Patient Preference and Adherence

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ORIGINAL RESEARCH

The Concizumab Pen-Injector is Easy to Use and Preferred by Hemophilia Patients and Caregivers: A Usability Study Assessing Pen-Injector Handling and Preference

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Introduction: Concizumab is a once-daily prophylactic treatment developed for patients with hemophilia A or B (HA/HB) with or without inhibitors. It is the first treatment for hemophilia patients to be delivered subcutaneously using a pre-filled, multi-dose pen-injector with a 4 mm, 32 G needle.

Aim: To investigate patient and caregiver handling and preference for the concizumab pen-injector compared with current injection systems used to treat hemophilia.

Methods: This preference and handling study was conducted in accordance with authority guidelines for approval of new devices and included adults and adolescents with HA/HB with or without inhibitors and caregivers currently administering factor replacement therapy or factor VIII mimetic (emicizumab) therapy. All participants underwent a training session, followed by a test session during which participants independently administered a single pen-injection into an injection pad or manikin. Time to train, time to prepare and inject, and number of complete independent injections handling the pen were assessed. Participants evaluated handling and preference via the Hemophilia Device Handling and Preference Assessment Questionnaire.

Results: 80 participants (44 adults, 21 adolescents, 15 caregivers) currently using factor replacement therapy (n=41, 51%) or emicizumab (n=39, 49%) participated. Average training time and time to complete an injection were 7 min 49s and 1 min 21s. In total, 98% of independent complete injections were achieved at first attempt. 98% (n=78; 95% confidence interval [CI] 91–100%) of participants assessed the pen-injector as either "easy" or "very easy" to use. 88% of participants preferred the pen-injector (n=70; 95% CI 78–94%) over their current injection system, and 9% (n=7) reported "no preference".

Conclusion: Participants found the concizumab pen-injector easy to learn and easy to use and preferred it over their current injection systems.

Plain Language Summary: People with hemophilia lack clotting factors that help stop bleeding after an injury. If left untreated, it can lead to life-threatening bleeding episodes. Treatment such as replacement therapy with clotting factors needs to be administered at regular intervals to prevent bleeding. The administration of intravenous (inside the vein) medication can be challenging due to the required skills, injection pain and availability of a good vein to inject into. Factor VIII mimetic therapy now allows people to inject medication under the skin (subcutaneously). However, using vials and syringes still poses challenges with the time to prepare and inject medication. Pen-injectors have been developed to address these challenges and provide additional benefits, including increased dose accuracy, portability, reduced discomfort, and less administration time. Concizumab is a medication developed for once-daily subcutaneous injection for people with hemophilia A or hemophilia B, with or without inhibitors, using a pen-injector. The objective of this preference and handling study was to understand patient and caregiver pen-injector handling experiences, and device preferences compared to their existing devices. In this study, most participants found it easy to learn to use the pen-injector. 98% of participants reported that the pen-injector was easy or very easy to use compared with their current device. 88% of participants reported

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a preference for the concizumab pen-injector over their current device. This shows that the pen-injector can easily and effectively be used to inject concizumab, providing more control and independence in patients' treatment while reducing the burden caused by intravenous modes of administration.

Keywords: concizumab, pen-injector, subcutaneous, preference and handling study, questionnaire

Introduction

Current management of hemophilia involves frequent intravenous (IV) infusions of factor replacement therapies or subcutaneous (SC) administration of non-factor replacement therapy using vial and syringe injection devices, which poses several treatment challenges. Well-known barriers to IV infusion are: (1) venous access; (2) frequent injections; (3) painful injections; (4) inconvenience of the administration, all of which result in reduced treatment adherence.[1–4] Other factors affecting adherence are the time-consuming nature of preparation, injection frequency, storage, and poor portability.[5–7]

Although SC administration of treatment using vial and syringe devices reduces barriers such as difficult venous access and pain, the use of vial and syringe devices still presents challenges with medication errors and longer administration times.[8,9] Overall, these factors impact the quality of life (QoL), including the impact on psychosocial well-being, and treatment adherence of patients.[4,10] Ultimately, a significant unmet need relating to current administration method exists.

To overcome the challenges associated with treatment administration, pen-injectors have been developed and widely used over the past four decades in other therapy areas.[11] The advantages of pen-injector use over traditional vial and syringe include improved dose accuracy, easier administration and better patient acceptability which may result in improved adherence.[12] Additionally, features that may influence a preference for pen-injectors include ease of use, which should be considered when developing devices for patients with manual dexterity impairment.[13] FlexTouch (PDS290) pen-injectors (Novo Nordisk A/S, Bagsværd, Denmark) comprise devices currently in use[14–16] that have been developed to specifically address feasibility concerns such as ease of use and long administration time, ensuring safe and effective use by all intended users.

Concizumab is the first prophylactic treatment for hemophilia patients to be delivered using a pen-injector and with a potential to address unmet need for all hemophilia patients. Concizumab is a novel anti-TFPI (tissue factor pathway inhibitor) monoclonal antibody, intended for once-daily SC prophylaxis in patients with hemophilia A or B (HA/HB), with or without inhibitors.[17] Concizumab is available as a liquid formulation with a shelf-life of 28 days after the first use and can be stored at room temperature below 30°C,[18] enabling its inclusion within a ready-to-use and easy-to-use pen-injector.[19,20] Thus, concizumab offers a novel approach, using SC administration with a pen-injector for patients with HA/HB, both with and without inhibitors.

The concizumab pen-injector is a pre-filled device with a dose setting mechanism and is used together with a single-use, disposable NovoFine® Plus 32G (0.23 mm/0.25 mm), 4 mm long needle (Figure 1). The aim of this preference and handling study was to investigate patient and caregiver handling and preference for the concizumab pen-injector compared with their current treatment injection systems (hereafter "current device"). As opposed to a clinical study, a medical device usability study aims at evaluating the device by testing it with representative participants who complete typical tasks and to evaluate the functionality and ease of use of the device in a simulated use environment. The study did not include evaluating use errors or root causes in case of incomplete injections.

Methods

Study Design and Participants

This preference and handling study was conducted by Novo Nordisk (NN) in collaboration with Research Collective in accordance with the Food and Drug Administration (FDA) accepted human factors principles outlined in the HE 75 document.[21,22] The study was facilitated by Research Collective in Tempe, Arizona and fielded in five locations in the United States of America (USA). Adult (≥18 years old) and adolescent (9–17 years old) patients with HA or HB, with or without inhibitors, and currently treated with factor replacement product or FVIII mimetic (emicizumab) treatment were

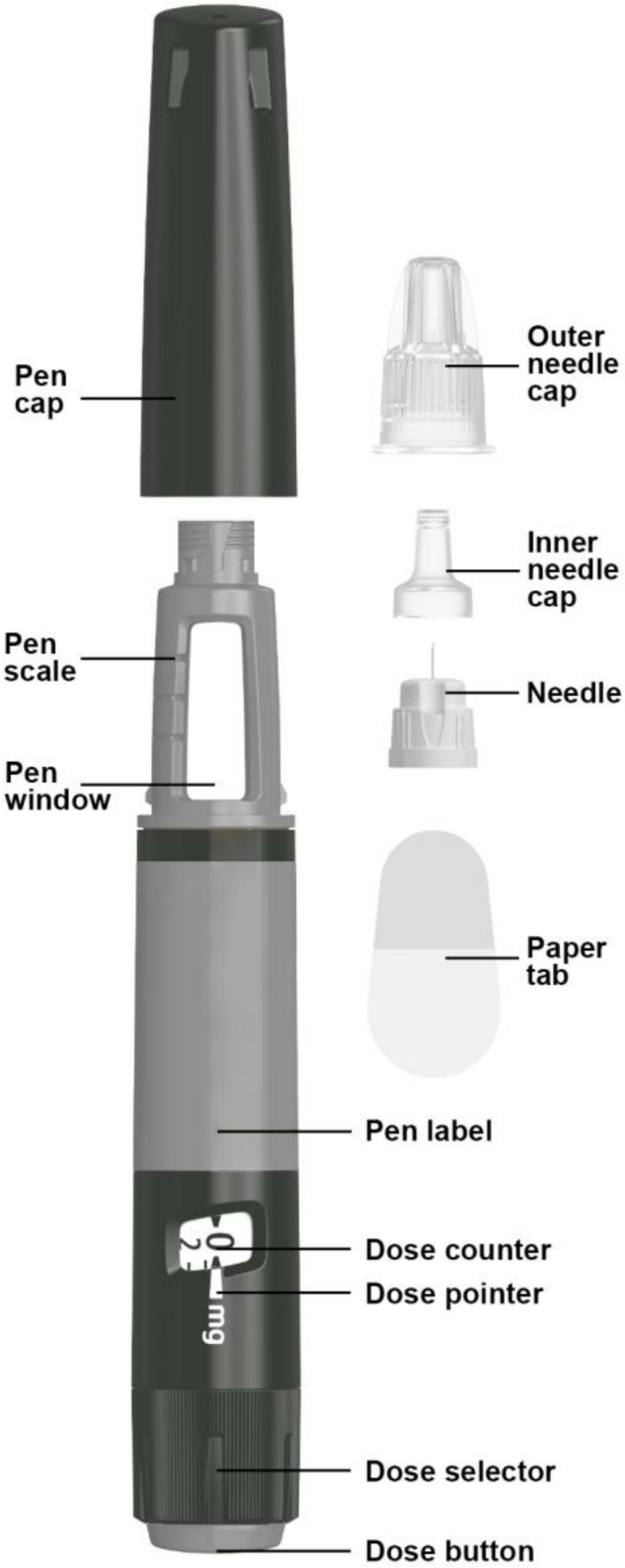


Figure 1 Concizumab pen-injector components. The concizumab pen-injector is shown with labelled individual components. Each pen-injector is supplied as a pre-filled pen containing 150 mg concizumab to be used with NovoFine® Plus 32G, 4 mm long injection needles, which come with inner and outer needle cap. The pen can deliver a maximum of 80 mg in one injection. The interval on the dose counter is 1 mg.

included in the study, along with the caregivers (≥18 years old) of this patient population. Patients who could self-administer injections independently or with support from caregivers were included. The majority of participants were pen-injector naïve. The exclusion criteria comprised: (1) mental or extreme physical incapacity, such as self-reported dementia and paralysis, respectively; (2) inability to read (eg, read a newspaper); (3) a barrier that precluded communication; (4) personal or family connection to the pharmaceutical industry; (5) occupation of clinical research in the medical device or pharmaceutical industry; (6) previous participation in a usability study within the past 6 months. Participants could withdraw from the study at any time without cause. Reasons could include but were not limited to: (1) feeling ill during the test; (2) withdrawing previously provided consent; (3) exhibiting cognitive impairment and/or inability to perform test activities. Participants were requested to participate in a 60–90 min usability study session. The study sessions took place in a test facility designed to be representative of the patient home environment, such as a living room. Research Collective LLC, an independent research company based in Tempe, AZ, USA, was responsible for recruiting participants via an Institutional Review Board (IRB) approved recruiting screener (see Supplementary Materials) that determined their inclusion in or exclusion from the study. All participants or, for patients under 18 years of age, parents or legal guardians, either provided informed consent or assent was obtained where appropriate, and approved a data processing form which gave consent to video recordings and still photographs being taken during the training or test session. Participants were compensated at a rate commensurate with local market value. This study was reviewed and approved by Castle IRB, an institutional review board offering review services in specific areas of research, including the rare disease space, located in Chesterfield, Missouri, USA. The study complies with the Declaration of Helsinki.

Study Objectives and Endpoints

The study had two main objectives. One objective was to determine whether the concizumab pen-injector is easy to learn how to use and easy to use. Endpoints included time to train, time to prepare and inject and the number of complete injections. Complete administration was achieved when a participant successfully demonstrated attaching the needle, removing the outer and inner needle caps, setting the intended dose, and injecting the full dose (Table 1). In addition, patient preference and ease of use of the concizumab pen-injector compared with their current device was assessed using the Hemophilia Device Handling and Preference Assessment (HDHPA) questionnaire.

Participant Training, Test Execution and HDHPA Questionnaire

All participants underwent a training session led by a certified nurse that lasted up to 15 min (Figure 2). The training encompassed a systematic overview of the instructions for use as well as an examination of the pen-injector components. The training session also included a practical demonstration of an injection being administered into an injection pad or manikin, followed by participants practicing the injection technique themselves. Before concluding the training session participants were provided with the chance to address any questions they might have. The training was followed by a test session during which participants independently administered a single injection into an injection pad or manikin. All

Table 1 Simulated Injection Steps

Injection Step	Contributed to Complete Injection (Yes/No)
1: Check your pen	No
2a: Attach the needle	Yes
2b: Remove outer and inner needle caps	Yes
3: Dial to "1" and test the flow	No
4: Set the intended dose (14 mg)	Yes
5: Inject the dose	Yes
6: Remove and dispose of the used needle	No
7: Put on the pen cap	No

Notes: Simulation injection steps contributing to complete injection.

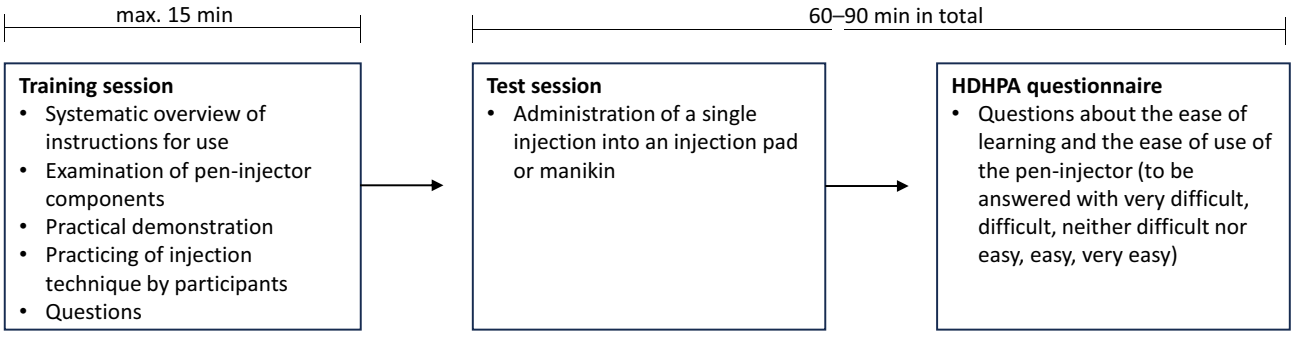


Figure 2 Overview of study design and implementation.

participants completed the HDHPA questionnaire on device handling and preference immediately after executing the test session. The Research Collective personnel responsible for conducting the test included a test administrator and a notetaker. NN personnel had the opportunity to unobtrusively observe the test session through a one-way mirror in a separate room, or remotely, without engaging directly with the participants. If needed, these individuals could request that the test administrator ask the participant additional questions of interest.

Participant Training

Training comprised three steps. First, an introduction to the pen-injector and instructions for use. This comprised an overview of (1) pen-injector components, (2) needle components, and (3) injection steps (Figure 1). Second, the trainer demonstrated the steps involved in completing the injection into an injection pad or a manikin (Table 1). Third, each participant practiced injection(s). Participants performed one or more injections into an injection pad placed on the patient's body using a VELCRO® strap or onto a manikin (for caregivers) until a complete injection was achieved during the training session (maximum duration 15 min).

Participant Test Execution

After being trained, participants performed one test injection independently and completed the HDHPA questionnaire, which together lasted 60 min to 90 min (Figure 2). The test execution included steps to prepare the pen-injector for a complete injection. Detailed steps that contribute to completing an injection are described in Table 1. After completing the injection, participants assessed the device handling and their preference for the concizumab pen-injector using the HDHPA questionnaire (see Supplementary Materials).

Hemophilia Device Handling and Preference Assessment (HDHPA) Questionnaire

The HDHPA questionnaire comprised questions related to ease-of-use, confidence in using the device, and preference for the pen-injector compared with the current device. Ratings on various aspects of device handling and preference were collected and recorded. To evaluate the comprehensiveness and relevance of the HDHPA questionnaire within this population, one-on-one cognitive interviews for a maximum of 60 min were conducted with approximately 10 adult and 5 adolescent patients with hemophilia and 5 caregivers. Specifically, the interviews were used to examine instrument instructions, items, response options, and recall period to establish evidence of content validity for the instrument's use in alignment with current scientific best practice guidance's from the Food and Drug Administration (FDA)[23] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Content Validity Task Force.[24,25] The results from the cognitive interviews will be reported elsewhere.

Data Analysis

All endpoints were summarized using standard descriptive statistics with 95% confidence intervals assessed using Clopper-Pearson interval methodology. Demographic data and background information were reported descriptively with mean and percentages. In addition, comments (eg, complaints, responses to interview questions) were organized

into related groups to reveal opinion patterns. All summaries were based on both the distinct user groups and on current treatment (factor replacement treatment or emicizumab).

Results

Study Participants

A total of 80 participants (44 adults, mean age: 28 years; 21 adolescents, mean age: 14 years; 15 caregivers, mean age: 40 years) were included in the study. Participants were either administering factor replacement products (n=41, 51%) or on emicizumab (n=39, 49%) (Table 2). The mean treatment period for adults was 25 years. The mean treatment period was 12 years for both adolescents and patients looked after by the caregivers included in the study (Table 2). The majority of the participants included in the study presented with HA without inhibitors (adults: n=34, 77%; adolescents: n=16, 76%) (Table 3). In addition, 87% (n=13) of caregivers included in the study cared for patients with HA without inhibitors (Table 3).

Training Time

The average training time across all participants was 7 min 49s, with a median of 7 min. The average training time for adult participants was 7 min 45s, with a median of 7 min. The average training time for adolescent participants was 7 min 37s, with a median of 7 min. The average training time for caregivers was 8 min 16s, with a median of 8 min (Table 4).

Table 2 Participant Demographic Details

Participant	Adult	Adolescent	Caregiver
N (%)	44 (55)	21 (26)	15 (19)
Mean age (years)	28	14	40
Gender	36 Male 8 Female	21 Male	3 Male 12 Female
Mean treatment period (years)	25	12	12
Highest employment status	Associate and PhD	12th grade	Associate

Abbreviation: N, number of participants.

Table 3 Participant Type of Hemophilia and the Current Treatment

Type of Hemophilia	Participants (n=80)		
	Adult (n=44)	Adolescent (n=21)	Caregiver (n=15)
Hemophilia A w/o inhibitors, n (%) Hemophilia A with inhibitors, n (%) Hemophilia B w/o inhibitors, n (%) Hemophilia B with inhibitors, n (%)	34 (77) – 10 (22) –	16 (76) 2 (10) 3 (14) –	13 (87) – 1 (7) 1 (7)
Type of current treatment Factor replacement products, n (%) Emicizumab (Factor VIII mimetic therapy), n (%)	 26 (59) 18 (41)	 9 (43) 12 (57)	 6 (40) 9 (60)

Abbreviations: w/o, without; n, number of participants.

Table 4 Measurements of Training Time, Time to Administer an Injection, and the Correct Execution of the Injection

	Average time	Range	Median
Training time			
Adult patients	7 min 45s	5–13 min	7 min 0s
Adolescent patients	7 min 37s	5–12 min	7 min 0s
Caregiver participants	8 min 16s	6–15 min	8 min 0s
Total	**7 min 49s**	**5–15 min**	**7 min 0s**
Time to prepare and inject			
Adult patients	1 min 19s	0 min 33s–4 min 3s	1 min 5s
Adolescent patients	1 min 13s	0 min 29s–2 min 0s	1 min 2s
Caregiver participants	1 min 40s	1 min 8s–2 min 45s	1 min 43s
Total	**1 min 21s**	**0 min 29s–4 min 7s**	**1 min 10s**
Completed injections	**Number of correctly executed injections (n; %)**		
Adult patients	43; 98%		
Adolescent patients	20; 95%		
Caregiver participants	15; 100%		
Total	**78; 98%**		

Notes: There was a total of 78 (98%) complete injections, with only 2 participants not completing a step (1 adult and 1 adolescent). In both cases the participants did not inject the full dose on the first attempt. This may be considered a test artefact.
Abbreviation: n, number of participants.

Administration Time

The time taken to successfully complete an injection across all participants was assessed. The time required to complete an injection with the concizumab pen-injector across all participants was 1 min 21s, with a median of 1 min 10s. The time required to complete an injection by adult participants was 1 min 19s, with a median of 1 min 5s. The time required to complete an injection by adolescent participants was 1 min 13s, with a median of 1 min 2s. The caregivers took 1 min 40s to complete an injection, with a median of 1 min 43s. Overall, complete injections were achieved by 98% (n=78) of the participants, with only 2 participants (1 adult and 1 adolescent) being unsuccessful due to a test artefact (medication was left in the pen-injector due to increased injection force, preventing flow of the fluid) (Table 4). When assessed individually, almost all participants (adult: n=43, 98%; adolescent: n=20, 95%; caregivers: n=15, 100%) successfully completed the injections (Table 4).

Ease-of-Learning to Use and Ease-of-Use of the Concizumab Pen-Injector

When participants were asked about the ease-of-learning to use the concizumab pen-injector, most rated that it was either easy or very easy (n=78, 97%) (Figure 3A). By category, all caregivers (n=15, 100%), 97% of adults (n=43), and 96% of adolescents (n=20) rated the pen-injector as either easy or very easy to learn to use (Figure S1). The pen-injector was considered to be easy or very easy to prepare for an injection (n=79, 99%) (Figure 3A). Most participants (n=76, 95%) rated the pen-injector as easy to carry and use outside their home (Figure 3A). In terms of usage, 85% of all participants (n=68; 95% CI: 75%–92%) reported that the concizumab pen-injector was very easy to use, and more broadly, 98% (n=78) of all participants (n=78; 95% CI: 91%–100%) reported that the concizumab pen-injector was either easy or very easy to use (Figure 3B). In all, 88% (n=36) of participants on factor replacement products and 82% (n=32) of participants on emicizumab reported that the concizumab pen-injector was very easy to use (Figure S2).

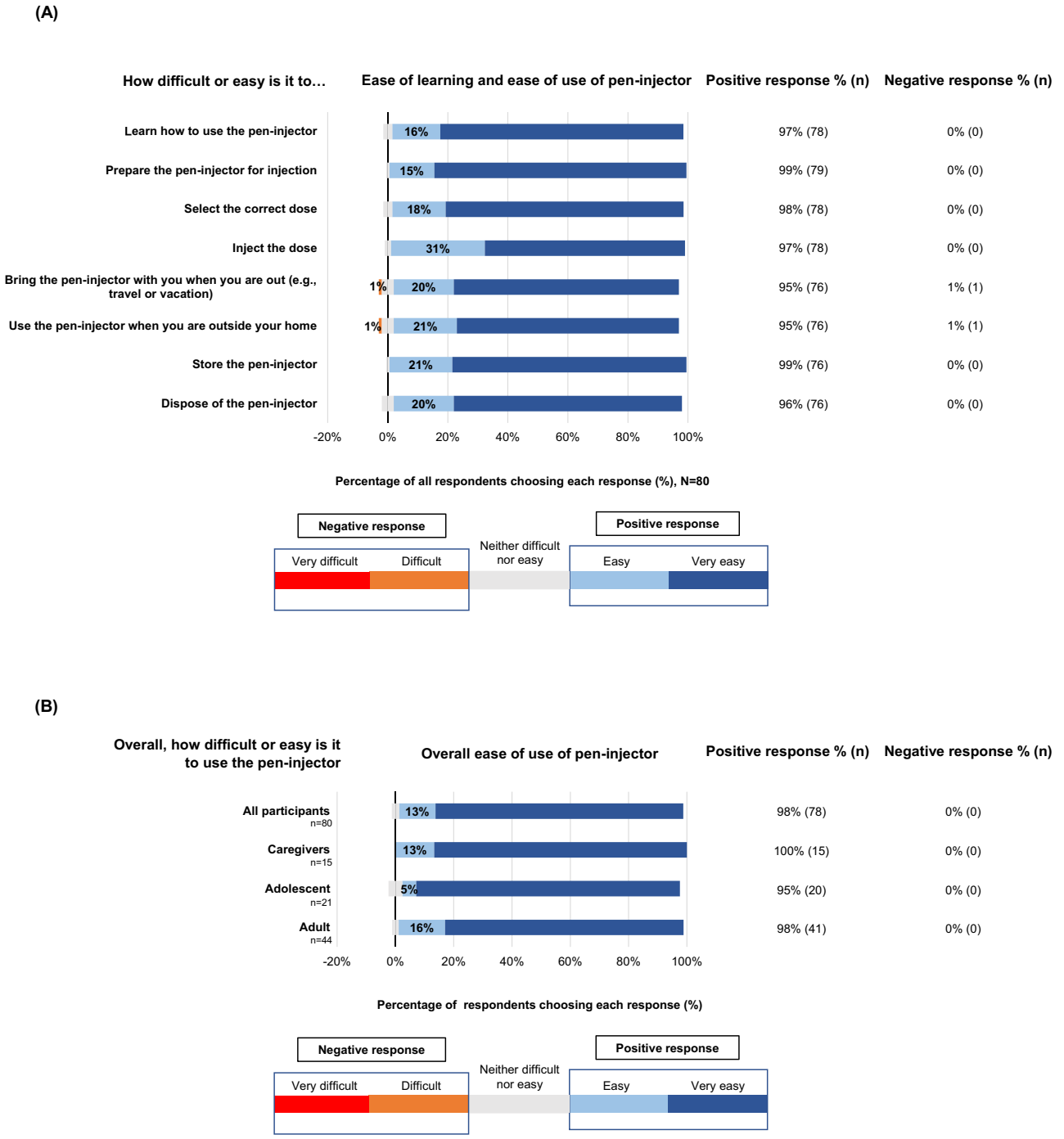


Figure 3 The ease of learning and ease of use of the pen-injector as assessed using the HDHPA questionnaire. (**A**) Responses from participants to HDHPA question 1 on factors associated with ease of handling and use of concizumab pen-injector. Participants were asked to select the response that most closely represented how they felt using the pen-injector. (**B**) Responses from participants to HDHPA question 2 on overall difficulty or ease of use of the concizumab pen-injector. Responses were assessed on a 5-point scale ranging from very difficult to very easy. Responses for very difficult and difficult were combined to represent negative results and the responses easy and very easy were combined to represent positive results. Data are presented as number of responses with percentages % (n).

Confidence in Using the Concizumab Pen-Injector

A total of 97% (n=77) of participants reported that they were either very confident or extremely confident to use the pen-injector correctly (Figure 4A). All the caregivers (n=15) and adolescents (n=21) responded that they were either very confident or extremely confident to use the pen-injector correctly (Figure 4A). In addition, 84% (n=67) of participants reported that they were either very or extremely confident that the pen-injector delivered the correct full dose (Figure 4B).

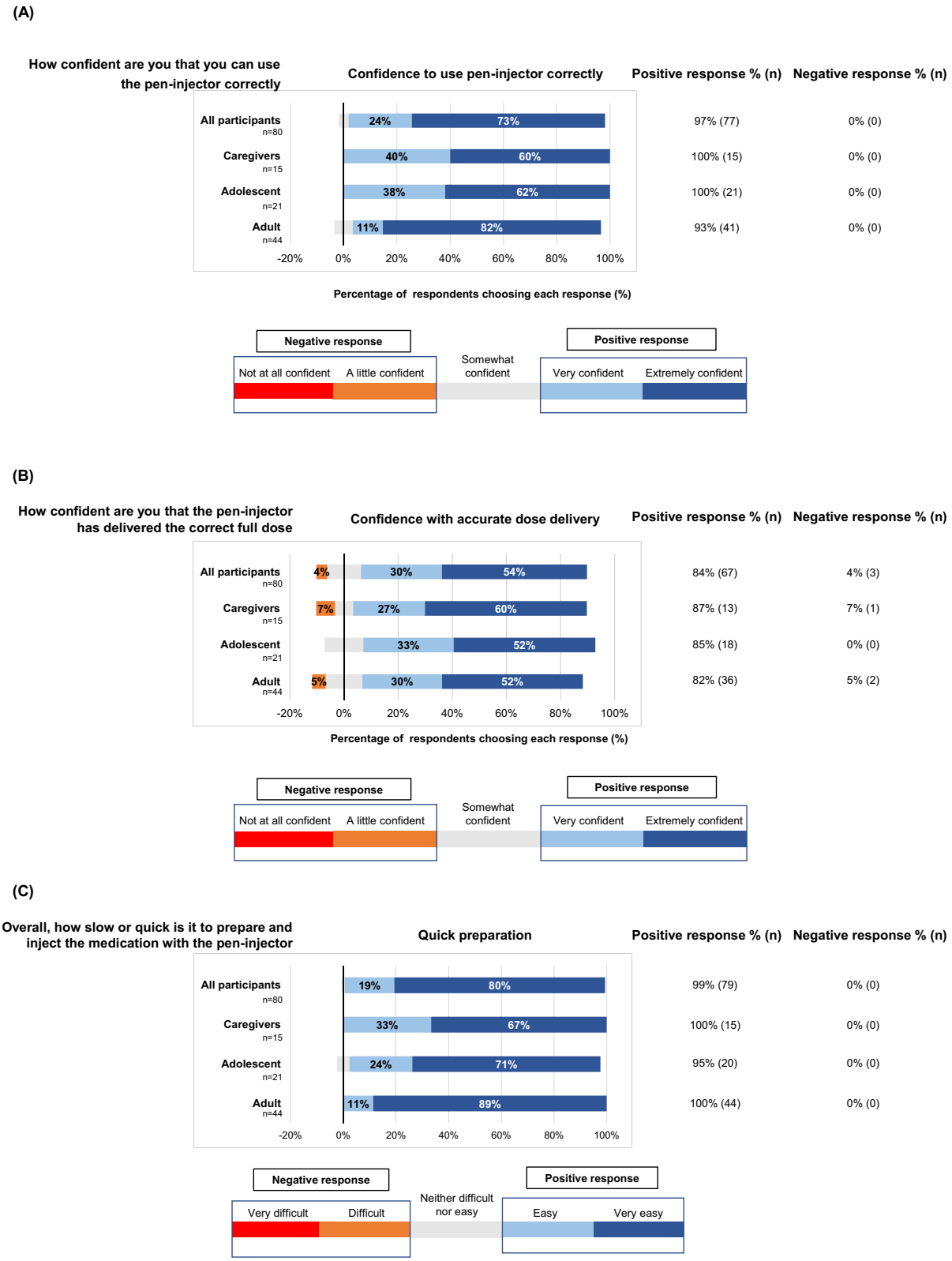


Figure 4 Confidence in using and quick preparation of the pen-injector. (**A**) Responses from participants to HDHPA question 3 on confidence in using the pen-injector correctly. (**B**) Responses from participants to HDHPA question 3 on confidence that the pen-injector delivered the correct full dose. Responses were assessed on a scale of 5 (not at all confident, a little confident, somewhat confident, very confident, extremely confident). Responses to not at all confident and a little confident were combined to represent negative results. Responses to very confident and extremely confident were combined to represent positive results. (**C**) Responses from participants to HDHPA question 4 on how slow or quick it was to inject with the concizumab pen-injector. Responses were assessed on a scale of 5 (very slow, slow, neither slow or quick, quick, very quick). Responses to slow and very slow were combined to represent negative results, and responses for quick and very quick were combined to represent positive results. Data are presented as number of responses with percentages % (n).

Another 12.5% (n=10) participants were somewhat confident that the correct full dose was delivered by the pen-injector. In total, 99% (n=79) of participants reported that preparing and administering the medication was either quick or very quick with the pen-injector (Figure 4C). Specifically, all of the caregivers (n=15, 100%) and adults (n=44, 100%) responded that it was either quick or very quick to prepare and inject the medication with the pen-injector (Figure 4C).

Comparison of the Pen-Injector with the Patient's Current Device

Compared with their current device, 92% (n=73) of participants reported that the pen-injector was either easier or much easier to learn to use (Figure 5A). This was also the case for participants who were currently on SC emicizumab treatment of whom 90% (n=35 out of 39) found that learning to use the pen-injector was easier or much easier to use. In terms of the overall ease of using the pen-injector, 96% of all participants (n=77; 95% CI: 89–99%) reported that the concizumab pen-injector was either easier or much easier to use than their current device (Figure 5B). Again, this also applied to participants currently using emicizumab with 95% (n=37 out of 39) of participants finding it easier or much easier to use the concizmab pen-injector than their current device. By category, 95% (n=42) of adults and 95% (n=20) of adolescents reported that it was either easier or much easier to use the pen-injector than their current device (Figure 5B). All of the caregivers (n=15, 100%) felt that it was either easier or much easier to use the pen-injector compared to their current device (Figure 5B).

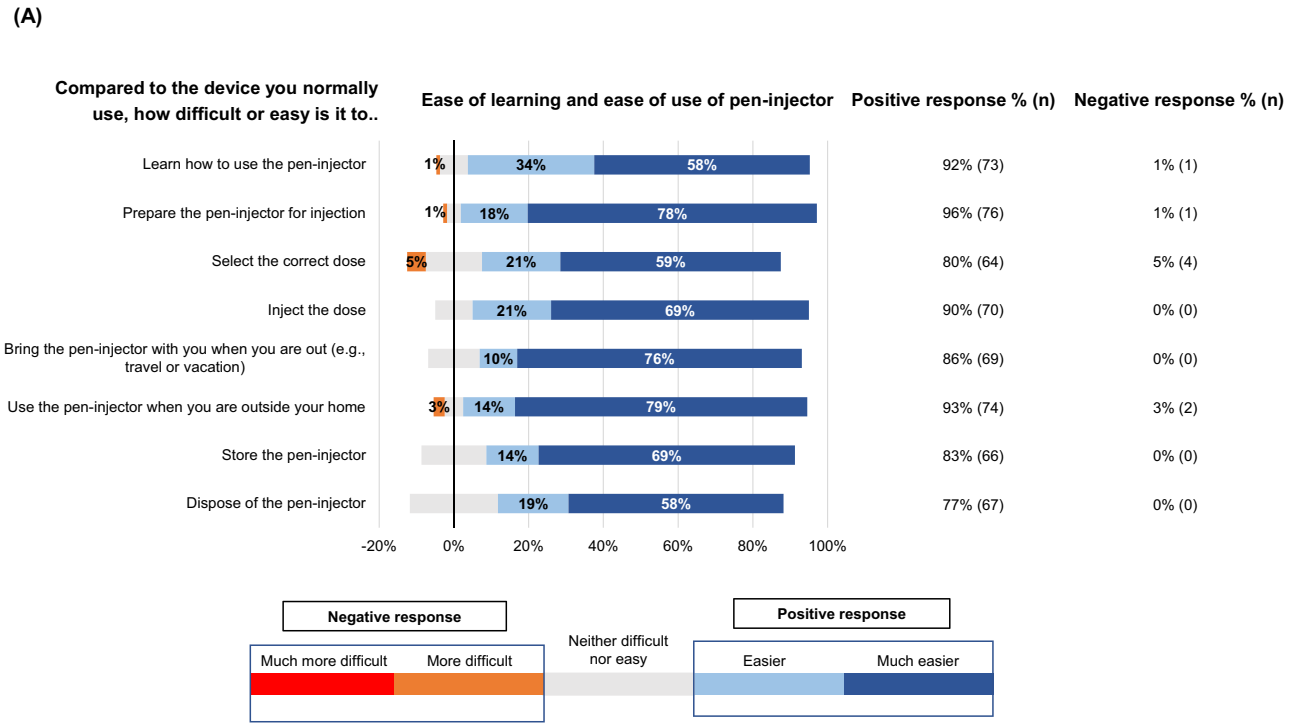
Preference for the Pen-Injector Over the Patient's Current Device

When participants were asked about their preference between the concizumab pen-injector and the current device they use to administer the treatment, 88% (n=70; 95% CI: 78–94%) of all participants expressed a preference for the concizumab pen-injector (Figure 6A). Specifically, 89% (n=39; 95% CI: 75–96%) of adults and 76% (n=16; 95% CI: 53–92%) of adolescents reported that they preferred the concizumab pen-injector to their current device (Figure 6A). All caregivers (n=15, 100%) expressed a preference for the concizumab pen-injector (Figure 6A). Only 9% (n=7) reported no preference and 4% (n=3) preferred their current device. Notably, 90% of participants who were on emicizumab or caring for a patient taking emicizumab preferred the concizumab pen-injector (Figure 6B). Of those who preferred the concizumab pen-injector, 97% (n=68) reported that their device preference was either very strong or fairly strong (Figure 6C).

Discussion

This usability study assessed the handling of and preference for the concizumab pen-injector in the management of hemophilia therapy. It should be noted that in contrast to a clinical trial, a usability study asks a fundamentally different question, namely whether patients can use a medical device safely and effectively as intended. Usability studies therefore are conducted under completely different requirements and follow other regulations. In this study, safety assessments and an evaluation of the root causes of use errors, if any, were not conducted. Patient and caregiver perspectives on treatment administration methods are very important, as the treatment is used as lifelong prophylaxis. In the study, 98% of participants successfully achieved an initial independent simulated injection, with an average time of 1 min 21s. The majority of participants rated that the concizumab pen-injector was either easy or very easy to learn to use (97%) and to use (98%). In all, 96% of participants found the pen-injector easier to use than their current device, and 88% of participants preferred to use the concizumab pen-injector. Easier use compared to the participants' current device was reported no matter whether participants were currently treated with IV factor product or SC emicizumab, with 98% (factor) or 95% (emicizumab) of participants finding the pen-injector easier to use, respectively. Eighty-five percent (factor) or 90% (emicizumab) of participants preferred the concizumab pen-injector over their current device. Of participants who preferred the concizumab pen-injector over their current device, 97% reported that the device preference was either fairly strong or very strong. This suggests that most participants felt comfortable both in learning to use and in using the pen-injector compared with their current device.

Participants received a face-to-face training session conducted by a certified nurse prior to using the pen-injector which can be perceived as a limitation of this study, as no other means of training such as videos or other materials were offered. This has to be seen in the light of this specific patient population being highly controlled with face-to-face



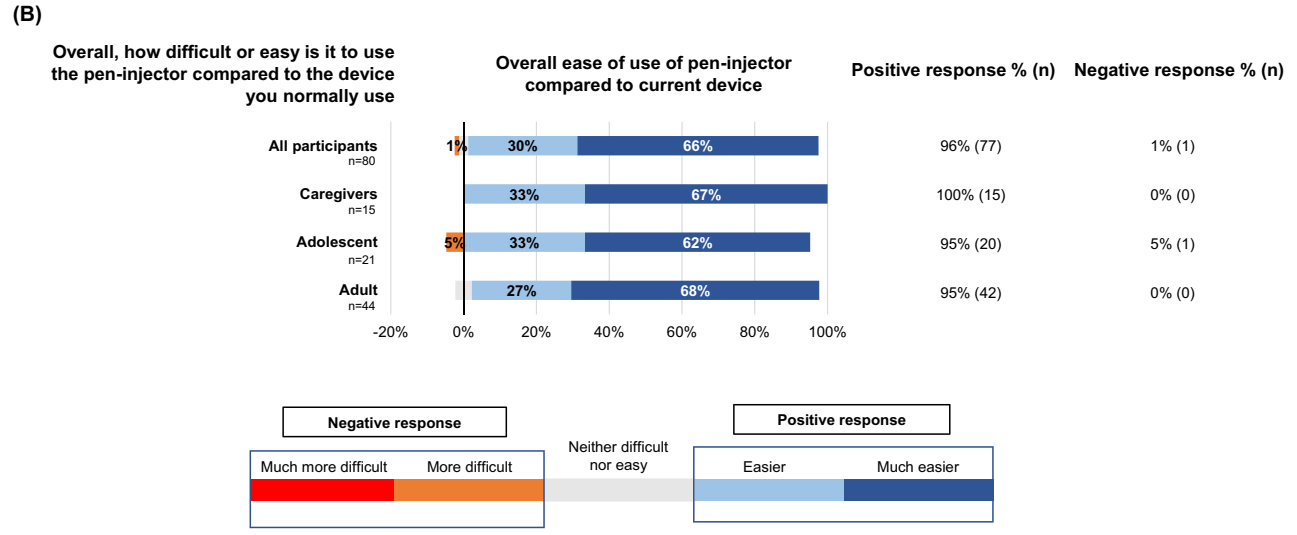


Figure 5 Comparison of the pen-injector to the patient's current device as assessed using the HDHPA questionnaire. (**A**) Responses from participants to HDHPA question 5 on factors associated with ease of handling and use of the concizumab pen-injector compared to their current device. (**B**) Responses from participants to HDHPA question 6 on overall ease or difficulty of use of the concizumab pen-injector compared to their current device. Responses were assessed on a scale of 5 (much more difficult, more difficult, neither more difficult nor easy, easier, much easier). Responses for much more difficult and more difficult were combined to represent negative results, and responses for easier and much easier were combined to represent positive results. Data are presented as number of responses with percentages % (n).

training for hemophilia treatment being received as standard. Study participants were therefore introduced to the device in a way that is similar to the way the training would have been conducted in the clinic. Nevertheless, such other training means may be available once the pen-injector has become a more established treatment modality.

The results obtained during this study are consistent with the results of two previous usability studies.[14,26] Those studies compared pen-injector to vial and syringe for the administration of insulin to people with type 1 or type 2

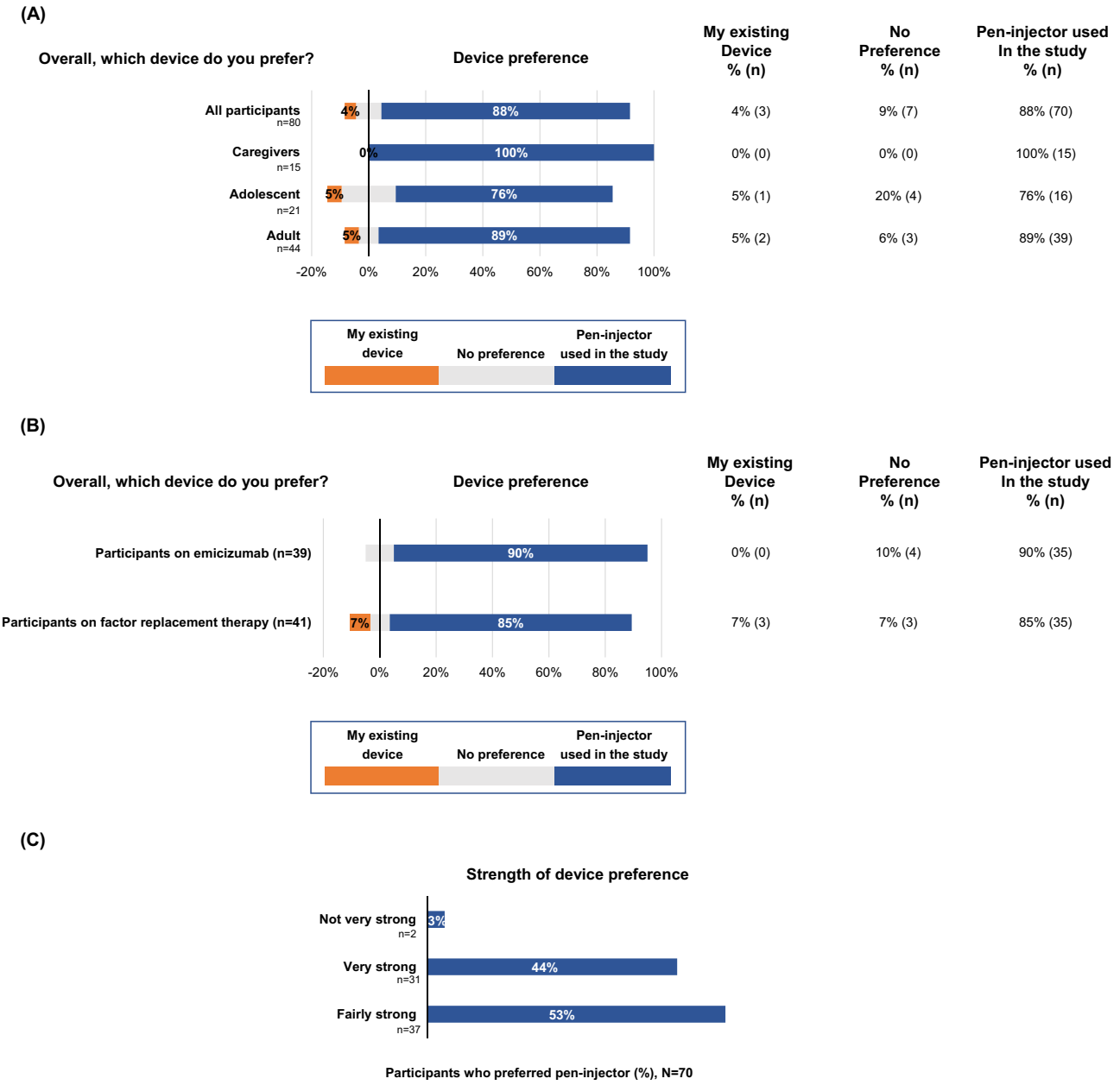


Figure 6 Preference for the pen-injector over the patient's current device. (**A**) Responses from participants to HDHPA question 9 on device preference. Device preference was recorded on a scale of 3 (pen-injector used in the study, no preference, my existing device). (**B**) Responses from participants either on factor replacement therapy or FVIII mimetic therapy (emicizumab) on device preference. (**C**) Responses from participants to HDHPA question 10 on strength of the device preference for those who preferred concizumab pen-injector (n=70) recorded on a scale of 3 (not very strong, fairly strong, very strong).

diabetes. Overall, 88% of respondents preferred a pen-injector compared with 5% who preferred vial and syringe, indicating high satisfaction with pen-injectors.[14,26] A survey of patients on regular growth hormone treatment, treating health care professionals, and caregivers demonstrated that pen-injectors are simple and easy to use, and reported an association between the use of the pen-injector and improved therapy adherence.[27]

One of the key outcomes of pen-injector use is the potential to maintain accurate dosages across different dose ranges. The FlexTouch® (from which the concizumab pen-injector is adapted) was shown to fulfil dosing accuracy as defined by ISO 11608–1 across a wide range of doses (10 microliters, 400 microliters and 800 microliters).[28] In this study, 84% (n=67) of participants were either very or extremely confident that the pen-injector delivered the correct full dose. Although this question resulted in the lowest positive response compared to all other questions, this has to be seen in the

light of the pen-injector being a completely new device with an unknown scale to this patient population. Another 12.5% (n=10) participants were somewhat confident that the pen-injector delivered the correct full dose.

In addition, pen-injectors reduce medication waste, increasing cost-effectiveness,[8] and require fewer resources compared with vials and syringes.[29] Therefore, the improved accuracy feature of pen-injectors will be particularly beneficial to patients who are visually or neurologically challenged, and for those who need to administer treatment on a daily basis.[30]

Despite significant advancements in hemophilia care, there have been multiple instances in which patients fail to adhere to their current treatment regimen. Some of the reasons reported include painful IV injections, the frequency of prophylaxis and the level of skill required for accurate dose administration.[5,31] One solution that could overcome these challenges is an SC mode of administration with pen-injectors, which are easier to use due to their portability, and cause less pain than IV infusions.[32] In addition, although hygiene measures such as aseptic techniques are required for both IV or SC administration routes, the consequences of not complying with these may be more harmful in the case of IV infusions considering the possibility of transferring blood-borne pathogens. Previous and current studies of SC prophylaxis with concizumab in explorer4,[33] explorer5,[33] explorer7,[34] and explorer8[35] indicated a trend towards improved health-related QoL and reduced treatment burden, suggesting a potential positive long-term outcome. In line with the explorer studies, the HAVEN 3 study for SC administration with emicizumab indicated a lower treatment burden and increased treatment satisfaction in persons with HA without FVIII inhibitors.[36] Similarly, reports on shared decision for administration methods conducted in patients with systemic lupus erythematosus taking non-steroidal anti-inflammatory drugs suggest that both physicians and patients preferred SC administration over IV injections.[37] Although considered the gold standard method for assessing device usability, simulated use models may not completely reflect the true experience of at-home use. In addition, it may be difficult for a participant to evaluate the pen-injector based on a single injection performed with an injection pad or manekin. It should further be noted that in usability studies like the one reported here participants are compensated at a rate commensurate with fair local market value, as opposed to Phase 3 clinical studies evaluating drugs for which participants are usually not compensated.

Conclusion

Overall, patients and caregiver participants found the concizumab pen-injector easy to learn to use and easy to use. Most participants were confident administering the dose correctly and found the process to be rapid. A majority of participants preferred the pen-injector over their current administration method. This study highlights the potential of the concizumab pen-injector to effectively address an unmet need experienced by caregivers and patients with HA/HB, irrespective of inhibitor status, thereby alleviating a treatment burden.

Data Sharing Statement

All of the individual participant data collected during the study will be made available upon reasonable request to the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported. This included the conception, study design, execution, acquisition of data, analysis and interpretation, drafting, revising or critically reviewing the article. All authors gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

Disclosure

NKR, BB, ASLC, JSN, GTB, and TS are employees of Novo Nordisk. EH and MG are employees of Research Collective, LLC, Tempe, Arizona, USA. Novo Nordisk is the sponsor of the trial. The study was conducted by an independent CRO. The authors report no other conflicts of interest in this work.

References

1. Mannucci PM. Hemophilia therapy: the future has begun. *Haematologica*. 2020;105(3):545–553. doi:10.3324/haematol.2019.232132
2. Callaghan MU, Negrier C, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. *Blood*. 2021;137(16):2231–2242. doi:10.1182/blood.2020009217
3. Okaygoun D, Oliveira DD, Soman S, Williams R. Advances in the management of haemophilia: emerging treatments and their mechanisms. *J Biomed Sci*. 2021;28(1):64. doi:10.1186/s12929-021-00760-4
4. Wiley RE, Khoury CP, Snihur AWK, et al. From the voices of people with haemophilia A and their caregivers: challenges with current treatment, their impact on quality of life and desired improvements in future therapies. *Haemophilia*. 2019;25(3):433–440. doi:10.1111/hae.13754
5. Remor E. Predictors of treatment difficulties and satisfaction with haemophilia therapy in adult patients. *Haemophilia*. 2011;17(5):e901–5. doi:10.1111/j.1365-2516.2011.02578.x
6. Spain CV, Wright JJ, Hahn RM, Wivel A, Martin AA. Self-reported barriers to adherence and persistence to treatment with injectable medications for type 2 diabetes. *Clin Ther*. 2016;38(7):1653–1664e1. doi:10.1016/j.clinthera.2016.05.009
7. Tischer B, Marino R, Napolitano M. Patient preferences in the treatment of hemophilia A: impact of storage conditions on product choice. *Patient Prefer Adherence*. 2018;12:431–441. doi:10.2147/PPA.S151812
8. Arora P, Muehrcke M, Hertig J. A cost-effectiveness study comparing ready-to-administer and traditional vial-and-syringe method for opioids. *Pain Ther*. 2022;11(3):937–950. doi:10.1007/s40122-022-00402-z
9. Lajara R, Guerrero G, Thurman J. Healthcare professional and patient perceptions of a new prefilled insulin pen versus vial and syringe. *Expert Opin Drug Deliv*. 2012;9(10):1181–1196. doi:10.1517/17425247.2012.721774
10. Lindvall K, Colstrup L, Wollter IM, et al. Compliance with treatment and understanding of own disease in patients with severe and moderate haemophilia. *Haemophilia*. 2006;12(1):47–51. doi:10.1111/j.1365-2516.2006.01192.x
11. Masierek M, Nabrdalik K, Janota O, Kwiendacz H, Macherski M, Gumprecht J. The review of insulin pens-past, present, and look to the future. *Front Endocrinol*. 2022;13:827484. doi:10.3389/fendo.2022.827484
12. Dang DK, Lee J. Analysis of symposium articles on insulin pen devices and alternative insulin delivery methods. *J Diabetes Sci Technol*. 2010;4(3):558–561. doi:10.1177/193229681000400308
13. Pfutzner J, Hellhammer J, Musholt P, et al. Evaluation of dexterity in insulin-treated patients with type 1 and type 2 diabetes mellitus. *J Diabetes Sci Technol*. 2011;5(1):158–165. doi:10.1177/193229681100500122
14. Campos C, Lajara R, Deluzio T. Usability and preference assessment of a new prefilled insulin pen versus vial and syringe in people with diabetes, physicians and nurses. *Expert Opin Pharmacother*. 2012;13(13):1837–1846. doi:10.1517/14656566.2012.713350
15. Hemmingsen H, Niemeyer M, Hansen MR, Bucher D, Thomsen NB. A prefilled insulin pen with a novel injection mechanism and a lower injection force than other prefilled insulin pens. *Diabetes Technol Ther*. 2011;13(12):1207–1211. doi:10.1089/dia.2011.0110
16. Wielandt JO, Niemeyer M, Hansen MR, Bucher D, Thomsen NB. FlexTouch: a prefilled insulin pen with a novel injection mechanism with consistent high accuracy at low- (1 U), medium- (40 U), and high- (80 U) dose settings. *J Diabetes Sci Technol*. 2011;5(5):1195–1199. doi:10.1177/193229681100500525
17. Shapiro AD. Concizumab: a novel anti-TFPI therapeutic for hemophilia. *Blood Adv*. 2021;5(1):279. doi:10.1182/bloodadvances.2019001140
18. Government of Canada. Summary basis of decision for alhemo; 2023. Available from: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/SBD1685635290781. Accessed July 16, 2024.
19. Eichler H, Angchaisuksiri P, Kavakli K, et al. Concizumab restores thrombin generation potential in patients with haemophilia: pharmacokinetic/pharmacodynamic modelling results of concizumab Phase 1/1b data. *Haemophilia*. 2019;25(1):60–66. doi:10.1111/hae.13627
20. Chowdary P, Lethagen S, Friedrich U, et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. *J Thromb Haemost*. 2015;13(5):743–754. doi:10.1111/jth.12864
21. Association for the Advancement of Medical Instrumentation. ANSI/AAMI HE75: 2009 (R2018) human factors engineering - design of medical devices. Available from: https://webstore.ansi.org/preview-pages/AAMI/preview_ANSI+AAMI+HE75-2009+(R2018).pdf. Accessed July 16, 2024.
22. US Food and Drug Administration. Applying human factors and usability engineering to medical devices: guidance for industry and food and drug administration staff. Available from: https://www.fda.gov/media/80481/download. Accessed July 16, 2024.
23. US Food and Drug Administration. FDA Patient-focused drug development guidance series for enhancing the incorporation of the patient's voice in medical product development and regulatory decision making. Available from: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical. Accessed June 4, 2023.
24. Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1--eliciting concepts for a new PRO instrument. *Value Health*. 2011;14(8):967–977. doi:10.1016/j.jval.2011.06.014
25. Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 2--assessing respondent understanding. *Value Health*. 2011;14(8):978–988. doi:10.1016/j.jval.2011.06.013
26. Bohannon NJ, Ohannesian JP, Burdan AL, Holcombe JH, Zagar A. Patient and physician satisfaction with the Humulin/Humalog Pen, a new 3.0-mL prefilled pen device for insulin delivery. *Clin Ther*. 2000;22(9):1049–1067. doi:10.1016/S0149-2918(00)80084-3
27. Sauer M, Abbotts C. A new pen device for injection of recombinant human growth hormone: a convenience, functionality and usability evaluation study. *Patient Prefer Adherence*. 2018;12:27–34. doi:10.2147/PPA.S149412

28. Abdel-Tawab M, Schmitz M, Kamlot S, Schubert-Zsilavecz M. Dosing accuracy of two disposable insulin pens according to new ISO 11608-1: 2012 requirements. *J Diabetes Sci Technol*. 2015;10(1):157–161. doi:10.1177/1932296815595983
29. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. *Clin Ther*. 2006;28(10):1712–1725. doi:10.1016/j.clinthera.2006.10.004
30. Santiago OM, Khutoryansky NM, Bilbo CM, Lawton SA, Kristensen CM. Accuracy and precision of the NovoPen 3 insulin delivery device after mechanical and temperature stresses. *Endocr Pract*. 2002;8(5):351–355. doi:10.4158/EP.8.5.351
31. Schrijvers LH, Uitslager N, Schuurmans MJ, Fischer K. Barriers and motivators of adherence to prophylactic treatment in haemophilia: a systematic review. *Haemophilia*. 2013;19(3):355–361. doi:10.1111/hae.12079
32. Usach I, Martinez R, Festini T, Peris J-E. Subcutaneous injection of drugs: literature review of factors influencing pain sensation at the injection site. *Adv Ther*. 2019;36(11):2986–2996. doi:10.1007/s12325-019-01101-6
33. Faller M, Tønder SM, Porstmann T. Improvement in health-related quality of life measures after long-term, daily, subcutaneous concizumab prophylaxis in patients with hemophilia A/B with and without Inhibitors: results from the main and extension parts of Phase 2 clinical trials. abstract. *Blood*. 2021;138(1):1041. doi:10.1182/blood-2021-152257
34. Shapiro AD, Abraham A, Linari S, et al. Health-related quality of life in patients with hemophilia A or B with inhibitors on concizumab prophylaxis: results from the phase 3 explorer7 study. *Blood*. 2022;140(Supplement 1):2732–2734. doi:10.1182/blood-2022-166306
35. Young G, Benson G, Eichler H, et al. OC 59.4 health-related quality of life, treatment burden and patient preference in patients with haemophilia A/B without inhibitors on concizumab prophylaxis: results from the phase 3 explorer8 study. *Res Pract Thromb Haemost*. 2023;7:100427. doi:10.1016/j.rpth.2023.100427
36. Kempton C, Trask P, Parnes A, et al. Development and testing of the satisfaction questionnaire with intravenous or subcutaneous haemophilia injection and results from the Phase 3 HAVEN 3 study of emicizumab prophylaxis in persons with haemophilia A without FVIII inhibitors. *Haemophilia*. 2021;27(2):221–228. doi:10.1111/hae.14222
37. Bell CF, Lau M, Lee M, Poulos C. Insights into the choice between intravenous infusion and subcutaneous injection: physician and patient characteristics driving treatment in SLE. *Clin Rheumatol*. 2021;40(2):581–590. doi:10.1007/s10067-020-05226-w