ (n=25, 64.1% of 39 patients), followed by ‘occurrence of AE/ADR’ (n=9, 23.1%). Three patients withdrew their consent (7.7%) and 1 patient was lost to follow-up (2.6%). Other reasons for early discontinuation were documented in 7 patients (17.9%). See Listing 16.2.1 for the specifications of ‘other’ reasons for early discontinuation. The most frequent ‘other’ reason was that a 2-year treatment period with immunoglobulin was completed, because the patient had been treated with another immunoglobulin prior to switching to Zutectra®. This was the case in 3 patients. One patient changed to another immunoglobulin, 1 patient stopped Zutectra® due to personal motives and in 2 patients the reason for early discontinuation was documented as ‘unknown’.

Six patients (3.1% of 195 patients) died during the observation period. Deaths were caused by various forms of cancer in 3 patients (death related to the neoplastic process that presented, glioblastoma, plasmablastic lymphoma). One patient died from massive splenic infarction and respiratory infection and another patient died from multiorgan failure. The cause of death in 1 patient was documented as ‘unknown’. Specifications of the causes of death are provided for the respective patients in Listing 16.2.1 and in Listing 16.2.7.1.1 (see also Section 11.4.5.5).

## 11.2 Descriptive Data

### 11.2.1 Demographic Characteristics

Table 3 summarises the demographic characteristics of the patients in the total FAS and for the patients in the HBV-HCC subgroup. Demographics for each patient are presented in Listing 16.2.2.2 (stand-alone document 1.5).

Total FAS

The majority of the patients were male (n=160, 82.1% of 195 patients), 35 patients were female (17.9%). The mean age of the patients at the time of providing their informed consent was 58.4 ± 10.5 years (n=195); the youngest patient was 19 and the oldest 81 years old. The BMI was derived from the patients’ height and the patients’ weight at baseline. The mean BMI of 179 patients with respective data available was 26.0 ± 4.8 kg/m$^2$, indicating that on average the patients were at the upper end of the normal BMI range. Ethnicity was not documented for the 122 patients from France as agreed with the ethics committee (‘not applicable’). Of the 73 patients from Spain, most were white (n=70), 2 patients were black and in 1 patient ethnicity was documented as ‘other: from Morocco’.

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

In the HBV-HCC subgroup, also most patients were male (n=69, 83.1% of 83 patients); only 14 patients were female (16.9%). The mean age was 59.7 ± 9.8 years (n=83), with a range between 19 and 78 years. The mean BMI was 26.3 ± 4.7 kg/m$^2$ (n=79).

**Table 3 Demographic characteristics**

| Characteristic | Statistics/ Category | FAS (N=195) Total (n=195) | FAS (N=195) Sub HBV-HCC (n=83) |
|---|---|---|---|
| Gender [n (%)][a] | Male | 160 (82.1%) | 69 (83.1%) |
| | Female | 35 (17.9%) | 14 (16.9%) |
| Ethnicity [n (%)][a,b] | White | 70 (35.9%) | 37 (44.6%) |
| | Black | 2 (1.0%) | 1 (1.2%) |
| | Asian | 0 | 0 |
| | Other | 1 (0.5%) | 1 (1.2%) |
| | n.a. | 122 (62.6%) | 44 (53.0%) |
| Age [years][c] | n | 195 | 83 |
| | Mean (SD) | 58.4 (10.5) | 59.7 (9.8) |
| | Median (Min, Max) | 59 (19, 81) | 61 (19, 78) |
| Height [cm] | n | 183 | 81 |
| | Mean (SD) | 170.4 (8.5) | 170.0 (9.3) |
| | Median (Min, Max) | 171 (140, 189) | 172 (149, 189) |
| Weight at baseline [kg] | n | 188 | 80 |
| | Mean (SD) | 75.1 (13.9) | 75.6 (13.6) |
| | Median (Min, Max) | 74 (43, 129) | 74 (49, 110) |
| BMI [kg/m$^2$][c] | n | 179 | 79 |
| | Mean (SD) | 26.0 (4.8) | 26.3 (4.7) |
| | Median (Min, Max) | 25.8 (16.4, 52.3) | 26.4 (17.6, 38.9) |

[a] Percentages are based on the number of patients in the total FAS or HBV-HCC subgroup.
[b] Ethnicity was not documented in France ('not applicable').
[c] Derived variable (see Section 10.4.4).
n.a. = not applicable
**Data source:** end-of-text Table 14.2.1 (stand-alone document 1.3, Appendix 1, Section 16.1).

### 11.2.2 Professional Activities

The frequencies of the patients' professional activities at baseline and at the last documented visit (FU last) are presented in Table 4. For frequencies at the 3-month FU and the 2-year FU visits and subgroup-specific results see end-of-text Table 14.2.2 (stand-alone document 1.3).

At baseline, 73 patients (37.4% of 195 patients) were retired, 39 patients (20.0%) were employed, 27 patients (13.8%) were not employed, 5 patients (2.6%) were on rehabilitation, and 1 patient was on training/education. Professional activities were unknown in 50 patients (25.6%).

At the last documented FU visit, data on professional activities were available for 193 patients. The proportions of employed patients, unemployed patients, and patients with unknown professional activities remained mostly similar between baseline and FU last. The greatest (but moderate) change was seen in the frequency of retirement: the proportion of retired patients increased from 37.4% (n=73) at baseline to 42.0% (n=81) at FU last.

**Table 4 Professional activities at baseline and last FU visit**

| Activities [n (%)][a] | Total FAS (n=195) | |
|---|---|---|
| | Baseline (n=195) | FU last (n=193) |
| Retired | 73 (37.4%) | 81 (42.0%) |
| Employed | 39 (20.0%) | 37 (19.2%) |
| Not employed | 27 (13.8%) | 24 (12.4%) |
| On rehabilitation | 5 (2.6%) | 0 |
| On training/education | 1 (0.5%) | 1 (0.5%) |
| Unknown | 50 (25.6%) | 50 (25.9%) |

[a] Percentages are based on the number of patients at the respective visit in the total FAS or HBV-HCC subgroup, respectively.
**Data source:** end-of-text Table 14.2.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

Changes from baseline in professional activities at each visit are presented by category in end-of-text Table 14.2.3 (stand-alone document 1.3). In the majority of patients, professional activities did not change between baseline and FU last (n=141, 73.1% of 193 patients; number and percentage derived from end-of-text Table 14.2.3 by adding up the number and percentages of patients with no change in the individual categories). The most frequent changes between baseline and FU last were seen in the categories ‘retired’ and ‘unknown’. In total, 17 patients were retired at FU last who had either been employed (n=4), not employed (n=6), or had been documented with unknown professional activity (n=7) at baseline. Likewise, for 17 patients, professional activities were unknown at FU last, but patients had been employed (n=7), not employed (n=5), or retired (n=7) at baseline. A total of 9 patients were not employed at FU last, but had either been retired (n=3) or professional activity had been unknown (n=6) at baseline. Nine patients were employed at FU last, of which 5 patients had been on rehabilitation at the baseline visit, 1 had not been employed, and for 3 patients, professional activities had been unknown. One patient remained on training/education throughout the study period.

Listing 16.2.2.3 presents the professional activities for each patient at the relevant study visits.

### 11.2.3 Medical History

#### *11.2.3.1 Liver Transplantation (Last and Prior), MELD Score, and Status of Liver Disease at the Time of LT*

Results on medical history of the patients related to the LT are summarised in Table 5 for the total FAS and the HBV-HCC subgroup.

Total FAS

The mean MELD score at the time of the last LT, calculated for 119 patients with data on MELD score available, was 16.6 ± 9.0 (median: 14.0). The lowest MELD score of a patient was 6 and the highest 40 (which corresponds to the possible range of the MELD score). Fourteen patients (7.2%) had undergone another LT, prior to the last LT. MELD scores at the time of the prior LT were available for only 6 of these patients (mean: 17.3 ± 6.9, median: 18.0). Listing 16.2.3. presents the dates and MELD scores of the last LT and the

prior LT. In patients #10303 and #21403, the dates of the prior LTs were only a few days (i.e. 2 and 4 days, respectively) before the dates of the last LTs. In other patients with dates available for the last and prior LTs (n=9), the time periods between both LTs ranged between approximately 1 and 21.5 years (see Listing 16.2.3).

The most frequent HBV-related main reason for the last LT was HBV-induced liver cirrhosis (n=100, 51.3% of 195 patients), followed by HBV-HCC (n=83, 42.6%), and HBV-induced fulminant hepatitis (n=12, 6.2%).

HBV-HCC was histopathologically determined in the explant in 91 patients (46.7% of 195 patients). In most of these patients (n=68), HBV-HCC had been the main reason for LT; in 22 patients, HBV-induced liver cirrhosis had been the main reason and in 1 patient HBV-induced fulminant hepatitis had been the main reason for LT (see Listing 16.2.3 for presentation of medical history data per patient). HBV-HCC was not detected in the explant in 72 patients (36.9%) and an examination for HCC was not done in 32 patients (16.4%).

The status of liver disease at the time of LT was 'compensated' in 89 patients (45.6%) and 'decompensated' in 106 patients (54.4%).

**Table 5 Medical history related to LT**

| Characteristics | Statistics/ Category | FAS (N=195) Total (n=195) | FAS (N=195) Sub HBV-HCC (n=83) |
|---|---|---|---|
| MELD score at the time of last LT | n | 119 | 66 |
| | Mean (SD) | 16.6 (9.0) | 12.2 (6.3) |
| | Median (Min, Max) | 14.0 (6, 40) | 10.0 (6, 35) |
| Patient had another LT prior to the last [n (%)][a] | Yes | 14 (7.2%) | 4 (4.8%) |
| | No | 181 (92.8%) | 79 (95.2%) |
| MELD score at the time of prior LT | n | 6 | 3 |
| | Mean (SD) | 17.3 (6.9) | 14.3 (8.4) |
| | Median (Min, Max) | 18.0 (9, 25) | 10.0 (9, 24) |
| HBV-related main reason for the last LT [n (%)][a] | HBV-induced liver cirrhosis | 100 (51.3%) | 0 |
| | HBV-induced fulminant hepatitis | 12 (6.2%) | 0 |
| | HBV-HCC | 83 (42.6%) | 83 (100.0%) |
| Histopathological determination of HBV-HCC in the explant [n (%)][a] | Yes | 91 (46.7%) | 68 (81.9%) |
| | No | 72 (36.9%) | 10 (12.0%) |
| | Not done | 32 (16.4%) | 5 (6.0%) |
| Status of liver disease at the time of last LT [n (%)][a] | Compensated liver disease | 89 (45.6%) | 58 (69.9%) |
| | Decompensated liver disease | 106 (54.4%) | 25 (30.1%) |

[a] Percentages are based on the number of patients in the total FAS or HBV-HCC subgroup.
**Data source:** end-of-text Table 14.3 (stand-alone document 1.3, Appendix 1, Section 16.1).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

The mean MELD score at the time of LT in the HBV-HCC subgroup was lower than in the total FAS: 12.2 ± 6.3 (median: 10), with a range between 6 and 35. Four patients (4.8% of

83 patients) had undergone another LT prior to the last LT with a mean MELD at the time of the prior LT of 14.3 ± 8.4 (n=3).

HBV-HCC was histopathologically determined in the explant in 68 patients (81.9% of 83 patients). Whereas HBV-HCC was not detected in the explant in 10 patients (12.0%) or the examination was not done in 5 patients (6.0%).

Compared to the total FAS, the proportion of patients with compensated liver disease was higher in the HBV-HCC subgroup: 58 patients (69.9%) had compensated liver disease and 25 patients (30.1%) had decompensated liver disease.

#### *11.2.3.2 Viral Co-infection*

Total FAS

At least one viral co-infection was documented in 57 patients in the total FAS (number derived from Listing 16.2.3). As shown in Table 6, HDV infection was the most frequent co-infection and was documented in 43 patients (22.1%); HCV infection was documented in 19 patients (9.7%) and HIV in 7 patients (3.6%). Six patients had co-infection with HDV and HCV, 1 patient with HCV and HIV, 1 patient with HDV and HIV, and 2 patients had co-infections with all three viruses (see Listing 16.2.3). Viral co-infection was documented as 'not applicable' in 138 patients (70.8%).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

Viral co-infection was documented in 18 patients (Listing 16.2.3). Infection with HDV was most frequently documented, i.e. in 14 patients (16.9%; Table 6). Infection with HCV was documented in 5 patients (6.0%) and HIV in 1 patient (1.2%). Two patients had co-infection with both HDV and HCV (Listing 16.2.3). Viral co-infection was documented as 'not applicable' in 65 patients (78.3%).

**Table 6 Viral co-infection**

| | | FAS (N=195) | |
|---|---|---|---|
| Characteristics | Statistics/ Category | **Total (n=195)** | **Sub HBV-HCC (n=83)** |
| Viral co-infection [n (%)][a] | HDV | 43 (22.1%) | 14 (16.9%) |
| | HCV | 19 (9.7%) | 5 (6.0%) |
| | HIV | 7 (3.6%) | 1 (1.2%) |
| | n.a. | 138 (70.8%) | 65 (78.3%) |

[a] Percentages are based on the number of patients in the total FAS or HBV-HCC subgroup.
n.a. = not applicable
**Data source:** end-of-text Table 14.3 (stand-alone document 1.3, Appendix 1, Section 16.1).

#### *11.2.3.3 Concomitant Non-HBV-related Liver Diseases and Non-hepatic Diseases*

The frequencies of concomitant non-HBV-related liver diseases and non-hepatic diseases at the time of the LT are presented for the total FAS and the HBV-HCC subgroup in Table 7.

Total FAS

The majority of the patients had no concomitant non-HBV-related liver diseases (n=144, 73.8% of 195 patients). Of the concurrent liver diseases, alcoholic liver disease was the most commonly reported (n=39, 20.0%). Seven patients (3.6%) had non-alcoholic steatohepatitis (NASH), 2 patients (1.0%) had autoimmune hepatitis, 2 patients (1.0%) had primary sclerosing cholangitis (PSC). Other individual concomitant liver diseases were reported in the category 'other' in 6 patients (3.1%). Specifications of these liver diseases are provided in Listing 16.2.3.

For approximately two thirds of the patients, it was reported that they had no concomitant non-hepatic diseases (n=121, 62.1% of 195 patients). Concomitant non-hepatic disorders were documented in 74 patients, of which 26 patients had more than one non-hepatic disease (see Listing 16.2.3). The most frequently reported concomitant non-hepatic disease was arterial hypertension (n=38, 19.5%), followed by diabetes mellitus (n=34, 17.4), and kidney disease (n=26, 13.3%). Allergy was reported in 10 patients (5.1%) and cancer in 3 patients (1.5%). Further details on concomitant non-hepatic diseases are provided by patient in Listing 16.2.3.

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

The majority of the patients in the HBV-HCC subgroup had no concomitant non-HBV-related liver diseases (n=66, 79.5% of 83 patients). Alcoholic liver disease was reported in 13 patients (15.7%); 5 patients (6.0%) had non-alcoholic steatohepatitis (NASH), 1 patient (1.2%) had primary sclerosing cholangitis (PSC), and 1 patient had hepatic artery thrombosis, which was documented in the category 'other' (see Listing 16.2.3).

Approximately half of the patients in the subgroup had no concomitant non-hepatic diseases (n=43, 51.8%). Arterial hypertension was the most common non-hepatic disease in the HBV-HCC subgroup (n=24, 28.9%), followed by diabetes mellitus (n=19, 22.9%).

**Table 7 Concomitant diseases at the time of liver transplantation**

| | | FAS (N=195) | |
|---|---|---|---|
| Characteristic | Category | **Total (n=195)** | **Sub HBV-HCC (n=83)** |
| Non-HBV-related liver diseases [n (%)][a] | Alcoholic liver disease | 39 (20.0%) | 13 (15.7%) |
| | Non-alcoholic steatohepatitis (NASH) | 7 (3.6%) | 5 (6.0%) |
| | Autoimmune hepatitis | 2 (1.0%) | 0 |
| | Primary sclerosing cholangitis (PSC) | 2 (1.0%) | 1 (1.2%) |
| | Other | 6 (3.1%) | 1 (1.2%) |
| | None | 144 (73.8%) | 66 (79.5%) |
| Non-hepatic diseases [n (%)][a] | Arterial hypertension | 38 (19.5%) | 24 (28.9%) |
| | Diabetes mellitus | 34 (17.4%) | 19 (22.9%) |
| | Kidney disease | 26 (13.3%) | 9 (10.8%) |
| | Allergy | 10 (5.1%) | 5 (6.0%) |
| | Cancer | 3 (1.5%) | 3 (3.6%) |
| | None | 121 (62.1%) | 43 (51.8%) |

[a] Percentages are based on the number of patients in the total FAS and HBV-HCC subgroup. Specified diseases are presented by frequency from highest to lowest in the total FAS.
**Data source:** end-of-text Table 14.3 (stand-alone document 1.3, Appendix 1, Section 16.1).

### 11.2.4 Donor and Donor Organ Characteristics

As shown in Table 8, a whole liver was transplanted in most cases (n=179, 91.8% of 195 patients). Eight patients (4.1%) received a split liver (deceased donor liver transplant), 5 patients (2.6%) received a living donor liver transplant, and 3 patients (1.5%) underwent liver and kidney co-transplantation.

The mean age of the donors was 51.7 ± 19.0 years (median: 52.0 years). The youngest donor was 12 years and the oldest was 87 years old.

Markers of HBV infection were tested positive in some of the donors: HBsAg was found in 3 donors (1.5% of 195 donors), anti-HBs was positive in 23 donors (11.8%), and anti-HBc was positive in 17 donors (8.7%). However, tests for HBV markers were not available for 41 to 103 donors (21.0% to 52.8%), depending on the variable.

No positive anti-HCV tests were reported; anti-HCV test results were not available for 40 donors (20.5%).

No positive anti-HIV1+2 tests or positive HIVAg tests were reported; anti-HIV1+2 test results were not available for 68 donors (34.9%) and HIVAg test results were not available for 116 donors (59.5%).

CMV IgG was tested positive in 97 donors (49.7%) and the test was not available for 46 donors (23.6%). CMV IgM, a marker of acute infection with cytomegalovirus, was positive in 15 donors (7.7%); for 141 donors (72.3%), CMV IgM test results were not available.

Individual test results, type of transplant by patient, and age of the donor are provided in Listing 16.2.6.

Results on donor and donor organ characteristics for the subgroup of patients with HBV-HCC as main reason for LT are summarised in end-of-text Table 14.6.1 (stand-alone document 1.3). The mean age of the donors in this subgroup was slightly higher than in the total FAS: 56.9 ± 17.6 years (median: 56.5 years), corresponding with the marginally higher mean age of the patients in this subgroup compared to the total FAS.

**Table 8 Characteristics of transplanted allograft and markers of viral infection of the donor**

| Characteristic | Statistics/ Category | **Total FAS (n=195)** |
|---|---|---|
| Transplant [n (%)][a] | Whole liver | 179 (91.8%) |
| | Split liver – deceased donor liver transplant | 8 (4.1%) |
| | Living donor liver transplant | 5 (2.6%) |
| | Liver and kidney co-transplant | 3 (1.5%) |
| Age of donor [years] | n | 179 |
| | Mean (SD) | 51.7 (19.0) |
| | Median (Min, Max) | 52.0 (12, 87) |
| HBsAg [n (%)][a] | Positive | 3 (1.5%) |
| | Not detectable | 151 (77.4%) |
| | Not available | 41 (21.0%) |
| Anti-HBs [n (%)][a] | Positive | 23 (11.8%) |
| | Not detectable | 69 (35.4%) |
| | Not available | 103 (52.8%) |
| Anti-HBc [n (%)][a] | Positive | 17 (8.7%) |
| | Not detectable | 130 (66.7%) |
| | Not available | 48 (24.6%) |
| Anti-HCV [n (%)][a] | Positive | 0 |
| | Not detectable | 155 (79.5%) |
| | Not available | 40 (20.5%) |
| Anti-HIV1+2 [n (%)][a] | Positive | 0 |
| | Not detectable | 127 (65.1%) |
| | Not available | 68 (34.9%) |
| HIVAg [n (%)][a] | Positive | 0 |
| | Not detectable | 79 (40.5%) |
| | Not available | 116 (59.5%) |
| CMV IgG [n (%)][a] | Positive | 97 (49.7%) |
| | Not detectable | 52 (26.7%) |
| | Not available | 46 (23.6%) |
| CMV IgM [n (%)][a] | Positive | 15 (7.7%) |
| | Not detectable | 39 (20.0%) |
| | Not available | 141 (72.3%) |

[a] Percentages are based on the number of patients (i.e. donors, respectively) in the total FAS.
Anti-HBc = hepatitis B core antibody, anti-HBs = hepatitis B surface antibody,
anti-HCV = hepatitis C antibody, anti-HIV = human immunodeficiency virus antibody, HIVAg = HIV antigen,
CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, Ig = immunoglobulin.
**Data source:** end-of-text Table 14.6.1 (stand-alone document 1.3, Appendix 1, Section 16.1).

### 11.2.5 Treatment of HCC before Liver Transplantation

As expected, most patients with documented data on bridging therapy, downstaging of HCC, and/or tumour characterisation were in the HBV-HCC subgroup. However, there were also a total of 16 patients with liver cirrhosis as main reason for LT who obviously also had liver tumours and for whom therapy data and/or tumour characteristics were documented (see Listing 16.2.5 for details on treatments of HCC before LT, tumour characteristics and TNM staging per patient).

#### *11.2.5.1 Bridging Therapy and HCC Downstaging*

Table 9 summarises the frequencies of bridging therapies and the number and percentages of patients with downstaging of HCC before the last LT in the total FAS and the subgroup of patients with HBV-HCC as main reason for LT.

Total FAS

Treatment of HCC before LT was documented as 'not applicable' in 131 patients (67.2% of 195 patients).

A total of 64 patients received bridging therapy for HCC before the last LT (individual treatments of HCC before LT are listed per patient in Listing 16.2.5). For most of these patients (n=59), HCC-HBV was documented as main reason for LT; for the remaining 5 patients, HBV-induced liver cirrhosis was the main reason for LT (see also Listing 16.2.3 for main reasons of LT). Most patients received one kind of bridging therapy, 14 patients received two different therapies, and 1 patient received three kinds of therapies (Listing 16.2.5).

The most frequent bridging therapy that patients received before LT was transarterial chemo-embolisation (TACE), which was documented in 42 patients (21.5% of 195 patients), followed by radiofrequency ablation (n=21, 10.8%). Selective internal radiation therapy (SIRT) was received by only 2 patients (1.0%) and sorafenib by only 1 patient (0.5%). Fourteen patients (7.2%) underwent other types of bridging therapies (e.g. liver resection), which were documented and counted in the category 'other' (see Listing 16.2.5 for details). Patients could have received more than one bridging therapy.

Downstaging of HCC to be within the Milan criteria before LT was performed in 18 patients (9.2%). Among these were 15 patients with HBV-HCC as main reason for LT and 3 patients with liver cirrhosis was main reason for LT. Downstaging was not performed in 41 patients (21.0%) and downstaging was reported as 'not applicable' in 134 patients (68.7%). Data on downstaging were missing for 2 patients (1.0%).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

In the HBV-HCC subgroup, treatment of HCC before LT was documented as 'not applicable' in 24 patients (28.9% of 83 patients).

The most frequent bridging therapy was TACE (n=38, 45.8%), followed by radiofrequency ablation (n=20, 24.1%). Other therapies were documented in 16 patients: SIRT (n=2, 2.4%), sorafenib (n=1, 1.2%); 'other' therapies (e.g. liver resection, n=13, 15.7%).

Downstaging of HCC was performed in 15 patients (18.1%), not performed in 31 patients (37.3%), and reported as 'not applicable' in 37 patients (44.6%).

**Table 9 Bridging therapy and downstaging before LT**

| Characteristic | Category | FAS Total (n=195) | FAS Sub HBV-HCC (n=83) |
|---|---|---|---|
| Type of treatment under bridging therapy [n (%)][a] | Transarterial chemo-embolisation (TACE) | 42 (21.5%) | 38 (45.8%) |
| | Radiofrequency ablation | 21 (10.8%) | 20 (24.1%) |
| | Selective internal radiation therapy (SIRT) | 2 (1.0%) | 2 (2.4%) |
| | Sorafenib | 1 (0.5%) | 1 (1.2%) |
| | Other | 14 (7.2%) | 13 (15.7%) |
| | Not applicable | 131 (67.2%) | 24 (28.9%) |
| Downstaging of HCC to be within the Milan Criteria [n (%)][a] | Yes | 18 (9.2%)[b] | 15 (18.1%) |
| | No | 41 (21.0%) | 31 (37.3%) |
| | Not applicable | 134 (68.7%) | 37 (44.6%) |
| | Missing data | 2 (1.0%) | 0 |

[a] Percentages are based on the number of patients in the total FAS or HBV-HCC subgroup.
[b] Downstaging documented as 'Yes' in 15 patients with HBV-HCC and 3 patients with liver cirrhosis as main reason for LT.
Treatments are presented by frequency from highest to lowest in the total FAS.
A patient could have received more than one kind of bridging therapy.
**Data source:** end-of-text Table 14.5 (stand-alone document 1.4, Appendix 1, Section 16.1).

#### *11.2.5.2 Tumour Characteristics*

Tumour characteristics of the liver/explant according to radiology and histopathology reports, respectively, are summarised in Table 10 for the total FAS and the HBV-HCC subgroup.

Total FAS

Data on number and sizes of tumour nodules according to the radiology reports were documented in 69 patients (of which 64 were in the HBV-HCC subgroup).[9] The mean number of tumour nodules at LT was 1.9 ± 1.2 and the mean total size of tumour nodules was 3.7 ± 2.4 cm. There were 4 additional patients (2.1% of 195 patients; all with HBV-HCC as main reason for LT) who were documented with 'multiple' nodules. Exact numbers of nodules and total sizes of nodules were not reported for patients with multiple nodules.

Histopathology report data were available for more patients than radiology report data. The mean number of nodules and the mean total size of nodules were calculated for 77 patients with at least 1 documented nodule in the explant.[10] The mean number of tumour nodules according to the histopathology reports was 2.2 ± 1.9 and the mean total size of tumour nodules was 4.0 ± 3.0 cm.

Results of TNM staging were available for 74 patients (of which 60 patients were in the HBV-HCC subgroup). Approximately half of these patients had a solitary tumour without vascular invasion (T1; n=39, 52.7% of 74 patients). The primary tumour was classified as

[9] For Patient #21408, the number of nodules was 0 according to the radiology report (RR; see Listing 16.2.5). This patient was omitted from the analysis of tumour characteristics according to the RR.
[10] For patient #21104, the number and total size of nodules was 0 according to the histopathology report (HR; see Listing 16.2.5). The patient was omitted from the analysis of tumour characteristics according to the HR.

T2 (solitary tumour with vascular invasion or multiple tumours, none > 5 cm) in 30 patients (40.5%). Higher T stages were documented in only 5 patients: T3a (multiple tumours > 5 cm) in 4 patients (5.4%) and T3b (single tumour or multiple tumours of any size involving a major branch of the portal or hepatic vein) in 1 patient (1.4%). Regional lymph nodes were not involved in 45 patients (60.8%) and regional lymph nodes could not be assessed in 29 patients (39.2%). There were no distant metastases (M0) in 73 patients (98.6%); distant metastasis (M1) was reported in 1 patient (1.4%).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

The tumour characteristics based on the radiology report were very similar between the HBV-HCC subgroup and the total FAS, because the patients in both analyses were almost identical (except for 5 patients). The mean number of tumour nodules at LT, calculated for 64 patients with data available, was 1.9 ± 1.2; the mean total size of tumour nodules was 3.7 ± 2.5 cm.

Histopathology report data were available for 63 subgroup patients. The mean number of tumour nodules detected in the explants was 2.1 ± 1.6 and the mean total size of tumour nodules was 4.2 ± 2.9 cm.

Results of TNM staging were available for 60 patients. The primary tumour was classified as T1 (solitary tumour without vascular invasion) in half of these patients (n=30, 50.0%). The primary tumour was classified as T2 (solitary tumour with vascular invasion or multiple tumours, none > 5 cm) in 26 patients (43.3%) as T3a (multiple tumours > 5 cm) in 3 patients (5.0%), and as T3b (single tumour or multiple tumours of any size involving a major branch of the portal or hepatic vein) in 1 patient (1.7%). There was no metastasis in regional lymph nodes in 34 patients (56.7%) and regional lymph nodes could not be assessed in 26 patients (43.3%). No distant metastases (M0) were seen in 59 patients (98.3%); 1 patient (1.7%) was reported with distant metastasis (M1).

**Table 10 Tumour characteristics**

| Characteristic | Statistics/ Category | FAS (N=195) Total (n=195) | FAS (N=195) Sub HBV-HCC (n=83) |
|---|---|---|---|
| Tumour characteristics at LT according to radiology report: | | | |
| Number of tumour nodules | n | 69 | 64 |
| | Mean (SD) | 1.9 (1.2) | 1.9 (1.2) |
| | Median (Min, Max) | 1.0 (1, 6) | 1.0 (1, 6) |
| Total size of tumour nodules [cm] | n | 69 | 64 |
| | Mean (SD) | 3.7 (2.5) | 3.7 (2.5) |
| | Median (Min, Max) | 3.2 (0.4, 12.2) | 3.1 (1.0, 12.2) |
| Tumour characteristics of the explant at LT according to histopathology report: | | | |
| Number of tumour nodules | n | 77 | 63 |
| | Mean (SD) | 2.2 (1.9) | 2.1 (1.6) |
| | Median (Min, Max) | 2.0 (1, 12) | 2.0 (1, 7) |
| Total size of tumour nodules [cm] | n | 77 | 63 |
| | Mean (SD) | 4.0 (3.0) | 4.2 (2.9) |
| | Median (Min, Max) | 3.3 (0.3, 14.2) | 3.5 (1, 14.2) |
| TNM staging [n (%)][a] | | | |
| Number of patients with TNM data [n] | | 74 | 60 |
| Primary tumour | T1 (Solitary tumour without vascular invasion) | 39 (52.7%) | 30 (50.0%) |
| | T2 (Solitary tumour with vascular invasion or multiple tumours, none > 5 cm) | 30 (40.5%) | 26 (43.3%) |
| | T3a (Multiple tumours > 5 cm) | 4 (5.4%) | 3 (5.0%) |
| | T3b (Single tumour or multiple tumours of any size involving a major branch of the portal or hepatic vein) | 1 (1.4%) | 1 (1.7%) |
| | T4 (Tumour(s) with direct invasion of adjacent organs other than gallbladder or with visceral peritoneum) | 0 | 0 |
| Regional lymph nodes | NX (Regional lymph nodes cannot be assessed) | 29 (39.2%) | 26 (43.3%) |
| | N0 (No regional lymph node metastasis) | 45 (60.8%) | 34 (56.7%) |
| | N1 (Regional lymph node metastasis) | 0 | 0 |
| Distant metastasis | M0 (No distant metastasis) | 73 (98.6%) | 59 (98.3%) |
| | M1 (Distant metastasis) | 1 (1.4%) | 1 (1.7%) |

[a] Percentages are based on the number of patients with TNM staging available in the total FAS or HBV-HCC subgroup.
**Data source:** end-of-text Table 14.5 (stand-alone document 1.3, Appendix 1, Section 16.1).

### 11.2.6 Immunosuppressive Treatment after Liver Transplantation

Table 11 presents the frequencies of Immunosuppressive treatments after LT in the total FAS and HBV-HCC subgroup. Details on immunosuppressive treatments, including total daily dose, frequency, start and stop dates, and any treatment changes are provided by patient in Listing 16.2.8.3.2.

Most patients received immunosuppressive treatments throughout the observation period: 194 patients (99.5% of 195 patients)[11] at baseline, 181 patients (100.0% of 181 patients) at the 3-month FU, and 146 patients (99.3% of 147 patients) at the 2-year FU. A patient could have been documented with more than one immunosuppressive medication at any study visit. The most frequently used immunosuppressive treatments after LT at all three documentation time points (baseline, 3-month FU, and 2-year FU) were calcineurin inhibitors (CNIs), followed by mycophenolated mofetil (MMF).

Total FAS

At baseline, 165 patients (85.1% of 194 patients) received CNI treatment and 131 patients (67.5%) received MMF. Corticosteroids and mTor inhibitor were less frequently given (corticosteroids: n=47, 24.2%; mTor inhibitor: n=27, 13.9%). Azathioprine was documented in only 2 patients (1.0%) and anti-IL-2 receptor antibody in only 1 patient (0.5%). At the 3-month FU, the proportion of patients who were treated with corticosteroids was smaller compared to baseline. The frequencies of other individual treatments were similar at the 3-month FU compared to baseline (Table 11). After two years of observation, the proportion of patients with corticosteroid therapy was decreased to 10.3% (n=15), while calcineurin inhibitors were still used by 79.5% (n=116) and MMF by 63.7% (n=93) of the patients with immunosuppressive treatment at this visit.

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

In patients with HBV-HCC as main reason for LT, the frequencies of immunosuppressive treatments were similar compared to the total FAS.

At baseline, 71 patients (85.5% of 83 patients) were treated with CNIs, 61 patients (73.5%) with MMF, 27 patients (32.5%) with corticosteroids, and 15 patients (18.1%) with mTor inhibitor. One patient (1.2%) received anti IL-2 receptor antibody and none of the patients were treated with azathioprine. At the subsequent study visits, the largest change in immunosuppressive treatments was seen in the therapy with corticosteroids, which was less frequent compared to baseline among the patients with immunosuppressive treatment at the 3-month FU (n=13, 16.7%) and only received by 3 patients (5.7%) at the 2-year FU.

[11] Immunosuppressive treatments listed at baseline for patient #20804 in Listing 16.2.8.3.2 have start/change dates more than 6 months after the patient's baseline visit. The patient was thus not counted with immunosuppressive treatment at baseline in the analysis.

**Table 11 Immunosuppressive treatment**

| Characteristic | FAS (N=195) Total (n=195) Baseline (n=195) | 3-month FU (n=181) | 2-year FU (n=147) |
|---|---|---|---|
| Number of patients with immuno-suppressive treatment [n (%)][a] | 194 (99.5%) | 181 (100.0%) | 146 (99.3%) |
| Treatment [n (%)][b] | | | |
| Calcineurin inhibitor | 165 (85.1%) | 154 (85.1%) | 116 (79.5%) |
| Mycophenolate mofetil (MMF) | 131 (67.5%) | 123 (68.0%) | 93 (63.7%) |
| Corticosteroids | 47 (24.2%) | 28 (15.5%) | 15 (10.3%) |
| mTor inhibitor | 27 (13.9%) | 26 (14.4%) | 25 (17.1%) |
| Azathioprine | 2 (1.0%) | 2 (1.1%) | 3 (2.1%) |
| Anti-IL-2 receptor antibody | 1 (0.5%) | 0 | 0 |
| | **Sub HBV-HCC (n=83)** | | |
| | Baseline (n=83) | 3-month FU (n=78) | 2-year FU (n=54) |
| Number of patients with immuno-suppressive treatment [n (%)][a] | 83 (100.0%) | 78 (100.0%) | 53 (98.1%) |
| Treatment [n (%)][b] | | | |
| Calcineurin inhibitor | 71 (85.5%) | 67 (85.9%) | 41 (77.4%) |
| Mycophenolate mofetil (MMF) | 61 (73.5%) | 58 (74.4%) | 38 (71.7%) |
| Corticosteroids | 27 (32.5%) | 13 (16.7%) | 3 (5.7%) |
| mTor inhibitor | 15 (18.1%) | 15 (19.2%) | 11 (20.8%) |
| Azathioprine | 0 | 0 | 0 |
| Anti-IL-2 receptor antibody | 1 (1.2%) | 0 | 0 |

[a] Percentages are based on the number of patients with the respective visit in the total FAS or HBV-HCC subgroup.
[b] Percentages are based on the number of patients with immunosuppressive treatment in the total FAS and HBV-HCC subgroup.
Treatments are presented by frequency from highest to lowest in the total FAS at baseline.
A patient could have been treated with more than one immunosuppressive medication.
**Data source:** end-of-text Table 14.8.3.3 (stand-alone document 1.3, Appendix 1, Section 16.1).

### 11.2.7 Prior and Concomitant Antiviral Medications

Listing 16.2.4 presents all documented prior and concomitant antiviral medications by patient, including daily dose, frequency, route of administration, start and stop dates, status (prior and/or concomitant), whether the intake was ongoing at the time of documentation, and any comments by the investigators.

#### *11.2.7.1 Prior Antiviral Medications*

A prior antiviral medication was defined as any medication of which at least one dose had been taken prior to the start of Zutectra® treatment. Table 12 presents the frequencies of

the documented prior antiviral medications by international nonproprietary name for the total FAS and the HBV-HCC subgroup.

Total FAS

At least one prior antiviral medication was documented in 189 patients (96.9% of 195 patients). The most frequent prior antiviral medication was hepatitis B immunoglobulin (intravenous [i.v]. or intramuscular [i.m.]), which had been given to over 80% of the patients with at least one prior antiviral medication (n=164, 86.8% of 189 patients). Therapy with at least one NUC had been received by 163 patients (86.2%). Of the documented NUCs, tenofovir disoproxil (n=69, 36.5%), entecavir (n=59, 31.2%), and lamivudine (n=59, 31.2%) were the most commonly used, followed by adefovir dipivoxil (n=20, 10.6%). All other documented NUCs and other antiviral medications were each reported in less than 5.0% of the 189 patients. Interferons as immunostimulants were also reported in only 2.6% of the patients (n=5).

Frequencies of prior antiviral medications were similar between Spain and France. In both countries prior hepatitis B immunoglobulin treatment was reported in over 80% of the patients (Spain: 84.9%; France: 87.9%). Of the NUCs, lamivudine was the most frequently used virostatic in Spain (41.1%) and tenofovir disoproxil in France (39.7%; end-of-text Table 14.4.1.1, stand-alone document 1.3).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

In the HBV-HCC subgroup, at least one prior antiviral medication was documented in most patients (n=82, 98.8% of 83 patients). Prior NUC therapy was documented in 76 patients (92.7% of 82 patients, corresponding to 91.6% of 83 patients). The frequencies of the four most used NUCs were as follows: 43.9% (n=36) tenofovir disoproxil, 39.0% (n=32) entecavir, 23.2% (n=19) lamivudine, and 12.2% (n=10) adefovir dipivoxil. Emtricitabine and tenofovir alafenamide had each been used by 6.1% (n=5). Prior hepatitis B immunoglobulin treatment was reported in over 80% of the patients (n=68, 82.9% of 82 patients). Only 2.4% (n=2) of the patients had been treated with interferons.

**Table 12 Frequencies of antiviral medications taken prior to Zutectra® treatment**

| Characteristic | FAS (N=195) Total (n=195) | FAS (N=195) Sub HBV-HCC (n=83) |
|---|---|---|
| Patients with at least one medication recorded [n (%)][a] | 189 (96.9%) | 82 (98.8%) |
| Individual medications by international nonproprietary name (INN) [n (%)][b]: | | |
| Hepatitis B immunoglobulin | 164 (86.8%) | 68 (82.9%) |
| Tenofovir disoproxil | 69 (36.5%) | 36 (43.9%) |
| Entecavir | 59 (31.2%) | 32 (39.0%) |
| Lamivudine | 59 (31.2%) | 19 (23.2%) |
| Adefovir dipivoxil | 20 (10.6%) | 10 (12.2%) |
| Emtricitabine | 9 (4.8%) | 5 (6.1%) |
| Tenofovir alafenamide | 7 (3.7%) | 5 (6.1%) |
| Interferons | 5 (2.6%) | 2 (2.4%) |
| Abacavir | 2 (1.1%) | 0 |
| Atazanavir | 2 (1.1%) | 0 |
| Ganciclovir | 2 (1.1%) | 0 |
| Lopinavir | 2 (1.1%) | 0 |
| Ritonavir | 2 (1.1%) | 0 |
| Dolutegravir | 1 (0.5%) | 0 |
| Etravirine | 1 (0.5%) | 0 |
| Famciclovir | 1 (0.5%) | 0 |
| Ledipasvir | 1 (0.5%) | 0 |
| Raltegravir | 1 (0.5%) | 0 |
| Ribavirin | 1 (0.5%) | 0 |
| Sofosbuvir | 1 (0.5%) | 0 |
| Telaprevir | 1 (0.5%) | 0 |
| Valaciclovir | 1 (0.5%) | 0 |
| Vidarabine | 1 (0.5%) | 0 |
| Patients with at least one NUC taken prior to start of Zutectra [n (%)][b] | 163 (86.2%) | 76 (92.7%) |

[a] Percentages are based on the number of patients in the total FAS and HBV-HCC subgroup.
[b] Percentages are based on number of patients with at least one medication recorded in the total FAS and HBV-HCC subgroup.
Medications are presented by frequency from highest to lowest in the total FAS.
**Data source:** end-of-text Table 14.4.1.1 (stand-alone document 1.3, Appendix 1, Section 16.1) and Listing 16.2.4 (stand-alone document 1.5, Appendix 1, Section 16.1).

### *11.2.7.2 Concomitant Antiviral Medications*

A concomitant antiviral medication was defined as any medication of which at least one dose had been taken after the start of Zutectra® treatment. Medications that were taken

before and after the start of Zutectra® treatment were counted as prior as well as concomitant medications. Table 13 presents the frequencies of the documented concomitant antiviral medications by international nonproprietary name for the total FAS and the HBV-HCC subgroup.

Total FAS

Most patients with concomitant antiviral medications had also received antiviral medications before the start of Zutectra® treatment and the majority of concomitant medications had also been taken prior to Zutectra® therapy by the patients (see Listing 16.2.4). There was only 1 patient (#21108) without any reported prior antiviral medications who started treatment with an antiviral drug (tenofovir disoproxil) after start of Zutectra® treatment.

At least one concomitant antiviral medication was documented in 162 patients (83.1% of 195 patients). NUCs were the most frequent concomitant antivirals: 159 patients (98.2% of 162 patients, corresponding to 81.5% of 195 patients) were documented with at least one NUC for concomitant therapy. The most commonly used individual NUCs were tenofovir disoproxil (n=63, 38.9% of 162 patients), entecavir (n=59, 36.4%), and lamivudine (n=39, 24.1%). Other concomitant NUCs were less frequently reported (< 5.0%). Protease inhibitors (atazanavir, ritonavir, telaprevir) and integrase inhibitors (dolutegravir, raltegravir) were each used in only 1 to 2 patients. Concomitant hepatitis B immunoglobulin treatment was reported in 18 patients (11.1%).

Tenofovir disoproxil, entecavir, and lamivudine were the most frequent concomitant virostatic drugs in both Spain and France with tenofovir disoproxil being the most commonly used medication of the three drugs in France (42.9%), whereas lamivudine was more common in Spain (35.2%). The frequency of concomitant hepatitis B immunoglobulin was similar between both countries (Spain: 12.7%, France: 9.9%; end-of-text Table 14.4.1.2, stand-alone document 1.3).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

In the HBV-HCC subgroup, 76 patients (91.6% of 83 patients) had used at least one concomitant antiviral medication. Concomitant NUC therapy was reported in 74 patients (97.4% of 76 patients, corresponding to 89.2% of 83 patients). Entecavir was the most frequently reported individual concomitant NUC (n=33, 43.4% of 76 patients), followed by tenofovir disoproxil (n=30, 39.5%), and lamivudine (n=10, 13.2%); emtricitabine and tenofovir alafenamide were each reported in 5 patients (6.6%), and adefovir dipivoxil in 2 patients (2.6%). Ten patients (13.2%) had received concomitant hepatitis B immunoglobulin.

**Table 13 Frequencies of concomitant antiviral medications**

| Characteristic | FAS (N=195) Total (n=195) | FAS (N=195) Sub HBV-HCC (n=83) |
|---|---|---|
| Patients with at least one medication recorded [n (%)][a] | 162 (83.1%) | 76 (91.6%) |
| Individual medications by international nonproprietary name (INN) [n (%)][b]: | | |
| Tenofovir disoproxil | 63 (38.9%) | 30 (39.5%) |
| Entecavir | 59 (36.4%) | 33 (43.4%) |
| Lamivudine | 39 (24.1%) | 10 (13.2%) |
| Hepatitis B immunoglobulin | 18 (11.1%) | 10 (13.2%) |
| Emtricitabine | 8 (4.9%) | 5 (6.6%) |
| Tenofovir alafenamide | 7 (4.3%) | 5 (6.6%) |
| Adefovir dipivoxil | 3 (1.9%) | 2 (2.6%) |
| Dolutegravir | 2 (1.2%) | 0 |
| Abacavir | 1 (0.6%) | 0 |
| Atazanavir | 1 (0.6%) | 0 |
| Raltegravir | 1 (0.6%) | 0 |
| Ribavirin | 1 (0.6%) | 1 (1.3%) |
| Ritonavir | 1 (0.6%) | 0 |
| Telaprevir | 1 (0.6%) | 0 |
| Valganciclovir | 1 (0.6%) | 1 (1.3%) |
| Patients with at least one concomitant NUC [n (%)][b] | 159 (98.2%) | 74 (97.4%) |

[a] Percentages are based on the number of patients in the total FAS and HBV-HCC subgroup.
[b] Percentages are based on number of patients with at least one medication recorded in the total FAS and HBV-HCC subgroup.
Medications are presented by frequency from highest to lowest in the total FAS.
**Data source:** end-of-text Table 14.4.1.2 (stand-alone document 1.3, Appendix 1, Section 16.1) and Listing 16.2.4 (stand-alone document 1.5, Appendix 1, Section 16.1).

### 11.2.8 Exposure (Treatment with Zutectra®)

Results of documented treatment with Zutectra® are summarised for the total FAS and the HBV-HCC subgroup in Table 14. Treatment changes, e.g. in dosing or frequency of administration, were possible during the observational period. All changes were to be documented by the participating physicians. Individual treatment changes, dosages, treatment intervals and administration data are provided in Listing 16.2.8.3.0. The dates of first and last treatment during the study, treatment duration, and the mean daily dose are presented for each patient in Listing 16.2.8.3.1.

Total FAS

The mean duration of Zutectra® treatment was 20.7 ± 7.4 months (median: 23.8 months). The shortest treatment duration in a patient during the study period was 0.2 months (i.e. 6 days) and the longest was 30.4 months.

The mean time to first treatment with Zutectra® after the last LT was 91.7 ± 94.1 months (median: 50.6 months). There was a very high variation regarding individual time periods

between LT and start of Zutectra® treatment with a range between 0.3 months (9 days) and 331.3 months (27.6 years).[12]

The mean average monthly dose of Zutectra® calculated from the data of 193 patients was 1171.4 ± 545.7 IU (median: 1087.1 IU). The lowest average monthly dose was 484.7 IU and the highest was 2528.8 IU.

Figure 1 illustrates the mean average daily dose of Zutectra® summarised per month over the course of the observation period. There was a decrease in the mean average daily dose during the first year after start of treatment from 52.1 ± 24.2 IU (n=193) to 34.9 ± 18.2 IU (n=166; see end-of-text Table 15.1.3, stand-alone document 1.4, for mean average doses). During the second year, the mean average dose remained at the same level. It should be noted that the analysis of the mean average daily dose over time was not based on the same sample of patients at each time point. The number of patients in the analysis decreased from 193 at month 1 to 115 at month 24 and was very small for the last months of the documented period.

The most common dosing interval of Zutectra® treatment was biweekly (n=134, 68.7% of 195 patients), followed by weekly (n=108, 55.4%), every 4 weeks/monthly (n=73, 37.4%), and every 3 weeks (n=66, 33.8%). At least one other dosing interval was reported in 12 patients (6.2%). Of these 'other' intervals, every 6 weeks (n=4, 33.3% of 12 patients), every 5 weeks (n=4, 33.3%), and every 10 days (n=3, 25.0%) were the most frequent (see end-of-text Table 14.8.3.1, stand-alone document 1.3). The dosing interval could have changed in a patient during the study period.

[12] Patient #20111: date of last LT was 26 August 1988 and date of first Zutectra® treatment was 05 April 2016.

**Table 14 Treatment with Zutectra® after LT (exposure and treatment administration)**

| Characteristic | Statistics/ Category | FAS (N=195) Total (n=195) | FAS (N=195) Sub HBV-HCC (n=83) |
|---|---|---|---|
| Duration of exposure [months][a] | n | 195 | 83 |
| | Mean (SD) | 20.7 (7.4) | 19.2 (7.7) |
| | Median (Min, Max) | 23.8 (0.2, 30.4) | 23.1 (0.2, 28.7) |
| Time to first treatment after LT [months][a] | n | 195 | 83 |
| | Mean (SD) | 91.7 (94.1) | 49.0 (64.9) |
| | Median (Min, Max) | 50.6 (0.3, 331.3) | 15.3 (0.5, 247.5) |
| Average monthly dose (over documentation period) [IU][a] | n | 193 | 82 |
| | Mean (SD) | 1171.4 (545.7) | 1165.7 (514.7) |
| | Median (Min, Max) | 1087.1 (484.7, 2699.3) | 1087.1 (500.0, 2361.8) |
| Frequency of administration [n (%)][b,c] | Biweekly | 134 (68.7%) | 59 (71.1%) |
| | Weekly | 108 (55.4%) | 42 (50.6%) |
| | Every 4 weeks/monthly | 73 (37.4%) | 28 (33.7%) |
| | Every 3 weeks | 66 (33.8%) | 24 (28.9%) |
| | Other | 12 (6.2%) | 6 (7.2%) |
| | Missing | 1 (0.5%) | 1 (1.2%) |
| Changes in treatment during documentation period [n (%)][b] | No change | 84 (43.1%) | 36 (43.4%) |
| | 1 change | 43 (22.1%) | 22 (26.5%) |
| | 2 changes | 31 (15.9%) | 11 (13.3%) |
| | 3 changes | 28 (14.4%) | 9 (10.8%) |
| | 4 changes | 4 (2.1%) | 3 (3.6%) |
| | 5 changes | 4 (2.1%) | 1 (1.2%) |
| | 6 changes | 1 (0.5%) | 1 (1.2%) |
| Self-administration [n (%)][e] | n' | 9021 | 3587 |
| | Yes | 6458 (71.6%) | 2775 (77.4%) |
| | No | 2563 (28.4%) | 812 (22.6%) |
| Home administration [n (%)][e] | n' | 9021 | 3587 |
| | Yes | 8514 (94.4%) | 3263 (91.0%) |
| | No | 507 (5.6%) | 324 (9.0%) |

[a] Derived variable (see Section 10.4.4).
[b] Percentages are based on the number of patients in the total FAS or HBV-HCC subgroup.
[c] Patients could be counted in more than one category due to changes in administration frequency during the observation period.
[d] Percentages are based on the total number of administrations (n') in the total FAS or HBV-HCC.
n' = total number of administrations during the observation period.
**Data source:** end-of-text Tables 14.8.3.1 and 14.8.3.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

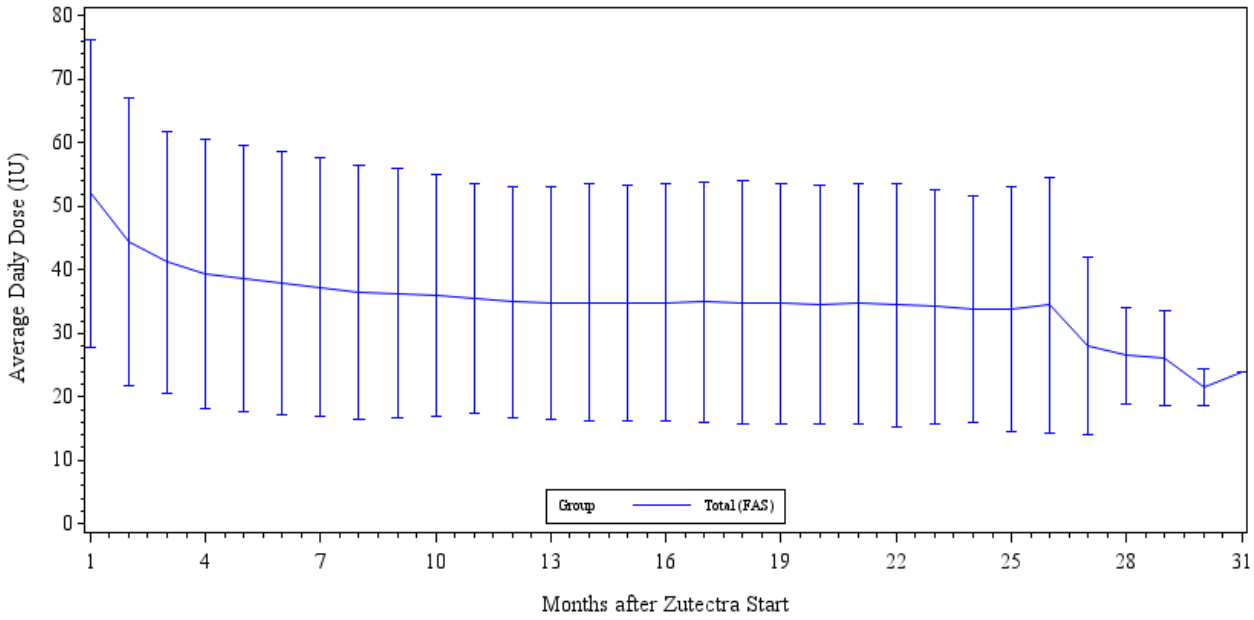


**Figure 1 Mean (± SD) average daily dose of Zutectra® over time**

Number of patients in the analysis at each time point (months after start of Zutectra® in grey rows):

| **Month** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **n** | 193 | 192 | 187 | 183 | 180 | 178 | 174 | 171 | 170 | 170 | 168 | 166 | 161 | 158 | 157 | 157 |
| | | | | | | | | | | | | | | | | |
| **Month** | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | |
| **n** | 157 | 154 | 151 | 150 | 147 | 144 | 133 | 115 | 84 | 45 | 21 | 10 | 7 | 3 | 1 | |

**Data source:** Figure 15.1.1 and end-of-text Table 15.1.3 (stand-alone document 1.4, Appendix 1, Section 16.1).

No changes in Zutectra® treatment during the study period were documented in 84 patients (43.1% of 195 patients); 43 patients (22.1%) had 1 change, 31 patients (15.9%) had 2 changes, 28 patients (14.4%) had 3 changes. Only 9 patients had more than 4 treatment changes: 4 changes (n=4, 2.1%), 5 changes (n=4, 2.1%), and 6 changes (n=1, 0.5%).

The majority of administrations of Zutectra® were self-administered by the patients (71.6% of administrations) and Zutectra® was mostly administered at home (94.4% of 9021 administrations). The mode and location of administration could have changed in a patient during the observation period (see Listing 16.2.8.3.0 for details on Zutectra® administration per patient and visit and for any documented comments by the physician on administration). With regard to country-specific differences in administration of Zutectra®, the data analysis showed that the percentage of self-administrations was considerably lower in France compared to Spain: 60.3% vs. 92.4% of administrations (end-of-text Table 14.8.3.1, stand-alone document 1.3). However, most administrations were performed at home in both countries: 96.0% (France) and 91.3% (Spain).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

The mean duration of Zutectra® treatment in the HBV-HCC subgroup was 19.2 ± 7.7 months (median: 23.1 months) with a range between 0.2 months (6 days) and 28.7 months.

The mean time to first treatment with Zutectra® after the last LT was 49.0 ± 64.9 months (median: 15.3 months). As in the total FAS, there was a high variation in individual time periods, ranging between 0.3 months (9 days) and 247.5 months (20.6 years); however,

the mean and median time to first treatment with Zutectra® was considerably lower in the subgroup than in the total FAS.

The mean average monthly dose of Zutectra® calculated from the data of 82 patients was 1165.7 ± 514.7 IU (median: 1087.1 IU; this is the same median average monthly dose as in the total FAS). The lowest average monthly dose was 500.0 IU and the highest was 2361.8 IU.

The most frequent dosing interval of Zutectra® treatment in the HBV-HCC subgroup was biweekly (n=59, 71.1% of 83 patients), followed by weekly (n=42, 50.6%), every 4 weeks/monthly (n=28, 33.7%), and every 3 weeks (n=24, 28.9%). Other dosing intervals were documented in 6 patients (7.2%) and information on dosing interval was missing in 1 patient (1.2%).

Zutectra® treatment was not changed during the study period in 36 patients (43.4% of 83 patients); 22 patients (26.5%) had 1 change, 11 patients (13.3%) had 2 changes, 9 patients (10.8%) had 3 changes, and the remaining 5 patients had up to 6 treatment changes.

## 11.3 Outcome Data

See Section 11.4.

## 11.4 Main Results

### 11.4.1 Hepatitis B Virus (HBV) Recurrence after Liver Transplantation

#### *11.4.1.1 Incidence of HBV Recurrence and Time to Recurrence*

The determination of the proportions of patients with and without HBV recurrence after LT, the incidence rate per year of HBV recurrence, and the time to recurrence were the primary objectives of effectiveness of this study.

Table 15 summarises the results of the primary variables for the total FAS, the HBV-HCC subgroup, and the subgroup of patients with HDV co-infection.

Total FAS

HBV recurrence was not documented in the CRF or derived from the results of the measurements of serum HBsAg and/or HBV DNA in 188 patients (96.4% of 195 patients in the FAS.

There were 7 patients (3.6% of 195 patients) with HBV recurrence after LT based on HBsAg or HBV DNA serum levels. In 2 of these patients, HBV recurrence was also documented in the CRF (see Listing 16.2.7.2). The observed 7 cases of HBV recurrence corresponded to an incidence rate of HBV recurrence per year of 2.01% (Table 15).

The mean time to HBV recurrence after LT, calculated for the 7 patients with HBV recurrence was 20.0 ± 7.6 months (median: 18.5 months); the shortest time was 13.1 months and the longest time was 34.6 months. Kaplan-Meier plots for time to HBV recurrence after LT can be found for the patients with HBV recurrence in the total FAS (including analyses by HBV marker and country-specific analysis) in Figures 15.5.1.1.1, 15.5.1.1.2, 15.5.2.1.1, 15.5.2.1.2, 15.5.3.1.1, and 15.5.3.1.2 (stand-alone document 1.4, Appendix 1, Section 16.1). In addition, Kaplan-Meier plots for the time to HBV recurrence after start of Zutectra® treatment for the patients with HBV recurrence are provided in Figures 15.5.1.2.1, 15.5.1.2.2, 15.5.2.2.1, 15.5.2.2.2, 15.5.3.2.1, and 15.5.3.2.2.

Table 15 also shows the number and percentages of patients with HBV recurrence based on HBsAg only (n=6, 3.1%) or HBV DNA only (n=1, 0.5%), respectively, as well as the corresponding incidence rates and times to HBV recurrence.

Listing 16.2.7.2 shows for each patient whether HBV recurrence since the last visit was diagnosed, documented clinical signs (if any), and the time to HBV recurrence (derived variable). Listing 16.2.7.3.1 presents for each of the 7 patients with HBV recurrence the date of recurrence and whether recurrence was derived from HBsAG or HBV DNA or both markers.

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

All 7 patients with HBV recurrence (based on HBsAg or HBV DNA levels) belonged into the HBV-HCC subgroup (8.4% of 83 patients). Based on the smaller number of patients in this subgroup compared to the total FAS, the calculated incidence rate per year of HBV recurrence was higher, i.e. 5.05% (Table 15). The mean time to HBV recurrence after LT was the same as in the total FAS: 20.0 ± 7.6 months (median: 18.5 months). Table 15 also shows incidence rate and time to HBV recurrence for the patients with HBV recurrence based on HBsAg only (n=6, 7.2%) or HBV DNA only (n=1, 1.2%), respectively.

Subgroup: HDV co-infection (Sub Co-HDV)

Three patients with HBV recurrence also had HDV co-infection (7.0% of 43 patients in this subgroup; Table 15). The calculated incidence rate per year in this subgroup was 4.12% and the mean time to HBV recurrence was 17.2 ± 5.5 months (median: 15.1 months). HBV recurrence in these patients was based on HBsAg values only.

**Table 15 HBV recurrence after LT**

| Characteristic | Statistics/ Category | FAS (N=195) Total (n=195) | Sub HBV-HCC (n=83) | Sub Co-HDV (n=43) |
|---|---|---|---|---|
| Patients with HBV recurrence after LT | | | | |
| HBsAg or HBV DNA | [n (%)][a] | 7 (3.6%) | 7 (8.4%) | 3 (7.0%) |
| | 2-sided 95% CI | 1.5 - 7.3% | 3.5 – 16.6% | 1.5 – 19.1% |
| HBsAg only | [n (%)][a] | 6 (3.1%) | 6 (7.2%) | 3 (7.0%) |
| | 2-sided 95% CI | 1.1 – 6.6% | 2.7 – 15.1% | 1.5 – 19.1% |
| HBV DNA only | [n (%)][a] | 1 (0.5%) | 1 (1.2%) | 0 |
| | 2-sided 95% CI | 0.0 – 2.8% | 0.0 – 6.5% | 0.0 – 8.2% |
| Incidence of HBV recurrence after LT per year | | | | |
| HBsAg or HBV DNA | Rate (%) | 2.01 | 5.05 | 4.12 |
| HBsAg only | Rate (%) | 1.73 | 4.33 | 4.12 |
| HBV DNA only | Rate (%) | 0.29 | 0.72 | 0 |
| Time to HBV recurrence after LT [months] | | | | |
| HBsAg or HBV DNA | n | 7 | 7 | 3 |
| | Mean (SD) | 20.0 (7.6) | 20.0 (7.6) | 17.2 (5.5) |
| | Median (Min, Max) | 18.5 (13.1, 34.6) | 18.5 (13.1, 34.6) | 15.1 (13.1, 23.5) |
| HBsAg only | n | 6 | 6 | 3 |
| | Mean (SD) | 17.5 (4.5) | 17.5 (4.5) | 17.2 (5.5) |
| | Median (Min, Max) | 16.8 (13.1, 23.5) | 16.8 (13.1, 23.5) | 15.1 (13.1, 23.5) |
| HBV DNA only | n | 1 | 1 | 0 |
| | Mean (SD) | 34.6 (n.a.) | 34.6 (n.a.) | n.a. |
| | Median (Min, Max) | n.a. | n.a. | n.a. |

[a] Percentages are based on the number of patients in the total FAS, HBV-HCC subgroup or HDV Co-infection subgroup, respectively.
n.a. = not applicable
**Data source:** end-of-text Table 14.7.1 (stand-alone document 1.3, Appendix 1, Section 16.1).

#### *11.4.1.2 Details on Patients with HBV Recurrence*

Table 16 presents the data related to the determination of HBV recurrence for each of the 7 patients. HBV recurrence was derived from the data on reported serum HBsAg and/or HBV DNA values during the observation period (see also Section 10.8.3 for definition and analysis rules of HBV recurrence). In 2 of the 7 patients, HBV recurrence was also documented in the CRF (‘Hepatitis B recurrence since last visit?’ was answered with ‘Yes’) at an interim or FU visit. Clinical signs of HBV recurrence were not seen in the 2 patients according to the investigators. HBV recurrence (‘hepatitis B’) was reported as an AE in patient #10804 (Listing 16.2.7.1.1).

**Table 16 Determination of (first) HBV recurrence and time to HBV recurrence after last LT per patient**

| | Patients with HBV recurrence (n=7) Patient ID | | | | | | |
|---|---|---|---|---|---|---|---|
| Characteristic | **#10804** | **#10806** | **#20107** | **#20120** | **#20508** | **#20803** | **#21305** |
| Age at study entry [yrs] | 40 | 51 | 35 | 64 | 75 | 55 | 61 |
| Sex | Male | Male | Male | Male | Female | Male | Male |
| HBV recurrence since last visit documented in CRF | Yes | Yes | No | No | No | No | No |
| Clinical signs of HBV recurrence | No signs | No signs | Not doc. | Not doc. | Not doc. | Not doc. | Not doc. |
| HBsAg [IU/mL] | Positive/ NA | Positive/ NA | ND | Positive/ NA | Positive/ 28 | Positive/ 199 | Positive/ NA |
| HBV DNA [IU/mL] | ND | ND | Positive/ 12 | ND | ND | ND | NA |
| Time to recurrence after LT [months] | 18.5 | 23.5 | 34.6 | 21.8 | 13.1 | 15.0 | 13.2 |
| Date of LT | 23Jan16 | 14Jun17 | 10May15 | 31Jul15 | 12Apr17 | 12Apr17 | 30Aug17 |
| Date of first Zutectra® treatment | 09Jul16 | 27Jun17 | 15Mar16 | 22Sep16 | 22May17 | 28Apr17 | 20Feb18 |
| Date of HBV recurrence[a] | 07Aug17 | 30May19 | 28Mar18 | 24May17 | 15May18 | 13Jul18 | 06Oct18 |
| Date of last Zutectra® treatment | 18Dec17 | 30May19 | 28Mar18 | 17Jul18 | 17May18 | 05Jul19 | 23Jan19 |
| Date of last study visit | 18Dec17 | 30May19 | 28Mar18 | 17Jul18 | 17May18 | 05Jul19 | 26Feb19 |

[a] Date of HBV recurrence as documented in the CRF or date of measurement of HBV DNA or HBsAg values indicating HBV recurrence.
NA = not available, ND = not detectable, Not doc. = not documented in CRF
**Data source:** Subject Data Listings 16.2.2.1, 16.2.2.2, 16.2.3, 16.2.7.2, 16.2.7.3.2, and 16.2.8.3.1 (stand-alone document 1.5, Appendix 1, Section 16.1).

The HBsAg test was positive during the observation period in 6 patients, but exact values were documented for only 2 of these patients (28 IU/mL and 199 IU/mL, respectively). HBV DNA was not detectable at the time of the positive HBsAg test (time of HBV recurrence) in

5 patients and HBV DNA test was not available in 1 patient. In 1 patient, the HBV DNA test was positive at the last FU visit (2-year FU) with a value of 12 IU/mL which was just above the detection limit. HBsAg was not detectable in this patient at this visit.

HBV recurrence occurred at the earliest after approximately 13 months following the LT (2 patients), after 15 months in 1 patient, after one and a half years (18.5 months) in 1 patient, after almost 2 years in 2 patients (21.8 and 23.5 months) and after almost 3 years (34.6 months) in another patient. All 7 patients had been treated with Zutectra® for at least 7 months (up to approximately 2 years) before HBV recurrence.

Table 17 presents the risks and protective factors in patients with HBV recurrence. Before LT, results of serologic tests of HBV markers were positive for HBsAg in 6 patients (with values available in 4 patients) and HBsAg test results were not available for 1 patient. HBV DNA was not detectable in 5 patients and detectable in 1 patient. Anti-HBs was not detectable in any patient. At the time of HBV recurrence, anti-HBs values were above 100 IU/L in 3 patients, below the threshold in 2 patients, and not available in the remaining 2 patients (in the latter 2 patients, last available values before recurrence were however above the threshold). Dosage intervals of Zutectra® (last documented dose and interval before HBV recurrence) differed between patients and ranged from weekly injection to injection every 5 weeks. The mean daily doses of Zutectra® averaged over the entire treatment period of a patient ranged between 20.8 IU and 64.3 IU. All 7 patients received concomitant antiviral treatment with either tenofovir or entecavir which was ongoing at the time of HBV recurrence.

All 7 patients had undergone LT for HBV-HCC as main reason for the LT. HCC was confirmed in the explant in 5 patients (examination was not done in 2 patients). Three patients were co-infected with hepatitis D virus.

**Table 17 Risk and protective factors in patients with HBV recurrence after LT**

| | Patients with HBV recurrence (n=7) Patient ID | | | | | | |
|---|---|---|---|---|---|---|---|
| Characteristic | **#10804** | **#10806** | **#20107** | **#20120** | **#20508** | **#20803** | **#21305** |
| Viral status before LT (as documented at baseline): | | | | | | | |
| HBV DNA [IU/mL] | ND | ND | Positive/ 20 | ND | ND | ND | ND |
| HBsAg [IU/mL] | Positive/ NA | Positive/ NA | Positive/ 2156 | Positive/ 56.6 | Positive/ 8500 | NA | Positive/ 3159 |
| Anti-HBs [IU/L] | ND | ND | ND | ND | ND | ND | ND |
| Anti-HBs at time of HBV recurrence [IU/L] | 108.2 | 22.6 | 167.9 | 100.1 | 29 | NA[a] | NA[a] |
| Zutectra® dose/interval at time of recurrence | 500 IU/ biweekly | 500 IU/ every 10 days | 500 IU/ every 5 weeks | 500 IU/ weekly | 500 IU/ biweekly | 500 IU/ once per month | 500 IU/ every 3 weeks |
| Mean daily Zutectra® dose[b] | 35.7 IU | 50.7 IU | 20.8 IU | 51.5 IU | 47.9 IU | 64.3 IU | 28.5 IU |
| Concomitant antiviral treatment | TDV | ETV | ETV | TDV | ETV | ETV | TDV |
| HBV-HCC in the explant of last LT | Yes | Yes | Yes | Not done | Yes | Yes | Not done |
| Viral co-infection | n.a. | HDV | n.a. | n.a. | HDV | HDV | n.a. |

[a] Last anti-HBs value available approx. 1 month before HBV recurrence in patient #20803 (172 IU/L) and approx. 4 months before HBV recurrence in patient #21305 (313 IU/L).
[b] Mean daily dose over entire treatment period of a patient.
ETV = entecavir, n.a. = not applicable, NA = not available, ND = not detectable, TDV = tenofovir
**Data source:** Subject Data Listings 16.2.7.3.2, 16.2.8.3.0, and 16.2.8.3.1 (stand-alone document 1.5, Appendix 1, Section 16.1).

### 11.4.2 Serological Test Results – Anti-HBs and Viral Status

Table 18 summarises the results of the patients' serologic tests of HBV markers at baseline, the 3-month FU, the 2-Year FU, and FU last for the total FAS and HBV-HCC subgroup. Baseline values are the last values determined before LT as documented at the baseline visit. In general, if several test results were available, the results dating closest to the respective visit date (including defined visit windows, see Section 10.4.4) were used in the analysis (baseline, 3-month FU, 2-year FU).

Changes from baseline in trough levels of serum anti-HBs, HBsAg, and HBV DNA at the post-baseline visits were analysed and statistically tested. The results are presented in end-of-text Table 14.8.4.2; none of the changes were statistically significant. However, as the number of patients with serum trough levels available at baseline and the respective post-baseline visit was so small for each parameter (between 1 and 10 patients) and due to the high inter-patient variability regarding the time to first Zutectra® treatment after LT, the test results for statistical significance should be regarded with caution and might not be meaningful.

Individual results of serological tests of HBV markers together with the date of measurement are presented by patient and visit in Listing 16.2.8.4.

Total FAS

*Anti-HBs*

Anti-HBs is routinely monitored in patients after LT under treatment with HBV immunoglobulin to ensure protective levels against HBV recurrence. Anti-HBs can also be used to indirectly measure adherence to treatment, especially if injections are performed at home by the patient or caregiver. Before LT (baseline), anti-HBs tests were positive in 18 patients (9.2% of 195 patients) and anti-HBs was not detectable in 105 patients (53.8%). In contrast, the proportions of patients with positive anti-HBs tests were > 90% after LT and after start of Zutectra® treatment: 170 patients (98.8% of 172 patients) at the 3 month-FU, 113 patients (95.8% of 118 patients) at the 2-year FU, and 184 patients (94.8% of 194 patients) at FU last (FU last corresponds to the last available test result documented as 'positive', 'not detectable' or 'not available'). There was only 1 patient at each post-baseline time point without detectable anti-HBs. HBs antibody test results were not available for 72 patients (36.9%) before LT, whereas during the observation period test results were not available for only a few patients: 1 patient (0.6%) at the 3-month FU, 4 patients (3.4%) at the 2-year FU, and 9 patients (4.6%) at FU last, respectively.

Table 19 summarises the serum anti-HBs trough levels at each visit. Inter-patient variability in trough levels was high at all time points. The median serum trough level of anti-HBs was 61.0 IU/L (n=11) before LT and was considerably higher at the post-baseline visits: 199.1 IU/L (n=170) at the 3-month FU, 144.0 IU/L (n=112) at the 2-year FU, and 140.1 IU/L (n=194) at FU last (FU last corresponds to the last available anti-HBs value documented in a patient). It should be noted that the number of patients with anti-HBs serum trough values available was very small at baseline compared to the post-baseline visits.

Table 20 shows the proportions of patients with serum anti-HBs trough levels below the threshold of 100 IU/L and ≥ 100 IU/L before LT (baseline) and after baseline. Of the 11 patients with anti-HBs values available before LT, 4 patients (3.4% of 116 patients) had levels ≥ 100 IU/L and 7 patients (6.0%) below the threshold. At all post-baseline time points, the vast majority of the patients with data available had serum anti-HBs trough values ≥ 100 IU/L: 146 patients (85.4% of 171 patients) at the 3-month FU, 84 patients (74.3% of 113 patients) at the 2-year FU, and 139 patients (71.6% of 194 patients) at FU last (FU last corresponds to the last available anti-HBs value or 'not detectable' test result documented in a patient). Below the threshold were 24 patients (14.0%) at the 3-month FU, 28 patients (24.8%) at the 2-year FU, and 54 patients (27.8%) at FU last.

**Table 18 Viral status – frequencies of positive serological tests of HBV markers**

| Marker | Statistics/ Category | FAS (N=195) Total (n=195) Baseline (before LT) (n=195) | 3-month FU (n=172) | 2-year FU (n=118) | FU last[b] (n=194) |
|---|---|---|---|---|---|
| **Anti-HBs** Test [n (%)][a] | Positive | 18 (9.2%) | 170 (98.8%) | 113 (95.8%) | 184 (94.8%) |
| | Not detectable | 105 (53.8%) | 1 (0.6%) | 1 (0.8%) | 1 (0.5%) |
| | Not available | 72 (36.9%) | 1 (0.6%) | 4 (3.4%) | 9 (4.6%) |
| **HBsAg** Test [n (%)][a] | Positive | 112 (57.4%) | 1 (0.6%) | 3 (2.5%) | 6 (3.1%) |
| | Not detectable | 16 (8.2%) | 111 (64.5%) | 73 (61.9%) | 117 (60.3%) |
| | Not available | 67 (34.4%) | 60 (34.9%) | 42 (35.6%) | 71 (36.6%) |
| **HBeAg** Test [n (%)][a] | Positive | 13 (6.7%) | 0 | 1 (0.8%) | 0 |
| | Not detectable | 76 (39.0%) | 36 (20.9%) | 15 (12.7%) | 21 (10.8%) |
| | Not available | 106 (54.4%) | 136 (79.1%) | 102 (86.4%) | 173 (89.2%) |
| **HBV DNA** Test [n (%)][a] | Positive | 42 (21.5%) | 0 | 1 (0.8%) | 1 (0.5%) |
| | Not detectable | 73 (37.4%) | 75 (43.6%) | 68 (57.6%) | 99 (51.0%) |
| | Not available | 80 (41.0%) | 97 (56.4%) | 49 (41.5%) | 94 (48.5%) |
| | | **Sub HBV-HCC (n=83)** Baseline (before LT) (n=83) | 3-month FU (n=71) | 2-year FU (n=47) | FU last[b] (n=83) |
| **Anti-HBs** Test [n (%)][a] | Positive | 4 (4.8%) | 71(100.0%) | 45 (95.7%) | 78 (94.0%) |
| | Not detectable | 59 (71.1%) | 0 | 0 | 0 |
| | Not available | 20 (24.1%) | 0 | 2 (4.3%) | 5 (6.0%) |
| **HBsAg** Test [n (%)][a] | Positive | 52 (62.7%) | 0 | 2 (4.3%) | 6 (7.2%) |
| | Not detectable | 7 (8.4%) | 53 (74.6%) | 29 (61.7%) | 48 (57.8%) |
| | Not available | 24 (28.9%) | 18 (25.4%) | 16 (34.0%) | 29 (34.9%) |
| **HBeAg** Test [n (%)][a] | Positive | 4 (4.8%) | 0 | 0 | 0 |
| | Not detectable | 43 (51.8%) | 13 (18.3%) | 4 (8.5%) | 8 (9.6%) |
| | Not available | 36 (43.4%) | 58 (81.7%) | 43 (91.5%) | 75 (90.4%) |
| **HBV DNA** Test [n (%)][a] | Positive | 14 (16.9%) | 0 | 1 (2.1%) | 1 (1.2%) |
| | Not detectable | 39 (47.0%) | 35 (49.3%) | 26 (55.3%) | 44 (53.0%) |
| | Not available | 30 (36.1%) | 36 (50.7%) | 20 (42.6%) | 38 (45.8%) |

[a] Percentages are based on the number of patients with the respective test results available at the respective visits (presented in brackets in header).
[b] FU last = last available non-BL result in a patient documented as 'positive', 'not detectable' or 'not available'.
Anti-HBs = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBeAg = hepatitis B envelope antigen.
**Data source:** end-of-text Table 14.8.4.1.1 (stand-alone document 1.3, Appendix 1, Section 16.1).

**Table 19 Summary statistics of serum anti-HBs trough levels**

| Marker | Statistics/ Category | FAS (N=195) | | | |
|---|---|---|---|---|---|
| | | Total (n=195) | | | |
| | | Baseline (before LT) | 3-month FU | 2-year FU | FU last[a] |
| Serum trough level [IU/L] | n | 11 | 170 | 112 | 194 |
| | Mean (SD) | 232.8 (315.2) | 237.8 (155.4) | 164.1 (107.2) | 172.0 (131.4) |
| | Median (Min, Max) | 61.0 (17, 1000) | 199.1 (36, 1000) | 144.0 (11, 558) | 140.1 (11, 1000) |
| | | Sub HBV-HCC (n=83) | | | |
| | | Baseline (before LT) | 3-month FU | 2-year FU | FU last[a] |
| Serum trough level [IU/L] | n | 3 | 71 | 44 | 83 |
| | Mean (SD) | 438.7 (504.3) | 253.3 (178.5) | 156.8 (104.7) | 175.3 (141.4) |
| | Median (Min, Max) | 292.0 (24, 1000) | 219.0 (53, 1000) | 131.1 (11, 545) | 146.0 (11, 1000) |

[a] FU last = the last available non-BL value of anti-HBs documented in a patient.

Note: at baseline and at the 2-year FU, the number of patients with available anti-HBs values was smaller than the respective number of patients with positive anti-HBs tests (tests were documented as 'positive', but values were not provided).
**Data source:** end-of-text Table 14.8.4.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

**Table 20 Frequencies of serum anti-HBs trough levels below/above the threshold of 100 IU/L**

| Category [n (%)][a] | FAS (N=195) | | | |
|---|---|---|---|---|
| | Total (n=195) | | | |
| | Baseline (before LT) (n=116) | 3-month FU (n=171) | 2-year FU (n=113) | FU last[b] (n=194) |
| Anti-HBs ≥ 100 IU/L | 4 (3.4%) | 146 (85.4%) | 84 (74.3%) | 139 (71.6%) |
| Anti-HBs < 100 IU/L | 7 (6.0%) | 24 (14.0%) | 28 (24.8%) | 54 (27.8%) |
| Not detectable | 105 (90.5%) | 1 (0.6%) | 1 (0.9%) | 1 (0.5%) |
| | Sub HBV-HCC (n=83) | | | |
| | Baseline (before LT) (n=62) | 3-month FU (n=71) | 2-year FU (n=44) | FU last[b] (n=83) |
| Anti-HBs ≥ 100 IU/L | 2 (3.2%) | 61 (85.9%) | 34 (77.3%) | 62 (74.7%) |
| Anti-HBs < 100 IU/L | 1 (1.6%) | 10 (14.1%) | 10 (22.7%) | 21 (25.3%) |
| Not detectable | 59 (95.2%) | 0 | 0 | 0 |

[a] Percentages are based on the number of patients with an anti-HBs value available or test result documented as 'not detectable' at the respective visits (presented in brackets in header).
[b] FU last = last available anti-HBs value or 'not detectable' result documented in a patient.
**Data source:** end-of-text Table 14.8.4.1.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

The time course of mean serum anti-HBs trough levels after the start of Zutectra® treatment is illustrated in Figure 2 (underlying data for each time point including number of patients, number of values, mean value, and SD are presented in end-of-text Table 15.2.2.3, stand-alone document 1.4). Mean serum anti-HBs trough levels decreased by approximately half during the first 6 months after treatment start and remained at a relatively constant level during the following one and a half years. Mean serum trough levels were above the threshold of 100 IU/L at any time point during the observation period. There were only two time points at the end of the documentation period (29 and 30 months after treatment start), with values below the threshold. However, these values were based on the data of only 2 patients (month 29) and 1 patient (month 30), respectively. Note that the mean serum trough levels over time were derived from patients with values available and still in the study at each time point; thus, the mean values were not based on the same sample of patients at each time point. In addition, all repeat measurements of a patient, if applicable, were included per patient and month. The number of patients in the analysis was considerably higher during the first months after treatment start than at later time points and was very small after month 27.

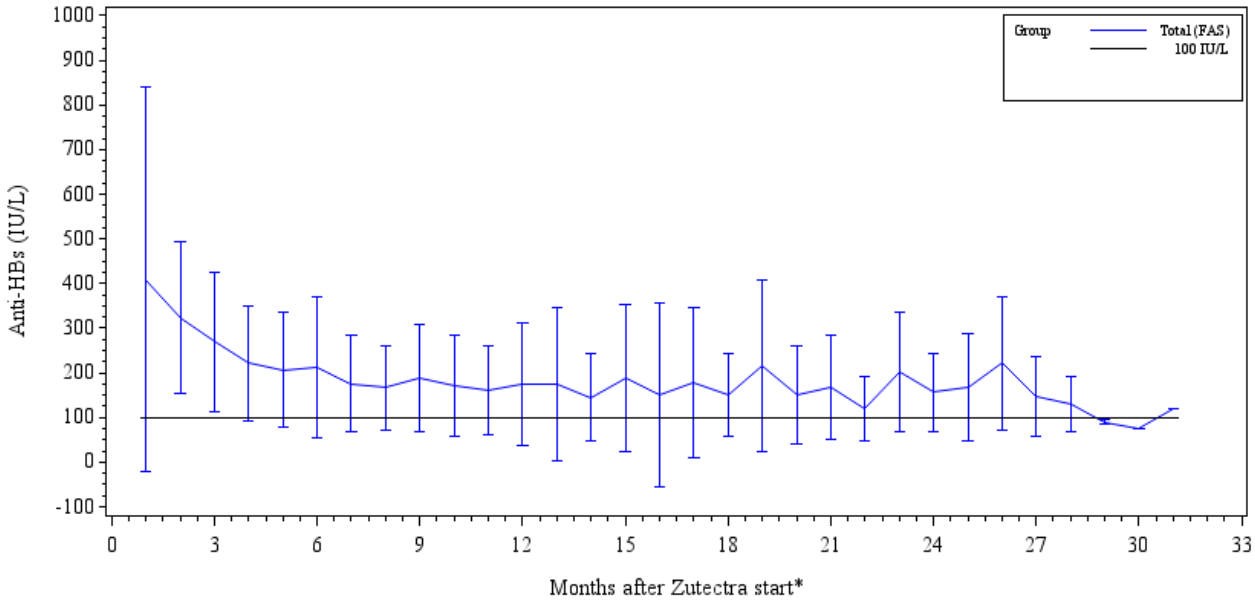


**Figure 2 Mean (± SD) serum anti-HBs trough levels over time after start of Zutectra® treatment**

Repeat measurements per patient and month are included.
Number of patients in the analysis at each time point (months after start of Zutectra® in grey rows):

| **Month** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **n** | 103 | 97 | 120 | 95 | 85 | 85 | 73 | 62 | 76 | 60 | 58 | 79 | 58 | 46 | 56 | 48 |
| | | | | | | | | | | | | | | | | |
| **Month** | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | |
| **n** | 49 | 43 | 39 | 37 | 41 | 31 | 40 | 38 | 31 | 18 | 10 | 3 | 2 | 1 | 1 | |

**Data source:** Figure 15.2.2.1 and end-of-text Table 15.2.2.3 (stand-alone document 1.4, Appendix 1, Section 16.1).

Similarly, in patients who had started Zutectra® treatment within 365 days after LT, mean serum anti-HBs trough levels were above the threshold of 100 IU/L over the entire period (starting at 0 months after LT) with a few exceptions at the end of the documentation period (Figure 15.2.1.1, stand-alone document 1.4). The number of patients per time point ranged between 1 and 20 patients (end-of-text Table 15.2.1.3, stand-alone document 1.4).

*HBsAg*

HBsAg is a marker of a new acute HBV infection. As shown in Table 18, HBsAg tests were positive in 112 patients (57.4% of 195 patients) before LT. After LT, positive HBsAg tests were documented in only very few patients, i.e. in 1 patient (0.6% of 172 patients) at the 3-month FU, in 3 patients (2.5% of 118 patients) at the 2-year FU, and in 6 patients (3.1% of 194 patients) at FU last. HBsAg was not detectable in 16 patients (8.2%) before LT, whereas at the post-baseline visits (including FU last analysis), HBsAg was not detectable in > 60% of the patients: 111 patients (64.5%) at the 3-month FU, 73 patients (61.9%) at the 2-year FU, and 117 patients (60.3%) at FU last. HBsAg tests were not available (missing) for approximately 34% to 37% of the patients at any of the analysis time points.

The median serum trough level of HBsAg was 1751.0 IU/L before LT, calculated for 25 patients with HBsAg values available at baseline (end-of-text Table 14.8.4.2). A HBsAg value was not available for the one patient with a positive test at the 3-month FU and was 22.5 IU/mL in 1 patient at the 2-year FU. The median HBsAg trough level calculated from the last available values documented in a patient (FU last) was 1256.0 IU/mL (n=12).

*HBeAg*

The presence of HBeAg indicates viral replication and serves as a marker for monitoring chronic HBV infection. Frequencies of positive/not detectable/not available test results are shown in Table 18. Before LT, 13 patients (6.7% of 195 patients) had a positive test. After baseline, no patient had a positive test result at the 3-month FU and there was only 1 patient (0.8% of 118 patients) with a positive test at the 2-year FU. There was also no patient with the last available test result documented as ‘positive’. HBeAg was not detectable in 76 patients (39.0%) before LT, in 36 patients (20.9%) at the 3-month FU, in 15 patients (12.7%) at the 2-year FU, and in 21 patients (10.8%) at FU last. HBeAg test results were not available for large proportion of the patients at each documentation time point: 106 patients (54.4% of 195 patients) before LT (baseline), 136 patients (79.1% of 172 patients) at the 3-month FU, 102 patients (86.4% of 118 patients) at the 2-year FU, and 173 patients (89.2%) at FU last.

Actual serum HBeAg values (trough levels) were not available for any of the patients at any documentation time point.

*HBV DNA*

The presence of HBV DNA in serum is a sign of active HBV replication. Before LT, positive HBV DNA tests were documented in 42 patients (21.5% of 195 patients), whereas after baseline, no positive test was documented at the 3-month FU and HBV DNA was detected in only 1 patient (0.8% of 118 patients) at the 2-year FU. There was also only 1 patient (0.5%) for whom the last available test after baseline (FU last) was documented as ‘positive’ (see Table 18). HBV DNA was not detectable in 73 patients (37.4%) before LT, in 75 patients (43.6% of 172 patients) at the 3-month FU, and in 68 patients (57.6% of 118 patients) at the 2-year FU. The last available test result was documented as ‘not detectable’ in 99 patients (51.0% of 194 patients). HBV DNA tests were not available for 41% to 56% of the patients at any documentation time point.

The median serum level of HBV DNA was 34.5 IU/mL (n=32) before LT (end-of-text Table 14.8.4.2). At the 3-month FU, there was no patient with a positive HBV DNA test. HBV DNA was 12.0 IU/mL in the one patient with a positive test at the 2-year FU. The median HBV DNA level calculated from the last available values documented in a patient (FU last) was 47.0 IU/mL (n=17).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

*Anti-HBs*

As shown in Table 18, there were only 4 patients (4.8% of 83 patients) with a positive anti-HBs test result before LT (baseline), whereas anti-HBs was not detectable in 59 patients (71.1%). Anti-HBs test results were not available in 20 patients (24.1%). After baseline, positive anti-HBs tests were documented in 71 patients (100% of 71 patients) at the 3-month FU, in 45 patients (95.7% of 47 patients) at the 2-year FU, and 78 patients (94.0% of 83 patients) at FU last. There were no patients without detectable anti-HBs at any of the FU visits. Anti-HBs test results were not available for only 2 patients (4.3%) at the 2-year FU and for 5 patients (6.0%) at FU last.

Inter-patient variability in serum trough levels of anti-HBs was high (Table 19). Mean and median levels were above 100 IU/mL at all time points (note: at baseline, analysis was based on the data of only 3 patients). The median serum trough level was 292.0 IU/L (n=3) before LT, 219.0 IU/L (n=71) at the 3-month FU, 131.1 IU/mL (n=44) at the 2-year FU, and 146.0 IU/L (n=83) at FU last.

Of the 3 patients with positive anti-HBs before LT, 2 patients (3.2% of 62 patients) had levels above the threshold (Table 20). After baseline, serum anti-HBs trough levels were ≥ 100 IU/L in more than 70% of the patients: 61 patients (85.9% of 71 patients) at the 3-month FU, 34 patients (77.3% of 44 patients), and 62 patients (74.7% of 83 patients) at FU last. Below the 100 IU/L threshold were the trough levels in 10 patients (14.1%) at the 3-month FU, in 10 patients (22.7%) at the 2-year FU, and in 21 patients (25.3%) at FU last.

*HBsAg, HBeAg, and HBV DNA*

Frequencies of test results ('positive', 'not detectable', or 'not available') of the HBV markers are presented in end-of-text Table 14.8.4.1.1 (stand-alone document 1.3) and summary statistics on the respective serum trough levels is shown in end-of-text Table 14.8.4.2.

Before LT, HBsAg tests were positive in 52 patients (62.7% of 83 patients), HBsAg was not detectable in 7 patients (8.4%), and test results were not available for 24 patients (28.9%). In contrast, none of the 71 patients at the 3-month FU had a positive HBsAg test while 53 patients (74.6% of 71 patients) had tests without detectable HBsAg. Likewise, tests were positive in only 2 patients (4.3% of 47 patients) at the 2-year FU and in 6 patients (7.2% of 83) at FU last, while HBsAg was not detectable in 29 patients (61.7%) at the 2-year FU and in 48 patients (57.8%) at FU last. Test results were not available at the post-baseline time points in 18 patients (25.4%) at the 3-month FU, in 16 patients (34.0%) at the 2-year FU, and in 29 patients (34.9%) at FU last.

HBeAg tests were positive in 4 patients (4.8% of 83 patients) before LT and in none of the patients at the post-baseline time points. HBeAg was not detectable in 43 patients (51.8%) before LT, in 13 patients (18.3% of 71 patients) at the 3-month FU, in 4 patients (8.5% of 47 patients) at the 2-year FU, and in 8 patients (9.6% of 83 patients) at FU last. HBeAg test results were not available in 36 patients (43.3%) before LT and in > 80% of the patients after baseline: 58 patients (81.7%) at the 3-month FU, 43 patients (91.5%) at the 2-year FU, and 75 patients (90.4%) at FU last.

HBV DNA was detected in serum in 14 patients (16.9% of 83 patients) before LT, but in none of the patients at the 3-month FU and in only 1 patient (2.1% of 47 patients) at the 2-year FU, and in 1 patient (1.2% of 83 patients) at FU last. HBV DNA was not detectable in 39 patients (47.0%) before LT, in 35 patients (49.3%) at the 3-month FU, in 26 patients (55.3%) at the 2-year FU, and in 44 patients (53.0%) at FU last. Test results were not

available for 30 patients (36.1%) before LT, 36 patients (50.7%) at the 3-month FU, 20 patients (42.6%) at the 2-year FU, and 38 patients (45.8%) at FU last.

### 11.4.3 Hepatocellular Carcinoma (HBV-HCC) Recurrence after Liver Transplantation

#### *11.4.3.1 Incidence of HBV-HCC Recurrence and time to HBV-HCC Recurrence*

Table 21 summarises the results of HBV-HCC recurrence for the total FAS, the HBV-HCC subgroup, and the subgroup of patients with HDV co-infection.

Total FAS

There were 4 patients (2.1% of 195 patients) with documented HBV-HCC recurrence during the observation period, corresponding to an incidence rate per year of 1.15%.

The mean time to recurrence of HBV-HCC after LT in the 4 patients was 17.4 ± 4.1 months (median: 17.5 months). The shortest time to recurrence was 12.5 months and the longest time was 22.2 months. Kaplan-Meier plots for time to HBV-HCC recurrence after LT can be found for the patients with HBV-HCC recurrence (including analyses by country) in Figures 15.6.1.1 and 15.6.1.2 (stand-alone document 1.4; Appendix 1, Section 16.1). In addition, Kaplan-Meier plots for the time to HBV-HCC recurrence after start of Zutectra® treatment for the 4 patients are appended in Figures 15.6.2.1, and 15.6.2.2.

The diagnosis of HBV-HCC recurrence was based on clinical diagnosis in all 4 patients. Recurrence of HBV-HCC manifested as extrahepatic dissemination in 3 patients (75.0% of 4 patients), and both in the liver and as extrahepatic dissemination in 1 patient (25.0%).

TNM staging was available for only 1 of the 4 patients. The patient presented with solitary tumour with vascular invasion or multiple tumours, none > 5 cm (T2). Regional lymph nodes could not be assessed (NX) and distant metastasis was present (M1).

Details related to HBV-HCC recurrence after LT, including date of diagnosis, manifestation of recurrence, tumour characteristics, and TNM staging, can be found for each patient in Listing 16.2.8.1.1.

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

All 4 patients with HBV-HCC recurrence belonged into the HBV-HCC subgroup (4.8% of 83 patients). Based on the smaller number of patients in this subgroup compared to the total FAS, the calculated incidence rate per year of HBV-HCC recurrence was higher, i.e. 2.88%. Results for time to HBV-HCC recurrence, manifestation of recurrent HBV-HCC, and TNM staging were identical to the results for the total FAS (Table 21).

Subgroup: HDV co-infection (Sub Co-HDV)

One of the 4 patients with HBV-HCC recurrence had HDV co-infection (2.3% of 43 patients). The calculated incidence rate per year in this subgroup was 1.37%. The time to recurrence of HBV-HCC in this 1 patient was 12.5 months, with extrahepatic manifestation (Table 21). TNM staging was not available.

**Table 21 Recurrence of HBV-HCC after LT**

| Characteristic | Statistics/ Category | FAS (N=195) Total (n=195) | Sub HBV-HCC (n=83) | Sub Co-HDV (n=43) |
|---|---|---|---|---|
| HBV-HCC recurrence after LT | | | | |
| Number of patients | [n (%)][a] | 4 (2.1%) | 4 (4.8%) | 1 (2.3%) |
| | 2-sided 95% CI | 0.6 – 5.2% | 1.3 – 11.9% | 0.1 – 12.3% |
| Incidence per year | Rate (%) | 1.15 | 2.88 | 1.37 |
| Time to HBV-HCC recurrence after LT [months] | n | 4 | 4 | 1 |
| | Mean (SD) | 17.4 (4.1) | 17.4 (4.1) | 12.5 (n.a.) |
| | Median (Min, Max) | 17.5 (12.5, 22.2) | 17.5 (12.5, 22.2) | n.a. |
| Manifestation of recurrent HCC [n (%)][b] | | | | |
| Extrahepatic dissemination | | 3 (75.0%) | 3 (75.0%) | 1 (100.0%) |
| Liver and extrahepatic dissemination | | 1 (25.0%) | 1 (25.0%) | 0 |
| TNM staging [n (%)][b] | | | | |
| Primary tumour | T2 | 1 (25.0%) | 1 (25.0%) | 0 |
| | Missing | 3 (75.0%) | 3 (75.0%) | 1 (100.0%) |
| Regional lymph nodes | NX | 1 (25.0%) | 1 (25.0%) | 0 |
| | Missing | 3 (75.0%) | 3 (75.0%) | 1 (100.0%) |
| Distant metastasis | M1 | 1 (25.0%) | 1 (25.0%) | 0 |
| | Missing | 3 (75.0%) | 3 (75.0%) | 1 (100.0%) |

[a] Percentages are based on the number of patients in the total FAS, HBV-HCC subgroup or HDV Co-infection subgroup, respectively.
[b] Percentages are based on the number of patients with HBV-HCC recurrence after LT in the respective group.
n.a. = not applicable
**Data source:** end-of-text Tables 14.8.1.1 and 14.8.1.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

### *11.4.3.2 Details on Patients with HBV-HCC Recurrence*

HBV-HCC had been the main reason for LT in all 4 patients with HBV-HCC recurrence. All 4 patients had received whole liver transplants (Listing 16.2.6). Table 22 presents some risk factors and concomitant factors/diseases in the 4 patients. One patient had HDV co-infection, but concomitant liver diseases were not present in any of the 4 patients. All patients had received bridging therapy for HCC before LT and downstaging had been performed in 1 patient. All patients were under concomitant antiviral therapy with NUCs. The serum anti-HBs through level around the time of HBV-HCC recurrence was above the threshold of 100 IU/L in 1 patient and below in 2 patients (anti-HBs value was not available for 1 patient).

**Table 22 Risks and concomitant factors in patients with HBV-HCC recurrence after LT**

| | Patients with HBV-HCC recurrence (n=4) Patient ID | | | |
|---|---|---|---|---|
| Characteristic | **#10804** | **#20120** | **#21305** | **#21410** |
| Age at study entry [yrs] | 40 | 64 | 61 | 67 |
| Sex | Male | Male | Male | Male |
| Viral co-infection | n.a. | n.a. | n.a. | HDV |
| Concomitant liver disease | None | None | None | None |
| Treatment of HCC before LT | TACE | TACE/ radio-frequency ablation | TACE | TACE |
| Downstaging of HCC | n.a. | No | n.a. | Yes |
| Number of nodules (RR) | 1 | 2 | Multiple | NA |
| Total size of nodules (RR) [cm] | 3.2 | 2.9 | - | NA |
| Concomitant antiviral treatment | TDV | TDV | TDV | ETV |
| Anti-HBs around time of HBV-HCC recurrence [IU/L] | 36.6 | 139 | 98.7 | NA |
| Date of anti-HBs measurement | 11Dec17 | 23Feb17 | 23Jan19 | n.a. |
| Date of HBV-HCC recurrence | 27Nov17 | 14Feb17 | 08Jan19 | 25Feb19 |

ETV = entecavir, n.a. = not applicable, NA = not available, TDV = tenofovir
**Data source:** Subject Data Listings 16.2.2.2 and 16.2.8.1.2 (stand-alone document 1.5, Appendix 1, Section 16.1).

### 11.4.4 Occurrence of any new Cancer(s) other than HCC after Liver Transplantation

The results of the occurrence of any new cancer(s) other than HCC are summarised in Table 23 for the total FAS, the HBV-HCC subgroup, and the subgroup of patients with HDV co-infection.

There were 4 patients (2.1% of 195 patients) in the total FAS for whom occurrence of new cancer(s) other than HCC since last visit was documented during the study period, corresponding to an incidence rate of occurrence of any new cancer per year of 1.15%.

The mean time to occurrence of any new cancer(s) other than HCC after LT, calculated for the 4 patients with documented occurrence, was 175.8 ± 83.4 months (median: 211.6 months). There was a wide individual range regarding the time to occurrence of any new cancer after LT: the shortest time period was 51.3 months and the longest was 228.8 months (19 years). Kaplan-Meier plots for time to recurrence of any new cancer other than HCC after LT can be found for the patients with occurrence of new cancer (including analyses by country) in Figures 15.7.1.1, and 15.7.1.2 (stand-alone document 1.4; Appendix 1, Section 16.1). In addition, Kaplan-Meier plots for the time to occurrence of any new cancer other than HCC after start of Zutectra® treatment for the 4 patients are provided in Figures 15.7.2.1, and 15.7.2.2.

The following specifications of new cancers were provided: invasive epidermoid carcinoma, poorly differentiated (larynx; patient #10313), basocellular carcinoma (skin; patient

#20106), glioblastoma (patient #20109), and suspicious undetermined nodule in the right upper lobe of the lung (patient #20115). At least 2 of the 4 patients (#10313 and #20109) died from cancer during the observation period (see also Section 11.4.5.5). Cause of death was reported as unknown in patient #20115[13] and patient #20106 was lost to follow-up.

In 1 of the 4 patients the main reason for LT was HBV-HCC (#20115, HBV-HCC subgroup). The incidence rate per year of new cancer other than HCC in this subgroup was therefore 0.72%. The patient did not develop HBV-HCC recurrence during the observation period).

None of the 4 patients had co-infection with HDV.

Details on the occurrence of new cancer(s) other than HCC after LT (e.g. date of diagnosis, specification of the tumour disease, and time to occurrence after LT) are provided by patient in Listing 16.2.8.2.

**Table 23 Occurrence of new cancer(s) other than HCC after LT**

| | | FAS (N=195) | | |
|---|---|---|---|---|
| Characteristic | Statistics/ Category | **Total (n=195)** | **Sub HBV-HCC (n=83)** | **Sub Co-HDV (n=43)** |
| Occurrence of new cancer(s) other than HCC | | | | |
| Known ('Yes') | [n (%)][a] | 4 (2.1%) | 1 (1.2%) | 0 |
| | 2-sided 95% CI | 0.6 – 5.2% | 0.0 – 6.5% | 0.0 – 8.2% |
| Unknown | [n (%)][a] | 10 (5.1%) | 9 (10.8%) | 1 (2.3%) |
| | 2-sided 95% CI | 2.5 – 9.2% | 5.1 – 19.6% | 0.1 – 12.3% |
| Incidence of any new cancer(s) other than HCC | | | | |
| Incidence per year | Rate (%) | 1.15 | 0.72 | n.a. |
| Time to occurrence of new cancer(s) other than HCC [months] | | | | |
| | n | 4 | 1 | 0 |
| | Mean (SD) | 175.8 (83.4) | 51.3 (n.a.) | n.a. |
| | Median (Min, Max) | 211.6 (51.3, 228.8) | n.a. | n.a. |

[a] Percentages are based on the number of patients in the total FAS, HBV-HCC subgroup or HDV Co-infection subgroup, respectively.
n-a- = not applicable
If 'unknown' and 'yes' were documented in a patient at different visits, the patient was counted with 'yes' for occurrence of new cancer.
**Data source:** end-of-text Table 14.8.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

### 11.4.5 Adverse Events and Adverse Drug Reactions

#### *11.4.5.1 Summary of AEs/SAEs and ADRs/SADRs*

Total FAS

A total of 342 AEs were reported in 111 patients (56.9% of 195 patients) during the study period (Table 24). Approximately one third of the patients had experienced at least one AE

[13] In patient #20115 nodule was considered as pulmonary carcinoma on 09 August 2017 (see Listing 16.2.7.1.1). Patient died on 07 September 2017 (cause of death was reported as unknown).

that was severe in intensity (n=38, 34.2% of 111 patients). The remaining patients had either experienced at least one AE of moderate intensity (n=42, 37.8%) or only mild AEs (n=31, 27.9%). A total of 133 AEs in 52 patients (26.7% of 195 patients) were assessed by the physicians as serious, including 6 SAEs with fatal outcome (see also Section 11.4.5.5).

AEs that were assessed by the physicians as having a possible causal relation to the treatment with Zutectra® were analysed as ADRs. There were 29 ADRs recorded in 16 patients (8.2% of 195 patients). Five patients (31.3%) had at least one severe ADR, 2 patients (12.5%) experienced at least one moderate ADR, but more than half of the patients with ADRs only had mild ADRs (n=9, 56.3% of 16 patients). Twelve of the ADRs were serious in 5 patients (2.6% of 195 patients). The criteria for seriousness of each SAE/SADR are provided in Listing 16.2.7.1.1. For more details on SADR cases, see also Section 11.4.5.4.

**Table 24 Summary of AEs/SAEs and ADRs/SADRs**

| Characteristics | Statistics/ Category | FAS (N=195) Total (n=195) | FAS (N=195) Sub HBV-HCC (n=83) |
|---|---|---|---|
| **Adverse Events (AEs)** | | | |
| Number of AEs | | 342 | 171 |
| Patients with AEs [n (%)][a] | | 111 (56.9%) | 55 (66.3%) |
| Patients with AEs by intensity [n (%)][b,c] | Mild | 31 (27.9%) | 15 (27.3%) |
| | Moderate | 42 (37.8%) | 19 (34.5%) |
| | Severe | 38 (34.2%) | 21 (38.2%) |
| **Serious Adverse Events (SAEs)** | | | |
| Number of SAEs | | 133 | 60 |
| Patients with SAEs [n (%)][a] | | 52 (26.7%) | 27 (32.5%) |
| **Adverse Drug Reactions (ADRs)** | | | |
| Number of ADRs | | 29 | 12 |
| Patients with ADRs [n (%)][a] | | 16 (8.2%) | 8 (9.6%) |
| Patients with ADRs by intensity [n (%)][b,c] | Mild | 9 (56.3%) | 6 (75.0%) |
| | Moderate | 2 (12.5%) | 0 |
| | Severe | 5 (31.3%) | 2 (25.0%) |
| **Serious Adverse Drug Reactions (SADRs)** | | | |
| Number of SADRs | | 12 | 6 |
| Patients with SADRs [n (%)][a] | | 5 (2.6%) | 3 (3.6%) |

[a] Percentages are based on the number of patients in the total FAS or HBV-HCC subgroup.
[b] Percentages are based on the number of patients with AEs or ADRs, respectively, in each group.
[c] If a patient experienced more than one AE/ADR, the patient was counted once with the maximum severity.
**Data source:** end-of-text Table 14.7.2.1 (stand-alone document 1.3, Appendix 1, Section 16.1).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

In the HBV-HCC subgroup, a total of 171 AEs were reported in 55 patients (66.3% of 83 patients) of which 21 patients (38.2% of 55 patients) had at least one severe AE, 19 patients (34.5%) had at least one moderate AE, and 15 patients (27.3%) had only mild AEs (Table

24). Serious AEs (SAEs) were reported in 27 patients (32.5% of 83 patients). The number of reported SAEs was 60. Two SAEs in 2 patients were fatal (see also Section 11.4.5.5).

There were 12 ADRs in 8 patients (9.6% of 83 patients). Most of the patients had only mild ADRs (n=6, 75.0% of 9 patients), 2 patients (25.0%) had at least one severe ADR, and none of the patients were reported with an ADR of moderate intensity. Six of the ADRs were serious in 3 patients (3.6% of 83 patients).

#### *11.4.5.2 Display of Frequent AEs and ADRs*

Table 25 shows frequent AEs and all reported ADRs by MedDRA System Organ Class (SOC) and by MedDRA Preferred Term (PT) in each SOC. Only those AEs are presented, which were documented in more than 1 patient (≥ 0.5%) in the total FAS (AEs that occurred in 1 patient are displayed in Table 25 only if the event was classified as an ADR). The frequencies of all AEs are presented for the total FAS and the HBV-HCC subgroup in end-of-text Table 14.7.2.2.

Details of all AEs, including MedDRA SOC, MedDRA PT, CRF verbatim, comments by the reporting physician, causal relationship to treatment with Zutectra®, seriousness criterion (in case of SAE), intensity, outcome, action taken, and whether liver- or kidney-related laboratory values were available, are provided in Listing 16.2.7.1.1. Onset and end dates of each event and the date of the last Zutectra® dose before the event are presented in Listing 16.2.7.1.2.

Total FAS

Overall, the most frequent AEs were recorded in the MedDRA SOC ‘gastrointestinal disorders’, i.e. 35 patients (17.9% of 195 patients) had at least one AE belonging into this SOC (Table 25). Other frequently affected SOCs, with AEs reported in > 10% of the patients, were ‘general disorders and administration site conditions’ (n=31, 15.9%), and ‘infections and infestations’ (n=29, 14.9%).

The most frequent AEs (reported in at least 4 patients) were diarrhoea (n=15, 7.7%), asthenia (n=12, 6.2%), back pain (n=7, 3.6%), headache (n=6, 3.1%), pyrexia (n=6, 3.1%), cholestasis (n=5, 2.6%), urinary tract infection (n=5, 2.6%), arthralgia (n=4, 2.1%), cholangitis (n=4, 2.1%), hepatocellular carcinoma (n=4, 2.1%), hypertension (n=4, 2.1%), neutropenia (n=4, 2.1%), and oedema peripheral (n=4, 2.1%).

The most frequent ADRs (reported in more than 1 patient) were: asthenia (n=3, 1.5%), back pain (n=2, 1.0%), headache (n=2, 1.0%), nausea (n=2, 1.0%), pyrexia (n=2, 1.0%), and rash pruritic (n=2, 1.0%). All other documented ADRs were single events and each reported in 1 patient only: arthralgia, blood pressure increased, decreased appetite, discomfort, dizziness, drug ineffective, erythema, fatigue, hepatitis B antibody abnormal, hepatitis surface antigen, hernia, muscle injury, myalgia, product dose omission issue, pruritus, vomiting.

In the 9 patients who discontinued the study early due to AEs/ADRs, the events for which action taken ‘permanent stop of Zutectra’ was documented were as follows (see also Listings 16.2.1, 16.2.7.1.1, and 16.2.8.3.1): nausea (SADR) and vomiting (SADR) in patient #10303 (treatment duration in study: 21.3 months), headache (ADR) and myalgia (ADR) in patient #10312 (treatment duration: 1.5 months), hepatitis B (SAE), hepatitis B surface antibody (SAE), hepatitis B surface antigen positive (SAE), and hepatocellular carcinoma (SAE) in patients #10804 (treatment duration: 17.3 months), drug ineffective (SADR) and hepatitis B surface antigen (SADR) in patient #10806 (treatment duration: 23.1 months), pyrexia (ADR) in patient #20308 (treatment duration: 1.1 months), rash pruritic (ADR) in

patient #20401 (treatment duration: 6.7 months), erythema (SADR), headache (SADR), pruritus (SADR), and rash pruritic (SADR) in patient #21402 (treatment duration: 1.9 months), decreased appetite (ADR) and nausea (ADR) in patient #21404 (treatment duration: 3.7 months), fatigue (ADR) in patient #21407 (treatment duration: 2.8 months).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

In the HBV-HCC subgroup, the most frequently reported AEs occurred in the MedDRA SOC ‘infections and infestations’ (n=18, 21.7% of 83 patients), followed by AEs in the SOC ‘general disorders and administration site conditions’ (n=17, 20.5%), and ‘gastrointestinal disorders’ (n=14, 16.9%) (Table 25).

The most frequent AEs (reported in at least 3 patients) were asthenia (n=7, 8.4%), diarrhoea (n=7, 8.4%), hepatocellular carcinoma (n=4, 4.8%), urinary tract infection (n=4, 4.8%), and pyrexia (n=3, 3.6%).

The most frequent ADR in the HBV-HCC subgroup was asthenia (n=2, 2.4%). All other ADRs were single cases only (n=1, 1.2%): discomfort, dizziness, drug ineffective, hepatitis B antibody abnormal, hepatitis surface antigen, nausea, product dose omission issue, pyrexia, rash pruritic, and vomiting.

**Table 25 Frequent AEs (PTs documented in > 1 patient in the total FAS)[a] and ADRs by MedDRA SOC and PT**

| System organ class (SOC) [n (%)][a,b] / Preferred term (PT) [n (%)][b,c] | FAS (N=195) | | | |
|---|---|---|---|---|
| | Total (n=195) | | Sub HBV-HCC (n=83) | |
| | AE | ADR | AE | ADR |
| **Gastrointestinal disorders** | **35 (17.9%)** | **2 (1.0%)** | **14 (16.9%)** | **1 (1.2%)** |
| Diarrhoea | 15 (7.7%) | 0 | 7 (8.4%) | 0 |
| Abdominal pain | 3 (1.5%) | 0 | 0 | 0 |
| Abdominal pain upper | 3 (1.5%) | 0 | 0 | 0 |
| Dyspepsia | 3 (1.5%) | 0 | 1 (1.2%) | 0 |
| Vomiting | 3 (1.5%) | 1 (0.5%) | 1 (1.2%) | 1 (1.2%) |
| GERD | 2 (1.0%) | 0 | 1 (1.2%) | 0 |
| Inguinal hernia | 2 (1.0%) | 0 | 2 (2.4%) | 0 |
| Nausea | 2 (1.0%) | 2 (1.0%) | 1 (1.2%) | 1 (1.2%) |
| **General disorders and administration site conditions** | **31 (15.9%)** | **9 (4.6%)** | **17 (20.5%)** | **5 (6.0%)** |
| Asthenia | 12 (6.2%) | 3 (1.5%) | 7 (8.4%) | 2 (2.4%) |
| Pyrexia | 6 (3.1%) | 2 (1.0%) | 3 (3.6%) | 1 (1.2%) |
| Oedema peripheral | 4 (2.1%) | 0 | 1 (1.2%) | 0 |
| Drug ineffective | 2 (1.0%) | 1 (0.5%) | 2 (2.4%) | 1 (1.2%) |
| Fatigue | 2 (1.0%) | 1 (0.5%) | 0 | 0 |
| Hernia | 2 (1.0%) | 1 (0.5%) | 1 (1.2%) | 0 |
| Pain | 2 (1.0%) | 0 | 1 (1.2%) | 0 |
| Discomfort | 1 (0.5%) | 1 (0.5%) | 1 (1.2%) | 1 (1.2%) |
| **Infections and infestations** | **29 (14.9%)** | **0** | **18 (21.7%)** | **0** |
| Urinary tract infection | 5 (2.6%) | 0 | 4 (4.8%) | 0 |
| Pneumonia | 3 (1.5%) | 0 | 2 (2.4%) | 0 |
| Cellulitis | 2 (1.0%) | 0 | 2 (2.4%) | 0 |
| Herpes zoster | 2 (1.0%) | 0 | 1 (1.2%) | 0 |
| Influenza | 2 (1.0%) | 0 | 1 (1.2%) | 0 |
| Pulmonary tuberculosis | 2 (1.0%) | 0 | 1 (1.2%) | 0 |
| Respiratory tract infection | 2 (1.0%) | 0 | 1 (1.2%) | 0 |
| **Musculoskeletal and connective tissue disorders** | **17 (8.7%)** | **3 (1.5%)** | **7 (8.4%)** | **0** |
| Back pain | 7 (3.6%) | 2 (1.0%) | 2 (2.4%) | 0 |
| Arthralgia | 4 (2.1%) | 1 (0.5%) | 1 (1.2%) | 0 |
| Muscle spasms | 3 (1.5%) | 0 | 2 (2.4%) | 0 |
| Musculoskeletal chest pain | 2 (1.0%) | 0 | 1 (1.2%) | 0 |
| Pain in extremity | 2 (1.0%) | 0 | 1 (1.2%) | 0 |
| Myalgia | 1 (0.5%) | 1 (0.5%) | 0 | 0 |

Table continued on next page

**Table 25 continued Frequent AEs (PTs documented in > 1 patient in the total FAS)[a] and ADRs by MedDRA SOC and PT**

| | FAS (N=195) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **System organ class (SOC) [n (%)][a,b]** | **Total (n=195)** | | | | **Sub HBV-HCC (n=83)** | | | |
| Preferred term (PT) [n (%)][b,c] | AE | | ADR | | AE | | ADR | |
| **Hepatobiliary disorders** | **16** | **(8.2%)** | **0** | | **9** | **(10.8%)** | **0** | |
| Cholestasis | 5 | (2.6%) | 0 | | 2 | (2.4%) | 0 | |
| Cholangitis | 4 | (2.1%) | 0 | | 1 | (1.2%) | 0 | |
| Cholangitis acute | 2 | (1.0%) | 0 | | 0 | | 0 | |
| Hepatic artery stenosis | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| Hepatocellular injury | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |
| **Metabolism and nutrition disorders** | **15** | **(7.7%)** | **1** | **(0.5%)** | **4** | **(4.8%)** | **0** | |
| Diabetes mellitus | 3 | (1.5%) | 0 | | 1 | (1.2%) | 0 | |
| Hypercholesterolaemia | 3 | (1.5%) | 0 | | 1 | (1.2%) | 0 | |
| Hyperkalaemia | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |
| Hypertriglyceridaemia | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| Obesity | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| Decreased appetite | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| **Nervous system disorders** | **14** | **(7.2%)** | **3** | **(1.5%)** | **7** | **(8.4%)** | **1** | **(1.2%)** |
| Headache | 6 | (3.1%) | 2 | (1.0%) | 1 | (1.2%) | 0 | |
| Tremor | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |
| Dizziness | 1 | (0.5%) | 1 | (0.5%) | 1 | (1.2%) | 1 | (1.2%) |
| **Renal and urinary disorders** | **14** | **(7.2%)** | **0** | | **7** | **(8.4%)** | **0** | |
| Acute kidney injury | 3 | (1.5%) | 0 | | 1 | (1.2%) | 0 | |
| Renal colic | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| Renal failure | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| Renal impairment | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| **Investigations** | **13** | **(6.7%)** | **3** | **(1.5%)** | **8** | **(9.6%)** | **2** | **(2.4%)** |
| Blood pressure increased | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| Hepatitis B antibody abnormal | 1 | (0.5%) | 1 | (0.5%) | 1 | (1.2%) | 1 | (1.2%) |
| Hepatitis B surface antigen | 1 | (0.5%) | 1 | (0.5%) | 1 | (1.2%) | 1 | (1.2%) |
| **Neoplasms benign, malignant and unspecified** | **11** | **(5.6%)** | **0** | | **7** | **(8.4%)** | **0** | |
| Hepatocellular carcinoma | 4 | (2.1%) | 0 | | 4 | (4.8%) | 0 | |
| Lung neoplasm malignant | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |

Table continued on next page

**Table25 continued Frequent AEs (PTs documented in > 1 patient in the total FAS)[a] and ADRs by MedDRA SOC and PT**

| System organ class (SOC) [n (%)][a,b] / Preferred term (PT) [n (%)][b,c] | FAS (N=195) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total (n=195) | | | | Sub HBV-HCC (n=83) | | | |
| | AE | | ADR | | AE | | ADR | |
| **Skin and subcutaneous tissue disorders** | **11** | **(5.6%)** | **2** | **(1.0%)** | **5** | **(6.0%)** | **1** | **(1.2%)** |
| Pruritus | 3 | (1.5%) | 1 | (0.5%) | 0 | | 0 | |
| Psoriasis | 2 | (1.0%) | 0 | | 0 | | 0 | |
| Rash puritic | 2 | (1.0%) | 2 | (1.0%) | 1 | (1.2%) | 1 | (1.2%) |
| Erythema | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| **Surgical and medical procedures** | **11** | **(5.6%)** | **0** | | **5** | **(6.0%)** | **0** | |
| **Blood and lymphatic system disorders** | **10** | **(5.1%)** | **0** | | **6** | **(7.2%)** | **0** | |
| Neutropenia | 4 | (2.1%) | 0 | | 1 | (1.2%) | 0 | |
| Eosinophilia | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |
| Lymphopenia | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| **Respiratory, thoracic and mediastinal disorders** | **9** | **(4.6%)** | **0** | | **4** | **(4.8%)** | **0** | |
| Cough | 3 | (1.5%) | 0 | | 1 | (1.2%) | 0 | |
| Dyspnoea | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| **Injury, poisoning and procedural complications** | **7** | **(3.6%)** | **2** | **(1.0%)** | **3** | **(3.6%)** | **1** | **(1.2%)** |
| Anastomotic stenosis | 2 | (1.0%) | 0 | | 0 | | 0 | |
| Product dose omission issue | 2 | (1.0%) | 1 | (0.5%) | 2 | (2.4%) | 1 | (1.2%) |
| Muscle injury | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| **Psychiatric disorders** | **6** | **(3.1%)** | **0** | | **3** | **(3.6%)** | **0** | |
| Depression | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| Insomnia | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |
| **Vascular disorders** | **6** | **(3.1%)** | **0** | | **3** | **(3.6%)** | **0** | |
| Hypertension | 4 | (2.1%) | 0 | | 2 | (2.4%) | 0 | |
| **Cardiac disorder** | **4** | **(2.1%)** | **0** | | **2** | **(2.4%)** | **0** | |
| **Reproductive system and breast disorders** | **3** | **(1.5%)** | **0** | | **3** | **(3.6%)** | **0** | |
| **Eye disorders** | **2** | **(1.0%)** | **0** | | **1** | **(1.2%)** | **0** | |
| **Ear and labyrinth disorders** | **1** | **(0.5%)** | **0** | | **0** | | **0** | |
| **Immune system disorders** | **1** | **(0.5%)** | **0** | | **1** | **(1.2%)** | **0** | |
| **Product issues** | **1** | **(0.5%)** | **0** | | **0** | | **0** | |

[a] Within a SOC, patients may have been reported with more than one PT.
[b] Percentages are based on the number of patients in the total FAS or HBV-HCC subgroup.
[c] A patient could have experienced a symptom (PT) more than once but was counted only once for such a symptom (for number of events per PT see end-of-text Table 14.7.2.2).
**Data source:** end-of-text Table 14.7.2.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

#### *11.4.5.3 Display of Frequent SAEs and SADRs*

Table 26 shows frequent SAEs and all reported SADRs by MedDRA SOC and MedDRA PT. Only those SAEs are presented, which were documented in more than 1 patient (≥ 0.5%) in the total FAS (SAEs that occurred in 1 patient are displayed in Table 26 only if the event was classified as an SADR). The frequencies of all SAEs are presented for the total FAS and the HBV-HCC subgroup in end-of-text Table 14.7.2.3.

Total FAS

Thirteen patients (6.7% of 195 patients) had SAEs occurring in the MedDRA SOC 'infections and infestations'. Other frequently affected SOCs, with AEs reported in ≥ 5% of the patients, were 'gastrointestinal disorders' (n=11, 5.6%), and 'neoplasms benign, malignant and unspecified' (n=10, 5.1%).

The most frequent SAEs (reported in at least 3 patients) were cholangitis (n=4, 2.1%), hepatocellular carcinoma (n=4, 2.1%), pyrexia (n=4, 2.1%), acute kidney injury (n=3, 1.5%), and diarrhoea (n=3, 1.5%).

All documented SADRs were single events and each reported in 1 patient (0.5%) only: arthralgia, back pain, drug ineffective, erythema, headache, hepatitis B antibody abnormal, hepatitis surface antigen, nausea, product dose omission issue, pruritus, rash pruritic, and vomiting.

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

In the HBV-HCC subgroup, SAEs were most frequently reported in the MedDRA SOC 'infections and infestations' (n=8, 9.6% of 83 patients), followed by 'neoplasms benign, malignant and unspecified' (n=7, 8.4%), and 'investigations' (n=6, 7.2%).

The most frequent SAE was hepatocellular carcinoma (n=4, 4.8%). SAEs reported in at least 2 patients (2.4%) were: cellulitis, lung neoplasm malignant, pneumonia, and pyrexia. Other SAEs were reported each in 1 patient (1.2%) only.

All documented SADRs were each reported in 1 patient (1.2%) only: drug ineffective, hepatitis B antibody abnormal, hepatitis surface antigen, nausea, product dose omission issue, and vomiting.

**Table 26 Frequent SAEs (PTs documented in > 1 patient in the total FAS)[a] and SADRs by MedDRA SOC and PT**

| System organ class (SOC) [n (%)][a,b] / Preferred term (PT) [n (%)][b,c] | FAS (N=195) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total (n=195) | | | | Sub HBV-HCC (n=83) | | | |
| | SAE | | SADR | | SAE | | SADR | |
| **Infections and infestations** | **13** | **(6.7%)** | **0** | | **8** | **(9.6%)** | **0** | |
| Cellulitis | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |
| Pneumonia | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |
| Pulmonary tuberculosis | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| Respiratory tract infection | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| **Gastrointestinal disorders** | **11** | **(5.6%)** | **1** | **(0.5%)** | **4** | **(4.8%)** | **1** | **(1.2%)** |
| Diarrhoea | 3 | (1.5%) | 0 | | 1 | (1.2%) | 0 | |
| Abdominal pain | 2 | (1.0%) | 0 | | 0 | | 0 | |
| Abdominal pain upper | 2 | (1.0%) | 0 | | 0 | | 0 | |
| Dyspepsia | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |
| Vomiting | 2 | (1.0%) | 1 | (0.5%) | 1 | (1.2%) | 1 | (1.2%) |
| Nausea | 1 | (0.5%) | 1 | (0.5%) | 1 | (2.4%) | 1 | (1.2%) |
| **Neoplasms benign, malignant and unspecified** | **10** | **(5.1%)** | **0** | | **7** | **(8.4%)** | **0** | |
| Hepatocellular carcinoma | 4 | (2.1%) | 0 | | 4 | (4.8%) | 0 | |
| Lung neoplasm malignant | 2 | (1.0%) | 0 | | 2 | (2.4%) | 0 | |
| **General disorders and administration site conditions** | **8** | **(4.1%)** | **1** | **(0.5%)** | **5** | **(6.0%)** | **1** | **(1.2%)** |
| Pyrexia | 4 | (2.1%) | 0 | | 2 | (2.4%) | 0 | |
| Drug ineffective | 1 | (0.5%) | 1 | (0.5%) | 1 | (1.2%) | 1 | (1.2%) |
| **Hepatobiliary disorders** | **8** | **(4.1%)** | **0** | | **2** | **(2.4%)** | **0** | |
| Cholangitis | 4 | (2.1%) | 0 | | 1 | (1.0%) | 0 | |
| Cholangitis acute | 2 | (1.0%) | 0 | | 0 | | 0 | |
| Cholestasis | 2 | (1.0%) | 0 | | 0 | | 0 | |
| **Surgical and medical procedures** | **8** | **(4.1%)** | **0** | | **3** | **(3.6%)** | **0** | |
| **Renal and urinary disorders** | **7** | **(3.6%)** | **0** | | **2** | **(2.4%)** | **0** | |
| Acute kidney injury | 3 | (1.5%) | 0 | | 1 | (1.2%) | 0 | |
| **Investigations** | **7** | **(3.6%)** | **2** | **(1.0%)** | **6** | **(7.2%)** | **2** | **(2.4%)** |
| Hepatitis B antibody abnormal | 1 | (0.5%) | 1 | (0.5%) | 1 | (1.2%) | 1 | (1.2%) |
| Hepatitis B surface antigen | 1 | (0.5%) | 1 | (0.5%) | 1 | (1.2%) | 1 | (1.2%) |
| **Respiratory, thoracic and mediastinal disorders** | **7** | **(3.6%)** | **0** | | **4** | **(4.8%)** | **0** | |
| Cough | 2 | (1.0%) | 0 | | 1 | (1.2%) | 0 | |

Table continued on next page

**Table 26 continued Frequent SAEs (PTs documented in > 1 patient in the total FAS)[a] and SADRs by MedDRA SOC and PT**

| | FAS (N=195) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **System organ class (SOC) [n (%)][a,b]** | **Total (n=195)** | | | | **Sub HBV-HCC (n=83)** | | | |
| Preferred term (PT) [n (%)][b,c] | SAE | | SADR | | SAE | | SADR | |
| **Injury, poisoning and procedural complications** | **4** | **(2.1%)** | **1** | **(0.5%)** | **2** | **(2.4%)** | **1** | **(1.2%)** |
| Anastomotic stenosis | 2 | (1.0%) | 0 | | 0 | | 0 | |
| Product dose omission issue | 1 | (0.5%) | 1 | (0.5%) | 1 | (1.2%) | 1 | (1.2%) |
| **Metabolism and nutrition disorders** | **3** | **(1.5%)** | **0** | | **0** | | **0** | |
| **Cardiac disorder** | **2** | **(1.0%)** | **0** | | **1** | **(1.2%)** | **0** | |
| **Musculoskeletal and connective tissue disorders** | **2** | **(1.0%)** | **1** | **(0.5%)** | **0** | | **0** | |
| Arthralgia | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| Back pain | 1 | (2.1%) | 1 | (0.5%) | 0 | | 0 | |
| **Nervous system disorders** | **2** | **(1.0%)** | **1** | **(0.5%)** | **1** | **(1.2%)** | **0** | |
| Headache | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| **Skin and subcutaneous tissue disorders** | **2** | **(1.0%)** | **1** | **(0.5%)** | **1** | **(1.2%)** | **0** | |
| Erythema | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| Pruritus | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| Rash puritic | 1 | (0.5%) | 1 | (0.5%) | 0 | | 0 | |
| **Blood and lymphatic system disorders** | **1** | **(0.5%)** | **0** | | **0** | | **0** | |
| **Product issues** | **1** | **(0.5%)** | **0** | | **0** | | **0** | |
| **Vascular disorders** | **1** | **(0.5%)** | **0** | | **1** | **(1.2%)** | **0** | |

[a] Within a SOC, patients may have been reported with more than one PT.
[b] Percentages are based on the number of patients in the total FAS or HBV-HCC subgroup.
[c] A patient could have experienced a symptom (PT) more than once but was counted only once for such a symptom (for number of events per PT see end-of-text Table 14.7.2.3).
**Data source:** end-of-text Table 14.7.2.3 (stand-alone document 1.3, Appendix 1, Section 16.1).

#### *11.4.5.4 Details on Cases of Serious Adverse Drug Reactions*

There were 5 patients (2.6% of 195 patients) with a total of 12 SADRs. Three of the patients were in the HBV-HCC subgroup (#10303, #10806, #21101). Table 27 provides an overview on all reported SADRs by patient. The criterion for seriousness according to the reporting physician was 'other medically important condition' for all 12 SADRs. At the time of reporting, 4 patients had recovered from the SADRs; two SADRs in 1 patient was not yet resolved.

**Table 27 Serious adverse drug reactions**

| Patient ID | Age [yrs]/ sex | Reaction (MedDRA PT) | Onset/ end date | Serious criterion | Intensity | Outcome | Last Zutectra® dose |
|---|---|---|---|---|---|---|---|
| #10303 | 65/ Male | Nausea | 01Jun2017/ 14Jun2017 | OMIC | Severe | Rec | 01Jun2017 |
| | | Vomiting | 01Jun2017/ 14Jun2017 | OMIC | Severe | Rec | 01Jun2017 |
| #10806 | 51/ Male | Drug ineffective | 30May2019/ Ongoing | OMIC | Mild | Not res | 20May2019 |
| | | HBsAg recurrence | 30May2019/ Ongoing | OMIC | Mild | Not res | 20May2019 |
| #20105 | 47/ Male | Arthralgia | 22Mar2016/ 25May2016 | OMIC | Mild | Rec | 22Mar2016 |
| | | Back pain | 22Mar2016/ 25May2016 | OMIC | Mild | Rec | 22Mar2016 |
| #21101 | 56 Male | Hepatitis B antibody abnormal | 08Nov2016 20Mar2017 | OMIC | Severe | Rec | 06Oct2016 |
| | | Product dose omission issue | 08Nov2016 19Mar2017 | OMIC | Severe | Rec | 06Oct2016 |
| #21402 | 80/ Male | Pruritus | 20Sep2016/ 15Mar2017 | OMIC | Severe | Rec | 20Sep2016 |
| | | Headache | 04Oct2016/ 15Mar2017 | OMIC | Not rep | Rec | Not rep |
| | | Erythema | 18Oct2016/ 15Mar2017 | OMIC | Not rep | Rec | Not rep |
| | | Rash pruritic | 15Nov2016/ Not rep | OMIC | Not rep | Rec | Not rep |

Not rep = not reported, not res= not resolved, OMIC = other medically important condition, rec = recovered.
**Data source:** Listings 16.2.2.2, 16.2.7.1.1 and 16.2.7.1.2.

### *11.4.5.5 Details on Cases of Death*

Six patients (3.1% of 195 patients) died during the observation period. Two of the patients (#20110, #20115) were in the HBV-HCC subgroup (2.4% of 83 patients). The 7 events leading to death in the 6 patients were reported as SAEs. None of the SAEs with fatal outcome were assessed as being related to the treatment with Zutectra® (Table 28). The most frequent cause of death was cancer: 1 patient died from malignant neoplasm progression (laryngeal cancer with lung and bone metastases), 1 patient died from glioblastoma, and 1 patient in the HBV-HCC subgroup died from plasmablastic lymphoma. Splenic infarction and respiratory tract infection were fatal in another patient. One patient with reported general physical health deterioration, acute kidney injury, and dialysis during the last five months before death died from multiple organ dysfunction syndrome. The cause of death was documented as unknown in one patient in the HBV-HCC subgroup (the

patient was reported with a pulmonary mass on 08 September 2016 which was diagnosed as pulmonary carcinoma on 09 August 2017, i.e. one month before his death).

**Table 28 Deaths**

| Patient ID | Age [yrs]/ sex | Reaction (MedDRA PT) | Onset/ end date | Serious criterion | Intensity | Relationship with Zutectra® treatment |
|---|---|---|---|---|---|---|
| #10313 | 61/ Male | Malignant neoplasm progression | 21Jun2016/ 26Dec2017 | Death/ OMIC | Severe | Not related |
| #10323 | 53/ Male | Splenic infarction | 02Jun2017/ 03Jun2017 | Death | Severe | Not related |
| | | Respiratory tract infection | 02Jun2017/ 03Jun2017 | Death | Severe | Not related |
| #20109 | 70/ Male | Glioblastoma | 16Sep2016/ 16Sep2016 | Death | Unknown | Not related |
| #20110 | 65/ Male | Plasmablastic lymphoma | 21Dec2016/ 05Jan2017 | Death | Severe | Not related |
| #20115 | 57/ Male | Death | 07Sep2017/ 07Sep2017 | Death | Unknown | Not related |
| #20511 | 72/ Female | Multiple organ dysfunction syndrome | 25Oct2018/ 05Dec2018 | Death | Severe | Not related |

OMIC = other medically important condition
**Data source:** Listings 16.2.2.2, 16.2.7.1.1 and 16.2.7.1.2.

### 11.4.6 Clinical Laboratory Tests for Liver and Kidney Function

Total FAS

Table 29 summarizes the results of the clinical laboratory tests for liver and kidney function at baseline, the 3-month FU, the 2-year FU, and FU last. Baseline values for safety laboratory parameters were defined as the last values determined before LT, i.e. prior to the start of the observation period of this study. On average, the period between the last LT and the start of Zutectra® treatment was rather long with a high inter-patient variability (91.7 ± 94.1 months). If several test results were available, the results dating closest to the respective visit date were used in the analysis (including defined visit windows, see Section 10.4.4). Results of the change vs. baseline analyses for each parameter are shown in end-of-text Table 14.8.5. However, due to the high inter-patient variability regarding the time to first Zutectra® treatment after LT, comparisons vs. baseline should be regarded with caution.

Inter-patient variability was very high for all three markers of liver function. The median liver enzyme values were at the upper end of the normal range or above the upper end before LT (baseline): 43.0 IU/L for ALT (n=178), 58.0 IU/L for AST (n=179), and 64.0 IU/L for GGT (n=166). Median values of all three enzymes were considerably lower at all post-baseline visits, i.e. during the treatment period with Zutectra® which started on average 91.7 months

after the LT. At FU last, the median values were 21 IU/L for ALT (n=192), 22.0 IU/L for AST (n=192), and 28.0 IU/L for GGT (n=192). Between baseline (last measurement before LT) and FU last, ALT decreased by a median of -22.0 IU/L (n=175), AST by a median of -33.0 (n=176), and GGT by a median of -28.5 IU/L (n=164) (see end-of-text Table 14.8.5 for changes vs. baseline). Mean and median values of all three liver enzymes remained stable between all post-baseline documentation time points under treatment with Zutectra® (Table 29).

**Table 29 Clinical laboratory tests for liver and kidney function**

| Characteristic | Statistics | FAS (N=195) | | | |
|---|---|---|---|---|---|
| | | Baseline (before LT)[a] | 3-month FU | 2-year FU | FU last |
| ALT [IU/L] | n | 178 | 166 | 134 | 192 |
| | Mean (SD) | 250.1 (982.5) | 25.2 (15.2) | 25.8 (23.9) | 26.3 (24.3) |
| | Median (Min, Max) | 43.0 (12, 7353) | 20.5 (5, 78) | 22.0 (8, 253) | 21.0 (5, 253) |
| AST [IU/L] | n | 179 | 166 | 134 | 192 |
| | Mean (SD) | 259.9 (946.6) | 25.6 (14.8) | 27.8 (22.0) | 26.8 (19.9) |
| | Median (Min, Max) | 58.0 (11, 7726) | 23.0 (9, 162) | 22.0 (9, 181) | 22.0 (9, 181) |
| GGT [IU/L] | n | 166 | 166 | 133 | 192 |
| | Mean (SD) | 100.6 (109.4) | 61.9 (87.0) | 56.1 (92.8) | 59.4 (93.0) |
| | Median (Min, Max) | 64.0 (12, 631) | 30.0 (6, 695) | 26.0 (9, 751) | 28.0 (9, 751) |
| Total bilirubin [µmol/L] | n | 178 | 163 | 133 | 191 |
| | Mean (SD) | 89.2 (143.7) | 11.4 (7.0) | 12.5 (8.2) | 12.0 (7.3) |
| | Median (Min, Max) | 30.0 (3.8, 981) | 10.0 (2.0, 45) | 10.3 (2.4, 61) | 10.3 (2.4, 61) |
| Albumin [g/L] | n | 130 | 98 | 65 | 139 |
| | Mean (SD) | 33.5 (7.8) | 43.0 (4.2) | 43.1 (4.7) | 42.3 (5.0) |
| | Median (Min, Max) | 34.0 (14, 47) | 43.0 (29, 52) | 43.0 (32, 53) | 43.0 (27, 53) |
| Serum creatinine [µmol/L] | n | 173 | 163 | 129 | 192 |
| | Mean (SD) | 103.0 (100.2) | 113.4 (71.8) | 103.6 (36.7) | 107.8 (53.5) |
| | Median (Min, Max) | 82.0 (20, 911) | 99.9 (52, 612) | 95.5 (6, 241) | 96.2 (13, 532) |
| eGFR (MDRD) [mL/min/ 1.73m$^2$] | n | 173 | 163 | 128 | 191 |
| | Mean (SD) | 86.1 (41.7) | 65.9 (22.2) | 84.6 (166.1) | 69.4 (50.7) |
| | Median (Min, Max) | 85.1 (5, 337) | 66.3 (8, 125) | 66.6 (20, 1822) | 66.5 (10, 704) |

[a] Baseline = last measurement before LT (documented at the baseline visit).
ALT = alanine aminotransferase, AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate, GGT = gamma glutamyl transferase, MDRD = Modification of Diet in Renal Disease.
**Data source:** end-of-text Table 14.8.5 (stand-alone document 1.3, Appendix 1, Section 16.1).

As observed for the liver enzymes, the median value of 30.0 µmol/L (n=178) of total bilirubin was above the upper limit of the normal reference range before LT (Table 29). Total bilirubin decreased between baseline (last measurement before LT) and FU last by a median of -17.3 µmol/L (n=174). At FU last, the median total bilirubin value was 10.3 µmol/L (n=191). Mean and median values of total bilirubin remained stable under treatment with Zutectra® and were within the normal reference range (Table 29).

The median value of albumin was 34.0 g/L before LT (n=130), i.e. slightly below the lower limit of the normal reference range. The median change in albumin between baseline (last measurement before LT) and FU last was 8.0 g/L (n=98). The median albumin value remained stable at 43.0 g/L at all documentation time points during the treatment period and was within the normal reference range (Table 29).

Kidney function was monitored by measurements of serum creatinine and determination of the eGFR (MDRD and CKD-EPI formulas). Overall, an increase in serum creatinine and a decrease in eGFR was seen between baseline (last measurement before LT) and all post-baseline time points. For example, the median changes at FU last were 13.1 µmol/L (n=170) for serum creatinine and -17.9 mL/min/1.73m$^2$ (n=170) for eGFR calculated with the MDRD formula (see end-of-text Table 14.8.5 for all changes vs. baseline).

The median value of serum creatinine was already at the upper limit of the normal reference range before LT: 82.0 µmol/L (n=173). During the observation period, the median and mean levels were above the upper limit of the normal reference range and were similar between the documentation time points with the highest median value at the 3-month FU (99.9 µmol/L, n=163; Table 29). The median eGFR (MDRD formula) was 85.1 mL/min/1.73m$^2$ before LT (n=173). Median eGFR values were lower at all post-baseline visits compared to baseline (last measurement before LT) but were stable under treatment with Zutectra®: 66.3 mL/min/1.73m$^2$ (n=163) at the 3-month FU, 66.6 mL/min/1.73m$^2$ (n=191) at the 2-year FU, and 66.5 mL/min/1.73m$^2$ (n=191) at FU last (Table 29). Results for the eGFR calculated with the CKD-EPI formula confirmed the results determined with the MDRD formula (see end-of-text Table 14.8.5).

Listing 16.2.8.5 presents all individual laboratory results by patient, visit, and date of measurement, including normal ranges, reference range indicator (stating whether the test result was below or above normal reference range), and changes from the baseline value at each FU visit.

<u>Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)</u>

The results of the liver and kidney function tests are summarised for the HBV-HCC subgroup in end-of-text Table 14.8.5 (stand-alone document 1.3).

As in the total FAS, an overall normalisation in liver function was seen between baseline (last measurement before LT) and the time points after the start of Zutectra® treatment based on the mean and median levels of liver enzymes, total bilirubin, and albumin values (see end-of-text Table 14.8.5 for changes vs. baseline). Mean and median values of all liver function parameters remained relatively stable during the treatment period.

Median ALT was 38.0 IU/L (n=79) before LT, 20.0 IU/L (n=71) at the 3-month FU, 19.0 IU/L (n=51) at the 2-year FU, and 19.0 IU/L (n=82) at FU last. Median AST was 50.0 IU/L (n=79) before LT, 22.0 IU/L (n=71) at the 3-month FU, 21.0 IU/L (n=51) at the 2-year FU, and 21.0 IU/L (n=82) at FU last. Median GGT was 74.0 IU/L (n=75) before LT, 30.0 IU/L (n=71) at the 3-month FU, 24.0 IU/L (n=51) at the 2-year FU, and 25.5 IU/L (n=82) at FU last.

Median total bilirubin was 21.0 µmol/L at baseline (n=80), i.e. above the upper limit of the normal reference range of 18 µmol/L, and < 10 µmol/L after LT: 8.7 µmol/L (n=70) at the 3-month FU, 9.9 µmol/L (n=51) at the 2-year FU, and 9.9 µmol/L (n=81) at FU last. Median albumin was 38.0 g/L (n=65) before LT, 44.0 g/L (n=49) at the 3-month FU, 44.0 g/L (n=28) at the 2-year FU, and 43.0 g/L (n=65) at FU last.

Changes between baseline (last measurement before LT) and post-baseline time points after LT in kidney function markers were also seen in the HBV-HCC subgroup, comparable to the changes observed in the total FAS (see end-of-text Table 14.8.5 for changes vs.

baseline). Median serum creatinine was 82.0 µmol/L (n=80) before LT. Higher median levels of serum creatinine were seen at all post-baseline visits: 105.0 µmol/L (n=69) at the 3-month FU, 95.9 µmol/L (n=50) at the 2-year FU, and 97.2 µmol/L (n=82) at FU last. The median eGFR (MDRD formula) was 84.4 mL/min/1.73m$^2$ before LT (n=80). During the observation period of this study, median eGFR values (MDRD formula) were lower compared to baseline but remained stable between all post-baseline visits: 63.0 mL/min/1.73m$^2$ (n=69) at the 3-month FU, 64.5 mL/min/1.73m$^2$ (n=50) at the 2-year FU, and 65.1 mL/min/1.73m$^2$ (n=82) at FU last.

### 11.4.7 Patient Satisfaction with Zutectra® Treatment

Total FAS

The frequencies of the responses on the Likert scales of the TSQM-11 are presented for each of the 11 items and per visit in end-of-text Table 14.8.7.1 (stand-alone document 1.3). At the start of the observation period (baseline), up to 140 patients (71.8% of 195 patients) completed the questionnaire (not every patient provided an answer to every single item). Responses to TSQM-11 items were available for up to 149 patients (76.4%) at the 3-month visit, for up to 89 patients (45.6%) at the 2-year visit, and for up to 166 patients (85.1%) at FU last (last available measurement).

The majority of the patients answered the two questions (items 10 and 11)[14] of the dimension ‘overall satisfaction’ with ‘satisfied’ (level 5) or higher. The following frequency results for items 10 and 11 were derived from end-of-text Table 14.8.7.1 by adding up the numbers and percentages of patients who were ‘satisfied’, ‘very satisfied’, and ‘extremely satisfied’ (i.e. at least satisfied). Percentages are based on the number of patients who answered the respective question at the respective visit. At baseline, 107 patients (78.1% of 137 patients) were at least satisfied that the good things about their medication outweighed the bad things (item 10); at the post-baseline time points, the proportions of patients who were at least satisfied were slightly higher: 130 patients (88.4% of 147 patients) at the 3-month FU, 77 patients (89.5% of 86 patients) at the 2-year FU, and 140 patients (86.4% of 162 patients) at FU last. The proportions of patients who were at least satisfied with the medication (item 11) were also slightly higher after baseline compared to the baseline visit: 110 patients (79.7% of 138 patients) at baseline, 131 patients (88.5% of 148 patients) at the 3-month FU, 78 patients (87.6% of 89 patients) at the 2-year FU, and 141 patients (85.5% of 165 patients) at FU last.

Table 30 presents the results of the four TSQM-11 dimension scores calculated from the respective responses to the questionnaire items at baseline and the FU visits, including the last available FU value (FU last).

The inter-patient variability was very high at all time points and for all dimension scores, ranging from 0 (extremely dissatisfied) to 100 (extremely satisfied) for the dimensions ‘effectiveness’, ‘convenience’, and ‘overall satisfaction’. The ‘side effect’ dimension scores were calculated only for patients with side effects (item 3 was answered with ‘yes’); thus, the numbers of patients in the analysis at each visit were considerably smaller as for the other three dimensions. The ‘side effect’ dimension score ranged from 25.0 to 100 at baseline, from 8.3 to 100 at the 3-month FU and FU last, and from 33.3 to 100 at the 2-year FU.

[14] Item 10: How satisfied are you that the good things about this medication outweigh the bad things?
Item 11: Taking all things into account, how satisfied or dissatisfied are you with this medication?

The median ‘effectiveness’ dimension score was 66.7 (n=135) at baseline, 66.7 (n=145) at the 3-month FU, 83.3 (n=81), at the 2-year FU, and 70.8 (n=156) at FU last. A numerical improvement of the median scores was seen between baseline and the 2-year FU and between baseline and FU last. However, the median changes were zero at all post-baseline visits (calculated for patients with data available at baseline and the respective FU). Statistical significance ($p<0.05$) for the change from baseline was reached only at the 2-year FU visit, based on the results of 64 patients (mean change from baseline: 6.4 ± 30.1).

The median ‘side effects’ dimension score was 75.0 at baseline (n=26) and all three post-baseline time points (13 to 23 patients with data). The changes from baseline could only be analysed for a very small number of patients with the respective data available: the median change was -8.3 (n=6) at the 3-month FU, and zero at the 2-year FU (n=2) and FU last (n=4). Statistical significance was not reached for the changes from baseline, but due to the small number of patients in the analysis, the results of the statistical test may not be meaningful.

The median ‘convenience’ dimension score was 66.7 (n=139) at baseline. Median scores were higher at later visits: 72.2 (n=149) at the 3-month FU, 77.8 (n=89) at the 2-year FU, and 72.2 (n=166) at FU last. The median changes from baseline were numerically identical (i.e. 5.6) at all three post-baseline visits and all improvements were statistically significant ($p<0.05$).

The median ‘overall satisfaction’ dimension score was also higher at the post-baseline time points than at baseline: 66.7 (n=137) at baseline, 75.0 (n=146) at the 3-month FU, 83.3 (n=86) at the 2-year FU, and 75.0 (n=161) at FU last. The median change was 8.3 between baseline and 2-year FU, and zero between baseline and the 3-month FU and between baseline and FU last, respectively. Nevertheless, the changes were statistically significant at all three post-baseline time points ($p<0.05$).

Individual answers to the 11 items of the TSQM are presented by patient and visit in Listing 16.2.8.7.

**Table 30 TSQM-11 dimension scores: results and changes from baseline**

| Dimension[a] | Statistics/ Category | FAS (N=195) | | | |
|---|---|---|---|---|---|
| | | Baseline | 3-month FU | 2-year FU | FU last |
| Effectiveness (Items 1-2) | n | 135 | 145 | 81 | 156 |
| | Mean (SD) | 66.6 (26.1) | 69.7 (25.1) | 72.6 (25.7) | 69.1 (25.6) |
| | Median (Min, Max) | 66.7 (0, 100) | 66.7 (0, 100) | 83.3 (0, 100) | 70.8 (0, 100) |
| Change from BL | n' | | 116 | 64 | 118 |
| | Median (Min, Max) [p-value[c]] | | 0.0 (-83.3, 83.3) [0.1855] | 0.0 (-83.3, 83.3) [<0.05] | 0.0 (-83.3, 83.3) [0.0792] |
| Side effects[b] (Items 3-6) | n | 26 | 16 | 13 | 23 |
| | Mean (SD) | 71.0 (22.9) | 66.1 (26.8) | 69.9 (20.0) | 69.2 (23.0) |
| | Median (Min, Max) | 75.0 (25, 100) | 75.0 (8.3, 100) | 75.0 (33.3, 100) | 75.0 (8.3, 100) |
| Change from BL | n' | | 6 | 2 | 4 |
| | Median (Min, Max) [p-value[c]] | | -8.3 (-16.7, 8.3) [0.1875] | -0.0 (-25.0, 25.0) [1.000] | 0.0 (-25.0, 25.0) [1.000] |
| Convenience (Items 7-9) | n | 139 | 149 | 89 | 166 |
| | Mean (SD) | 64.4 (22.6) | 70.4 (20.3) | 71.4 (23.1) | 70.9 (21.5) |
| | Median (Min, Max) | 66.7 (0, 100) | 72.2 (0, 100) | 77.8 (0, 100) | 72.2 (0, 100) |
| Change from BL | n' | | 119 | 71 | 128 |
| | Median (Min, Max) [p-value[c]] | | 5.6 (-66.7, 77.8) [<0.05] | 5.6 (-77.8, 66.7) [<0.05] | 5.6 (-77.8, 77.8) [<0.05] |
| Overall satisfaction (Items 10-11) | n | 137 | 146 | 86 | 161 |
| | Mean (SD) | 67.7 (22.1) | 72.3 (20.2) | 75.6 (21.8) | 72.9 (21.3) |
| | Median (Min, Max) | 66.7 (0, 100) | 75.0 (0, 100) | 83.3 (0, 100) | 75.0 (0, 100) |
| Change from BL | n' | | 116 | 68 | 123 |
| | Median (Min, Max) [p-value[c]] | | 0.0 (-66.7, 75.0) [<0.05] | 8.3 (-100.0, 100.0) [<0.05] | 0.0 (-100.0, 100.0) [<0.05] |

[a] Each dimension score ranges from 0 (extremely dissatisfied) to 100 (extremely satisfied).
[b] Side effect dimension scores were calculated only for patients with side effects (item 3: 'yes').
[c] Wilcoxon signed rank test for change vs. BL (level of significance: 5%).
BL = baseline, n= number of patients for whom the respective score could be calculated, n' = number of patients with data at BL and respective FU visit (used for calculation of change from BL).
**Data source:** end-of-text Table 14.8.7.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

The results of the TSQM-11 questionnaire for the HBV-HCC subgroup are presented in end-of text Tables 14.8.7.1 (frequency of responses to the 11 items on Likert scales) and 14.8.7.2 (results for the dimension scores).

As shown in end-of text Table 14.8.7.2, the median dimension scores at baseline and the post-baseline visits were in a similar range compared to those in the total FAS. The median 'effectiveness' dimension score was 66.7 (n=62) at baseline, 70.8 (n=60) at the 3-month FU, 75.0 (n=32) at the 2-year FU, and 66.7 (n=68) at FU last. The median 'side effects' dimension score was 70.8 (n=10) at baseline, 62.5 (n=8) at the 3-month FU, 66.7 (n=7) at the 2-year FU, and 70.8 (n=12) at FU last. The median 'convenience' dimension score was 66.7 (n=63) at baseline, 72.2 (n=61) at the 3-month FU, 77.8 (n=34) at the 2-year FU, and 72.2 (n=70) at FU last. The median 'overall satisfaction' dimension score was 66.7 (n=63) at baseline, 75.0 (n=61) at the 3-month FU, 83.3 (n=34) at the 2-year FU, and 79.2 (n=70) at FU last.

Changes from baseline were not statistically significant at the 5% level except for the improvements in the 'convenience' dimension score from baseline to the 3-month FU (median change: 5.6, n=52) and the 'overall satisfaction' dimension score from baseline to the 2-year FU (median change: 8.3, n=26).

### 11.4.8 Quality of Life

Total FAS

Any of the five individual dimensions of the EQ-5D were completed by up to 174 patients (89.2% of 195 patients) at baseline, by 151 patients (77.4%) at the 3-month FU, by 90 patients (46.2%) at the 2-year FU, and by 167 patients (85.6%) at FU last.

As shown in Table 31, the frequencies per level of perceived problem were similar at the start and the patients' individual end of the documentation period for all five dimensions. No noteworthy changes were also seen at the other two post-baseline visits (see end-of-text Table 14.8.6.1, stand-alone document 1.3, for the frequency results at the 3-month and 2-year FU visits). No problems (level 1) were most frequently observed for the dimension 'self-care' at all time points (> 90% of the patients who completed the respective dimension at the respective visit). Some problems (level 2) were most frequently seen for the dimension 'pain/discomfort' (between 44.7% and 50.6%), followed by the dimension 'anxiety/depression' (between 24.7% and 32.7%). Only very few patients reported extreme problems (level 3) for any dimension and at any visit: between 0 and 3 patients for the dimensions 'mobility', 'self-care', and 'usual activities', up to 5 patients (3.0% at FU last) for the dimension 'pain/discomfort', and up to 6 patients (3.6% at FU last) for the dimension 'anxiety/depression'. A slight shift in frequencies towards the lowest level of perceived problems was seen between baseline and FU last, especially in the three dimensions 'usual activities', 'pain/discomfort', and 'anxiety/depression'. However, when comparing different time points, it should be taken into account that the analyses at different time points were not based on the exact same set of patients.

**Table 31 Frequencies of EQ-5D dimension scores at baseline and FU last**

| Dimension | Category/ Level | FAS (N=195) | |
|---|---|---|---|
| | | Baseline | FU last |
| Mobility [n (%)][a] | Patients with data, n' | 173 | 167 |
| | 1 - no problems | 137 (79.2%) | 135 (80.8%) |
| | 2 - some problems | 36 (20.8%) | 31 (18.6%) |
| | 3 - extreme problems | 0 | 1 (0.6%) |
| Self-care [n (%)][a] | Patients with data, n' | 171 | 165 |
| | 1 - no problems | 163 (95.3%) | 161 (97.6%) |
| | 2 - some problems | 8 (4.7%) | 3 (1.8%) |
| | 3 - extreme problems | 0 | 1 (0.6%) |
| Usual activity [n (%)][a] | Patients with data, n' | 173 | 166 |
| | 1 - no problems | 128 (74.0%) | 132 (79.5%) |
| | 2 - some problems | 42 (24.3%) | 32 (19.3%) |
| | 3 - extreme problems | 3 (1.7%) | 2 (1.2%) |
| Pain/discomfort [n (%)][a] | Patients with data, n' | 174 | 167 |
| | 1 - no problems | 82 (47.1%) | 86 (51.5%) |
| | 2 - some problems | 88 (50.6%) | 76 (45.5%) |
| | 3 - extreme problems | 4 (2.3%) | 5 (3.0%) |
| Anxiety/depression [n (%)][a] | Patients with data, n' | 171 | 165 |
| | 1 - no problems | 113 (66.1%) | 115 (69.7%) |
| | 2 - some problems | 56 (32.7%) | 44 (26.7%) |
| | 3 - extreme problems | 2 (1.2%) | 6 (3.6%) |

[a] Percentages are based on the number of patients with data available for the respective dimension at the respective visit (n').
**Data source:** end-of-text Table 14.8.6.1 (stand-alone document 1.3, Appendix 1, Section 16.1).

Table 32 presents the results of the EQ-5D total and VAS scores derived from the questionnaire answers provided at baseline, the 3-month FU, the 2-year FU, and FU last. Individual questionnaire results including level of perceived problem per dimension, total score (index), and VAS score are shown for each patient in Listing 16.2.8.6.

At baseline, the mean EQ-5D total score was 0.81 ± 0.19 (median: 0.80, n=170), which corresponds to a relatively high quality of life among the patients in the total FAS at the time of treatment start (a total score of 1.00 indicates a perfect health state). Self-assessed overall quality of life remained at a similarly high level over the course of the entire observation period. The mean total scores were 0.83 ± 0.19 (median: 0.81, n=148) at the 3-month FU, 0.82 ± 0.19 (median: 0.81, n=87) at the 2-year FU, and 0.82 ± 0.22 (median: 0.81, n=163) at FU last. The mean changes from baseline were between 0.007 and 0.023 (calculated for patients with questionnaire data available at baseline and the respective FU visit); median changes from baseline were zero at all post-baseline visits and the changes were not statistically significant (p≥0.075).

The results obtained from the 5 dimensions of the EQ-5D are reflected in the results of the patients' self-assessment of their health state on a scale (VAS) from 0 (worst health state) to 100 (best health state). A slight numerical increase (improvement) was seen in the mean VAS score over the course of the study period: 75.2 ± 17.1 (n=172) at baseline, 76.9 ± 16.8

(n=147) at the 3-month FU, 79.3 ± 16.0 (n=90) at the 2-year FU, and 78.0 ± 16.1 (n=165) at FU last. The median VAS score was 80.0 at all visits. The mean changes from baseline were between 1.4 and 2.1 points; median changes from baseline were zero at all post-baseline visits. None of the changes from baseline were statistically significant (p≥0.1794).

**Table 32 EQ-5D total score and VAS score: results and changes from baseline**

| Score | Statistics/ Category | FAS (N=195) | | | |
|---|---|---|---|---|---|
| | | Baseline | 3-month FU | 2-year FU | FU last |
| Total score[a] | n | 170 | 148 | 87 | 163 |
| | Mean (SD) | 0.81 (0.19) | 0.83 (0.19) | 0.82 (0.19) | 0.82 (0.22) |
| | Median (Min, Max) | 0.80 (0.2, 1.0) | 0.81 (0.0, 1.0) | 0.81 (0.2, 1.0) | 0.81 (-0.4, 1.0) |
| Change from BL | n' | | 138 | 77 | 146 |
| | Median [p-value[c]] | | 0.0 [0.0750] | 0.0 [0.4374] | 0.0 [0.4072] |
| VAS score[b] | n | 172 | 147 | 90 | 165 |
| | Mean (SD) | 75.2 (17.1) | 76.9 (16.8) | 79.3 (16.0) | 78.0 (16.1) |
| | Median (Min, Max) | 80.0 (28, 100) | 80.0 (29, 100) | 80.0 (39, 100) | 80.0 (20, 100) |
| Change from BL | n' | | 138 | 81 | 150 |
| | Median [p-value[c]] | | 0.0 [0.2519] | 0.0 [0.2412] | 0.0 [0.1794] |

[a] Total score of 1.00 corresponds to a perfect health state.
[b] VAS score range: 0 = worst imaginable health, 100 = best imaginable health.
[a] Wilcoxon signed rank test for change vs. BL (level of significance: 5%).
BL = baseline, n' = number of patients with data at BL and respective FU visit (used for calculation of change from BL).
**Data source:** end-of-text Table 14.8.6.2 (stand-alone document 1.3, Appendix 1, Section 16.1).

Subgroup: HBV-HCC as main reason for LT (Sub HBV-HCC)

The results of the EQ-5D questionnaire for the HBV-HCC subgroup are presented in end-of text Tables 14.8.6.1 and 14.8.6.2 (stand-alone document 1.3).

As in the total FAS, no noteworthy changes were seen in the frequency distributions over the course of the documentation period for all five dimensions (end-of text Table 14.8.6.1).

The overall quality of life and health state, as indicated by the mean and median EQ-5D total and VAS scores, remained at a constantly high level throughout the observation period (end-of text Table 14.8.6.2). The number of subgroup patients for whom questionnaire data were available ranged from 73 patients (88.0% of 83 patients) at baseline) to 37 patients (44.6%) at the 2-year FU.

The mean total scores were 0.83 ± 0.16 (n=73) at baseline, 0.82 ± 0.17 (n=62) at the 3-month FU, 0.84 ± 0.14 (n=36) at the 2-year FU, and 0.80 ± 0.23 (n=72) at FU last. The median changes from baseline (calculated for patients with data available at the respective visits) were zero at all post-baseline visits (p≥0.4821).

The mean VAS scores were 76.2 ± 17.6 (n=73) at baseline, 75.4 ± 18.1 (n=58) at the 3-month FU, 81.8 ± 14.8 (n=37) at the 2-year FU, and 77.9 ± 17.6 (n=71) at FU last. There were no statistically significant changes in the VAS score from baseline at any post-baseline visit (p≥0.6793); median changes were zero at all post-baseline visits.

## 11.5 Other Analyses

### 11.5.1 Acute Rejection Episodes

Only 1 patient (0.5% of 195 patients; patient #10402 from Spain, total FAS and HBV-HCC subgroup) experienced an acute rejection episode during the observation period (approximately 7 months after the last LT and approximately 5 months after start of Zutectra® treatment). The episode was characterised by endothelitis, lymphocytic infiltration in the liver, and bile duct damage (end-of-text Table 14.8.8, stand-alone document 1.3).

Details on acute rejection episodes including date of diagnosis are presented in Listing 16.2.9.1.

### 11.5.2 Chronic Rejection and Other Complications

None of the 195 FAS patients experienced chronic rejection during the observation period (end-of-text Table 14.8.9, stand-alone document 1.3).

Complications other than transplant rejection were documented in 48 patients (24.6% of 195 patients). These patients had between 1 and 6 complications during the observation period (see Listing 16.2.9.2). Details on any complications had to be documented by the participating physicians in the AE/ADR section of the CRF and were thus not further analysed as ‘complications’ but as AEs/ADRs (see Section 11.4.5).

Of the 48 patients with other complications, 30 patients were in the HBV-HCC subgroup (36.1% of 83 patients, end-of-text Table 14.8.9).

### 11.5.3 Overall Survival and Disease-Free Survival

#### *11.5.3.1 Overall Survival after LT*

The detailed results of the Kaplan-Meier analysis of the overall survival time (defined as the time between LT and death during the 2-year observation period) can be found in end-of-text Table 14.9.1 (stand-alone document 1.3) and the respective Kaplan-Meier plots can be found for the total FAS and by country in Figures 15.3.1.1 and 15.3.1.2 (stand-alone document 1.4, Appendix 1, Section 16.1). Note: Additional plots for overall survival after start of Zutectra® treatment are appended in Figures 15.3.2.1 and 15.3.2.2.

The median (Kaplan-Meier) overall survival time (months) could not be calculated as the number of patients with an event (death) during the 2-year observation period was too small (n=6). The survival times of the remaining 189 patients are censored observations and were calculated as the respective difference between the date of the last LT and the date of the end of the documentation period. The mean overall survival time was 266.2 ± 3.7 days (n=195; end-of-text Table 14.9.1).

The overall survival time after LT varied considerably between the 6 patients who died during the observation period, with a range between 5.8 months and 273.9 months (22.8 years; Table 33). In 3 of the 6 patients, the last LT dated back more than 17 years before the start with Zutectra® treatment within this study.

**Table 33 Time to death after last LT in the affected patients**

| | Patients with an event (death) (n=6) | | | | | |
|---|---|---|---|---|---|---|
| Characteristic | **#10313** | **#10323** | **#20109** | **#20110** | **#20115** | **#20511** |
| Age at study entry [yrs] | 61 | 53 | 70 | 65 | 57 | 72 |
| Sex | Male | Male | Male | Male | Male | Female |
| Date of last LT | 12Oct1998 | 10Dec2016 | 01Feb1999 | 19Jan2015 | 31Jul2012 | 07Feb1996 |
| Start date of Zutectra® treatment | 04Jan2016 | 20Mar2017 | 30Mar2016 | 08Mar2016 | 20Apr2016 | 24Jul2017 |
| Date of death | 26Dec2017 | 03Jun2017 | 16Sep2016 | 05Jan2017 | 07Sep2017 | 04Dec2018 |
| Time to event (death) [months] | 230.5 | 5.8 | 211.5 | 23.6 | 61.3 | 273.9 |

**Data source:** Subject Data Listings 16.2.1, 16.2.2.2, 16.2.3, and 16.2.8.3.1 (stand-alone document 1.5, Appendix 1, Section 16.1).

#### *11.5.3.2 Disease-free Survival*

The disease-free survival time was defined as the time between LT and the event of recurrence of HBV, HBV-HCC, or any new cancer, or death during the 2-year observation period. The results of the Kaplan-Meier analysis can be found in end-of-text Table 14.9.1 (stand-alone document 1.3); respective Kaplan-Meier plots for the total FAS and by country are appended in Figures 15.4.1.1 and 15.4.1.2 (stand-alone document 1.4, Appendix 1, Section 16.1). Additional plots for disease-free survival after start of Zutectra® treatment are appended in Figures 15.4.2.1 and 15.4.2.2.

The median disease-free survival time could not be calculated as the number of patients with a recurrence of HBV, HBV-HCC, or any other cancer, or who died during the observation period was too small (n=15). The disease-free survival times of the remaining 180 patients are censored observations and were calculated as the respective difference between the date of the last LT and the date of the end of the documentation period. The mean disease-free survival time was 253.1 ± 5.5 months (n=195; end-of-text Table 14.9.1).

The disease-free survival time in the 15 patients with an event ranged between 5.8 months and 273.9 months (22.8 years).

# 12. DISCUSSION

## 12.1 Key Results

All key results (primary and secondary variables) summarised below refer to the total FAS (n=195), except if otherwise stated. The mean age of the FAS patients at the time of informed consent was 58.4 ± 10.5 years (range 19 to 81 years). The majority of the patients were male (n=160, 82.1%).

Two subgroups were analysed based on the FAS: the subgroup of patients with HBV-HCC as main reason for LT comprised 83 patients and the subgroup of patients with HDV co-infection comprised 43 patients.

### 12.1.1 Key Results of Primary Variables

*HBV Recurrence after Liver Transplantation*

HBV recurrence after LT was not documented or observed based on non-detectability of serum HBsAg and/or HBV DNA in most patients during the observation period and under treatment with Zutectra® with and without concomitant NUC therapy (n=188, 96.4%).

HBV recurrence after LT was detected in 7 patients (3.6%) based on serum HBsAg and/or HBV DNA levels. The incidence rate of HBV recurrence per year was 2.01%. The mean time to HBV recurrence after LT was 20.0 ± 7.6 months (median: 18.5 months, range: 13.1 to 34.6 months).

HBV recurrence based on HBV DNA detectability alone was determined in only 1 patient (0.5%). The corresponding incidence rate of HBV recurrence per year was 0.29%.

Subgroup analysis: All 7 patients with HBV recurrence belonged into the HBV-HCC subgroup (8.4% of 83 patients in the HBV-HCC subgroup). The incidence rate of HBV recurrence in the HBV-HCC subgroup was 5.05%. Three patients with HBV recurrence had HDV co-infection (7.0% of 43 patients in the HDV co-infection subgroup). The incidence rate of HBV recurrence in this subgroup was 4.12% and the mean time to HBV recurrence was 17.2 ± 5.5 months.

*Adverse Events and Adverse Drug Reactions*

AEs were reported in 111 patients (56.9%; number of AEs: 342) during the observation period; serious AEs were observed in 52 patients (26.7%; number of SAEs: 133). Six patients (3.1%) died during the study period; none of the SAEs with fatal outcome were related to treatment with Zutectra®. At least one AE of severe intensity was reported in 38 patients; AEs were either mild or moderate in the remaining 73 patients.

AEs with a possible causal relation to the treatment with Zutectra® (ADRs) were reported in 16 patients (8.2%; number of ADRs: 29). Serious ADRs were seen in 5 patients (2.6%; number of SADRs: 12). At least one ADR of severe intensity was reported in 5 patients; ADRs were either mild or moderate in the remaining 11 patients.

The most frequent AEs were diarrhoea (n=15, 7.7%) and asthenia (n=12, 6.2%). The most frequent SAEs were cholangitis (n=4, 2.1%), hepatocellular carcinoma (n=4, 2.1%), pyrexia (n=4, 2.1%), acute kidney injury (n=3, 1.5%), and diarrhoea (n=3, 1.5%).

ADRs reported in more than 1 patient were: asthenia (n=3, 1.5%), back pain (n=2, 1.0%), headache (n=2, 1.0%), nausea (n=2, 1.0%), pyrexia (n=2, 1.0%), and rash pruritic (n=2, 1.0%). Of these, back pain, headache, nausea, and rash pruritic were each reported in 1

patient (0.5%) as SADR. All other documented ADRs (and SADRs) were each reported in 1 patient only: arthralgia (SADR), blood pressure increased, decreased appetite, discomfort, dizziness, drug ineffective (SADR), erythema (SADR), fatigue, hepatitis B antibody abnormal (SADR), hepatitis surface antigen (SADR), hernia, muscle injury, myalgia, product dose omission issue (SADR), pruritus (SADR), vomiting (SADR).

### 12.1.2 Key Results of Secondary Variables

*Frequency of Positive Anti-HBs Test Results and Serum Trough Levels of Anti-HBs*

Anti-HBs was positive in 18 patients (9.2% of 195 patients) and not detectable in 105 patients (53.8%) before LT (baseline). At each post-baseline time point (i.e. after start of Zutectra® treatment) > 90% of the patients had a positive anti-HBs test: 170 patients (98.8% of 172 patients) at the 3 month-FU, 113 patients (95.8% of 118 patients) at the 2-year FU, and 184 patients (94.8% of 184 patients) at FU last. There was only 1 patient at each post-baseline time point without detectable anti-HBs. The median serum anti-HBs trough level was 61.0 IU/L (n=11) before LT, 199.1 IU/L (n=170) at the 3-month FU, 144.0 IU/L (n=112) at the 2-year FU, and 140.1 IU/L (n=194) at FU last (FU last corresponds to the last available anti-HBs value documented in a patient). Anti-HBs trough levels were ≥ 100 IU/L in 4 patients (3.4% of 116 patients with anti-HBs value available or with 'not detectable' anti-HBs) before LT, in 146 patients (85.4% of 171 patients) at the 3-month FU, in 84 patients (74.3% of 113 patients) at the 2-year FU, and in 139 patients (71.6% of 194 patients) at FU last.

*Recurrence of HBV-HCC after LT*

HBV-HCC recurrence after LT was documented in 4 patients (2.1%) during the observation period. The incidence rate of HBV-HCC recurrence per year was 1.15%. The mean time to recurrence of HBV-HCC after LT in the 4 patients was 17.4 ± 4.1 months (median: 17.5 months; range: 12.5 to 22.2 months). HBV-HCC had been the main reason for LT in all 4 patients with HBV-HCC recurrence.

*Occurrence of any new Cancer(s) other than HCC after LT*

Occurrence of new cancer(s) other than HCC after LT was observed in 4 patients (2.1%). The corresponding incidence rate per year was 1.15%. The mean time to occurrence of any new malignancies after LT in the 4 patients was 175.8 ± 83.4 months (median: 211.6 months; range: 51.3 to 228.8 months). HBV-HCC had been the main reason for LT in 1 of the 4 patients with new cancer(s) other than HCC after LT.

*Exposure to Zutectra®*

The mean duration of exposure to Zutectra® was 20.7 ± 7.4 months (median: 23.8 months; range: 0.2 to 30.4 months). The mean time to start of Zutectra® treatment after LT was 91.7 ± 94.1 months (median: 50.6 months; range: 0.3 to 331.3 months). The mean average monthly dose of Zutectra® was 1171.4 ± 545.7 IU (median: 1087.1 IU; range: 484.7 to 2528.8 IU). The most common dosing interval of Zutectra® was biweekly (n=134, 68.7%), followed by weekly (n=108, 55.4%), every 4 weeks/monthly (n=73, 37.4%), and every 3 weeks (n=66, 33.8%); other dosing intervals were reported in 12 patients (6.2%). Dosing intervals could have changed during the study period. At least one change in Zutectra® treatment was documented in 111 patients (56.9%).

The majority of administrations of Zutectra® were self-administered by the patients (71.6% of administrations) and Zutectra® was mostly administered at home (94.4% of 9021 administrations).

*Concomitant Antiviral Treatment*

At least one concomitant antiviral medication was documented in 162 patients (83.1% of 195 patients). NUCs were the most frequent concomitant antivirals (n=159, 98.2% of 162 patients) with tenofovir disoproxil (n=63, 38.9%), entecavir (n=59, 36.4%), and lamivudine (n=39, 24.1%) being the most common individual drugs. Other concomitant NUCs were less frequently reported (< 5.0%). Concomitant hepatitis B immunoglobulin treatment (i.v. or i.m.) was reported in 18 patients (11.1%).

*Immunosuppressive Treatment after LT*

Most patients received immunosuppressive treatments throughout the observation period: 194 patients (99.5% of 195 patients) at baseline, 181 patients (100.0% of 181 patients) at the 3-month FU, and 146 patients (99.3% of 147 patients) at the 2-year FU. The most frequently used immunosuppressive treatments after LT at all three documentation time points (baseline, 3-month FU, and 2-year FU) were CNIs, followed by MMF.

*Safety Laboratory Parameters of Liver and Kidney Function*

Safety laboratory parameters changed between baseline (here: last measurement before LT) and all documentation time points during the observation period. Median changes between baseline and at FU last were: -22.0 IU/L (n=175; ALT), -33.0 IU/L (n=176; AST), -28.5 IU/L (n=164; GGT), -17.3 µmol/L (n=174; total bilirubin), 8.0 g/L (n=98; albumin), 13.1 µmol/L (n=170; serum creatinine), and -17.9 mL/min/1.73m2 (n=170, eGFR, MDRD formula).

In contrast, median and mean values of all documented safety laboratory parameters remained stable during the entire observation period, i.e. under treatment with Zutectra®.

*Patient Satisfaction*

The inter-patient variability was very high at all time points and for all TSQM-11 dimension scores, ranging from 0 (extremely dissatisfied) to 100 (extremely satisfied) for the dimensions ‘effectiveness’, ‘convenience’, and ‘overall satisfaction’.

The median ‘effectiveness’ dimension score was 66.7 (n=135) at baseline, 66.7 (n=145) at the 3-month FU, 83.3 (n=81), at the 2-year FU, and 70.8 (n=156) at FU last. Median changes from baseline were zero at all post-baseline time points (calculated for patients with data available at baseline and the respective FU). Statistical significance ($p<0.05$) for the change from baseline was reached only at the 2-year visit, based on the results of 64 patients.

The median ‘side effects’ dimension score was 75.0 at baseline (n=26) and all three post-baseline time points (13 to 23 patients with data). The analysis of change from baseline was based on a very small number of patients with data available at baseline and the respective post-baseline visit (2 to 6 patients). Changes from baseline were not statistically significant.

The median ‘convenience’ dimension score was 66.7 (n=139) at baseline. Median scores were higher at later visits: 72.2 (n=149) at the 3-month FU, 77.8 (n=89) at the 2-year FU, and 72.2 (n=166) at FU last. The median changes from baseline were numerically identical

(i.e. 5.6) at all three post-baseline visits and all improvements were statistically significant ($p<0.05$).

The median 'overall satisfaction' dimension score was 66.7 (n=137) at baseline, 75.0 (n=146) at the 3-month FU, 83.3 (n=86) at the 2-year FU, and 75.0 (n=161) at FU last. The median change was 8.3 between baseline and 2-year FU, and zero between baseline and the 3-month FU or FU last, respectively. The changes were statistically significant at all three post-baseline time points ($p<0.05$).

*Quality of Life*

Self-assessed overall quality of life, as indicated by the total EQ-5D score, was at a relatively high level throughout the entire observation period. The median EQ-5D total score was 0.80 (n=170) at baseline, 0.81 (n=148) at the 3-month FU, 0.81 (n=87) at the 2-year FU, and 0.81 (n=163) at FU last. The median changes from baseline were zero at all post-baseline visits. None of the changes were statistically significant ($p\geq0.075$).

The patients' self-assessed health state as indicated by the EQ-5D VAS scores remained stable over the course of the observation period. The median VAS score was 80.0 at baseline and all post-baseline time points. All median changes from baseline were zero and none of the changes from baseline were statistically significant ($p\geq0.1794$).

## 12.2 Limitations

Limitations of this study include those generally associated with the observational, non-interventional character of this study, such as the lack of a control group for the evaluation of effectiveness, confounding, selection and information bias, and bias due to dropout and missing data.

Early study discontinuation was documented in 39 FAS patients (20.0%). However, treatment with Zutectra® lasted for almost 2 years in 7 of these patients and for more than 12 months in 14 discontinued patients (see Listing 16.2.8.3.1). When regarding the total FAS, a treatment duration of less than 3 months within this study was observed in only 9 patients (Listing 16.2.8.3.1).[15] This is reflected in the median duration of exposure (23.8 months), which is very close to the planned 2-year observation period.

Missing data may cause under- or overestimation of outcomes in the statistical analysis. Data were complete or the proportions of patients with missing data were very low (< 2%) for most documented variables in this study. However, serological test results for anti-HBs were not available for approximately 37% of the patients before LT (at post-baseline time points, the number of patients with unavailable test results was small). Test results for HBsAg, HBeAg, and HBV DNA as markers of HBV (re-) infection were not available for a considerable proportion of patients at all documentation time points, i.e. for approximately 34% to 37% (HBsAg), 54% to 89% (HBeAg), and 41% to 56% (HBV DNA) of the patients, respectively. As determination of HBV recurrence was based on the evaluation of HBsAg and/or HBV DNA serum levels, the number of patients with actual HBV recurrence may have been underestimated based on these criteria. On the other hand, it should be mentioned that the question 'HBV recurrence since last visit?' was answered with 'no' in most patients and at most visits (except for 2 patients, for whom also positive HBsAg test results were available). Furthermore, clinical signs of HBV recurrence were not documented in any of the study patients. In some patients with positive test results, the

[15] There was 1 FAS patient (#20307) with a documented 2-year FU visit but with a documented Zutectra® treatment duration of only 6 days. One patient (#10323) died after approx. 2,5 months and the remaining 7 patients discontinued the study within the first 3 months.

corresponding serum values were missing. As the number of patients with available serum trough levels at baseline and at the post-baseline time points (only exception: post-baseline anti-HBs) was so small for each parameter (between 1 and 10 patients), the results of the statistical tests for changes vs. baseline were not meaningful.

The time period between the patients' last LT and start of Zutectra® treatment was not predefined and differed considerably between study patients (range: 9 days to 27.6 years). The median time between LT and treatment start with Zutectra® was rather long, i.e. 50.6 months (approximately 4 years), as there were 34 patients who had their last LT in the 1990s and 1 patient in 1988 (see Listing 16.2.3 for LT dates). Thus, there may have been a selection bias towards patients whose condition after LT was stable over a long period. In the patients with HBV recurrence, the time between LT and treatment start varied between approximately 2 weeks and 14 months. In addition to the differences in the length of the time periods between LT and Zutectra® treatment, there may have been considerable differences regarding previous and concomitant treatments and treatment regimens between the patients. For example, 6 of the 7 patients with HBV recurrence had received i.m. or i.v. HBIg before Zutectra® but treatment durations differed between 1 day and approximately 14 months (see Listing 16.2.4 for prior antiviral treatment). Thus, several factors, such as the time to first treatment, prior and concomitant antiviral treatments, and the presence or absence of other risk factors for HBV recurrence (including HCC, positive HBV DNA at LT), may have influenced the likelihood of developing HBV recurrence among study patients.

Visits in this study were performed based on clinical routine. Although the post-baseline documentation time points 3 months and 2 years after treatment start with Zutectra® were planned and predefined in the protocol and CRF, the actual time periods between treatment start and of the post-baseline visits documented as 3-month or 2-year FU did not always match the planned intervals. Thus, for most of the analyses, those results or values were attributed to the respective visits, which were gathered within predefined time windows for the respective post-baseline visits. For the questionnaires (TSQM-11 and EQ-5D) and professional status, investigator's classifications of the visits were used. Thus, the actual intervals between treatment start and the post-baseline documentation may have been longer or shorter than 3 months or 2 years in some patients for these variables. Furthermore, patients with a documented 2-year FU visit may have had an actually shorter observation time, whereas some patients with a documented early discontinuation visit had actual observation times that were > 23 months.

Selection bias could play a role in the examination of optional self-assessed measures such as the questionnaires for treatment satisfaction and quality of life. Patients' replies (and willingness to reply to certain questions) may be influenced by numerous factors including the patients' motivational level, educational level, state of mind, or general state of health. Furthermore, scales such as the EQ-5D VAS are based on subjective perception and may be interpreted differently among patients. The EQ-5D and the TSQM-11 questionnaires are instruments for measuring quality of life and treatment satisfaction in non-specific patient groups and health conditions. Although widely used and established, especially the EQ-5D questionnaire may not have captured specific health problems and other aspects in patients after LT such as chronic physical fatigue, coping with restrictions in lifestyle and/or diet, or mental stress.

## 12.3 Interpretation

*Effectiveness and Adherence*

According to the European Association for the Study of the Liver (EASL), NUC and HBIg combination therapy after LT reduces the risk of graft infection to < 5% [26]. In this real-life population under treatment with Zutectra® and with concomitant NUC therapy in approximately 82% of the patients, HBV recurrence after LT was detected in 7 patients (3.6%) based on serum HBsAg and/or HBV DNA. All 7 HBV recurrent patients had received either concomitant entecavir or tenofovir. Using a less strict definition of HBV recurrence (detection of HBV DNA alone) the incidence of HBV recurrence was very low (0.5%) in this study with only 1 HBV recurrent patient and an incidence per year of 0.29%.

In previous studies in liver transplant patients, HBV recurrence rates below as well as above 5% were observed. In a retrospective data collection in 371 patients with LT for HBV-associated conditions and treated with HBIg (either Zutectra®, i.v. HBIg or other HBIg preparations) with or without concomitant NUC therapy for at least 12 months after LT, a HBV recurrence rate of 4.3% was seen over a median documentation time of 7.0 years [27]. In a systemic literature review including 46 studies in over 2162 patients who underwent LT for HBV-related liver diseases and received HBIg and NUCs as prophylaxis, HBV recurrence was detected in 6.6% of the patients during a median follow-up of 21 months [28]. Of 99 HBsAg positive patients who underwent orthotopic LT for cirrhosis and being treated with HBIg with and without NUC(s), 14 patients (14.1%) showed HBV recurrence during a median period of 15 months after LT [29]. No HBV recurrence was seen in clinical phase III studies with Zutectra® treatment over periods between 18 and 48 weeks [21, 22]. Comparisons between the above-mentioned studies may be difficult, however, because of the different designs and settings, such as differences in HBIg/NUC combination therapies, status of treatment at time of recurrence (i.e. still under HBIg therapy or not), and follow-up periods.

EASL guidelines recommend lifelong combination therapy in patients who are at a high risk for HBV recurrence, i.e. patients who are HBV DNA positive at the time of LT, who are HBeAg positive, have HCC or viral co-infection with HDV or HIV [26]. All 7 HBV recurrent patients had at least one risk factor for HBV recurrence, i.e. all had undergone LT for HBV-HCC as main reason for the LT, 3 patients had a HDV co-infection, and 1 patient had a positive HBV DNA test at LT. A study by Faria and colleagues also showed a higher HBV recurrence rate in patients with HCC post-LT: 11 of 31 patients with HCC at the time of LT and 3 of 68 without HCC at LT [29].

The rate of HBV-HCC recurrence after LT was low (n=4, 2.1%). All 4 patients had undergone LT due to HBV-HCC (HBV-HCC subgroup) and 3 of the 4 patients also developed HBV recurrence during the observation period. In 2 patients, HBV recurrence was detected prior to HBV-HCC recurrence (3.1 and 3.7 months prior, respectively). In the remaining patient, HBV-HCC recurrence was observed 3.2 months before detection of HBV recurrence. However, results of serologic tests around the time of and approximately 2.5 months before HBV-HCC recurrence were not available for HBsAg, HBeAg, and HBV DNA (HBV DNA was not detectable in one measurement). Associations between HBV-HCC pre-LT, HBV-HCC recurrence, and HBV recurrence after LT were found in several previous studies [29, 30, 31, 32]. The retrospective chart review by Campsen and colleagues showed that HBV recurrent patients were 3.6 times more likely than patients without HBV reinfection to have HCC recurrence [30]. Furthermore, HBV recurrence may be a predictor of HCC recurrence in patients who underwent LT due to HCC, at least in those patients with exceeding Milan criteria [31].

The minimum threshold of anti-HBs for protection against HBV re-infection in patients treated with HBIg of ≥ 100 IU/L was achieved in 85.4% of the patients at the 3-month FU and in 74.3% at the 2-year FU (percentages are based on patients with an anti-HBs value available or test result documented as 'not detectable' at the respective visit). There was only 1 patient with undetectable levels of anti-HBs at any post-baseline time point, whereas anti-HBs values were below the threshold in the remaining patients (14.0% at the 3-month FU and 24.8% at the 2-year FU). The reasons for low anti-HBs levels in these patients cannot be deduced from the analysed data. Suboptimal dosing regimens or non-adherence to the prescribed dosages are likely explanations. More than 70% of the injections administered within this study were self-administered by the patients (mostly at home). Adherence to treatment was not specifically monitored or analysed in this study. Monitoring of adherence was at the discretion of the participating physicians by means of their routinely applied measures, e.g. patient treatment diaries. Thus, conclusions on adherence can only be drawn indirectly by assessing the results of serum anti-HBs measurements. Of the 7 patients with HBV recurrence, 3 patients had anti-HBs levels above the protective threshold, 2 patients at inadequate levels, and results were missing in another 2 patients (in the latter 2 patients, last available values before recurrence were however above the threshold).

*Safety*

Zutectra® has been shown to be safe and well tolerated in four clinical studies and one previous NIS-PASS [20, 21, 22, 23, 24]. In these previous studies, treatment periods were shorter (up to 48 weeks) than in the present study. Thus, due to the prolonged observation period, more ADRs may have been observed. For example, of the 9 patients who discontinued treatment with Zutectra® due to AEs/ADRs, 3 patients experienced the respective AEs after more than 1 year of treatment (after 17.3, 21.2, and 23.1 months).

In previous studies, injection site reactions were the most frequently reported ADRs (≥ 1/100 to < 1/10), followed by headache and upper abdominal pain (both (≥ 1/1000 to < 1/100). In contrast to previous studies, injection site reactions were not an issue in this study. Whether they did not occur, or the patients and physicians did not report or document them, because such reactions were deemed a common side effect of s.c. (self-) injection, is not clear. There were only 2 patients with ADRs that possibly were injection site reactions: 1 patient with rash pruritic (comment by the physician: 'pruritus without specific topography but with pink rash outside of injection site') and 1 patient with erythema ('on belly') and rash pruritic. Overall, asthenia was the most frequently documented ADR, being observed in 3 patients (1.5%), followed by back pain, headache, nausea, pyrexia, and rash pruritic (each being observed in 2 patients, 1.0%). All other documented ADRs were each single cases only. Most of the documented ADRs, such as arthralgia, dizziness, lower back pain, nausea, and vomiting, have also been reported in previous studies with Zutectra® or have been associated with other human immunoglobulin preparations.

There were 2 patients with 4 SADRs relating to dose omission and lack of efficacy. In patient #21101 the SADRs 'product dose omission issue' and 'hepatitis B antibody abnormal' were reported. It was noted that HBIg decreased below 100 IU/L and that there was a potential lack of protection. The last dose of Zutectra® was documented approximately 1 month before the onset of the events. The patient was followed subsequently without Zutectra® treatment for 4 months and HBV recurrence was not seen in this patient during the observation period. Patient #10806 was reported with the SADRs 'drug ineffective' and 'Hepatitis B surface antigen'. Reappearance of HBsAg in the blood was noted and the patient was identified as HBV recurrent. The last dose of Zutectra® was

documented in this patient 10 days before the event and the treatment regimen had changed shortly before the recurrence from 500 IU weekly to every 10 days (self-administration at home). Whether dosing had been performed correctly by the patient could not be deduced from the documented data.

The most frequent ADR in the HBV-HCC subgroup was asthenia, reported in 2 patients. All other ADRs in the subgroup were single cases.

Overall, the frequency and nature of observed ADRs support the very good safety profile of Zutectra®.

The results of the clinical laboratory tests for liver and kidney function showed improvements in the markers of liver function between baseline (last measurements before LT) and all post-baseline time points after LT and after start of Zutectra® treatment. However, it should be kept in mind that the period between the last LT and the start of Zutectra® treatment was on average rather long with a high inter-patient variability (91.7 ± 94.1 months). Thus, changes in liver enzyme values during such a long period may be multifactorial, including the impact of successful transplantation. All post-baseline mean and median levels of liver enzymes, total bilirubin, and albumin remained stable over the entire treatment period with Zutectra® and indicated overall normal liver function in the total FAS.

An overall decrease in kidney function as measured by serum creatinine and eGFR was observed between the last measurement before LT and the post-baseline time points after start of Zutectra® treatment (on average 91.7 months after LT). Several factors may have contributed to this observation. During the time period prior to the start of Zutectra® treatment, immunosuppressive treatment after LT was continuously provided and may be associated with nephrotoxicity, particularly the therapy with calcineurin inhibitors [27]. In this study, calcineurin inhibitors were used by more than 80% of the patients throughout the observation period. In addition, numerous patients may have been on immunosuppressive therapy for very long periods as their last LT and hence their baseline kidney function had been performed years (in some cases even decades) before the start of this study. During this time, pre-existing kidney disease may have worsened or chronic renal dysfunction may have developed. The study population included 26 patients (13.3%) with concomitant kidney disease and in at least half of these patients a worsening in the markers of kidney function occurred between baseline (before LT) and post-baseline time points (see Listing 16.2.8.5 for results of clinical laboratory tests). As the period between LT and study start was very long in numerous patients, aging of the patients could also have had an impact on the worsening of kidney function markers, at least regarding the eGFR, which usually decreases progressively with age [33]. However, mean and median serum creatinine and eGFR values were similar between all post-baseline visits.

Overall, the stability of the mean and median clinical safety laboratory values during the 2-year treatment period with Zutectra® did not indicate towards any deterioration of liver or kidney function or problems with liver or kidney toxicity under Zutectra® treatment in combination with NUCs and other antiviral and/or immunosuppressive medications.

*Patient Satisfaction and Quality of Life*

Good treatment acceptance and satisfaction with HBIg therapy may considerably impact the patients' long-term adherence and ultimately reduce the risk of HBV recurrence. Patient satisfaction with treatment as measured with the TSQM-11 was good throughout the observation period. Significant improvements were seen regarding the perceived effectiveness of the treatment between baseline and the 2-year FU. Regarding

convenience and overall satisfaction, statistically significant improvements vs. baseline were seen at all post-baseline time points. As patients were given the questionnaire for optional completion at the baseline visit, treatment with Zutectra® was just about to begin or had not yet started in most patients. Thus, patients probably assessed their previous and/or concomitant antiviral therapy at that time. A large proportion of patients (86.8%, 164 of 189 patients with prior antiviral treatment) had received i.v. or i.m. HBIg before start of Zutectra® treatment. The switch to s.c. injections, which could be self-administered by the patient at home (probably after a short while of training and getting used to self-injecting) may have contributed to the improvement in the convenience dimension. A recent observational study investigating patient satisfaction and changes in quality of life after switching from i.v. or i.m. HBIg to s.c. HBIg in patients who had undergone LT one year before study entry, showed positive effects of the s.c. route on side effects, negative feelings, and patient autonomy [34]

Quality of life as measured by the EQ-5D was overall already at a high level at baseline indicated by both the total score with a median of 0.80 (1.00 indicating perfect health) and the VAS score with a median of 80.0 (100 indicating best imaginable health). Successful liver transplantation should usually improve the patients' health substantially. The subjectively perceived quality of life may be comparatively high in patients after coming through critical illness and major surgery. The results of the EQ-5D identified pain/discomfort as the dimension where patients most frequently reported any problems, followed by the dimension 'anxiety and depression'. These two dimensions also have been shown to contribute to a worse general health status in liver transplant recipients one year after LT in a longitudinal study in 30 patients [35]. The generally high level of self-assessed quality of life in the current study could be maintained until the end of the observation period, with slight numerical improvements in some of the EQ-5D dimensions (shift in frequencies towards the lowest level of perceived problem) and mean total and VAS score.

### 12.4 Generalisability

The results of this study may be generalisable to other similar populations of patients treated with a combination of self-administered s.c. HBIg and NUCs after LT for HBV-related liver diseases such as fulminant hepatitis B, HBV-induced liver cirrhosis, and HBV-HCC. The study was performed under real-life conditions, reflecting the participating physicians' standard of care. To ensure a representative selection of participating clinics, hepatic centres performing LT were distributed over two different European countries.

## 13. OTHER INFORMATION

Not applicable.

## 14. CONCLUSION

In this NIS performed in France and Spain, a low rate of HBV recurrence (3.6%) was observed over a 2-year period in patients treated with Zutectra® after LT (mostly in combination with NUC therapy) for HBV-induced liver diseases. All 7 HBV recurrent patients had received NUC therapy at the time of recurrence and had at least one risk factor for graft re-infection (all had undergone LT for HBV-HCC, 3 patients had HDV co-infection, and 1 patient had positive HBV DNA at LT). Under Zutectra®, which was mostly self-

administered at home, anti-HBs levels were adequately high for protection against HBV recurrence in more than 70% of the patients at all documentation time points.

Zutectra® was well tolerated and no new safety signal was observed in this study.

Patient satisfaction as measured with the TSQM-11 was good throughout the observation period with significant improvements vs. baseline regarding convenience and overall satisfaction already after 3 months of Zutectra® treatment. The high level of self-assessed quality of life established around the time of therapy start was maintained until the end of the observation period.

Overall, the results of this NIS support the evidence that Zutectra® in combination with NUC therapy is efficacious in the long-term prophylaxis of HBV recurrence in liver transplant patients under real-life conditions and is well tolerated and accepted by the patients.

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# 16. APPENDICES

## 16.1 Appendix 1. List of stand-alone documents

| Number | Document reference number | Date | Title |
|---|---|---|---|
| 1 | 1.1 | 17-Aug-2015 | Observation plan, final version 2.0 |
| 2 | 1.2 | 16-Feb-2021 | Statistical analysis plan, final version 2.0 |
| 3 | 1.3 | 29-Apr-2021 | End-of-text tables (file: NIS Zutectra Tables 2021-04-29) |
| 4 | 1.4 | 29-Apr-2021 | Figures (file: NIS Zutectra Figures 2021-04-29) |
| 5 | 1.5 | 29-Apr-2021 | Subject data listings (file: NIS Zutectra Listings 2021-04-29) |
| 6 | 1.6 | | List of participating physicians |

## 16.2 Appendix 2. Additional information

Not applicable.