

**EXPERT
OPINION**

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An analysis of product wastage arising from dosing increment granularity in four modern growth hormone administration devices

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Objective: Human growth hormone (hGH) delivery systems differ in the size of the dose increments that can be set by the patient, affecting proximity to the target (i.e., prescribed) dose which can be attained. We investigated differences in dosing increment granularity in NordiFlex[®], FlexPro[®], NordiPen[®] (all multiple dose devices) and MiniQuick[®] (single dose) delivery systems.

Methods: A simulation model was developed to project hGH dosing in pediatric patients with growth hormone deficiency, small for gestational age or Turner syndrome, calculating the nearest dose above the target dose administrable by each device in typical EU and US cohorts and projecting the excess dose (hGH wastage) over 1 year of typical use.

Results: The device with the smallest dosing increment (FlexPro 5 mg; 0.025 mg dosing increment) was projected to administer doses < 1% above the target across all indications. MiniQuick (0.2 mg dosing increment) was projected to deliver between 5 and 6% above the target dose. None of the sensitivity analyses changed the conclusion that larger dosing increments result in more hGH wastage.

Conclusions: In addition to increasing dosing accuracy, finer dosing increments may result in reductions in unnecessary hGH usage, which may in turn result in reductions in the cost of hGH treatment borne by the health-care payer.

Keywords: computer simulation, drug delivery systems, growth hormone, injections, subcutaneous

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1. Introduction

Short stature is a consequence of a variety of medical conditions, including growth hormone deficiency (GHD), Turner syndrome (TS), children born small for gestational age (SGA) and other growth disorders. Short stature associated with these conditions can be treated with daily injections of recombinant human growth hormone (hGH). Numerous formulations of hGH are available commercially, differing primarily in the expression systems used during manufacturing and the buffering and preservative agents used in the final injectable hGH solution. Choice of treatment is generally influenced by the value-added patient support services offered by the manufacturer, the characteristics of the hGH delivery systems and the price per milligram of active substance [1].

Since the introduction of hGH for treatment of growth-related diseases, hGH delivery systems have evolved from conventional vials and syringes (which have been associated with reduced adherence and increased product wastage) to more

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user-friendly pen injection devices [1-3]. Even with modern pen delivery systems, there are a number of differences among the devices and formulations that may lead to different patient preferences such as ease of use (including, e.g., a need to reconstitute the medication), pain at the injection site, storage requirements, and the ability to record injection history and missed doses [3-8]. At the same time, there are a number of device characteristics that may drive preference from a prescriber and payer perspective, such as device reliability, granularity of dosing increments and hGH wastage during dose setting or injection [1,9]. Over the course of long-term treatment with hGH, these factors can affect the number of prescription refills required by a patient, which may, in turn, have an effect on the cost borne by the health-care payer. The aim of the present study was to investigate the effect of dosing increment granularity on hGH wastage in four modern hGH delivery systems: NordiFlex, FlexPro, NordiPen (all capable of delivering multiple hGH doses) and MiniQuick (a single-use device). While recent analyses have focused on evaluating the cost of hGH wastage in specific health-care settings, the aim of the present analysis was to quantify excess GH usage alone in a series of hypothetical GHD, TS and SGA cohorts such that health-care authorities and payers may apply the findings to their own patient populations, factoring in the local cost of hGH [1,10].

2. Methods

The present study investigated differences in hGH wastage arising from dose increment size in four hGH administration devices: NordiFlex, NordiPen, FlexPro (Novo Nordisk A/S, Bagsværd, Denmark) and MiniQuick (Pfizer, Inc., New York, NY). NordiFlex and FlexPro are prefilled devices containing 5, 10 or 15 mg of liquid Norditropin[®] with dosing increments ranging from 0.025 to 0.1 mg (Novo Nordisk A/S, Bagsværd, Denmark). NordiPen is a durable device, also available in 5, 10 and 15 mg strengths of liquid Norditropin. NordiFlex, FlexPro and NordiPen allow delivery of multiple doses of hGH. MiniQuick is a disposable device used to mix and administer a single dose of Genotropin[®] lyophilized powder (Pfizer, Inc., New York, NY) available in 10 dose sizes from 0.2 to 2.0 mg in 0.2 mg increments. Characteristics of the four devices are presented in Table 1. These devices were selected to include a wide range of hGH dosing increments, from 0.025 mg (NordiFlex and FlexPro) to 0.2 mg (MiniQuick), allowing the results to be more easily extrapolated to other devices with similar dosing increments. Furthermore, devices were chosen to capture a representative device from each device category: prefilled, reusable devices (such as NordiFlex and FlexPro); durable devices, which accept cartridges of hGH (such as NordiPen); and prefilled, single-use devices (such as MiniQuick).

A computer-based cohort simulation model was constructed in Microsoft[®] Excel[®] (Microsoft Corp., Redmond, WA) to estimate the mean annual hGH wastage per patient

in hypothetical US and European cohorts of pediatric patients with GHD, SGA or TS. The model captured hGH wastage arising from different device dosing increments in simulated cohorts of patients in the US and European settings. hGH doses were taken from the NordiNet[®] International Outcome Study (IOS) and the American Norditropin[®] Studies Web Enabled Research (ANSWER Program[®]) for the EU and US settings, respectively [11]. Specifically, the mean doses in the European setting were 0.032, 0.038 and 0.044 mg/kg/day for patients with GHD, SGA and TS, respectively. In the US setting, mean doses in patients with GHD, SGA and TS were 0.048, 0.053 and 0.051 mg/kg/day, respectively.

Wastage calculations were conducted in typical US and European cohorts of pediatric patients with GHD, TS and born SGA using country-specific bodyweight assumptions. In the US, mean bodyweight was taken to be 35 kg with a standard deviation (SD) of 5 kg, while in the European setting bodyweight was assumed to be 30 kg (SD 4 kg). Based on these parameters, the model calculated the proportion of the cohort in 1 kg bins, assuming a Gaussian distribution of bodyweight. Where possible, the model assumed that patients would take one dose per day, that is, that the daily dose would be delivered in a single injection. In the case of the single-use MiniQuick devices, each 1 kg bodyweight bin was assumed to use the MiniQuick device with the lowest hGH content that either met or exceeded the calculated target dose.

To calculate the excess dose arising from the device dosing increments, the target daily hGH dose was first calculated by multiplying the lower bound of each bodyweight bin by the recommended daily dose per kilogram, multiplying the resulting values by the proportion of patients in each 1 kg bin and summing them to give the mean daily dose over the whole cohort. To calculate the actual administered dose (which differs from the target dose as a result of the device dosing increments), the model assumed that all patients would dose to the nearest dose increment above the recommended dose. The modeled administered dose was therefore calculated by finding the nearest integer number of dose increments that would meet or exceed the target dose and multiplying it by the size of the dose increment.

2.1 Sensitivity analyses

In computer simulation modeling, sensitivity analyses are typically conducted to establish how the model responds to changes in key inputs. To establish the extent to which doses from the NordiNet IOS and ANSWER Program[®] were driving model outcomes, sensitivity analyses were performed around the mean daily dose assumptions. The magnitude of the effect that the average dose had on the absolute projected wastage was calculated for each device to establish whether the dose assumptions biased the analysis in favor of devices with certain dosing increments. Doses were varied from 0.01 to 0.07 mg/kg/day in 0.001 mg/kg/day increments and the projected wastage for devices with dosing increments of 0.025, 0.05, 0.075 mg, 0.1 and 0.2 mg were plotted at each dose.

Table 1. Device characteristics.

| Device | Growth hormone content (mg) | Dosing increment size (mg) | Maximum dose (mg) |
|-----------------------------|-----------------------------|----------------------------|-------------------|
| <i>Base case analyses</i> | | | |
| NordiPen [®] | 5 | 0.050 | 1.25 |
| | 10 | 0.100 | 2.50 |
| | 15 | 0.100 | 4.00 |
| NordiFlex [®] | 5 | 0.025 | 1.50 |
| | 10 | 0.050 | 3.00 |
| | 15 | 0.075 | 4.50 |
| FlexPro [®] | 5 | 0.025 | 2.00 |
| | 10 | 0.050 | 4.00 |
| | 15 | 0.100 | 8.00 |
| MiniQuick [®] | 0.2 – 2 (single use) | 0.200 | 2.00 |
| <i>Sensitivity analyses</i> | | | |
| FlexPro* | 30 | 0.100 | 8.00 |
| NordiFlex | 30 | 0.100 | 6.00 |

*FlexPro[®] 30 mg/3 ml is currently pending approval by the US FDA.

Table 2. Additional administered growth hormone arising from coarse dosing increments expressed as absolute mass of human growth hormone per patient and as a percentage of the annual per-patient target dose in the US setting.

| | FlexPro [®] 5 mg | FlexPro 10 mg | FlexPro 15 mg | MiniQuick [®] |
|--------------------------------|---------------------------|---------------|---------------|------------------------|
| Turner syndrome (mg) | 5.23 | 5.50 | 14.63 | 32.91 |
| Turner syndrome (%) | 0.80 | 0.84 | 2.24 | 5.05 |
| Growth hormone deficiency (mg) | 4.63 | 7.60 | 16.64 | 34.76 |
| Growth hormone deficiency (%) | 0.76 | 1.24 | 2.71 | 5.66 |
| Small for gestational age (mg) | 4.45 | 9.47 | 19.31 | 38.92 |
| Small for gestational age (%) | 0.66 | 1.40 | 2.85 | 5.75 |

US mean annual target dose per patient for growth hormone deficiency = 613.62 mg, small for gestational age = 677.54 mg, Turner syndrome = 651.97 mg.

The analysis was conducted using both European and US bodyweight assumptions. Sensitivity analyses were also conducted in which wastage was modeled in FlexPro 30 mg and NordiFlex 30 mg, both of which have dosing increments of 0.1 mg (Table 1).

3. Results

Over the course of 1 year, the modeling analysis showed substantial differences in the administered hGH dose between MiniQuick and Norditropin devices in all settings (Table 2). Excess dosing was calculated both in terms of absolute additional hGH and as a percentage of the annual target dose and, overall, the analysis showed that devices with smaller dosing increments resulted in reduced excess hGH dosing. In line with the model setting to ensure that at least the recommended dose was delivered with each simulated injection, every device dosed a volume of hGH either equal to or above the target dose. However, the magnitude of this difference varied between the devices as illustrated in Figures 1, 2 and 3.

3.1 United States

In the US setting, the model calculated that, over the course of 1 year, patients in the simulated cohort would require an average of 613.62 mg hGH for GHD, 677.54 mg hGH for SGA and 651.97 mg hGH for TS (Table 2 and Figure 1). Over the 1-year time horizon, excess hGH dosing in the GHD cohort varied from 4.63 mg (0.76% of the annual target dose) with FlexPro 5 mg (0.025 mg dosing increment) up to 34.76 mg (5.66% of the annual target dose) with MiniQuick. FlexPro 10 and 15 mg devices exhibited wastage of 7.60 and 16.64 mg in the simulated GHD cohort, respectively, corresponding to 1.24 and 2.71% of the annual target dose. Findings in the TS and SGA cohorts were similar when expressed as a percentage of the target dose, with FlexPro 5 mg resulting in 0.80% wastage in the TS cohort and 0.66% in the SGA cohort (based on absolute wastage of 5.23 and 4.45 mg per annum, respectively). FlexPro 10 mg was projected to result in wastage of 5.50 mg (0.84% of the annual target dose) and 9.47 mg (2.24%) in the TS and SGA cohorts respectively, while FlexPro 15 mg resulted in

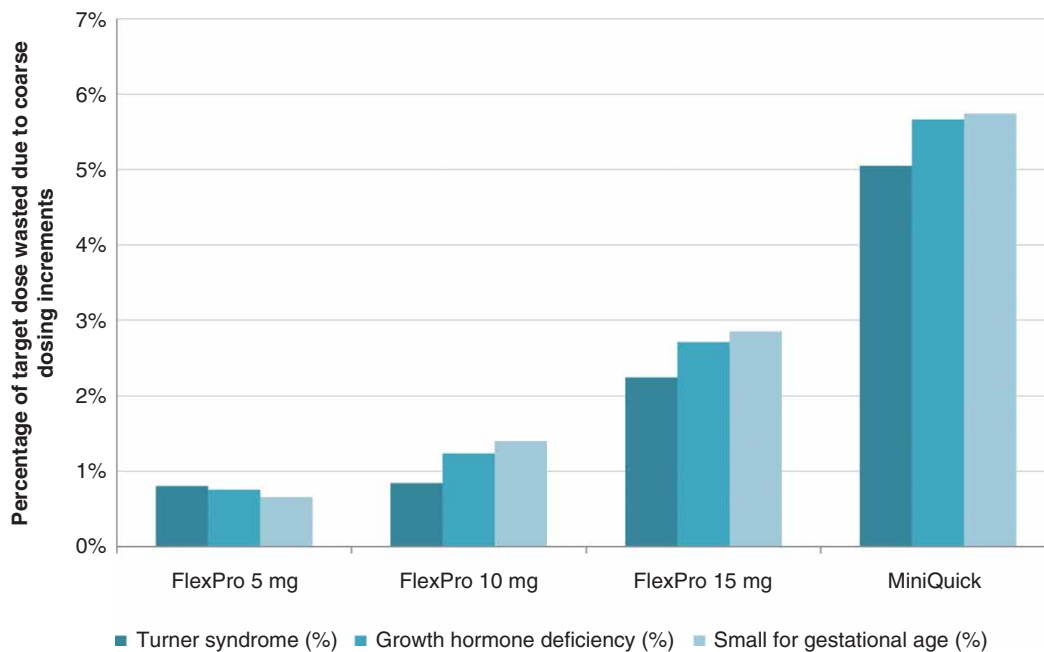


Figure 1. Annual wastage arising from coarse dosing increments in the US setting.

wastage of 14.63 mg (2.24%) and 19.31 mg (2.85%) in the same cohorts. The equivalent values for MiniQuick were 5.05% (based on 32.91 mg of wastage) in the TS cohort and 5.75% (based on 38.92 mg of wastage) in the SGA cohort.

3.2 Europe

Findings in the modeled European cohort were broadly comparable to those in the US setting (Table 3 and Figure 2). In the TS cohort, annual wastage from the Norditropin devices ranged from 4.75 mg with FlexPro 5 mg and NordiFlex 5 mg (0.99% of the mean annual target dose of 482.13 mg) to 17.16 mg with NordiPen 10 mg, NordiPen 15 mg and FlexPro 15 mg (3.56% of the target dose), compared with 37.39 mg (7.76%) with the MiniQuick devices. For the GHD cohort in the European setting, the absolute wastage values were lower than the TS cohort, but were higher when expressed as a percentage of the target dose of 350.64 mg per annum, with Norditropin devices resulting in wastage of between 1.19% (with FlexPro 5 mg and NordiFlex 5 mg) and 4.33% (with FlexPro 15 mg, NordiPen 10 mg and NordiPen 15 mg), compared with 9.42% with MiniQuick.

3.3 Sensitivity analysis

Sensitivity analyses in which the mean daily dose varied from 0.01 to 0.07 mg/kg/day showed the model to be relatively sensitive to the assumed daily dose. Across the full range doses with US bodyweight assumptions (35 kg with a SD 5 kg), devices with a 0.025 mg dosing increment were projected to

waste between 0.0 and 5.2 mg of growth hormone annually, while devices with 0.2 mg dosing increments were projected to waste between 27.4 and 44.4 mg of growth hormone per year (Figure 4). In the analysis of 0.025 mg dosing increments, the model projected 0.0 mg of wastage in the case of a 0.025 and 0.050 mg/kg/day doses as the integer units of bodyweight always yielded total prescribed daily doses that were exactly divisible by the dosing increment. The same analysis was conducted with European bodyweight assumptions, yielding similar results (Figure 3). While the model was sensitive to changes in mean daily dose, smaller dosing increments consistently resulted in less wastage.

Analyses in which wastage was modeled in 30 mg devices yielded the same results as FlexPro 15 mg in both the US and EU settings and across all indications, owing to equivalent dosing increments (0.1 mg) across the devices.

4. Discussion

Currently available hGH administration devices have a number of characteristics that can be used to differentiate between them from prescriber, payer and patient perspectives. In the present study, we investigated the effect of dosing increment granularity on the annual delivered hGH dose. While the dosing increments between devices vary only by amounts < 1 mg, modeling these differences over 1 year in representative GHD, SGA and TS populations showed substantial differences in the annual quantity of administered hGH between devices. Excess dosing was higher in the

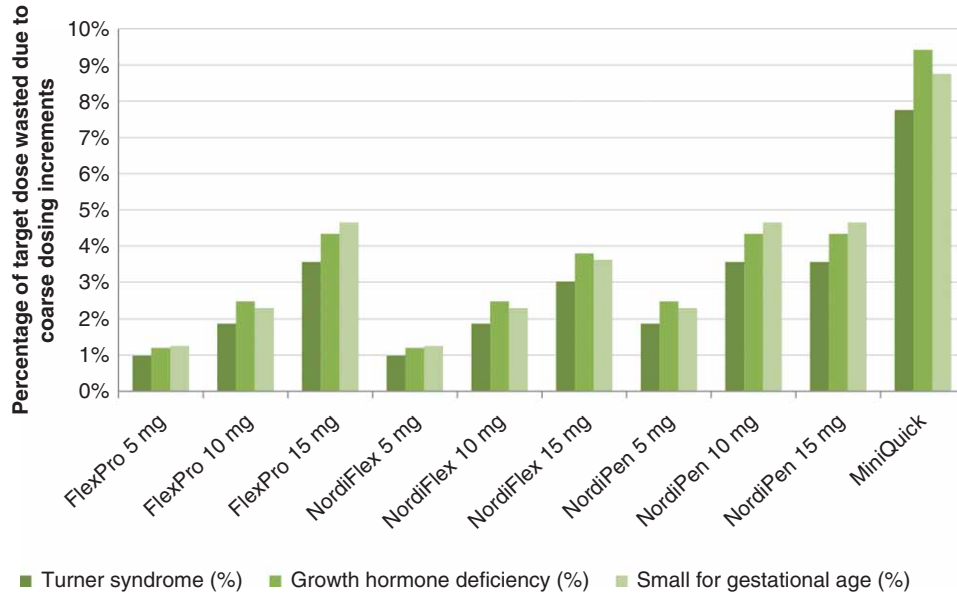


Figure 2. Annual wastage arising from coarse dosing increments in the European setting.

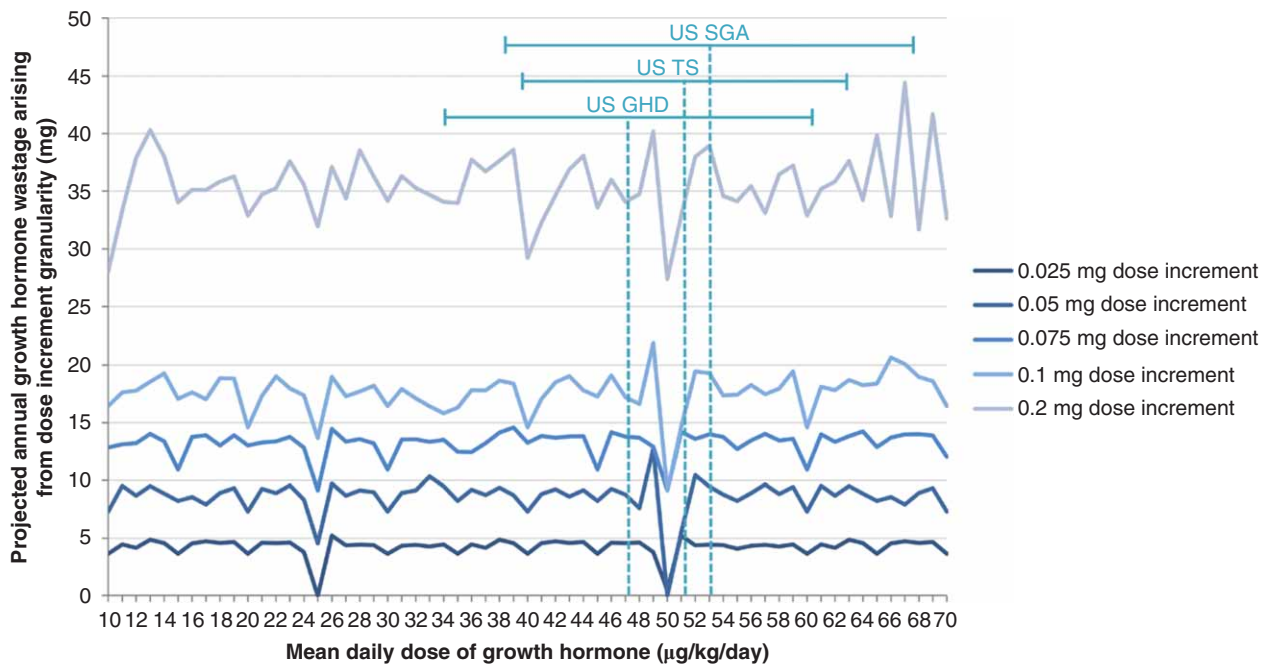


Figure 3. Sensitivity analysis showing projected growth hormone wastage across a range of mean doses (10 – 70 µg/kg/day) for five different dosing increments assuming a mean bodyweight of 35 kg. Overlaid lines represent mean doses (± 1 standard deviation) for patients with GHD, SGA and TS from the ANSWER Program.

GHD: Growth hormone deficiency; SGA: Small for gestational age; TS: Turner syndrome.

European setting than in the US setting, with FlexPro 5 mg (which has a 0.025 mg dosing increment) exhibiting excess dosing of between 0.66 and 0.80% of the target dose in the US setting compared with excess of between 0.99 and

1.25% of the target dose in the European setting. Corresponding figures for the disposable MiniQuick devices were between 5.05 and 5.75% in the US, compared with between 7.76 and 9.42% in the European setting. Sensitivity analysis

Table 3. Additional administered growth hormone arising from coarse dosing increments expressed as absolute mass of human growth hormone per patient and as a percentage of the annual per-patient target dose in the European setting.

| | FlexPro® 5 mg | FlexPro® 10 mg | FlexPro® 15 mg | NordiFlex® 5 mg | NordiFlex® 10 mg | NordiFlex® 15 mg | NordiPen® 5 mg | NordiPen® 10 mg | NordiPen® 15 mg | Mini Quick® |
|--------------------------------|------------------|-------------------|-------------------|--------------------|---------------------|---------------------|-------------------|--------------------|--------------------|----------------|
| Turner syndrome (mg) | 4.75 | 8.99 | 17.16 | 4.75 | 8.99 | 14.55 | 8.99 | 17.16 | 17.16 | 37.39 |
| Turner syndrome (%) | 0.99 | 1.86 | 3.56 | 0.99 | 1.86 | 3.02 | 1.86 | 3.56 | 3.56 | 7.76 |
| Growth hormone deficiency (mg) | 4.19 | 8.65 | 15.20 | 4.19 | 8.65 | 13.30 | 8.65 | 15.20 | 15.20 | 33.04 |
| GHD (%) | 1.19 | 2.47 | 4.33 | 1.19 | 2.47 | 3.79 | 2.47 | 4.33 | 4.33 | 9.42 |
| Small for gestational age (mg) | 5.22 | 9.51 | 19.37 | 5.22 | 9.51 | 15.07 | 9.51 | 19.37 | 19.37 | 36.46 |
| SGA (%) | 1.25 | 2.28 | 4.65 | 1.25 | 2.28 | 3.62 | 2.28 | 4.65 | 4.65 | 8.76 |

EU mean annual target dose per patient for growth hormone deficiency = 350.64 mg, small for gestational age = 416.39 mg, Turner syndrome = 482.13 mg. GHD: Growth hormone deficiency; SGA: Small for gestational age.

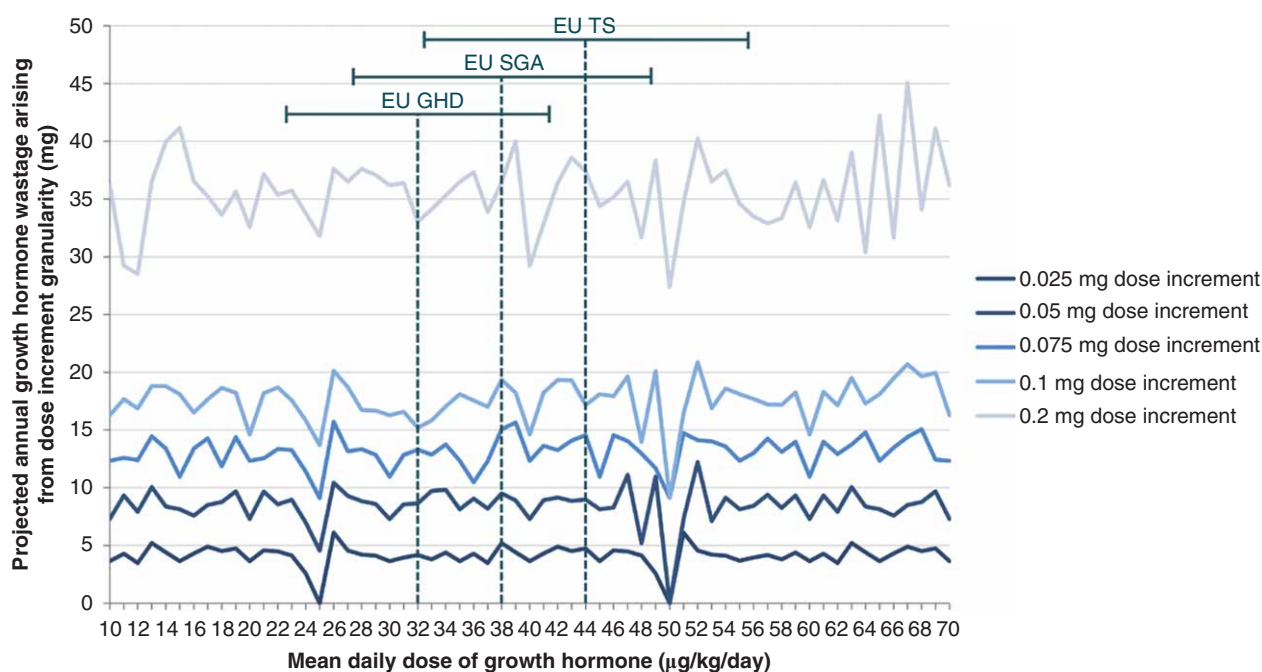


Figure 4. Sensitivity analysis showing projected growth hormone wastage across a range of mean doses (10 – 70 µg/kg/day) for five different dosing increments assuming a mean bodyweight of 30 kg. Overlaid lines represent mean doses (± 1 standard deviation) for patients with GHD, SGA and TS from the NordiNet® International Outcome Study.

GHD: Growth hormone deficiency; SGA: Small for gestational age; TS: Turner syndrome.

showed that the model was sensitive to changes in the mean daily dose assumptions, but no modeled dose between 0.01 and 0.07 mg/kg/day changed the finding that larger dosing increments result in increased hGH wastage.

While we have developed the model to represent a robust simulation of hGH usage in pediatric patients with GHD, SGA and TS, the analysis makes a number of assumptions that may not reflect the real-world use of hGH delivery systems. Notably, the model assumed that patients follow dosing

instructions accurately and will always administer the first incremental dose above the target dose (to ensure that the full prescribed dose is administered). The model also assumed that all dispensed hGH product is used; in the case where a patient is unable to inject a full dose using the hGH remaining in a pen/syringe, the remainder of the pen content would be injected and the full dose made up from a new device. In the case of the MiniQuick device, this assumption results in an underestimation of wastage, as the single-use nature of

the device would result in any remaining hGH in a second device (where required) going to waste, making the analysis conservative with respect to the Norditropin device comparisons. Despite these assumptions, we consider the model to be a reasonable representation of hGH use and that, while the assumptions made around hGH dosing may affect the absolute estimates of wastage, any incremental differences arising as a result of the assumptions would be negligible.

One important consideration when interpreting the findings of the present analysis is the weight-based hGH dosing assumption. While this reflects current clinical practice in pediatric patients, the results may not be applicable in adult patients, in whom hGH is typically either administered to normalize IGF-I levels appropriate for age and sex, or adjusted in stepwise, fixed-dose increments from an age-adjusted daily starting dose [12,13]. Particularly in the latter fixed dose increment titration strategy, prescribed doses could be aligned exactly with device dose increments, eliminating any discrepancies between the prescribed and administered doses.

One further consideration in interpreting the results of the analysis is the clinical effect of over- or under-dosing hGH, which is well understood at the two extremes: nonadherence and high-dose hGH therapy (up to 0.1 mg/kg/day). In the former case, patients classified as nonadherent may experience reduced height velocity and subsequent cardiovascular and metabolic consequences [14-17]. Conversely, high-dose hGH therapy has been shown to have a similar safety profile to standard-dose treatment while increasing near-adult height [18-21]. However, these effects would be unlikely to manifest as a result of systematic deviations from the prescribed dose on the scale of a single device dose increment; further clinical research would be required to definitively establish what effect, if any, such small-scale changes in dose may have on GHD, SGA or TS patients.

Regarding the generalizability of the findings, if the assumption is made that all other factors contributing to hGH wastage are the same across devices, the model framework used in the present analysis could be used to estimate wastage in a wide variety of hGH administration devices. Indeed, under that assumption, the present analysis of NordiPen 10 mg could be applied to, for instance, the Genotropin Pen[®] 5 pen or Nutropin AQ[®] NuSpin[™] 10, which also have a 0.1 mg dosing increment [22,23]. However, care should be exercised in making the assumption that other factors are equivalent as characteristics such as priming volumes and

wastage during needle attachment can also affect hGH utilization [1,10].

Given that current commercially available hGH products contain the same active substance and are generally considered to be clinically equivalent, health-care prescribers and payers may currently look to other differentiators when deciding which hGH products to prescribe. As noted in previous studies, product differentiation generally focuses on the formulation (including the buffering and preservative agents and their effects on room temperature stability, and whether the hGH is supplied as an injectable solution or must be reconstituted from lyophilized powder), administration devices, patient support services offered by each manufacturer as well as patient preference and the quality of the injection device [1,4-7].

5. Conclusion

As illustrated in the present study, in addition to patient-centric considerations such as device storage and handling, injection-site pain, and injection history recording, there are differences between the hGH delivery systems that may affect the volume of hGH that is available for injection relative to the nominal content. Such differences may lead to cost savings that would not be apparent from the per-milligram list prices of the various hGH products.

Declaration of interest

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