



User assessment of Norditropin NordiFlex[®], a new prefilled growth hormone pen: a Phase IV multicenter prospective study

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Background/aim: In growth disorders, ensuring long-term growth hormone therapy (GHT) remains a challenge that might compromise the clinical outcome. Consequently, strategies aiming at alleviating the burden of daily injection might improve the treatment benefit. The study reported here was performed to assess the ease of use of Norditropin NordiFlex[®] (Novo Nordisk, Princeton, NJ, USA) compared with that of the devices previously used in children treated with GHT with recombinant somatropin.

Methods: This Phase IV prospective, multicenter, open-label study was conducted in France. All patients received Norditropin NordiFlex for 6 weeks. Oral questionnaires were administered by the physician to the patients and/or the parents at inclusion and at the final visit.

Results: This study included 103 patients aged between 6 and 17 years. The patients assessed Norditropin NordiFlex as significantly easier to use than their previous device (median value = 7.5, $P < 0.001$). Almost three-quarters of patients (64.4%) preferred Norditropin NordiFlex to their previous device. Among physicians and nurses, 73% assessed Norditropin NordiFlex training as “very easy” and 26% as “easy.” Norditropin NordiFlex improved patient autonomy, with 41% of patients able to self-inject the treatment.

Conclusion: This study has shown that Norditropin NordiFlex is reliable, safe, and easy to use and most study patients preferred it to their previous device. These characteristics may improve the adherence to GHT.

Keywords: growth hormone therapy, adherence, injection devices, preference, ease of use

Introduction

In France, growth hormone therapy with recombinant somatropin (of rDNA origin) (rhGH) is indicated for several growth disorders in children, including growth hormone deficiency (GHD), affecting 1/2000 births in case of partial GHD and 1 in 10,000 births in severe GHD; Turner syndrome, occurring in 1/2000 female births; chronic renal insufficiency, affecting 30 to 35 cases per year; small-for-gestational-age babies, occurring in fewer than 1/1000 births; and Prader–Willi syndrome, of which there are 25 to 50 cases per year.¹

Early and long-term growth hormone therapy (GHT) improves clinical outcome, with many patients reaching normal adult height or approaching their target height.² GHT requires daily subcutaneous injection to achieve an optimal clinical benefit. Therefore, adequate and improved methods of rhGH injection have been developed to suit pediatric use and to manage the potential fear of syringes and needles in this population.³ However, previous studies have shown that poor compliance with GHT is frequent in children treated with rhGH.^{4–6} Between 23% and 33% of patients

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receive <80% of their expected growth hormone (GH) injections.⁶⁻⁸

A prefilled pen with a liquid formulation of rhGH, Norditropin NordiFlex[®] (Novo Nordisk, Princeton, NJ, USA), has been developed to alleviate the injection burden. The reconstitution procedure required prior to injection in some devices is thus avoided with Norditropin NordiFlex. Moreover, the quick setup and administration make Norditropin NordiFlex easy to teach and to use. Additionally, Norditropin NordiFlex requires less injection force than previous devices, meaning that children can easily inject themselves.⁹ All these properties are expected to improve comfort and adherence to treatment, since patient autonomy has been found to be a positive factor in adherence to GHT.^{5,10,11}

This study was performed for three main reasons: (1) to assess the ease of use of Norditropin NordiFlex compared with that of other GH injection devices previously used to treat children with rhGH, (2) to describe how the properties of this pen are perceived by both parents and health care professionals, and (3) to delineate the putative impact of these properties on daily treatment.

Patients and methods

We conducted a Phase IV, prospective, multicenter, open-label study throughout France. Participating centers were specialized in pediatric endocrinology. Inclusion criteria were: being a child aged 6 years or older, receiving GHT for at least 1 year prior to inclusion, and eligibility for Norditropin NordiFlex treatment according to the "Summary of product characteristics."¹² Exclusion criteria included suffering from a life-threatening disease, using any investigational medicine within 3 months prior to inclusion, and being pregnant or intending to be pregnant. All patients had to receive Norditropin NordiFlex for 6 weeks. Ethics committee approval was obtained from Le Comité de Protection des Personnes (CPP) Sud-Ouest et Outre Mer III before the study started and written informed consent was obtained before each patient was included in the study.

The main objective of the study was to compare the ease of use of Norditropin NordiFlex with the device usually used by the patients or their parents. Secondary objectives included the ease of learning how to administer Norditropin NordiFlex, patient autonomy assessment, patient or parent preference for GH injection device, adherence, and the safety of Norditropin NordiFlex.

The study consisted of two visits: the inclusion visit and the final visit. At inclusion, demographics and information regarding GHT and related diseases were collected

by the physician. Technical characteristics of the device used prior to inclusion were recorded according to the generic nomenclature used for its registration in the French Health Agency. An oral questionnaire was administered by the physician to patients and/or parents at inclusion and final visit (Figure S1). This questionnaire considered respondents' perceptions of the simplicity of the injection device and patient autonomy and preference. Adherence was assessed using patient/parent diaries.

Ease of use (the primary endpoint of the study; assessed at the final visit) was measured using a quantitative scale ranging from 0 (= far less easy) to 10 (= far more easy). Secondary outcomes were assessed at inclusion and the final visit. The primary endpoint was analyzed using the Wald test, comparing the average value of the numerical scale to the neutral value 5. Categorical variables involving paired samples were compared using McNemar's test or logistic regression for matched-pair data. Descriptive statistics were supplied according to the variable nature. Continuous variables are presented as mean, standard deviation, median, and range. Categorical variables are presented as frequency and percentage. The level of significance was 0.05.

Results

Between November 2010 and January 2011, 38 centers participated in the study and 28 centers enrolled at least one patient (Figure S2). The majority of the study centers were departments of pediatric endocrinology at public hospitals, while eight centers were outpatient private clinics. A total of 103 patients were included. Four patients did not complete the study as planned. The reasons for premature study withdrawal were: patient/parent choice to discontinue the treatment ($n = 3$) and patient lost to follow-up ($n = 1$).

Patient characteristics and GHT at inclusion

The main demographic characteristics are summarized in Table 1. The median age was 12 years (range 6–17, lower quartile $Q1 = 9$, upper quartile $Q3 = 14$) and 58.3% were male. The median body mass index was 18.1 ± 4.3 kg/m² (median = 17.7, range 12.6–47.8). Median height and weight standard deviation scores were -1.2 (range -4.4 to 1.7) and -0.8 (range -2.5 to 11.0), respectively.

All patients had received GHT for a median duration of 3.6 years (range 0.5–14.3, $Q1 = 1.9$, $Q3 = 5.8$) prior to inclusion (Table 2). Median daily dose was 1.60 mg (range 0.5–4.5, $Q1 = 1.08$, $Q3 = 2.14$). The indications for GH treatment were: GHD ($n = 43$, 41.7%), having been a

Table 1 Patients' characteristics at inclusion (n = 103)

Sex (male), n (%)	60 (58.3)
Age (years)	11.7 ± 2.9
Height (cm)	141 ± 16.5
Height (SDS)	-1.2 ± 1.0
Weight (kg)	37.3 ± 16.0
Weight (SDS)	-0.5 ± 1.6

Note: Results are presented as mean ± standard deviation unless otherwise indicated.

Abbreviation: SDS, standard deviation score.

small-for-gestational-age baby (n = 51, 49.5%), and Turner syndrome (n = 9, 8.8%). Prior to inclusion, 90.3% (n = 93) of the patients had been using a durable pen with prefilled cartridges; the remaining patients (n = 10, 9.7%) had been using a durable pen requiring product reconstitution.

Ease of use

The patients assessed Norditropin NordiFlex as being significantly easier to use than their previous system (median value = 7.5, lower quartile = 5, upper quartile = 9 [interquartile range IQR = 4], $P < 0.001$). The mean value was 6.89 ± 2.52 , with a 95% confidence interval of 6.39–7.38.

Patients' and parents' ratings of the ease of the injection steps with Norditropin NordiFlex are presented in Figure 1. The dose selection and injection using Norditropin NordiFlex were considered "very easy" by 68 (66.7%) and 64 (62.7%) patients, respectively. The dose modification in case of error with Norditropin NordiFlex was rated as "very easy" by 84 (84%) patients.

For 95 (~93%) patients, the injection preparation time took <5 minutes. Of the remaining patients, six (6%) were able to prepare the device for injection in 5 to 10 minutes and only one patient (1%) needed 10 to 20 minutes.

Patient autonomy

With reference to the different steps of GHT administration, parents ensured dose selection in 30.4% of cases and dose

Table 2 Growth hormone (GH) therapy at inclusion (n = 103)

Reason for GH therapy, n (%)	
Small for gestational age	51 (49.5)
GH deficiency	43 (41.7)
Turner syndrome	9 (8.7)
Duration of GH treatment (years), mean ± SD	4.2 ± 2.8
Daily dose (mg/day), mean ± SD	1.67 ± 0.72
Type of injection device prior to inclusion, n (%)	
Durable pen with needle and prefilled cartridge	93 (90.3)
Durable pen with needles and containers for single use	10 (9.71)

Abbreviation: SD, standard deviation.

modification in 44.6% of cases, whereas 38.2% of parents were in charge of the injection step. However, when compared with the previous devices, patients were more often autonomous with the Norditropin NordiFlex system, with 42 (41.2%) patients being in sole charge of all GHT administration steps while only 29 (28.2%) were so with their previous device ($P = 0.005$, odds ratio = 8, 95% confidence interval 1.836–34.793).

Ease of training

The persons in charge of training the patients and/or parents how to use Norditropin NordiFlex were the physician in 52 (50.5%) of cases, nurses in 48 (46.6%) cases, and both the physician and nurse in three (2.9%) cases. In 60.4% of cases, both patients and parents were trained, while only the patient was trained in 11.9% of cases and only the parents were trained in 27.7% of cases.

Physicians and nurses considered the Norditropin NordiFlex training as "very easy" in 72.8% of cases, "easy" in 26.2%, and "difficult" in only 1% of cases (Figure 2). In 66% of cases, the training took from 5 to 15 minutes; in 30%, from 15 to 30 minutes; and, in 4%, >30 minutes. According to the health care professionals, the benefits of Norditropin NordiFlex were ranked as follows: overall simplicity (82.5%), dose adjustment (64.1%), dose selection (35.0%), improvement in adherence (27.2%), ease of injection (26.2%), and maximum dose available (15.5%). No benefits of the Norditropin NordiFlex were reported in 4.9% of cases.

Patient preference

At inclusion, 62.1% of patients reported their device as absolutely reliable: 65.6% in the subgroup using durable pens with prefilled cartridges and 30.0% in the subgroup using devices with a reconstitution step. Table 3 illustrates patients' and parents' perceptions of Norditropin NordiFlex. In the durable pen/prefilled cartridges subgroup, the perception of Norditropin NordiFlex's reliability was close to that observed for the previous device: 57.1% rated it "absolutely reliable" and 35.2% "quite reliable." However, in the subgroup using devices with a reconstitution step, the perception of reliability was higher than that for the previous device: 70.0% versus 30.0%.

The majority of patients expressed no fear of the injections with Norditropin NordiFlex (69.6%) and lack of pain was recorded in 57.8% of cases (Table 3).

Further, the majority of patients (64.4%, n = 65) declared Norditropin NordiFlex to be their preferred system for GHT,

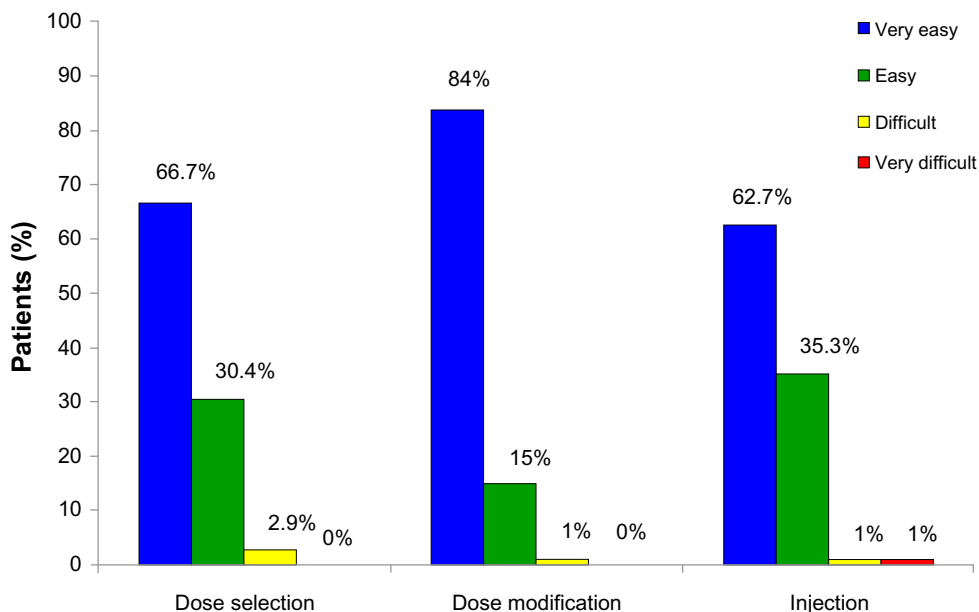


Figure 1 Parents'/patients' ratings of the ease of injection steps with Norditropin NordiFlex® (Novo Nordisk, Princeton, NJ, USA) at the 6-week visit.

with 100% of patients previously using a device requiring reconstitution indicating that they preferred the new system (Figure 3).

Adherence and safety

After 6 weeks, according to patient/parent diaries, 65/92 (70.6%) of patients were considered “absolutely adherent,” meaning no daily dose was skipped during the 6-week study period, while 14.1% had skipped only one GH injection during the past 6 weeks.

The majority of patients (91 [90.1%]) stated that injections with Norditropin NordiFlex were well tolerated

locally versus 78 (76.5%) who indicated that injections with their previous system were so.

No serious adverse events (AEs) or medical events of special interest were reported in the study. One adverse event was reported relating to the device (an injection site hematoma).

Overall, 15 patients experienced at least one AE during the study. The total number of AEs was 19. Of these, one was severe (influenza). The most common AEs were “infections and infestations” (ten), which included influenza (four), ear infection (three), gastroenteritis (one), rhinitis (one), and upper respiratory tract infection (one). Other AEs were

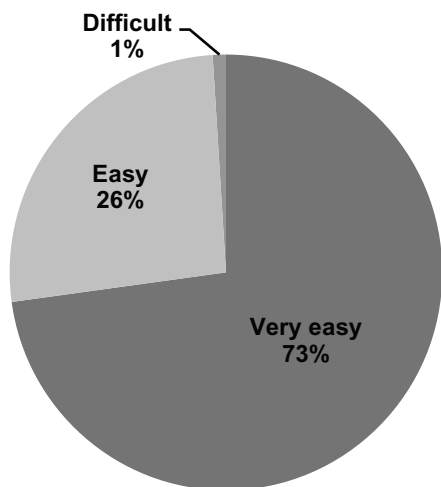


Figure 2 Norditropin NordiFlex® (Novo Nordisk, Princeton, NJ, USA) ease of training assessed by the health care professionals (physician or nurse) in charge of giving device instructions to patients/parents.

Table 3 Patients' and parents' ratings of reliability, fear, and pain regarding Norditropin NordiFlex® (Novo Nordisk, Princeton, NJ, USA) at the 6-week visit (n = 102)

Reliability of Norditropin NordiFlex	
Absolutely reliable	59 (58.4)
Quite reliable	35 (34.7)
Quite unreliable	6 (5.9)
Absolutely unreliable	1 (1.0)
Patient fear of injection	
None	71 (69.6)
Slight	10 (9.8)
Fair	8 (7.8)
Significant	13 (12.7)
Patient pain or discomfort	
None	59 (57.8)
Slight	21 (20.6)
Fair	10 (9.8)
Significant	12 (11.8)

Note: Results are presented as n (%).

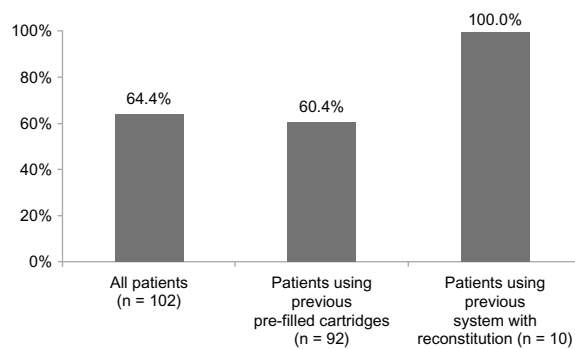


Figure 3 Patients' preference for Norditropin NordiFlex® (Novo Nordisk, Princeton, NJ, USA) at the 6-week visit.

mainly “general disorders and administration site conditions” (three) and these included an injection site hematoma (one), pyrexia (two), and “gastrointestinal disorders” (two).

Discussion

This study confirmed the ease of use of Norditropin NordiFlex in children being treated with GH. Indeed, patients, parents, and health care professionals considered that Norditropin NordiFlex was quick to learn and easy to use.

With only two steps required to prepare the injection (dose selection/adjustment and injection), almost all patients considered that the device was “easy” or “very easy” to use. They were able to administer the injection in <5 minutes. Interestingly, ease of use and the number of preparation steps have been ranked among the most important device characteristics by both patients and health care professionals.¹³

Moreover, in this study, Norditropin NordiFlex was considered by patients and parents to be significantly easier to use than their previous device. When asked to consider which type of device would best meet their needs, a majority preferred Norditropin NordiFlex than their previous device. Of those who had previously used a device requiring a reconstitution step, 100% indicated they preferred Norditropin NordiFlex.

Adherence to GHT has a significant impact on clinical outcomes. In a group of patients poorly compliant, growth rates were significantly lower than in patients who missed fewer doses.⁸ It has also been shown that missing more than two injections per week is significantly correlated with declined height and weight velocity.⁶ Adherence in this study was remarkably high. Although the device is easy to use, this adherence may be due to the attention study patients received and to patient selection. However, previous studies have emphasized the influence of the mode of treatment

administration on the adherence level.^{5,6,14,15} With respect to GHT, it has been demonstrated that simplicity of the GHT administration is predictive of good adherence to treatment.^{5,6,14,15} Thus, the high level of ease with which Norditropin NordiFlex can be used might have a positive impact on patient adherence during chronic GHT. In fact, when asked about the added value of Norditropin NordiFlex, nearly 30% of health care professionals suggested a positive impact on adherence.

Device reliability and its ability to allow patient autonomy are clearly key factors contributing to a good adherence.^{5,11} In line with these observations, patients and their parents quickly learned to use the device in an accurate and reliable manner. Almost all health care professionals in charge of providing instructions (99%), including physicians and nurses, found the training process with Norditropin NordiFlex “very easy” or “easy.” This observation is certainly of interest keeping in mind that, if an appropriate training remains mandatory to ensure efficacy, safety, and adherence, extensive training can be time consuming and costly for health facilities.

The observation supporting the quick and easy training is that a good number of patients (41%) were able to self-inject without assistance, and that the preparation and injection process took <5 minutes for almost all patients. As the device is easy to learn and use, this may potentially lead to safer and more accurate use and the prevention of dosing errors.

It should also be noted that self-injection was significantly higher with Norditropin NordiFlex than with patients' previous devices. Considering the short period of observation (6 weeks), this greater autonomy may be due to the ease of use of Norditropin NordiFlex rather than to change in age. Moreover, autonomy and adherence may be affected further by several factors related to patient or disease, but these were not assessed in this study.

Lack of pain is also considered an important feature in GHT as well as in other chronic injected treatment^{9,13} and may directly affect adherence.⁸ Reduced needle diameter has been shown to reduce pain during injection.¹⁶ Norditropin NordiFlex, which uses a thin needle (30 gauge or smaller), is designed to make the injection process painless. In the present study, almost 80% of patients reported injections as not, or only slightly, painful. Overall, only twelve patients declared they experienced significant pain with the injections. This small number may be due to the Norditropin solution containing histidine as a buffer, which appears preferable to citrate for dispensing GH. Previous data have shown that solutions containing histidine as a buffer cause less pain

after subcutaneous injection than solutions using citrate for this purpose.¹⁷

Lastly, the high level of acceptance of Norditropin NordiFlex by both parents/patients and health care professionals was associated with a favorable safety profile and no reporting of technical complaints.

It should be noted that the limitations of this industry-funded trial include its open-label, uncontrolled design and short-term follow-up.

Conclusion

This study has shown that Norditropin NordiFlex is easy to use, reliable, and safe in children with GH deficiency. That a preference for Norditropin NordiFlex was indicated by the majority of the study patients suggests that device properties play an important role in GHT. Their positive impact on adherence should therefore be considered. Norditropin NordiFlex may improve adherence and consequently can be recommended as an option for GHT; however, a controlled randomized trial is needed to confirm this observation.

Acknowledgments

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Disclosure

DJ is an employee of Novo Nordisk and the other authors are investigators in the NordiFlex study and have no other conflicts of interest.

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Supplementary figures

1. How do you assess the ease of use of Norditropin NordiFlex® compared with the previous system?										
0	1	2	3	4	5	6	7	8	9	10
↑					↑					↑
NordiFlex is less simple					Equivalent		NordiFlex is more simple			
2. Please specify the person who completes the following actions.										
<i>a. Dose selection</i>										
<input type="checkbox"/> Patient			<input type="checkbox"/> Parents			<input type="checkbox"/> Nurse		<input type="checkbox"/> Other, specify _____		
<i>b. Dose correction in case of error</i>										
<input type="checkbox"/> Patient			<input type="checkbox"/> Parents			<input type="checkbox"/> Nurse		<input type="checkbox"/> Other, specify _____		
<i>c. Injection</i>										
<input type="checkbox"/> Patient			<input type="checkbox"/> Parents			<input type="checkbox"/> Nurse		<input type="checkbox"/> Other, specify _____		
3. Please specify the simplicity of the following actions.										
<i>a. Dose selection</i>										
<input type="checkbox"/> Very easy			<input type="checkbox"/> Easy		<input type="checkbox"/> Difficult		<input type="checkbox"/> Very difficult			
<i>b. Dose correction in case of error</i>										
<input type="checkbox"/> Very easy			<input type="checkbox"/> Easy		<input type="checkbox"/> Difficult		<input type="checkbox"/> Very difficult			
<i>c. Injection</i>										
<input type="checkbox"/> Very easy			<input type="checkbox"/> Easy		<input type="checkbox"/> Difficult		<input type="checkbox"/> Very difficult			
4. Indicate the time you spend to prepare the injection.										
<input type="checkbox"/> <5 minutes			<input type="checkbox"/> 5–10 minutes			<input type="checkbox"/> 10–20 minutes		<input type="checkbox"/> >20 minutes		
5. Indicate the level of reliability that the Nordiflex system provides you.										
<input type="checkbox"/> Absolutely reliable			<input type="checkbox"/> Quite reliable			<input type="checkbox"/> Quite unreliable		<input type="checkbox"/> Unreliable		
6. Indicate the level of tolerance at the injection site.										
<input type="checkbox"/> Very good			<input type="checkbox"/> Good			<input type="checkbox"/> Bad		<input type="checkbox"/> Very bad		
7. Does this system improve:										
<i>a. Apprehension</i>										
<input type="checkbox"/> Not at all			<input type="checkbox"/> Slightly			<input type="checkbox"/> Fairly		<input type="checkbox"/> Very much		
<i>b. Fear or discomfort</i>										
<input type="checkbox"/> Not at all			<input type="checkbox"/> Slightly			<input type="checkbox"/> Fairly		<input type="checkbox"/> Very much		
8. Which system do you prefer to continue using for growth hormone treatment?										
NordiFlex.....										<input type="checkbox"/>
Previous system										<input type="checkbox"/>
Neither of these systems										<input type="checkbox"/>

Figure S1 Questionnaire administered by the physician to the patient/parents.

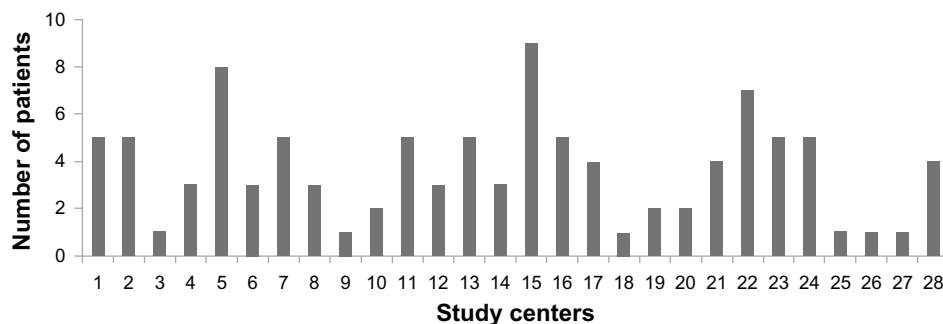


Figure S2 Distribution of included patients across study centers.

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