Study 974 - EudraCT Number: 2008-007625-39

Synopsis

Name of Sponsor/Company: Biotest AG			
Title of study: An open, prospective, single-arm study investigating feasibility of home self-treatment, safety and efficacy of subcutaneous application of the human hepatitis B immunoglobulin BT088 in liver transplanted patients			
Study Number: 974			
Coordinating Investigator: Prof. Franco Filipponi, MD, U. O. Chirurgia Generale e Trapianti Di Fegato, Ospedale Cisanello, Via Paradisa 2, I - 56124 Pisa, Italy **Principal Investigators:** F. Filipponi/Pisa, [redacted], G. Rossi/Milan, [redacted], [redacted], S.Fagiuoli/Bergamo, L.G. De Carlis/Milan, G. Di Costanzo/Naples/			
Study centre(s): 7 centres in Italy			
Publication (reference): Filipponi et al. (2011), Calise et al. (2011), Strignano et al. (2012)			
Studied period (years):	2 years	**Clinical phase:**	III
(date of first enrolment)	04-JUN-2009		
(date of last completed)	15-JUN-2011		
Objectives: Feasibility of home self-treatment including patient compliance Safety and efficacy of subcutaneous application of BT088 in patients after liver transplantation			
Methodology: Open, prospective, single-arm, multicentre			
Number of patients (planned and analysed): It was planned to enrol about 60 male or female patients (age 18-75 years) after liver transplantation to achieve a total number of at least 50 evaluable patients in this trial. 72 patients were screened in this study. 66 patients entered this study and were treated with BT088 at least once. 58 patients completed both Part A (day1-169/24 weeks) and Part B (day176-337/48 weeks) of the study.			
Diagnosis and main criteria for inclusion: 1. Male and female patients (age 18-75 years) 2. ≥ 3 months after liver transplantation 3. HBsAg negative/ HBV-DNA negative in two determinations during the last 3 months (patients with known hepatitis D superinfection may be included) 4. After the last i.v. or i.m. administration of HBIg serum HBs antibody concentration between 200 IU/L and 350 IU/L or between 300 IU/L and 500 IU/L (protocol version 2.0/amendment 01) prior to the first dosing of BT088 at day 1 5. Regular long-term i.v. or i.m. HBIg prophylaxis (combined re-infection prophylaxis) with stabilised HBIg dosage and administration intervals with i.v. or i.m hepatitis B immunoglobulins 6. Stable liver function 7. Written informed consent			

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Test product, dose and mode of administration, batch number:

Test product: BT088, human hepatitis B immunoglobulin (HBIg)

Dose and mode of administration: Subcutaneous injections of approx. 500 IU (1 mL) BT088 per week for patients with bodyweight < 75 kg and 1000 IU (2 mL) BT088 per week for patients with bodyweight ≥ 75 kg; dosage was to be adapted individually, if necessary, according to the serum anti-HBs concentrations.

Batch numbers: A098037A; A098028; B798010

Duration of treatment:
Weekly subcutaneous injections of BT088 during 24 weeks (Part A)
Facultative extension: continuation of the therapy for another 24 weeks (Part B)

Reference therapy, dose and mode of administration, batch number:
Not applicable

Criteria for evaluation

Feasibility:
- Percentage of self-administration in hospital/home
- Time to first self-administration in hospital/home
- Time to complete self-administration in hospital/home
- Patient compliance during home self-administration

Efficacy:
- Trough serum anti-HBs levels ≥ 100 IU/L
- Number of hepatitis B related infections

Safety:
- Number and nature of adverse events including safety laboratory parameters

Statistical methods:

Analyses of feasibility of home self-treatment were performed for the Intention-To-Treat (ITT) population, additionally, sensitivity analyses were performed for the Feasibility (FB) population.

Analyses of efficacy were performed for the ITT population. Sensitivity analyses for efficacy parameters were additionally performed for the Per-Protocol (PP) population.

The safety analysis was performed for the safety population.

Quantitative data were analysed by the statistical parameters valid N, mean, standard deviation (SD) and the following quantiles: minimum, median and maximum. Qualitative and ordinal data were analysed by absolute and relative frequency distributions.

SUMMARY – CONCLUSIONS

Feasibility of home self-treatment

With the exception of the 6 patients who withdrew prior to D36 and/or had no post D29 injection, all 60 patients achieved complete hospital and home self-administration: 60/66

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patients (90.9%) of the ITT population and 60/60 patients (100%) of the FB population. No patient prematurely discontinued the study due to lack of feasibility of home self-treatment. On D36, i.e. immediately after the end of the 4-weeks training period, 54/60 patients (90.0% of FB population) were in complete hospital/home-self administration; on D43, all except 2 patients (56/60, 96.7%). These 2 patients achieved complete home self-administration on D50 and D141, respectively.

Efficacy

During the 48-weeks treatment phase constant serum HBs antibody concentrations above the minimum safety trough level of ≥ 100 IU/L were measured in all patients with mean values of: 317.0 ±111.7 IU/L on D1, 321.0 ±88.1 IU/L at the end of the obligatory training period on D29, 325.2 ±107.0 IU/L on D169 and 312.0 ±103.5 IU/L at the end of the facultative extension period on D337. In 7/66 patients (10.6%) a total of 10 serum HBs antibody concentrations below 150 (range 112-148) IU/L were observed that required an adaptation of BT088 dosing.

Protective levels were maintained independent from the type of administration (investigator, patient in hospital, patient at home). The individual patient data demonstrate the efficacy of BT088 during long-term home self-treatment without dose adaptations in the majority of patients.

No clinical signs of a hepatitis B re-infection were reported and no patient was tested HBsAg positive during the study which confirms that effective protection against Hepatitis B virus re-infection was provided by subcutaneous administration of BT088.

Safety:

There was no death reported in this study. A total of 4 serious TEAEs occurred in 3/66 patients (4.5%); wrist fracture, acute cholangitis, cholangitis/fever in 1 patient each. All these events were assessed as not related to the administration of BT088, were of moderate intensity and resolved during the study.

No HBV re-infection was observed in Study 974.

A total of 335 TEAEs were reported in 52/66 patients (78.8%).

The most frequently reported TEAEs (MedDRA PT) by patient were headache in 24/66 patients (36.4%), injection site haematoma in 9/66 patients (13.6%), pyrexia in 9/66 patients (13.6%), nasopharyngitis in 9/66 patients (13.6%), and injection site erythema in 7/66 patients (10.6%).

A total of 102 TEAEs assessed as related to BT088 were reported in 29/66 patients (43.9%). TEAEs assessed as related that occurred in more than a single patient were injection site haematoma in 9 patients (13.6%), injection site erythema and headache in 7 patients each (10.6%), nausea in 4 patients (6.1%), erythema in 3 patients (4.5%), vertigo, vomiting and injection site oedema in 2 patients each (3%). The nature and frequency of related non serious TEAEs was comparable to previous studies.

In 4 patients, a total of 10 TEAEs were reported leading to withdrawal from the study: hereof 5 events in 2 patients were assessed as related to study medication by the investigator (hypersensitivity in 1 patient; vomiting, nausea, headache, hypertension in 1 patient). The other 5 events were assessed as not related to BT088 (lymphadenopathy in 1 patient; increased GOT/GPT/gamma-GT and pruritis in 1 patient).

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CONCLUSIONS: Overall, the results of the present study demonstrate the feasibility of home self-administration with BT088 during a treatment period of 48 weeks. A training period of 4-5 weeks was sufficient in all but 2 patients. Serum HBs antibody concentrations above the minimum safety trough level of ≥ 100 IU/L were reached in all patients at all assessments. No hepatitis B related infection (HBsAG positive) was observed during the study which confirms that effective protection against Hepatitis B virus re-infection was provided by subcutaneous administration of BT088. Treatment with BT088 was well tolerated and safe. Overall findings of physical examinations, vital signs and laboratory investigations confirmed safety of BT088 in a broader population of stable patients during long-term treatment for prophylaxis against re-infection of a transplanted liver. **Date of report:** 15-AUG-2012

Name and the address of the consenting investigators pursuant to Section 4a of the Federal Data Protection Act

Coordinating Investigator (and investigators at site 001) **15 patients screened, 13 treated**	Prof. Franco Filipponi, MD U. O. Chirurgia Generale e Trapianti Di Fegato Ospedale Cisanello Via Paradisa 2 56124 Pisa Italy
Investigators at site 002 **22 patients screened, 20 treated**	[redacted] Cardarelli Hospital Department of Hepato-Biliary Surgery & Liver Transplantation Unit Via Antonio Cardarelli, 9 / block,building D 80131 Naples Italy

Investigators at site 003 **5 patients screened, 3 treated**	Dr. Giorgio Rossi, MD Ospedale Policlinico di Milano Unità Operativa Chirurgia, Generale e trapianto di fegato, Padiglione Zonda I piano Via Francesco Sforza 28 20122 Milan Italy
Investigators at site 004 **9 patients screened, 9 treated**	Dr. Stefano Fagiuoli, MD Ospedale di Bergamo Unità strutturale complessa USC -Gastroenterologia, DAY HOSPITAL Largo Barozzi, 1 24128 Bergamo Italy
Investigators at site 005 **10 patients screened, 10 treated**	[redacted] Azienda Ospedaliera Universitaria Centro Trapianti Fegato, San Giovanni Battista Corso Bramante, 88/90 10126 Turino Italy
Investigators at site 006 **5 patients screened, 5 treated**	Dr. Luciano Gregorio De Carlis, MD Ospedale Niguarda di Milano Chirurgia Generale 2 e Trapianti, BLOCCO SUD Piazza Ospedale Maggiore 3 20762 Milan Italy
Investigators at site 007 **6 patients screened, 6 treated**	Prof. Dr. Giovan Giuseppe Di Costanzo, MD Azienda Ospedaliera di Rilievo, Nazionale A Cardarelli U. O. C. Chirurgia Epatobiliare e Trapianto di Fegato Via Antonio Cardarelli, 9 80131 Naples Italy

Overview of substantial protocol amendments

Amen. No./ Prot. Vers.	Date	Sections concerned	Rationale
01	09 Oct 2009	Cover Page, Synopsis, Section 7.2, 8, 12.1, 12.2, 13.2, 14	**Substantial Changes** • The primary objective was changed reflecting the feasibility of home self-treatment of the subcutaneous mode of application of BT088 in liver transplanted patients. • The sample size was reduced from 110 to approximately 50 evaluable cases as a consequence of the change of the primary study objective. • The inclusion criterion 4 was adapted to the recommendations in the submitted SPC for Zutectra concerning the anti-HBs serum levels prior to first dosing (above 300 – 500 IU/L).

Interruption and early termination of the clinical trial

Not applicable