2 Synopsis

Trial registration ID-number GH-3826	**UTN :** **EudraCT number :** 2009-017387-16
Title of trial Norditropin NordiFlex® device compared with the device previously used by patients or parents.	
Investigator(s) [redacted]	
Trial site(s) Thirty eight trial sites participated in the trial and 28 sites enrolled at least one patient.	
Publications Not applicable.	
Trial period Initiation date: 17 November 2010 (first patient enrolled) Completion date: 18April 2011(last patient completed)	**Development phase** Phase 4

Objectives

Primary objective:

- The relative ease-of-use of Norditropin NordiFlex® comparing with the previous device used by patients and parents.

Secondary objectives:

- Overall easiness of Norditropin NordiFlex® comparing with the previous device
- Ease of learning of Norditropin NordiFlex® administration
- Patient autonomy in the injection steps comparing with the previous device
- Patient/parent preference for Norditropin NordiFlex® and criteria of preference
- Compliance
- Clinical and technical safety of Norditropin NordiFlex®.

Methodology

This was a phase 4, prospective, multi-centre, open label, non-randomised trial. Approximately, 40 centres in France were supposed to participate in the study. Patients who fulfilled all the inclusion/exclusion criteria received Norditropin NordiFlex® for 6 weeks. The duration of participation in the study for each patient was 6 weeks. The study consisted of 2 visits: inclusion visit and final visit. During these visits, all information concerning the treatment system were collected.

Number of subjects planned and analysed

This study was expected to include 200 patients. As the end of inclusion was planned for 31 January 2011, 103 patients were included in the trial. No amendment was done to extend the inclusion period. Four patients did not complete the trial as planned. The reasons for premature study withdrawn were: request from the patients or their parents to discontinue the treatment (n=3) and patient not present at the final visit (n=1). However, all patients (n=103) were included in the analysis.

Diagnosis and main criteria for inclusion

Inclusion criteria

- Only children eligible for Norditropin® treatment according to the product labelling were to be included in this study
- Children receiving growth hormone therapy for at least one year
- Age ≥ 6 years
- Informed consent obtained before any trial-related activities.

Exclusion criteria

- Contraindications to Norditropin® growth hormone therapy as stated in the summary of product characteristics.

- Known or suspected hypersensitivity to trial product(s) or related products
- Patients who have previously been enrolled in this study.
- The use of any investigational medicinal product within 3 months prior to this trial.
- Suffering from a life threatening disease (cancer or specify).
- Pregnancy or intent to become pregnant.

Investigational medicinal product and/or investigational medical device, dose and mode of administration, batch number

The NordiFlex™ pen is a prefilled, multi-dose, disposable pen available in 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL, and 30 mg/3 mL dosage forms. The NordiFlex™ pens come in increments of 0.075 mg.

Dosing with NordiFlex™ pens was individualized.

Norditropin NordiFlex® 15 mg/1.5 mL delivery pen was used in this study. The batch number was YY50073.

Duration of treatment

The patients were supposed to take the treatment for 6-week duration.

Reference therapy and/or non-investigational medical device, dose and mode of administration, batch number

Not applicable.

Criteria for evaluation – efficacy criteria

Ease-of-use (primary endpoint)

The ease of injection using Norditropin NordiFlex® compared with the device previously used was measured using a quantitative scale ranging from "Far less easy" (score = 0) to "Far more easy" (score = 10).

Ease of learning

Ease of learning of Norditropin NordiFlex® administration were to be scored with a 4-points Likert scale by the member of the investigator team in charge of teaching, ranging from very easy to very difficult.

Patient autonomy

Patient autonomy was measured by the number of operations performed by the patient and the proportion of patients achieving all of these operations in comparison to the device previously used.

Patient preference

Patient preference was assessed using the proportion of patients wishing to continue treatment with Norditropin NordiFlex® over any other system.

Criteria for evaluation – safety

All the adverse events, serious adverse events and medical events of special interest were to be collected during the study. The tolerance at site injection was evaluated by the patient/parent.

Technical complaints were also collected.

Statistical methods

Determination of sample size

The minimum necessary to demonstrate an average difference of the numerical scale greater than or equal to 1 compared with the value 5, with at least a power $(1 - \beta) = 0.80$ and a standard deviation less than or equal to 3.5 , using an approximation of normal distribution (two-sided) is 193 patients. It was therefore decided to include 200 patients.

This sample is realistic if we take into account the population treated in France, the inclusion criteria, the number of centres and the expected timing of the study.

Definition of analysis set

- Intent-to-Treat Set (ITT): All subjects included in the study, i.e., having signed the informed consent form (n=103).
- Per Protocol Set (PP): All subjects in the ITT set using Norditropin NordiFlex® and completed the trial and did not significantly violate the inclusion/exclusion criteria or any other aspect of the protocol considered to potentially affect the efficacy results (n=98).
- Safety set: All subjects included in the study and having taken at least one dose of study treatment (n=103).

Statistical analysis

Missing data were not to be replaced. Descriptive statistics were supplied according to the criteria nature, for the whole set:

- Quantitative variable: Sample size, arithmetic mean, median, standard deviation, minimum and maximum.

- Qualitative variable: Sample size, frequency and percentage.

For statistical tests, the level of significance was 0.05.

Descriptive statistics on the ease-of-use compared with the device previously used were produced for the ITT and PP sets. The ease-of-use was measured by a quantitative scale ranging from "Far less easy" (score = 0) to "Far more easy" (score = 10). This primary endpoint was to be analyzed by the Wald test; comparing the average value of the numerical scale to the neutral value 5 (Norditropin NordiFlex® is equivalent to previous device). The relative ease-of-use was to be compared between groups defined by the system used previously using Student t-test.

Demography of trial population

Patient age was 11.7 ± 2.94 years in average (range 6-17) and 58.3% of patients were male. They had a mean body mass index of 18.1 ± 4.26 (range 12.6-47.8). Patients were at 1.2 standard deviation below the general mean height and at 0.5 standard deviation below the general mean weight.

Overall, 64.1% of patients had at least one medical history; of these 56.2% were ongoing. The most common disorders reported were endocrine disorders (16.5% of patients), congenital, familial and genetic disorders (14.6%), and respiratory, thoracic, and mediastinal disorders (12.6%).

All patients were receiving growth hormone therapy prior to inclusion, over 4.18 ± 2.81 years in average. The main reasons for growth hormone treatment were: growth hormone deficiency (41.7%), small for gestational age (49.5%) and Turner Syndrome (8.8%). Mean daily dose was 1.67 ± 0.72 mg.

Almost all patients (90.3%) were using a pen with needle and prefilled cartridge as an injection device; the remaining patients (9.7%) were using pen, with needles and containers for single-use and requiring product reconstitution.

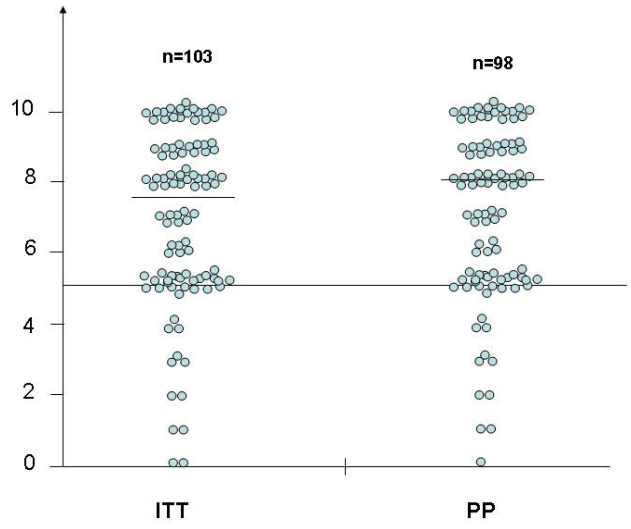
Efficacy results

Primary endpoint

The objective of this study was to evaluate the ease-of-use of Nordiflex® system, comparing with other systems.

The patients assessed that Nordiflex® system was significantly easier to use than other systems ($p<0.001$). This assessment was done using a quantitative scale ranging from 0 to 10 with 0= Nordiflex® far less simple, 5=equivalent simplicity, 10=Nordiflex® far more simple. The relative easiness of Nordiflex® system was evaluated as 6.89 ± 2.52 in average in ITT population.

Same results were obtained in PP population, concerning the ease-of-use of Nordiflex® system with a mean of 6.98 ± 2.46 on the quantitative scale. The median of the relative ease-of-use measure is presented in the following figure in ITT and PP population.



Simplicity of use

No significant differences were found between the previous device and Nordiflex® system concerning the dose selection easiness (p=0.677), the injection easiness (p=0.143) and the time spent in the injection preparation (p=0.120) in ITT population. However, the dose modification, in case of error, was assessed as easier when using the Nordiflex®

system ($p<0.001$). Same results were obtained in the subgroup of patients having used prefilled cartridges previously. No difference was found in the subgroup of patients having used a system with product reconstitution previously. However, the number of patients in this subgroup (n=10) might not be sufficient to demonstrate any difference.

Ease-of-learning

The ease-of-learning was considered "very easy" in 72.8% and "easy" in 26.2% of cases, by the person who was in charge of teaching the patient or parent how to use Nordiflex® (physician or nurse). The time to learning was in the majority of cases between 6 and 15 minutes.

According to physicians or nurses, the added value of Nordiflex® system was overall simplicity (82.5%) and dose adjustment (64.1%). No added value was reported in approximately 5% of cases.

Patient autonomy

In general, patients were more autonomous when using Nordiflex® system comparing with previously used system: 41.2% vs. 28.2%, p=0.005. Similarly, a significant difference concerning patient autonomy was observed in prefilled cartridge subgroup (39.1% vs. 29.0%, p=0.019), but not in system with product reconstitution subgroup (p=0.996).

Patient preference

The majority of patients (64.4%) preferred to continue with Nordiflex® system for the growth hormone treatment. Interestingly, all patients having used the system with product reconstitution preferred to continue with Nordiflex®.

The majority of patients considered that Nordiflex® system is reliable and didn't feel any pain or discomfort with the system.

Safety results

All the patients were exposed to Nordiflex® system for at least one dose. Daily dose was between 0.2 and 4 mg.

No serious adverse events or medical events of special interest were recorded during the trial. Overall, 15 patients had experienced at least one adverse event. The number of total adverse events was 19. The main reported adverse events were: "infections and infestations" and "general disorders and administration site conditions". Only one adverse event was severe (influenza) and [redacted]; and another one was reported as probably related to Nordiflex® system (mild injection site hematoma) and [redacted].

Local tolerance at the injection site was considered "very good" to "good" in almost all patients. This tolerance was likely better than with the previously used system.

Finally, 13 patients had technical complaints with Nordiflex® system, of these 10 were with the pen mate.

Conclusions

This study showed that Nordiflex® system was safe and easy to use.

- Patients assessed that Nordiflex® was globally easier to use than other systems, possibly because it requires less steps to be performed. According to patients, the dose modification in case of error was significantly easier with Nordiflex® system, than other systems.
- Growth hormone injection was more frequently self-administered with Nordiflex® system comparing with previous system. More patients were completely autonomous using Nordiflex® system. Ease-of-use and patient autonomy might subsequently improve the treatment compliance.
- Patients or parents need to learn how to perform injections in an accurate and reliable manner. Nordiflex® system was assessed as "easy" or "very easy" to learn, by the majority of physicians and nurses. In fact, when devices are easier for caregivers to learn and use, it may also be easier for patients to be adherent to medication regimens.
- This study showed that Nordiflex® system was safe and well tolerated. No serious adverse events were reported during the study. Fifteen patients (15%) experienced at least one adverse event. Of the reported adverse events (n=19), only one adverse event was assessed as probably related to the trial treatment.

The trial was conducted in accordance with the Declaration of Helsinki 1964 (amended in Somerset west, 1996) *and ICH Good Clinical Practice.*

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