CTR synopsis

Trial registration ID-number: NCT01706159	**UTN:** U1111-1120-3824 **EudraCT number:** 2011-001568-22

TITLE OF TRIAL

A multicenter, randomised, double-blind, placebo-controlled, multiple-dose trial with rFXIII administered to subjects with mild to moderate active ulcerative colitis.

INVESTIGATORS

One principal investigator was appointed at each of the 12 trial sites in the trial. The following investigator was designated signatory investigator for the trial, and was responsible for reviewing and approving the clinical trial report:

- Dr. [redacted], MD, PhD, [redacted].

TRIAL SITES

The trial was conducted at 12 sites in 6 countries as follows: Bulgaria (4 sites), Denmark (1 site), Hungary (1 site), Poland (4 sites), Russian Fed.(1 site) and Ukraine (1 site). These 12 sites randomised/assigned subjects to treatment.

PUBLICATIONS

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

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 09 October 2012 (first patient first visit) Termination date: 25 June 2013 (decision to terminate the trial prematurely) / 10 July 2013 (last patient last visit)	Phase 2a

DATA CUT-OFF DATE

The results presented reflect the data available in the clinical database as of 26 September 2013.

OBJECTIVES

Primary objective:

- To assess the effects of rFXIII on mucosal healing

Secondary objectives:

- To assess effects of rFXIII on clinical disease activity
- To assess the safety of rFXIII
- To assess the pharmacokinetics (PK) of rFXIII by FXIII activity systemically

METHODOLOGY

The trial was a multi-centre, double-blind, randomised, placebo-controlled, parallel-group, 2-arm trial designed to assess the effects of rFXIII on mucosal healing in male and female subjects with mild to moderate active ulcerative colitis (UC) (i.e., ulcerative colitis disease activity index [UC-DAI]) score of 4−10).

The doses were to be administered every other week for a total of 4 doses. The trial was planned to consist of 8 visits (screening visit, 4 dosing visits, follow-up visits after first and last dosing and end-of-trial visit). Furthermore, for the first 15 randomised subjects 2 additional visits (24 and 72 hours after first dosing) were planned for blood sampling for PK assessment. The total length of the trial was planned to 10 weeks from first dosing until last visit, excluding the screening period, which could be maximally 4 weeks. Subjects were randomised to receive either rFXIII (35 IU/kg) or placebo intravenously (i.v.), in a 2:1 ratio. Randomisation was stratified into 2 strata, based upon screening levels of FXIII using the Berichrom® assay (below 43% or between 43 and 75%, both inclusive).

The trial was terminated earlier than planned. After having screened 119 subjects of which 99 were screening failures, Novo Nordisk evaluated the data and in contrast to the published literature, the data from the screened subjects did not provide any relationship between the FXIII level and the disease activity of UC. Thus, the medical hypothesis this trial was based on could not be confirmed.

An interim PK analysis was planned to be performed when the first 15 subjects (10 on active trial drug) had completed the visit at Week 6, and at least 80% of the samples from each subject had been obtained. The trial was terminated

before the planned sample size for PK analysis was reached, and therefore no interim analysis was performed.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

Only 18 out of 90 planned subjects were exposed to trial product (rFXIII or placebo). The subject disposition is summarised in **Table 1.** The full analysis set (FAS) and the safety analysis set was identical and consisted of all 18 subjects exposed to trial product. The completer analysis set (CAS) consisted of the 9 subjects who had an available Baron score at Week 8.

Table 1 Subject disposition

	Placebo	rFXIII 35 IU/kg	Total
Screened Subjects, N			119
Randomised Subjects, N (%)	6 (100.0)	14 (100.0)	20 (100.0)
Exposed Subjects, N (%)	5 (83.3)	13 (92.9)	18 (90.0)
Completed Subjects, N (%)	4 (66.7)	6 (42.9)	10 (50.0)
Withdrawn Subjects, N (%)	2 (33.3)	8 (57.1)	10 (50.0)
- Withdrawal Criteria, N (%)	1 (16.7)	2 (14.3)	3 (15.0)
- Other reason, N (%)	1 (16.7)	6 (42.9)	7 (35.0)
Completer Subjects (with Baron Score at Week 8), N (%)	3 (50.0)	6 (42.9)	9 (45.0)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Key inclusion criteria:

- Male and female subjects between 18 and 64 years of age
- Diagnosis of UC for at least 3 months from the time of initial diagnosis. The diagnosis must have been confirmed by historical endoscopy and histology. The severity of disease must have been confirmed by endoscopy at screening
- Currently receiving oral aminosalicylates at approved doses for at least 6 weeks of at least 2 g/day. Doses of oral aminosalicylates should be stable for at least two weeks prior to dosing (Visit 2)

Key exclusion criteria:

- Diagnosis of UC limited to the rectum (ulcerative proctitis only, defined as < 15 cm from the anal verge)
- Requiring hospitalisation for current episode of severe UC
- Use of biologic therapies for the treatment of UC within 12 weeks prior to dosing (Visit 2)
- Treatment failures to anti-TNF-α agents (e.g. infliximab, adalimumab)
- Use of immunosuppressant agents (e.g. azathioprine) within 4weeks prior to dosing (Visit 2)
- Use of corticosteroids (oral, intravenous (i.v.), intramuscular (i m.), or rectal) within 14 days prior to dosing (Visit 2)
- Use of enemas (corticosteroid or aminosalicylate) within 14 days prior to screening (Visit 1)
- Use of cyclosporine, tacrolimus, D-penicillamine, leflunomide, methotrexate, mycophenolate mofetil, or thalidomide within 4 weeks prior to dosing (Visit 2)
- Currently receiving total parenteral nutrition

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

The trial products were supplied by Novo Nordisk A/S, Denmark:

- rFXIII, 2500 IU/vial (15 mg), powder for solution for injection (Batch no. YR40345)
- rFXIII placebo 0 IU/vial (0 mg), powder for solution for injection (Batch no. BR40118)
- Sterile water for injection, European Pharmacopoeia (Ph. Eur.) (Batch no. AR40227)

The investigational medical product (rFXIII), also named NNC8717-0001, was supplied as a sterile lyophilized powder for injection. Each vial was reconstituted with 3.2 mL sterile water for injection to give a concentration in the reconstituted vial of 833 IU/mL. The placebo and active drug were visually identical.

DURATION OF TREATMENT

All subjects were planned to receive an i.v. dose of rFXIII (35 IU/kg) or placebo every second week for a total of 4 doses. Due to the early termination of this trial, not all randomised subjects received all 4 planned doses of trial product; for further details, please refer to safety results.

CRITERIA FOR EVALUATION – EFFICACY/PHARMACOKINETICS/PHARMACODYNAMICS

Efficacy:

Endoscopic assessment of mucosal healing:

- Modified Baron score
- Ulcerative colitis endoscopic index of severity (UCEIS) score

Endoscopic and clinical assessment:

- Modified Sutherland score, also known as disease activity index (DAI) and UC disease activity index (UC-DAI)

Histology of mucosal biopsies:

- Riley index score
- Geboes score

Pharmacokinetics:

- rFXIII plasma activity (analysed by Berichrom® assay)

Pharmacodynamics:

- C-reactive protein (CRP) level in blood
- Calprotectin level in faeces

HRQoL:

- Inflammatory bowel disease questionnaire (IBDQ)

CRITERIA FOR EVALUATION – SAFETY

- Adverse events (AEs)
- Vital signs, physical examination and electrocardiogram (ECG)
- Clinical laboratory safety: haematology, biochemistry, urinalysis, coagulation-related parameters and antibodies against rFXIII

STATISTICAL METHODS

Sample size calculation

Under assumption that the placebo response for the FAS was 10% and the treatment response was 25% above the placebo response, the number of subjects with a 2:1 randomisation ratio (treatment to placebo) needed to ensure approximately 80% power to detect a difference between active and placebo treatment at Week 8 (at a two-sided significance level of 10%) was equal to 90 (60:30).

Definition of analysis sets

The following analysis sets were defined in the protocol:

- Full analysis set (FAS) – included all randomised and treated subjects.
- Safety analysis set – the safety analysis set was identical to the FAS.
- Completer analysis set (CAS) - all subjects with a modified Baron score available at Week 8.

Primary endpoint:

- Endoscopic remission defined as a modified Baron score of 0 at Week 8

The primary endpoint was the binary variable ("responder" vs. "non-responder") where "responders" were the subjects with endoscopic remission (endoscopic mucosal healing) at Week 8, defined as a modified Baron score of 0, while subjects with a modified Baron score ≥1 were designated as “non-responders”. For dropouts, the score at the end-of-trial visit (if available) was to be used instead of the score at Week 8. If the baseline score (at screening) was the only score available for a subject then this subject would be considered a non-responder.

The primary endpoint was analysed using both the FAS and CAS, as specified in the protocol. The following model was used for the analysis: logistic regression for the binary outcome (responder vs. non-responder) with treatment and stratum as factors, and the baseline modified Baron score as a covariate. Estimates of the primary endpoint proportions

for the treatment groups were obtained based on this model. The odds ratio of the proportions for rFXIII and placebo treatments was estimated along with its 90% confidence interval to allow for testing the null hypothesis of "no treatment difference" at a significance level of 0.1 (two-sided testing).

Secondary endpoints

Disease activity endpoints:

- Remission (clinical and endoscopic) defined by a UC-DAI score of ≤ 1 with 0 for rectal bleeding and 0 for stool frequency and no mucosal friability (modified Baron score ≤ 1) at Week 8

This key secondary endpoint was analysed in a similar manner as the primary endpoint.

Other secondary endpoints investigating improvement in disease activity at Week 8 included the UC-DAI and UCEIS scores as well as histology assessments (Riley index and Geboes score).

PK endpoints:

FXIII activity in plasma after a single dose of rFXIII (up to 72 hours post-dose), based on the Berichrom® assay:

- CL, $t_{½}$, $AUC_{0-\infty}$, V_z, MRT, AUCτ, C_{trough} and C_{max}

PK endpoints were presented using descriptive statistics.

PD endpoints:

- Levels of CRP in blood at Week 8
- Levels of faecal calprotectin at Week 8

PD endpoints were presented using descriptive statistics.

HRQoL endpoints:

- IBDQ score at Week 8

Results were presented using descriptive statistics.

Safety endpoints

All safety endpoints were presented using descriptive statistics.

All secondary endpoints were analysed using the FAS, except the safety and immunogenicity endpoints which were based on the safety analysis set. Furthermore, selected key secondary efficacy endpoints were analysed using the CAS; this was not specified in the protocol, but was done since the trial was terminated prematurely and not all randomised subjects completed the trial.

DEMOGRAPHY OF TRIAL POPULATION

There were 9 males and 9 females included in the FAS and 5 males and 4 females included in the CAS. Subjects included in the FAS had a mean age of 39.2 years (range: 21−61 years) and a mean body mass index (BMI) of 24.8 kg/m^2 (range: 19.1−32 kg/m^2). Subjects included in the CAS had a mean age of 38.9 years (range: 25−60 years) and a mean BMI of 25.3 kg/m^2 (range: 21.3−31.2 kg/m^2). All subjects were White.

The distribution of males and females differed slightly between the placebo and rFXIII groups as 80% (FAS) or 67% (CAS) were females in the placebo group and 39% (FAS) or 33% (CAS) were females in the rFXIII group. Otherwise there were no marked differences in demographics and baseline characteristics between the placebo and rFXIII groups.

EFFICACY/PHARMACOKINETIC/PHARMACODYNAMIC RESULTS

Efficacy:

Primary endpoint

- No effect of rFXIII was demonstrated on the primary endpoint, endoscopic remission defined as modified Baron score of 0 at Week 8 (**Table 1**).

Table 1 Analysis of responders - defined as modified Baron score of 0 at Week 8

Analysis set	rFXIII	Placebo	rFXIII Events	Placebo Events	Fishers exact test†	Logistic regression ϕ		
	N	N	N (%)	N (%)	P-value	Odds Ratio (OR)	90% CI	P-value
FAS	13	5	1 (8%)	1 (20%)	0.4902	0.16	[0.01; 3.05]	0.3056
CAS	6	3	1 (17%)	1 (33%)	1.00	NA‡	NA‡	NA‡

‡ Logistic regression analysis was not conducted due to an insufficient sample size.

Secondary endpoints

- No effect of rFXIII was demonstrated on the secondary efficacy endpoints when using clinical and endoscopic tools at Week 8.
- A non-statistically significant improvement in histopathology scores as assessed by Riley index and Geboes score was seen in subjects treated with rFXIII when compared to placebo.

Pharmacokinetics:

- It was not possible to obtain reliable single dose PK profiles for rFXIII in this trial.
- No consistent increase in trough FXIII activity levels was seen after multiple dosing with rFXIII.

Pharmacodynamics:

- There was no improvement in CRP serum levels or faecal calprotectin levels after administration of rFXIII when compared to placebo.

Health-related quality of life:

- Based on descriptive statistics of the IBDQ no difference between the rFXIII and placebo groups could be concluded.

SAFETY RESULTS

- Due to the early termination of this trial, not all randomised subjects received all planned doses of trial product; 11 out of 18 dosed subjects received all 4 planned i.v. doses (4 placebo and 7 rFXIII), 2 subjects received 3 doses (rFXIII), 2 subjects received 2 doses (1 placebo and 1 rFXIII) and 3 subjects received 1 dose (rFXIII).
- A total of 11 AEs were reported in 5 out of 18 dosed subjects; 7 events in 3 (23%) subjects receiving rFXIII and 4 events in 2 (40%) subjects receiving placebo.
- One SAE of exacerbation of UC was recorded in a subject receiving rFXIII. The event was judged to be unlikely related to trial product by the investigator and of severe severity. All other events were of mild or moderate severity.
- One event of peripheral oedema in a subject receiving rFXIII was judged to be possibly related to trial product by the investigator. All other AEs were judged to be unlikely related to trial product.
- The majority of events were characterised by full recovery.
- There were no relevant differences in the frequency and type of AEs between rFXIII and placebo groups. However, due to the small sample size the AE analysis should be interpreted with caution.
- No deaths occurred in this trial. No significant AEs were recorded.
- No anti-rFXIII antibodies were detected in this trial.
- Results on laboratory safety parameters, vital signs, physical examination and ECG did not indicate clinically significant changes as a result of rFXIII administration.

CONCLUSIONS

- The trial was terminated earlier than planned as the hypothesis of a correlation between low levels of FXIII and disease activity of UC could not be confirmed. Thus, only 18 out of 90 planned subjects with mild to moderate UC were dosed with rFXIII (35 IU/kg) or placebo in this trial. Only 9 of these subjects (3 placebo and 6 rFXIII) completed the trial and had a modified Baron score available at Week 8. Based on the low number of subjects, the conclusions should be interpreted with caution.
- No effect of rFXIII was demonstrated on the primary efficacy endpoint, endoscopic remission defined as a modified Baron score of 0 at Week 8.
- No effect of rFXIII was demonstrated on the secondary efficacy endpoints when using clinical and endoscopic tools at Week 8. However, there was a non-statistically significant improvement in histopathology scores in subjects treated with rFXIII when compared to placebo.
- No reliable PK for single dose of rFXIII could be established in this trial. No consistent increase in rFXIII through concentrations was seen after multiple dosing of rFXIII.
- No safety concerns were raised.

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996).