

EVALUATION OF THE SAFETY OF A NEEDLE-FREE INJECTION DEVICE GENOTROPIN ZIP TIP™ (INJEX™*) COMPARED WITH A NEEDLE INJECTION DEVICE (GENOTROPIN PEN®) FOR ADMINISTRATION OF RECOMBINANT HUMAN GROWTH HORMONE (GH) IN CHILDREN WITH GH DEFICIENCY

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Introduction

- GH treatment often requires daily subcutaneous injections over several years; long-term treatment with needles can lead to difficulties in compliance and patient acceptance¹ which may be obviated by the use of needle-free jet injectors²
- The Genotropin ZipTip™ device was selected to offer a needle-free delivery method for Genotropin (figure 1)
- A phase I study suggests that Genotropin delivered via the Genotropin ZipTip™ device is bioequivalent to conventional subcutaneous injection³

Figure 1.—The Genotropin ZipTip™ device.



- The majority of patients found the presence or absence of other injection site symptoms (pain, bruising, soreness) to be the same for Genotropin ZipTip™ and needle injection, although noninferiority of the needle-free device was not statistically supported (Table 3)

Objective

To compare the safety of the Genotropin ZipTip™ needle-free device to a needle injection device for the administration of Genotropin to pediatric patients with GHD currently receiving Genotropin

Methods

Study Design

- A multicenter (n = 6), randomized, two-period crossover study (2 + 2 weeks)
- The GH deficiency dose, 0.24 mg/kg per week, was given with the 0.178-mm-orifice needle-free device or a fine-gauge (29, 30, or 31 G) needle device for 2 weeks; then patients were switched to the other device for 2 weeks. All patients received between 0.05 and 0.3 mL once daily
- Genotropin was administered either by the patient or the parent/guardian
- On average, patients had used a needle device for > 4 years; the Genotropin Pen was used by more than 95% of patients
- To avoid bias, patients were excluded if they had previous experience with a needle-free device

Safety Assessment

- Incidence of bleeding at the injection site (primary safety variable)
- Adverse events; physical examination of injection site symptoms (bleeding, injection site pain, soreness, and bruising) associated with the needle-free or the needle device collected on a daily diary card
- Pain recorded at the time of injection; soreness and bleeding recorded immediately after the device removal, and 10 and 30 minutes post injection; bruising recorded 24 hours following the previous injection and prior to the next injection
- At study conclusion, subjects' preference for the needle-free or needle-injection device was ascertained

Statistical Analysis

- Intent-to-treat (ITT) population (n = 133) defined as all patients receiving at least 1 dose of study medication with their allocated device
- Per-protocol (PP) population (n = 117) defined as ITT subjects who provided diary cards at second week of each treatment period and who had no major protocol violations
- Noninferiority of the needle-free device compared with the patient's usual needle-injection device (defined as a difference in injection site bleeding incidence rates of 10%) required that the upper 95% confidence limit for the needle device: the needle-free device odds ratio for no bleeding not exceed 1.49 in the PP population

Results

Demographics

- Both treatment groups had similar exposure profiles to GH, in terms of mean treatment duration, usual daily dose, and frequency of injections
- The Genotropin Pen was the most recent device for 95.7% (112/117) of patients

Toxicity—Injection site

- At week 2, the majority of patients considered the bleeding response at each time point after injection to be the same with both injection devices; the injection site bleeding responses at week 1 showed a similar profile to that of week 2 (Table 1)
- The upper 95% confidence limits for the analysis of injection site bleeding (odds ratio, needle to the needle-free device, for absence of symptoms) at week 2 exceeded the limit of 1.49; therefore, the study did not support the hypothesis of noninferiority of the needle-free device to the needle-injection device (Table 1)
- The average bleeding severity at the time of injection was recorded as "None" by the majority of patients with both the Genotropin ZipTip™ and with the needle device. Mild-to-moderate bleeding severity was recorded by 56/117 (47.9%) with the needle-free device and by 12/116 (10.3%) with the needle-injection device (Table 2)

Toxicity—Adverse Events

- The majority of adverse events were of mild or moderate intensity; the overall frequency of adverse events was similar for the Genotropin ZipTip™ (31/132 patients, 23.5%) and needle devices (16/130 patients, 12.3%)
- No clinically relevant change from baseline occurred in the mean values of any vital sign in either treatment group
- No serious adverse events were reported; 5 patients in the ITT cohort (5/133, 3.8%) prematurely discontinued treatment; 2 of these discontinuations were due to an adverse event: 1 patient during treatment with the needle-free device, the other during treatment with the needle-containing device.

Device Preference

- Overall, 22.2% (26/117) of patients preferred the Genotropin ZipTip™ device
- Approximately 20% elected to continue on the Genotropin ZipTip™ device instead of their usual needle device at the end of the study

Table 1.—Patient Assessment of Injection Devices for the Absence or Presence of Injection Site Bleeding Among the PP Population

	Better on Genotropin ZipTip™		Same		Better on Needle		OR (U95L)
	n	%	n	%	n	%	
Week 1							
At time of injection	2	1.7	75	64.1	40	34.2	8.43 (16.27)
10 minutes after	8	6.8	77	65.8	32	27.4	3.51 (6.16)
30 minutes after	3	2.6	107	91.5	7	6.0	2.09 (5.87)
Week 2							
At time of injection	9	7.8	72	62.1	35	30.2	2.74 (4.39)
10 minutes after	5	4.3	86	74.1	25	21.6	3.51 (6.59)
30 minutes after	3	2.6	105	90.5	8	6.9	2.15 (5.48)

OR = odds ratio for no injection site bleeding (needle device: Genotropin ZipTip™); PP = per protocol; U95L = upper 95% confidence limit for odds ratio.
Source: Data on file, Pharmacia Corp.

Table 2.—Average Bleeding Severity (Week 2) Among Patients in the PP Population

Device	None	Mild	Moderate
Genotropin ZipTip™, n (%)	61/117 (52.1)	53/117 (45.3)	3/117 (2.6)
Needle, n (%)	104/116 (89.7)	12/116 (10.3)	0/116 (0)

PP = per protocol.

Table 3.—Patient Assessment of Pain, Bruising, and Soreness (Week 2, PP Population)

Parameter	Genotropin ZipTip™	Better on Same	Better on Needle
Pain (at time of injection), n (%)	13/117 (11.1)	83/117 (70.9)	21/117 (17.9)
Bruising (at time of injection), n (%)	10/116 (8.6)	74/116 (63.8)	32/116 (27.6)
Soreness			
At time of injection	1/116 (0.9)	83/117 (71.6)	32/117 (27.4)
10 min postinjection	5/116 (4.3)	80/117 (68.4)	32/117 (27.4)
30 min postinjection	8/116 (6.8)	82/117 (70.1)	27/117 (23.1)

Summary/Discussion

- Overall, no safety concerns that would preclude use of the needle-free device to administer Genotropin were seen. During week 2, the majority of patients reported equivalent bleeding, pain, bruising, and soreness with Genotropin ZipTip™ as with their usual needle device
- At the end of the study, approximately 20% elected to continue on the Genotropin ZipTip™ device instead of their usual needle device
- In terms of statistical analysis for injection site symptoms, the data did not support noninferiority of Genotropin ZipTip™ compared with a needle device for administration of Genotropin to GH-deficient children
- The study enrolled patients comfortable and skilled in the use of a needle device; enrollment of needle-phobic patients in the study was seen as unethical as they would have had to use a needle injection device for a 2-week period

Conclusion

- The Genotropin ZipTip™ device is a safe and useful alternative to subcutaneous needle injection for patients unable or unwilling to use needles for GH administration
- The Genotropin Pen is still the device of choice in the majority of patients

REFERENCES

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- Gonzalez JL, Verrips GH, Fekkes M, Hirasings RA, Groth M. *Today Ther Trends*. 1998;16:53-71.
- Pharmacia Corp. Data on the file, abstract 2313.

*The device is marketed as Injex by Rösch AG, Medizintechnik, Berlin Germany, for other applications.