Adv Ther (2019) 36:3409–3423
https://doi.org/10.1007/s12325-019-01112-3

ORIGINAL RESEARCH

Co-Creation of a Lanreotide Autogel/Depot Syringe for the Treatment of Acromegaly and Neuroendocrine Tumours Through Collaborative Human Factor Studies

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Received: August 7, 2019 / Published online: October 14, 2019

ABSTRACT

Introduction: Although the previous lanreotide autogel/depot syringe had been well received, feedback indicated that improvements could be made to make it more user-friendly. Additionally, the view that patients should have greater involvement in the research and development process is echoed by the International Neuroendocrine Cancer Alliance. A series of studies aimed to develop and validate a new syringe that works better for patients, caregivers and healthcare professionals (HCPs) by involving these groups at key stages in the development and testing process.

Methods: The multicentre, international, human factor studies, consisted of four formative studies and one validation study. The formative studies collected patient, caregiver and HCP feedback on the lanreotide autogel/depot syringe on the market at the time, and on newly designed prototypes. The validation study was conducted to evaluate the final syringe to confirm that it can be used effectively and safely in the intended environment, by the intended user, for the intended purpose.

Results: Overall, 213 individuals participated in the studies; 145 contributed to the formative studies and 68 to the validation study. The validated new-generation syringe included several important updates compared with the lanreotide autogel/depot syringe currently on the market, including the flanges, which are now larger and have a better grip; the overcap, which is white, ridged, opaque and bigger; the plunger

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Electronic Supplementary material The online version of this article (https://doi.org/10.1007/s12325-019-01112-3) contains supplementary material, which is available to authorized users.

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supports and the thermoformed tray. No participant hurt themselves or others during the validation study (although several misuses were reported), and all participants succeeded in delivering a complete dose and activating the safety system.
Conclusion: With collaboration, a new syringe was developed to meet the needs of patients, caregivers and HCPs, whilst ensuring lanreotide was delivered effectively and safely. These studies highlight the importance of involving patients, caregivers and HCPs in clinical evaluation studies to develop medical products that address their concerns and meet their needs.
Funding: Ipsen.
Plain Language Summary: Plain language summary available for this article.

Keywords: Acromegaly; Autogel; Caregivers; Depot; Lanreotide; Neuroendocrine tumours; Nurses; Patients; Syringe

PLAIN LANGUAGE SUMMARY

Lanreotide autogel (lanreotide depot in the USA) is a medication that can be used to treat acromegaly or neuroendocrine tumours (NETs):

Acromegaly	A condition where a pituitary tumour produces excessive growth hormone and causes enlarged hands/feet/face.
NETs	Slow-growing cancers that usually originate in the gastrointestinal system and can secrete hormones.

To work properly, lanreotide must be injected correctly into fatty tissue under the skin using a syringe. The syringe must be easy to use for patients with acromegaly and large hands or joint problems who self-inject (outside the USA), caregivers and nurses wearing gloves.

To see if the syringe design could be improved to make it easier for everyone to use, 145 patients, caregivers and nurses were asked for feedback on the current syringe and the suggested changes. Using their feedback, we developed a new syringe with the following key features:

- Larger flanges (finger supports for pushing the plunger down).
- A larger, ridged, non-transparent cap that fits over the needle (instead of a see-through needle shield).
- New plunger supports.
- New protective tray.

A separate group of 68 patients, caregivers and nurses tested the new syringe to make sure they could use it easily and correctly.

- Everyone succeeded in delivering an injection properly and safely.

This work shows the importance of considering the needs of those who will be using medical products. By working together, we improved the syringe to meet the needs of patients, caregivers and nurses, and ensured that lanreotide was delivered properly and safely.

INTRODUCTION

Somatostatin analogues are indicated for the treatment of acromegaly and neuroendocrine tumours (NETs), providing hormone and tumour control for acromegaly, tumour control for NETs, and symptom control for both diseases [1, 2]. Two long-acting somatostatin analogue formulations are currently available: lanreotide autogel (Europe and other countries outside the USA)/depot (USA) (Ipsen) and octreotide long-acting release (LAR) (Novartis). Lanreotide autogel/depot is administered as a deep subcutaneous injection via a ready-to-use syringe, whilst octreotide LAR is a preparation that needs reconstitution before intramuscular injection.

In a previous study, the key factors for effective treatment delivery and efficient patient management when using somatostatin analogues were identified as ease of use, safety and speed of administration [3]. Nurses indicated that the most important attributes of syringes for injecting patients with acromegaly or NETs are easy and convenient preparation and injection, low clogging risk and high product efficacy [3]. Although intramuscular

octreotide LAR injections achieved a higher mean evaluation score for plunger sturdiness, subcutaneous lanreotide autogel/depot received a significantly higher score for overall nurse preference, for the significantly shorter preparation and administration time, lower clogging risk and higher confidence that a full dose had been delivered [3]. Furthermore, in a study of patients switching from octreotide LAR to lanreotide autogel/depot, the latter was preferred by more than 80% of patients, and was described as very convenient by 75% of them [4].

Convenience is considerably increased by ready-to-use syringes that allow self-injection or partner-injection. Indeed, patients with acromegaly were reported to value injectable treatments that fit around their everyday lives, with prefilled injectable preparations that save administration time and treatments that can be administered at home, allowing greater independence [5]. An important concern for healthcare professionals (HCPs) is that patients receive their full therapeutic doses. Since a poor injection experience can reduce patient adherence to the recommended treatment and affect treatment outcomes, HCPs value simple ready-to-use syringes that help facilitate patient adherence to therapy [6].

Although the previous lanreotide autogel/depot syringe had been well received following its approval [7, 8], interviews with nurses [3] and patient surveys (unpublished data) identified several aspects that could be improved for some users, particularly those with acromegaly, who tend to have large hands and fingers, or people who wished to self-inject more easily. It has been highlighted that patients in general should be more involved in the research and development process, a view echoed specifically for patients with NETs by the International Neuroendocrine Cancer Alliance, to ensure, for example, that clinical trials are conducted to improve treatment options [9–11]. Therefore, the presented series of studies aimed to develop and validate a new syringe that works better for all patients, caregivers and HCPs by involving these groups at key stages in the development and testing process.

METHODS

Four formative studies were conducted in Europe and the USA to collect feedback from patients, caregivers and HCPs on the lanreotide autogel/depot syringe on the market at the time, and on successive prototypes designed specifically for this purpose. The process for developing the new syringe included retaining attributes of the previous lanreotide autogel/depot delivery system that were already well received (prefilled/ready-to-use syringe, automatic needle guard and overall transparency of the delivery system) [3]. A validation study was conducted to evaluate the final syringe and confirm that it could be used effectively and safely in the intended environment, by the intended users, for the intended purpose.

All participants were required to be 18 years or older (no upper age limit), have the capacity to understand study risks, and be available and willing to participate in the study (including a willingness to be video-recorded during the study). Recruitment throughout all studies allowed a mix of genders, hand size and hand dominance (more right than left) in order to reflect the general population of users. Participants were excluded from the study if they were employed by the sponsor (Ipsen) or a pharmaceutical company. Further exclusion criteria included participants with uncorrected sensory, cognitive or physical disabilities that would preclude the participant from attempting to administer an injection.

As the prevalence of acromegaly and gastroenteropancreatic (GEP)-NET is rare, it would have been logistically difficult to recruit sufficient participants with experience for these studies. Therefore, patients, caregivers and HCPs were also represented via surrogates which, in addition to the criteria above, had the same injection experience and relevant clinical conditions and attributes of each group that would impact the syringe use (detailed below).

Formative Studies

Formative studies were conducted in France, Germany, the UK and the USA between 17 June 2015 and 29 September 2016.

All formative studies were face-to-face interviews with patients with GEP-NETs or acromegaly, lay caregivers of patients with these conditions and HCPs. Some of the formative studies also included patient and/or caregiver *representatives*. Representatives of patients with acromegaly were individuals with conditions that mimic the dexterity problems (e.g. large fingers, pain in joints) experienced by patients with acromegaly, e.g. those with a diagnosis of diabetic neuropathy, carpal tunnel syndrome or arthritis and self-described "large" or "very large" hands and "thick" or "very thick" fingers. Representatives of patients with GEP-NETs were defined as those willing to administer injections, as patients with GEP-NETs did not have any specific characteristics expected to affect use of the syringe. Caregiver representatives were defined as individuals willing to administer injections. Vision-related ailments were allowed in patients and patient representatives, but not in caregivers or caregiver representatives.

Formative Study 1

Formative study 1 included patients with GEP-NETs, patients with acromegaly and HCPs from France, Germany, the UK and the USA. It assessed the user experience of the current on-the-market lanreotide autogel/depot syringe and also provided a comparison with the octreotide LAR syringe to identify challenges and areas of improvement for the lanreotide autogel/depot syringe. As such, participants were only eligible for inclusion if they had injected lanreotide autogel/depot or octreotide LAR in the month prior to the study. HCPs were required to have administered either product to at least five patients. Patients and HCPs were excluded if they had recently taken part in marketing research on NETs or acromegaly.

Participants were also asked to provide feedback on four new early prototypes (developed via 3D printing), each with a set of unique attributes related to the body of the syringe, the thumb position, finger flanges and completion indicator, to understand which features were important for patients and their HCPs.

Formative Study 2

Formative study 2 was conducted in the UK and included a subset of the HCPs that participated in formative study 1. The aim was to gather feedback on a prototype that had been developed using results from formative study 1. On the basis of the results, five different colour prototypes were then developed for formative study 3.

Formative Study 3

Formative study 3 was carried out in France, Germany, the UK and the USA, in patients with acromegaly or GEP-NETs and HCPs. All were real-life users of lanreotide autogel/depot or octreotide LAR. HCPs were required to have administered either product to at least four patients.

Participants provided feedback on the five prototypes and the instructions for use (IFU). They also evaluated the impact of colour and the presence of rubber on the finger flanges/overcap on the participants' experience. Patients and HCPs in Europe could administer a simulated injection to assess the potential for self-injection, demonstrate the level of understanding of the IFU, and identify potential use errors and areas for improvement.

Formative Study 4

Formative study 4 was conducted in the USA (HCPs only) and Europe (patients with acromegaly and GEP-NETs or patient representatives and caregivers or their representatives). The latest versions of the prototype were presented, with the aim of evaluating each updated syringe–user interface. Participants conducted a simulated injection, then were asked a series of knowledge task questions and were interviewed to determine the root causes of any misuses that occurred. They then provided subjective feedback of their experience with syringes, to confirm whether any further changes needed to be incorporated in the syringe design (specifically

focusing on the plunger support and the overcap).

Validation Study

A simulated-use validation study was conducted in May and June 2017 in the USA (HCPs only) and in Germany (with representatives of patients with acromegaly, patients with GEP-NETs and caregiver representatives). HCPs were required to have prior injection experience, though not necessarily with lanreotide autogel/depot. It was not compulsory for patients with GEP-NETs to have experience with lanreotide autogel/depot or other somatostatin therapies. In the USA, the study aimed to include mostly nurses (although other HCPs including physicians, physician assistants, nursing and medical assistants were recruited) and preferentially chose HCPs employed at an endocrinology practice (although HCPs from other practices were also included). Individuals involved in any prior formative testing of the syringe were excluded.

The validation study assessed the misuses associated with preparing and administering an injection using the updated syringe according to a critical task list (Supplementary Table S1). Possible misuses were identified during a risk assessment using the Failure Mode and Effect Analysis (FMEA) tool, conducted to evaluate and analyse all hazard situations related to use of the syringe. Projected risks were rated following the International Organization for Standardization (ISO) 14971:2013 ("Medical devices—Application of risk management to medical devices").

Participants in the acromegaly, GEP-NET and caregiver groups in Germany followed a training session of 30 min under the supervision of a nurse. This consisted of reviewing the IFU and warnings and precautions, and administering their first simulated injection under nurse supervision. Some of the HCPs in the US study also received a 30-min training session that included reviewing the IFU, familiarising themselves with the syringe, receiving answers to any questions they may have had and watching a nurse demonstrate an injection (if requested).

Following training, all participants (including untrained HCPs) were presented with a use scenario requiring preparation and administration of the drug to evaluate all the misuses that participants had with the product. During each session, participants administered two injections (one dose of 60 mg and one of 120 mg, the order of which was evenly distributed between participants) of a simulated gel (designed to mimic the characteristics of lanreotide autogel/depot) into an injection pad placed on their chosen injection site on a mannequin. The injection site was dependent on whether the participant would self-administer the injection (not approved in the USA following the extension indication for NET, it was initially permitted for the acromegaly indication) or whether they would be injecting someone else. Therefore, HCPs (enrolled in the US study) were expected to place the pad on the upper, outer, external quadrant of the buttock of the mannequin (the site for injecting someone else) before making the injection, whilst participants in the acromegaly group were expected to place the pad on the upper outer thigh of the mannequin (self-injection site) before injecting. Participants in the GEP-NET and caregiver group injected in both sites; one injection mimicked self-injection whilst the other simulated injecting someone else.

Two different environments were created to help simulate the injection experience: a clinical environment for HCPs, and a home environment for patients self-administering the injections and for caregivers. Requirements for the environments included the area being well lit, quiet, 18–24 °C and with a humidity between 15% and 85%.

Data Analyses

For the validation study, the number of participants in each group (minimum of 15) was determined according to Annex B from the Food and Drug Administration (FDA) guidance, Applying Human Factors and Usability Engineering to Medical Devices. Demographic

information collected for the validation study included gender, age, professional title (for HCPs), experience with lanreotide autogel/depot, hand size and handedness. Descriptive analyses are presented and categorical variables are presented as frequency counts. The numbers of misuses are compared between trained and untrained HCPs, and between HCPs and patients/representatives/caregivers.

Ethics

All participants provided written informed consent prior to enrolment in any of the studies. As they were not interventional clinical studies and the injections were simulated, no ethics review or committee approval was required. The validation studies were conducted in accordance with FDA draft guidance, Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, issued February 2016 and European Standard: Application of usability engineering to medical devices EN62366–1:2015.

RESULTS

Participants

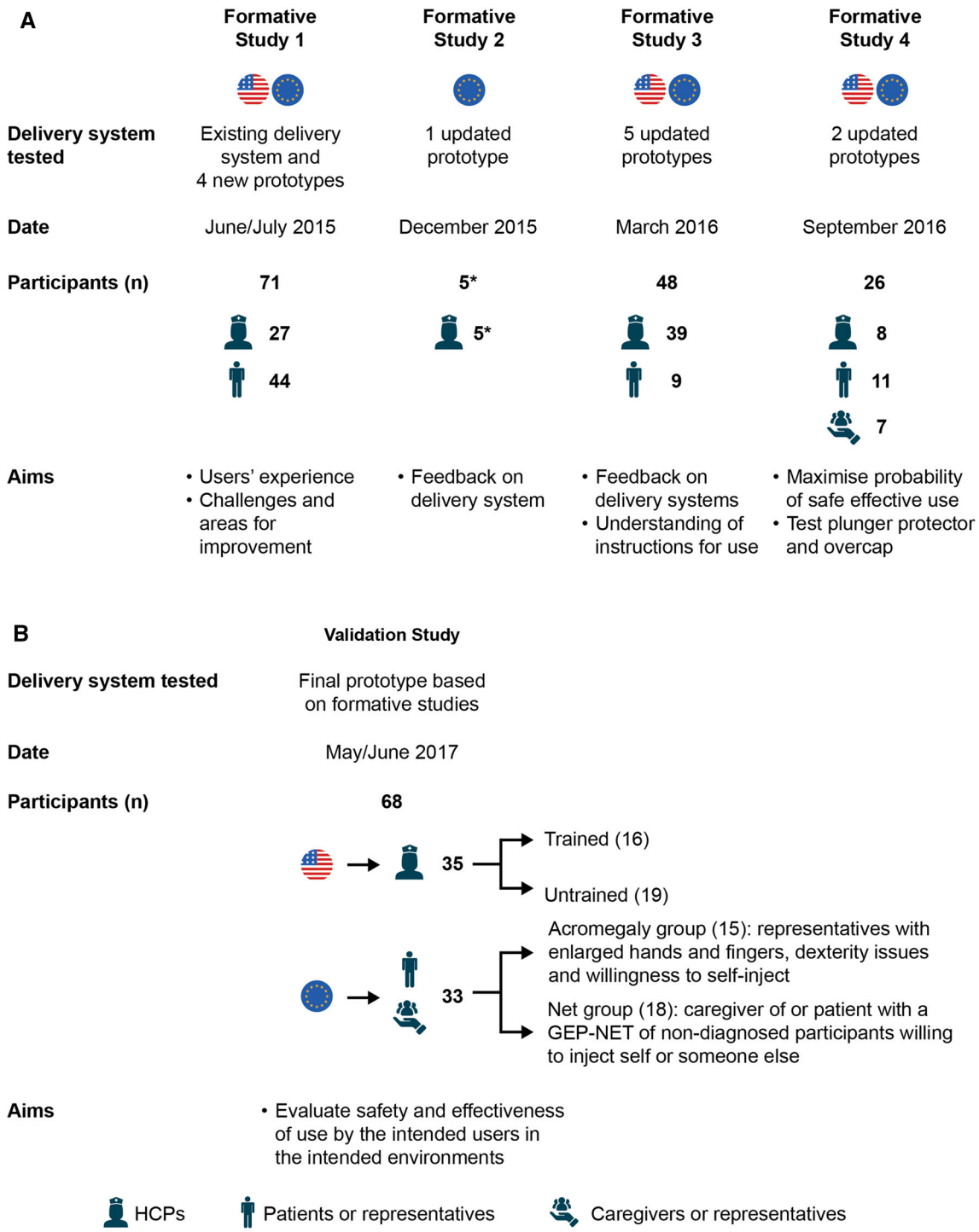
A total of 213 participants took part in the studies, including 33 patients with acromegaly and 28 patients with NETs (Fig. 1). The formative studies consisted of a total of 145 participants. In formative study 1, there were 71 participants (29 patients with acromegaly, 15 patients with GEP-NETs and 27 HCPs). In formative study 2, there were five participants (all endocrine nurses, all of whom participated in formative study 1). In formative study 3, there were 48 participants (three patients with acromegaly, six patients with NETs and 39 HCPs). In formative study 4, there were 26 participants (two patients with acromegaly, four representatives of patients with acromegaly, five representatives of patients with GEP-NET, three caregivers, four caregiver representatives, six HCPs specialising in endocrinology and two other HCPs). In the validation study, there were 68 participants (15 representatives of patients with acromegaly, seven patients with GEP-NETs, 11 representatives of patients with GEP-NETs or their caregivers, and 35 HCPs [12 HCPs specialising in endocrinology and 23 other HCPs]). Of these HCPs, 16 (46%) were trained and 19 (54%) were untrained.

Participant characteristics and experience with injections, specifically lanreotide autogel/depot for the validation study, are shown in Table 1. Participant characteristics for the formative studies are shown in Supplementary Tables S2, S3 and S4. In the validation study, most HCPs (30/35, 86%) were female; 24 (69%) were aged between 35 and 60 years, and nine (26%) had previous experience with lanreotide autogel/depot. The majority of participants in the GEP-NET group (11/18, 61%) were also female; 14 (78%) were aged between 18 and 60 years, and six (33%) had previous experience with lanreotide autogel/depot. Around half of the participants in the acromegaly group (8/15, 53%) were female; seven (47%) were aged between 35 and 60 years, but none had previous experience with lanreotide autogel/depot.

Formative Studies: Development of the New Syringe

Results of the formative studies were used to design the prototype that was assessed in the validation study. All changes incorporated are presented in Table 2.

Formative study 1 optimised the development of the new syringe with respect to end user (patient, caregiver or HCP) preferences. Participants indicated that an ideal injection device would have an easy setup for administration, take an acceptable amount of time to inject a complete dose and have a clearly labelled drug name and dose. Furthermore, the device should be intuitive to use from start to finish and have a needle that is easy to withdraw from the skin after the dose has been administered. Nurses specified the importance of an intuitive grip, whilst patients stipulated they would prefer a device that provided clear feedback when the dose had been administered.



A, the formative studies; B, the validation study. *These HCPs also participated in Formative Study 1. GEP-NET, gastroenteropancreatic neuroendocrine tumours; HCP, healthcare professional.

Fig. 1 Study design.

Table 1 Human factor validation study participant demographics

	HCPs			GEP-NET group[a] (n = 18)	Acromegaly group[b] (n = 15)
	Untrained HCPs (n = 19)	Trained HCPs (n = 16)	All (n = 35)		
Gender					
Male	4	1	5	7	7
Female	15	15	30	11	8
Age					
18–34	5	5	10	8	4
35–60	13	11	24	6	7
60+	1	0	1	4	4
Professional title					
RN	12	10	22	–	–
Physician	5	4	9	–	–
NP	2	2	4	–	–
Injection experience					
Experienced	19	16	35	12	10
Inexperienced	0	0	0	6	5
Experience with lanreotide autogel/depot[c]					
Yes	4	5	9	6	0
No	15	11	26	12	15
Hand size[d]					
Small	7	8	15	7	3
Medium	7	7	14	7	7
Large	5	1	6	4	5
Handedness					
Right	18	13	31	15	12
Left/ ambidextrous	1	3	4	3	3

HCP healthcare professional, *GEP-NET* gastroenteropancreatic neuroendocrine tumour, *RN* registered nurse, *NP* nurse practitioner

[a] Includes patients with GEP-NETs (n = 7) and caregivers/representatives (n = 11)

[b] Representatives with acromegaly had carpal tunnel syndrome (n = 7), diabetic neuropathy (n = 4) and osteoarthritis (n = 6)

[c] Participants were asked: have you ever used a product called Somatuline® autogel/depot (lanreotide)? Have you ever used any other types of somatostatin therapies? If so, which one?

[d] Participants subjectively provided hand size

Table 2 Summary of design changes following the formative studies

Formative study	Comments during user study	Impact on design
1	Small and simple needle cap with grids	Development of grey cap with a rubber grid material
	No needle shroud	No needle shroud will be added owing to development of needle cap
	Curved finger flanges with heavy texture/rubber grips	Two prototypes created (mono-material and biomaterial for cover and overcap)
	Plunger protector	Plunger protector is retained
	Clear and relatively thin body	Body of the device will remain clear
	Visual completion indicator on the middle of the device	Visual indicator to show dose delivery is not necessary. Retain transparent body so participant can see if dose has been delivered
	Audible completion indicator	Audible sound was not added (implementation could be difficult and could increase the risk of misuse)
2	Clear, useful and easy to find drug label	No impact on the design
	Font label on device label was too small	No design change. Font label updated and evaluated in formative study 4
	Clear device cover allows for visual inspection of drug integrity	Syringe body will stay transparent
	Larger design of device cover was sturdier than currently marketed version	No impact on the design
	Concave, ribbed thumb pad on plunger provides more stability	No impact on the design
	Needle was easy to remove after injection	No impact on the design
	Plunger protector with arrows is intuitive to use and remove	Plunger protector is kept with arrows
	Plunger was too long and may be difficult for smaller hands to use	Nurses were able to inject correctly but expressed concerns about the device size; further investigation in formative study 4
	Rubber coating on finger flanges is not necessary	Rubber on the flanges removed
	Would prefer to have a needle retraction mechanism	No needle shroud. Needle retraction safety system is kept
	Overcap was difficult to remove; would prefer a "twist-and-pull" method of removal	Verify ergonomics of the overcaps in formative study 3
	Would prefer an audible click to signal injection is complete	Audible sound not added to the device owing to technical evaluation ruling it could increase the risk of misuse (and would be difficult to implement)

Table 2 continued

Formative study	Comments during user study	Impact on design
3	The rubber coating would increase the perception of the quality of the device	Rubber grip is nice to have but is not a must-have
	Raise user's attention to the importance of pressing plunger until total administration of the dose. Provide clear instructions to avoid misuse	The sentence 'give plunger a final push to make sure you cannot depress the plunger further' is in the current IFU and will be in the IFU of the new injection system
	The coloured arrow would help user to remove the plunger protector	Arrows on the plunger protector are nice to have but not a must-have. No misuse was reported linked to non-coloured arrow. The user study 4 will be done without the coloured arrows to assess the necessity
	The IFU is already clear but still fine-tuning to be made	No impact on the device design
	The coloured device will optimise visibility and usage. Yellow is the preferred colour	Colour of the device is nice to have but is not a must-have. Following evaluation, there is a recommendation not to change the colour of the plunger
	New device is better suited for self-injection compared to current devices	No impact on the design
4	All participants succeeded in engaging the needle safety mechanism	No impact on the design
	All participants succeeded in pushing the plunger to the bottom of the syringe without breaking the plunger	No impact on the design
	All participants succeeded in delivering a full dose	No impact on the design
	One participant initially tried to inject without removing the plunger protector and overcap, considering the device as auto-injector	Plunger protector is replaced by a tray following a risk evaluation
	Most participants did not initially remove the IFU from the box and indicated they would not normally refer to the IFU prior to delivering the injection	The risk is identical to the current marketed product. Modification of the drawings of the IFU
	Some participants did not visually check that a full dose had been administered, but rather considered the tactile feedback of the plunger reaching the bottom of the syringe to be sufficient confirmation	Different ways permit confirmation that the plunger is pushed completely: transparent body and cover; tactile feedback of the plunger reaching the bottom of the syringe; indication on IFU to give a final push
		All participants were able to inject a full dose because the safety mechanism was activated. No impact on the device
	Some participants initially tried to twist the overcap rather than pull	No safety issue because participants were able to remove the overcap at the end. No change on the overcap design
	A few participants pinched the skin rather than flattening the injection site	The risk is identical to the current marketed product. Modification of the illustrations and instructions of the IFU
	Participants did not wash hands either before or after the injection	The risk is identical to the current marketed product. Modification of the illustrations of the IFU
	One EU participant accidentally pulled out the plunger support whilst trying to remove the needle cap	Syringe body: improvement of the interface between the proximal end of the syringe body and the tip of the plunger rod to prevent tear off

IFU instructions for use

The comparison between lanreotide autogel/depot and octreotide LAR showed no clear preference for either syringe; participants preferred the easy setup and needle safety feature of lanreotide autogel/depot, but found octreotide LAR easier to hold and to inject with. Participant feedback on the four prototypes indicated that a number of key features should be incorporated to produce an 'ideal device', including a clear and relatively thin body with comfortable grip, textured finger flanges, an indicator on the body of the device, a plunger protector, and a small and simple overcap with grips.

Following the first formative study, participants of formative study 2 identified both advantages and disadvantages of the prototype design to further refine the syringe. Advantages included the clear, useful and easy-to-find drug label; the clear and sturdier device cover; the thumb pad on the plunger and the large finger flanges for stability; and the needle being easy to remove after injection. Disadvantages included the small font on the label, the long plunger, the unnecessary rubber coating on finger flanges and the overcap being difficult to remove.

Overall feedback for formative study 3 was positive; participants thought the prototypes were easy-to-use, safe and robust. They also described the IFU as detailed, user-friendly, straightforward and intuitive, with clear wording and well-laid-out images. One of the most popular syringe features was the needle safety mechanism (already present in the previous lanreotide autogel/depot syringe), differentiating this syringe from other products. To improve the IFU, participants suggested that images associated with the injection site should be clarified. Additionally, they recommended that emphasis be placed on the need for users to flatten the skin and maintain pressure on the plunger until the needle is fully removed.

No areas of the syringe were identified as requiring significant improvement; however, participants suggested potentially refining the design by making the syringe and needle smaller. European participants indicated that the new design would make them feel slightly more comfortable self-injecting, but the most important feature to address to further encourage self-injection would be the thickness of the needle. Nevertheless, needle gauge and length (18 gauge needle/20 mm) were retained from the previous lanreotide autogel/depot syringe, as reducing needle gauge and length could increase injection force and risk of injection failure to reach the deep subcutaneous tissue. Simulated-use testing in formative study 3 indicated the occurrence of possible misuses, including failure to check for expiration date or drug integrity; failure to remove overcap prior to injection; failure to flatten the skin at the injection site; failure to maintain pressure on the plunger whilst removing the needle, and not fully depressing the plunger to activate the needle safety mechanism. The risks of these specific failures were assessed during the next formative study and the validation study.

In formative study 4, participants assisted in finalising the design of the syringe by taking part in use scenarios. All participants succeeded in gripping and removing the needle cap, engaging the needle safety mechanism, pushing the plunger to the bottom of the syringe without breaking the plunger and delivering a full dose. The most common misuses were not visually checking that a full dose had been administered (the tactile feedback of the plunger reaching the bottom of the syringe was considered sufficient confirmation; $n = 22$, 85%) and trying to twist the overcap rather than pulling it (difficulty was quickly resolved; $n = 11$, 42%). Following the latter, participants indicated preferring an overcap that can twist off, and dark arrows on an opaque plunger protector that twists off. Additionally, a few participants pinched the skin rather than flattening the injection site ($n = 6$, 23%).

On the basis of the feedback from all four of the formative studies, the new generation of syringe included several important updates compared with the lanreotide autogel/depot syringe currently on the market (Fig. 2). These included larger flanges; the overcap (replacing the transparent needle shield), which is white, ridged, opaque and bigger; and the plunger supports. The last modification to be incorporated following formative study 4 was the thermoformed tray.

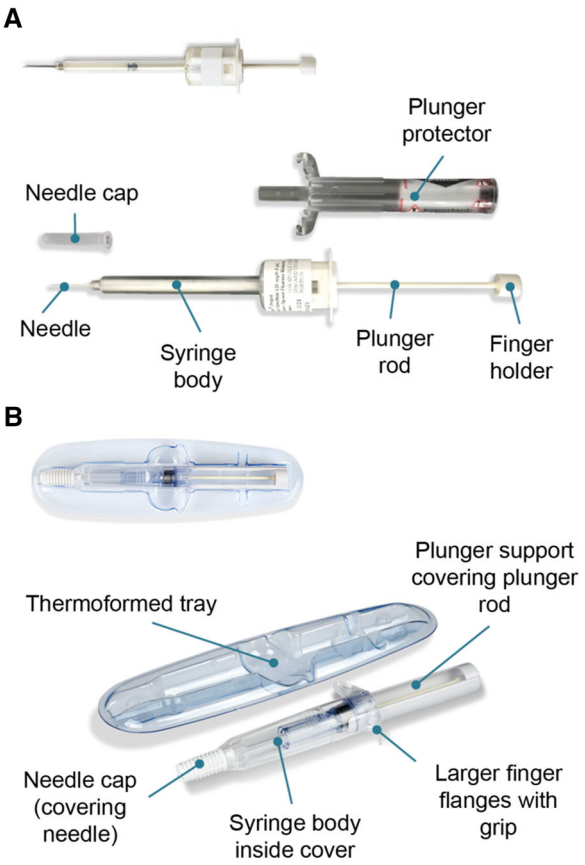


Fig. 2 Comparison of the **A** currently marketed and the **B** updated lanreotide autogel/depot syringe

Validation Study: Safety and Effective Use of Updated Syringe

No participant hurt themselves or others (no accidental needlestick injuries were observed); all participants succeeded in delivering a complete dose and activating the safety system. Misuses were made by 21/35 HCPs; 15 in the untrained group and six in the trained group. Untrained HCPs had misuses in 13 tasks and trained HCPs in three tasks (Supplementary Table S5). A total of 16 task misuses were reported for the GEP-NET and caregivers group, whilst there were 19 task misuses for the acromegaly group. The most common misuses included failure to follow the correct procedure if the syringe was dropped (HCPs: $n = 12$, 34%; acromegaly group: $n = 9$, 60%; GEP-NET and caregiver group: $n = 14$, 78%) and failure to inspect the product before administration (check the drug colour and that there is nothing inside the gel in the syringe; HCPs: $n = 12$, 34%; acromegaly group: $n = 7$, 47%; GEP-NET and caregiver group: $n = 8$, 44%). Additionally, participants in the GEP-NET and caregiver groups reported uncertainty about how to store the syringe in the fridge (in the box vs the pouch; $n = 5$, 28%). Misuses that occurred were not specific to this syringe; they are common misuses that can occur with all syringes [12].

DISCUSSION

The involvement of end users of lanreotide autogel/depot syringe (i.e. patients with acromegaly or GEP-NETs, caregivers and nurses) from various countries resulted in a number of improvements being made to the current model, and increased the perception of the new syringe being more ergonomic, robust, intuitive to use and with a better safety profile. Additionally, patients and HCPs were asked for feedback in a stepwise manner to check that adaptions made to the product addressed their needs. These improvements also resulted in key factors identified for effective treatment delivery being addressed: device usability, safety and speed of administration [3].

During the human factor studies, only the relevant and feasible ideas were carried forward from each formative study. Some modifications in the earlier studies were not retained if they were considered unnecessary in later studies. However, numerous relevant changes were identified as important improvements by the participants. Finger flanges were made larger than those on the previous marketed lanreotide autogel/depot syringe, improving the finger placement. This in turn increases comfort when users push the plunger rod with the thumb and stabilised the syringe during the 20 s of the injection. The addition of a plunger support improved the sturdiness of the syringe. A thermoformed tray was added to protect the syringe, preventing unintended depression of the plunger during transport and handling, thus removing the need for a 'twist-off' plunger protector. Special recessed areas within the tray allow the user to take the syringe from the tray

safely, improving handling. However, in order to accommodate the thermoformed tray, the box packaging for the new syringe has been made slightly bigger.

The new designed overcap, the surface of which is ridged, was considered easier to grip and to pull off than in the previous marketed version, reducing the risks associated with preparation of the syringe for lanreotide autogel/depot administration. The overcap is more robust (made of polypropylene, a hard plastic, instead of the soft plastic needle shield on the current marketed syringe), but the interface between the needle shield and the syringe was kept the same to maintain the same tightness of fit. Furthermore, the visibility of the needle before injection is restricted by the white opaque overcap (which protects the needle before injection), and after injection the needle is retracted into the transparent syringe body (though the needle is visible).

The updated syringe and the IFU were found to be safe and effective for the intended use by the intended users in the intended setting. A number of misuses occurred across the groups; however, the misuses were not specific to this syringe; they were common misuses that occur with all syringes [12]. Needle fear and anxiety occur frequently in patients and can result in delay or avoidance of therapy [13]. Moderate-to-severe anxiety before injections was reported more frequently by octreotide-treated patients (11%) than lanreotide-treated patients (2%) in the observational Somatostatin TReatment ExperiencE Trial (STREET: NCT02788565) [14], and attributes of the new syringe are likely to reduce the anxiety levels even further, as improvements were made in response to specific feedback from patients and nurses. The updated syringe is more stable to administer than the prior lanreotide autogel/depot syringe and has improved the user experience by making administration easier and more intuitive. Administration of the full dose with the new syringe is consistent with the previous syringe (same effect achieved, as all participants administered the full dose during simulated injections). A PREference STudy of the new lanreOtide autogel syringe (PRESTO) is currently in progress to compare the new syringe with the octreotide LAR syringe currently on the market in a simulated-use study with nurses.

It has been highlighted that products and devices can most likely be improved to meet the patient needs by incorporating changes following feedback from users; however, surveys have shown that patients are not involved enough in research and development [9]. A better understanding of patient priorities, their expectations from research and the impact of treatment on their lives will result in a better treatment experience [6]. Conducting human factor studies is one way of involving patients and ensuring that their needs are met, and this type of study has previously been used to optimise the design of a self-injection device for the anti-tumour necrosis factor drug certolizumab [15].

Patients and HCPs enrolled in these studies were good representatives for the end users of the new lanreotide autogel/depot syringe. In the absence of patients with acromegaly or NETs, representatives of these patients who exhibited similar symptoms and disabilities (e.g. large hands and fingers resulting in comparable dexterity problems) were enrolled to provide feedback relevant to the intended end users. A number of different locations (within Europe and the USA) were included so feedback would be representative of the diseases and of patient needs (and not limited by authorisation at a specific location). These studies provide evidence that including patients and HCPs in the early development stages of products can be beneficial in creating a device that meets patient and HCP requirements.

The distribution of participants across the USA and Europe could be considered a limitation as there are considerable differences in clinical practices. However, to improve the syringe design for as many people as possible, it was deemed important to include a wide variety of users in this study. Patients who self-injected could not be evaluated in the USA as lanreotide autogel/depot is only licensed to be administered by HCPs in the USA; therefore, the self-injection evaluation was part of the study conducted in Europe. It is also possible that a bias could have been introduced in the validation study as the HCP group only included

participants from the USA whereas participants from the patient and caregiver groups were all from Europe. However, the design of the presented series of studies was intended to evaluate the new syringe in the most relevant user groups for each world region (HCPs only in the USA, and patients or caregivers in Europe).

CONCLUSION

By collaborating with patients, caregivers and HCPs in the clinical evaluation process, we developed a new lanreotide autogel/depot syringe to meet their needs and it was subsequently validated to ensure that lanreotide was delivered effectively and safely in the intended environment, by the intended user, for the intended purpose.

ACKNOWLEDGEMENTS

The authors would like to thank all patients, caregivers and HCPs involved in the study, as well as the investigators and research staff in the participating institutions.

Funding. Sponsorship for these studies, the Rapid Service fee and open access fees were provided by Ipsen. All authors had full access to all of the data in these studies and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Medical Writing and Editorial Assistance. The authors thank Rachel Dobb, PhD, of Watermeadow Medical, an Ashfield Company, for providing medical writing and editorial support, which was funded by Ipsen in accordance with Good Publication Practice guidelines.

Disclosures. Daphne T. Adelman: Consultant for Pfizer and Novo Nordisk; advisory board for Ipsen, Crinetics, Novo Nordisk. Dirk Van Genechten: Board member of INCA, and NET & MEN Kanker Belgium vzw. Clémentine M. Megret: Employee of Ipsen. Xuan-Mai T. Truong Thanh: Employee of Ipsen. Philippa Hand: Consultant/advisory board member for Pfizer, Novartis and Ipsen. Wendy A. Martin: Honoraria from Ipsen and Novartis for academic talks; advisory board for Novartis.

Compliance with Ethics Guidelines. All participants had to provide written informed consent prior to enrolment in any of the studies. The studies conformed to the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. However, as they were not interventional clinical studies and the injections were simulated, no ethics review or committee approval was required. Validation studies were conducted in accordance with the FDA draft guidance, Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, issued February 2016 and European Standard: Application of usability engineering to medical devices EN62366–1:2015.

Data Availability. Where patient data can be anonymised, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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