CTR synopsis

Trial registration ID-number NCT 01392547	**UTN – U1111-1118-2228** **IND number – BB–IND#13,317** **EudraCT number – 2010-023803-92** **Japanese registration number – JapicCTI-111595**

TITLE OF TRIAL

Efficacy and safety of NNC 0078-0000-0007 in treatment of acute bleeding episodes in patients with congenital haemophilia and inhibitors

INVESTIGATORS

A primary investigator was appointed for each of the 49 sites initiated. [redacted] was appointed signatory investigator and approved the clinical trial report on behalf of all investigators.

TRIAL SITES

Patients were recruited from a total of 46 sites globally in 18 countries, including Austria, Brazil, Croatia, Greece, Hungary, Italy, Japan, Malaysia, Poland, Romania, Russia, Serbia, South Africa, Taiwan, Thailand, Turkey, United Kingdom and United States.

PUBLICATIONS

No publications were available at the time of this clinical trial report synopsis.

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 07-Jul-2011 Completion date: 13-Aug-2012	Phase 3

OBJECTIVES

Primary objective:

- To demonstrate the efficacy of vatreptacog alfa in controlling acute bleeds in patients with congenital haemophilia with inhibitors

Secondary objectives:

- To confirm the safety of vatreptacog alfa when administered for treatment of acute bleeds
- To evaluate the immunogenicity of vatreptacog alfa (formation of neutralising antibodies)

METHODOLOGY

- The trial was designed as a global multi-centre, double-blind, cross-over, confirmatory phase 3 trial, in which bleeding episodes were randomly assigned to a treatment regimen of vatreptacog alfa (1−3 doses of 80 µg/kg) or an active comparator (1–3 doses of 90 µg/kg rFVIIa). Patient eligibility was assessed after signing informed consent at a screening visit (Visit 1). Eligible patients received a patient number.
- The trial consisted of scheduled visits, during which a single dose of vatreptacog alfa was administered in a non-bleeding state, and home-treatment of acute bleeding episodes with vatreptacog alfa or rFVIIa.
- During the scheduled visits (prior to home treatment and at 3-month intervals), safety was monitored by clinical and laboratory assessments including antibody screening (pre-dose) and assessment of recovery of rFVIIa activity (10 minutes post-dose) as a potential indicator of formation of neutralising antibodies. In addition, patients were trained in drug reconstitution, safety reporting, assessment of efficacy, and the use of an eDiary.
- All bleeds that occurred during the trial period were to be treated with trial product, regardless of localisation and severity. Each bleeding episode was randomised to be treated with either vatreptacog alfa or rFVIIa (randomisation 3 vatreptacog alfa: 2 rFVIIa). The initial dose of trial product was to be administered as soon as the patient recognised the symptoms of a bleed and preferably within 2 hours of onset of bleed. The patient received up to 3 doses of trial product, separated by a dosing interval of 3 hours. If haemostasis had not been achieved after 3 doses, the patient was to be treated with other haemostatic agents according to local standard care.
- The treatment of bleeds was primarily done at home to allow for treatment as early after bleeding onset as possible. Home-treatment could be initiated when the patient and/or caregiver had, at the scheduled dose visit(s), demonstrated

their capability of treatment and evaluation of bleeds. In situations where home treatment was not feasible the treatment with trial product could occur at the haemophilia treatment centre.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

- A total 500 bleeds were planned to be treated with trial product (including 300 bleeds treated with vatreptacog alfa and 200 bleeds treated with rFVIIa) *and* a minimum of 15 patients were to have at least 10 exposure days to vatreptacog alfa during the trial. Recruitment was competitive between countries and trial sites.
- A total of 567 bleeds were treated in 69 patients.

Screened	80
Exposed	
Total	72 (100.0)
Scheduled visits	72 (100.0)
Bleeds	69 (95.8)
Withdrawals	
Total	8 (11.1)
Adverse event	2 (2.8)
Non-compliance	2 (2.8)
Withdrawal criteria	3 (4.2)
Other	1 (1.4)
Completed	64 (88.9)
Safety analysis set	72 (100.0)
Full analysis set	69 (95.8)

Number of patients (proportion of exposed patients)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Inclusion criteria

- Male patient with clinical diagnosis of congenital haemophilia A or B and inhibitors to coagulation factors VIII or IX
- Minimum of five bleeds requiring haemostatic drug treatment within the previous 12 months at trial start

Exclusion criteria

- Previous participation in this trial defined as withdrawal after administration of trial product
- Patient has received an investigational medicinal product within 30 days prior to this trial
- Congenital or acquired coagulation disorders other than haemophilia A or B
- Any clinical signs or known history of arterial thrombotic events or of deep venous thrombosis or pulmonary embolism (as defined by available medical records)
- Platelet count of less than 50,000 platelets/mcL (at the screening visit)
- ALAT (alanine transaminase) of more than 3 times the upper normal limit (according to laboratory reference ranges)
- Factor VIII/IX immune tolerance induction regimen planned to occur during the trial
- Ongoing bleeding prophylaxis regimens or planned bleeding prophylaxis to occur during the trial
- HIV (human immunodeficiency virus) positive with current $CD4^+$ count of less than 200/mcL (defined by medical records)

INVESTIGATIONAL MEDICINAL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

- Activated recombinant vatreptacog alfa was provided as a sterile freeze-dried powder in single-use vials of 2 mg/vial (batch nos. AR40096, AR40097 and AR40367) to be reconstituted with 2.1 mL of histidine solvent (batch no. AR40007) for intravenous injection.

DURATION OF TREATMENT

- Each bleeding episode was randomised to be treated with either vatreptacog alfa or rFVIIa (randomisation 3 vatreptacog alfa: 2 rFVIIa). The initial dose of trial product was to be administered as soon as the patient recognised the symptoms of a bleed and preferably within 2 hours of onset of bleed. The patient received up to 3 doses of trial product, separated by a dosing interval of 3 hours. If haemostasis had not been achieved after 3 doses, the patient was to be treated with other haemostatic agents according to local standard care.
- The total number of bleeds treated with trial products ranged from 1 to 42 bleeds. A total of 57 patients had a total of 1 to 16 bleeds treated with rFVIIa and 67 patients had 1 to 26 bleeds treated with vatreptacog alfa.
- The patients were planned to be in the trial for approximately 10−21 months, followed by 1 month for antibody assessment, dependent on the time of enrolment.

Number of treated bleeds with vatreptacog alfa and rFVIIa - full analysis set

	rFVIIa	vatreptacog alfa
Number of patients treated	57	67
Number of bleeds treated, N (%)		
1	10 (17.5)	12 (17.9)
2	11 (19.3)	13 (19.4)
3	14 (24.6)	8 (11.9)
4	7 (12.3)	9 (13.4)
5	6 (10.5)	3 (4.5)
6	1 (1.8)	4 (6.0)
7		5 (7.5)
8		4 (6.0)
9	1 (1.8)	1 (1.5)
10	2 (3.5)	
11	2 (3.5)	1 (1.5)
12	2 (3.5)	2 (3.0)
15		1 (1.5)
16	1 (1.8)	1 (1.5)
18		1 (1.5)
20		1 (1.5)
26		1 (1.5)

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

- Activated recombinant FVII (rFVIIa) was provided as a sterile, freeze-dried powder in single-use vials of 2.3 mg (batch no. AR40098) to be reconstituted with 2.1 mL of histidine solvent (batch no. AR40007) for intravenous injection.

CRITERIA FOR EVALUATION – EFFICACY

The primary objective of the trial was to demonstrate the efficacy of vatreptacog alfa in controlling acute bleeds in patients with congenital haemophilia with inhibitors. Primary and secondary efficacy endpoints were defined to fulfil this objective.

The primary efficacy endpoint was effective bleeding control, defined as no additional haemostatic medication (other than trial product) given within 12 hours after first dose of trial product.

Secondary efficacy endpoints included:

- effective and sustained bleeding control (no use of additional haemostatic medication to treat the same bleed within 24 hours after initiation of treatment)
- number of doses of trial product given for each bleed
- use of additional haemostatic medication to treat the same bleed within 48 hours after first dose of trial product
- change in pain assessments over time (change between the pain assessments after 1, 3, 6 and 9 hours after first dose of trial product and baseline pain immediately prior to initial dose).

CRITERIA FOR EVALUATION – SAFETY

- A secondary objective was to confirm the safety of vatreptacog alfa when administered for treatment of acute bleeds. In order to reflect this objective, adverse events (non-serious and serious adverse events) were defined as a secondary safety endpoint in the trial. Monitoring for adverse events included assessments of biochemistry, haematology, coagulation-related parameters, vital signs and physical examination at regular intervals throughout the trial. All events meeting the definition of an adverse event were to be collected from the first trial-related activity until the end of participation in the trial. Treatment-emergent non-serious adverse events were defined as events occurring from the time of initial dose of trial product (for treatment of bleed) until 7 days after initial dose. Treatment-emergent serious adverse events were defined as all events collected from a patient's first administration of trial product to the end of patient's participation in the trial. Treatment-emergent adverse events were assigned to the most recent administration of trial product. All antibody adverse events were classified as treatment emergent, even if they were detected more than 7 days from last dose of trial product. Antibody adverse events were allocated to the product that they were antibodies against, and hence not necessarily the most recent trial product used. Bleeding episodes and pain in connection with bleeding episodes evaluated by the investigator as part of the underlying disease should not be reported as adverse events unless evaluated as related to trial product. In case of fatal outcome, the bleeding episodes and pain were to be reported as a serious adverse event.
- Another secondary objective of the trial was to evaluate the immunogenicity of vatreptacog alfa. A secondary safety endpoint of immunogenicity specified as development of neutralising antibodies against vatreptacog alfa and/or FVII was included to reflect this objective. In addition, FVIIa activity (recovery) was included as a secondary efficacy endpoint.

STATISTICAL METHODS

Sample size

- Assuming a true success rates of 97% for vatreptacog alfa and 90% for rFVIIa, 300 bleeding episodes treated with vatreptacog alfa and 200 bleeding episodes on rFVIIa would give over 99% power to demonstrate non-inferiority with a 15% non-inferiority bound. Power to subsequently demonstrate superiority was 90%. This was based on simulations with the binomial distribution.

Analysis sets

- All patients exposed to at least one dose of trial product was included in the safety analysis set. Patients in the safety set contributed to the evaluation "as treated".
- All exposed patients for whom at least one of the efficacy variables was available were included in the full analysis set (FAS). In exceptional cases patients from the FAS may be excluded. In such cases the exclusion will be justified and documented prior to database lock. The statistical evaluation of the FAS followed the intention-to-treat principle and patients contributed to the evaluation "as randomised".

Analyses

- Effective bleeding control was analysed by a logistic regression model adjusting for treatment, type of bleed (joint or non-joint) and baseline pain score. Patient was included as a random variable by use of a repeated statement in proc Genmod in SAS. Exchangeable working matrices were applied. The primary test was a non-inferiority test of vatreptacog alfa compared to rFVIIa using a non-inferiority bound for the log odds ratio corresponding to a non-inferiority bound of 15% on the absolute scale. If, and only if, non-inferiority was established, superiority of vatreptacog alfa over rFVIIa (null-hypothesis: Effect of vatreptacog alfa is equal or worse than the effect of rFVIIa) was to be tested in the same model based on a 1-sided test on a 2.5% alpha level.
- The secondary endpoints were analysed by a logistic regression model similar to the primary analysis.
- Safety endpoints were presented using summary statistics.

DEMOGRAPHY OF TRIAL POPULATION

- A total of 72 patients from 46 sites in 18 countries were enrolled including 66 patients with haemophilia A and 6 patients with haemophilia B.
- All patients were male, and the age at screening ranged from 12 to 71 years. A total of 11 adolescent patients (below the age of 18 years) were included in the trial.
- Approximately 2 out of 3 of patients were White (Caucasian), ~20% were Asian, 17% were Black or African-American and [redacted] patients were of other race ([redacted]). Almost half ([redacted] out of [redacted]) of the adolescent patients were Asian. The majority of patients (~92%) were not of Hispanic or Latino ethnicity.

EFFICACY RESULTS

- A total of 72 patients from 46 sites in 18 countries received trial products including 66 patients with haemophilia A and 6 patients with haemophilia B. Of these 69 patients received trial products for treatment of acute bleeds including 1−3 doses of vatreptacog alfa (5−80 µg/kg) or the comparator (90 µg/kg rFVIIa).
- A total of 56 of 69 patients (81.2%) had no treatment failures, i.e., effective bleeding control was achieved with 1 to 3 doses of vatreptacog alfa (80 µg/kg) or rFVIIa (90 µg/kg). For 322 out of 340 (93.5%) bleeds treated with vatreptacog alfa, effective bleeding control was achieved with the per-protocol 1−3 doses. Of the 227 bleeds treated with rFVIIa, bleeding control was obtained in 211 (93.0%) bleeds with the per-protocol 1−3 doses.
- Vatreptacog alfa was shown to be effective (non-inferior to rFVIIa) on the primary efficacy endpoint, effective bleeding control, defined as no additional haemostatic medication (other than trial product) given within 12 hours after first dose of trial product.
- Vatreptacog alfa was not superior to rFVIIa on the primary efficacy endpoint (p=0.9703).
- A statistically significantly better effect of vatreptacog compared to rFVIIa was shown for all secondary efficacy endpoints including:
  - Sustained bleeding control evaluated at 24 and 48 hours after first dose of trial product (p=0.0223 and p=0.0102, respectively)
  - Pain relief at 6 and 9 hours after first dose of trial product (p=0.0058 and p=0.0230, respectively)
  - Number of doses of trial product used to treat bleed (p=0.0304)

	80 µg/kg vatreptacog alfa	90 µg/kg rFVIIa
Bleeding episodes	340 (100.0)	227 (100.0)
Primary endpoint		
No additional haemostatic agents given within 12 hours	318 (93.5)	211 (93.0)
Secondary endpoints		
Sustained control		
- No additional haemostatic agents given within 24 hours	306 (90.8)	194 (86.2)
- No additional haemostatic agents given within 48 hours	268 (83.5)	163 (76.2)
Pain[a]		
- Pre-dose	27.8 (26.0)	25.2 (25.6)
- Change in pain 1 hour post-dose(SD)	-4.1 (8.1)	-4.0 (8.8)
- Change in pain 3 hours post-dose(SD)	-8.4 (12.5)	-6.7 (14.1)
- Change in pain 6 hours post-dose(SD)	-14.1 (17.0)	-10.7 (19.7)
- Change in pain 6 hours post-dose(SD)	-17.6 (21.5)	-13.7 (24.7)
Number of doses		
- Bleeds treated with 1 dose	51 (15.0)	23 (10.1)
- Bleeds treated with 2 doses	94 (27.6)	62 (27.3)
- Bleeds treated with 3 doses	195 (57.4)	142 (62.6)
- Mean doses/bleed (SD)	2.42 (0.74)	2.52 (0.67)

a: Pain associated with a bleed was assessed by a VAS scale ranging from "no pain"(score: 0) to "pain as bad as you can imagine"(score: 100). Change in pain was rated based on baseline/pre-dose pain

SAFETY RESULTS

- Overall, vatreptacog alfa was safe and well tolerated, with a low frequency of adverse events.
- A total of 8 (11%) patients developed antibodies against vatreptacog alfa, and an *in vitro* neutralising activity against vatreptacog alfa (approximately 60% in vitro remaining activity corresponding to 0.2 U of vatreptacog alfa) was reported in 1 blood sample from 1 of these patients.
- In the 4 patients with anti-vatreptacog alfa antibody titre above 16, low-titre cross-reactivity against rFVIIa was seen. Binding of the antibodies against rFVIIa could in all cases be competed out by vatreptacog alfa, suggesting that these rFVIIa antibodies had been induced by vatreptacog alfa but were cross-binding with lower affinity to rFVIIa because of the high amino acid sequence homology (only 3 amino acids difference).
- One (1) patient with negative test results for antibodies against vatreptacog alfa had borderline negative results for

rFVIIa-binding antibodies at [redacted] and [redacted], and low-titre anti-rFVIIa antibodies just above assay cut-off point in one sample collected at [redacted].

- Tests for antibodies neutralising endogenous FVII were negative for all patients at all visits, and all antibody positive patients with bleeds after occurrence of antibodies responded well to treatment with trial product while being active in the trial.
- Most adverse events (other than anti-drug antibody formation) were related to concomitant illnesses and the underlying disease (haemophilia) and consequences hereof. Overall, the type and frequency of adverse events reported following exposure to vatreptacog alfa did not appear to differ from the well-established adverse event profile of rFVIIa. Hence, no adverse events specific to vatreptacog alfa, besides antibody formation, were identified.
- One (1) event of arteriovenous fistula thrombosis was reported as a serious adverse events (and medical event of special interest) evaluated to be possibly related to rFVIIa administration. The patient was withdrawn from the trial due to the event.
- Except for immunogenicity, no safety signals were revealed by any of the laboratory safety parameters.

CONCLUSIONS

- Vatreptacog alfa (1–3 doses of 80 µg/kg) was effective in controlling acute bleeds in patients with congenital haemophilia with inhibitors. A statistically significantly better effect of vatreptacog alfa compared to rFVIIa was demonstrated for all secondary endpoints, including sustained bleeding control (24 and 48 hours after initial dose), pain relief (6 and 9 hours after initial dose) and number of doses used to treat bleeds.
- Vatreptacog alfa was generally well-tolerated. A high incidence of anti-drug antibody development (11%) was however observed among patients receiving vatreptacog alfa, indicating that even very small changes to the molecule can significantly change the immunogenicity profile of rFVIIa products.
- In the light of the proven safety of rFVIIa, the risks associated with anti-drug antibody formation against vatreptacog alfa in the investigated patient population were evaluated as unacceptable.

The trial was conducted in accordance with the Declaration of Helsinki (World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 59th WMA General Assembly, Seoul, October 2008) and ICH Good Clinical Practice (01-May-1996, Geneva, Switzerland. 1996).

The results presented reflect the data available in the clinical database as of 25 October 2013.