Medical Devices: Evidence and Research Dovepress

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Investigation into the Acceptability of Moderate-to-Large Volume Subcutaneous Injections in Healthy Volunteers: Results from a Single-Center Randomized Controlled Study

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Purpose: Therapeutic proteins are often delivered by subcutaneous (SC) autoinjector to enable self-administration. Autoinjectors typically deliver up to 1 mL injected volumes per dose. Delivery of larger volumes may be limited by injection site discomfort, including pain, swelling, and redness. Delivery at a slower rate may mitigate this discomfort. This single-center, randomized, crossover study evaluated the acceptability and tolerability of varying volumes and delivery rates of SC saline in healthy volunteers.

Patients and Methods: Eligible participants were adults (18–65 years) with a body mass index of 18.5–32.0 kg/m^2. Participants (N = 24) were randomized to multiple sequences of infusions over five visits, with infusions ranging from 1 to 5 mL at rates of 1.50–6.00 mL/minute (min) and including a 1 mL SC infusion in 10 seconds (s) at a rate of 6.00 mL/min. The primary objective was to identify acceptable volume and delivery rates of SC saline, as assessed by visual analogue scale (VAS) pain scores, a tolerability and acceptability questionnaire, and infusion leakage.

Results: Infusions that met the acceptability criteria were 1 mL in 10s, 4 mL in 58s, and 3 mL in 2 mins. Higher delivery volumes and rates were associated with higher VAS pain scores but remained within the VAS acceptability criteria.

Conclusion: These findings may support the development of larger-volume injectors for self-administration of future medicines.

Keywords: drug delivery system, skin, formulation, pain scores, tolerability and acceptability questionnaire

Introduction

Therapeutic proteins such as monoclonal antibodies typically have high dose requirements, often exceeding 100 mg per dose.[1] This can lead to a variety of challenges, including those related to delivery to the patient.[2] Strategies to deliver such high doses include high-concentration formulations, multiple injections per dose, and high-volume injections.[1] High-concentration formulations are limited by the exponential relationship between concentration and viscosity, while multiple injections per dose increase the risk of non-adherence, reducing the likelihood that the patient will receive the full effective dose.[3]

High-volume injections can be delivered intravenously; however, in many cases, a subcutaneous (SC) injection is preferable because it enables self-administration by the patient, reduces the risk of systemic infection, and also reduces the cost of treatment.[4,5] These factors could lead to less need to travel to healthcare facilities, better patient compliance, and better quality of life for the patient. In addition to these benefits, multiple studies have shown that patients prefer SC administration compared with IV infusions.[6–9] Autoinjectors are commonly used to self-administer SC injections; volumes were historically limited to 1 mL or less, but recent developments have enabled increases to ~3 mL, while

Received: 24 May 2024
Accepted: 11 October 2024
Published: 25 October 2024

larger-volume injectors are generally on-body devices.[10] The delivery time for autoinjectors is typically less than 15 seconds (s);[11] however, there is concern that SC injection of larger volumes over this timescale would not be tolerated due to increasing injection pain, as supported by studies reporting an increase in pain for injections exceeding 0.8 mL.[12,13] These studies, which involved injection rates between 8 and 48 mL/minute (min), found no relationship between the rate of SC injection and pain.[12,13]

Large-volume SC delivery is an established technique for hydration and nutrition.[14,15] In a review of this technique, the delivery of 500 mL of fluid in 2 hours (h) was reported to be possible with expected transient local oedema and minimal patient discomfort.[16] This equates to a delivery rate of around 4 mL/min, implying that similar injection rates could be acceptable for the SC delivery of therapeutic proteins, assuming their formulation is tolerable.

Several human subject trials have assessed injection pain for SC injection volumes greater than 1 mL at a variety of injection rates. In one study,[17] volumes of up to 3.5 mL were delivered at rates of up to 3.5 mL/min, while in another study, an injection volume of 3 mL was delivered at a rate of up to 18 mL/min.[18] In both studies, these SC injections were well tolerated and acceptable. Nevertheless, in a review of these and other studies, it has been argued that the tolerability of SC injection volumes higher than 3.5 mL should be further explored.[19] More recently, 5 mL injections at a constant speed of 1.2 mL/min were demonstrated to be well tolerated and acceptable.[20]

In the current study, we examined the acceptability and tolerability of SC saline injection volumes of up to 5 mL over a delivery time of up to 3 minutes via infusion pump into the abdomen of healthy volunteers.

Materials and Methods

Trial Design

This was a single-center, randomized, single-blind, crossover, adaptive design study to evaluate the tolerability and acceptability of varying volumes and delivery rates of SC infusions of saline solution in healthy volunteers. Since registration of Methodology studies is not required as per ClinicalTrials.gov or EU regulations, no trial registration is available for this study (GSK study 209488).

Participants

Twenty-four healthy male and female participants aged between 18 and 65 years with a body mass index of 18.5–32.0 kg/m^2 were recruited. Before being enrolled, participants were required to undergo routine clinical assessments to determine their general health status and eligibility for inclusion into the study. Key exclusion criteria included sensitivity or severe allergic responses to any medication, or any of the components/excipients used in the study; relevant skin conditions (eg, recent history of eczema or recurrent eczema, keloid, skin allergies, psoriasis, atopic dermatitis, and vitiligo) and/or blood disorders which, in the opinion of the investigator, could pose safety issues or cause interference with the study procedures; presence of abdominal tattoos which, in the opinion of the investigator, could affect the evaluation of the infusion site; relevant concomitant medication deemed by the investigator to be prohibited for the study; and a phobia of needles.

This study was conducted according to the principles of the Declaration of Helsinki, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) and was approved by the Wales Research Ethics Committee 2 (Cowbridge Road, East Cardiff, Wales). All participants gave their informed consent with the option to withdraw at any time if they wished. Participation in the study was entirely voluntary.

Interventions

The screening visit involved participants undergoing routine clinical assessments to determine their general health status and eligibility for inclusion into the study. Eligible participants attended five study visits, with a minimum of one week between visits. During each visit, two infusions of saline solution (0.9%, viscosity of approximately 1 cP at room temperature) were administered to the SC tissue of the abdomen, with at least 3 h between infusions. Alternate sites were used for each infusion, and these were predefined using a diagrammatic representation of the abdomen divided into four

quadrants (R1, R2, L1, and L2) to mark the injection sites. This process ensured that the injection sites were evenly distributed throughout the infusion period.

Participants were randomized at baseline to 16 injection sequences. Infusions A and B were the predefined starting infusions and were administered at Visits 1 and 2 (A [1 mL in 10s at a constant rate of 6.00 mL/min, 62s hold time]; B [5 mL in 1.2 min at a constant rate of 4.17 mL/min, 0s hold time]). For subsequent study visits, the infusion volumes and rates were determined iteratively with the limits of flow rate/volume defined by the acceptability of prior infusions. Acceptability was based on a review of available data by the study decision committee, which comprised the principal investigator (or appropriate designee) and relevant representatives of the study sponsor. If a given infusion was deemed tolerable and acceptable, the delivery rate for subsequent infusions was increased by up to 1.00 mL/min. Following this approach, six further injections were defined during conduct of the trial, giving a total of eight different infusions (combinations of infusion volume and infusion rate) administered (infusions A, B, C [4 mL in 58s at a constant rate of 4.14 mL/min, 62s hold time], D [5 mL in 2 mins at a constant rate of 2.50 mL/min, 0 s hold time], E [5 mL in 3 mins at a constant rate of 1.67 mL/min, 0 s hold time], F [5 mL in 2 mins 5s at a constant rate of 2.40 mL/min, 55s hold time], G [4 mL in 2 mins at a constant rate of 2.00 mL/min, 30s hold time], and H [3 mL in 2 mins at a constant rate of 1.50 mL/min, 30s hold time]). Different infusion sequences, volumes, injection times, and rates are provided in Figure 1. For infusions assessed during the study, the maximum delivery volume per infusion was 5 mL and the maximum delivery rate was 6.00 mL/min. Hold times were included for blinding purposes and to ascertain if leakage would be minimized.

Outcomes

The primary objective was to identify acceptable delivery rates for the SC infusion of between 5–8 mL of saline solution to participants based on a combination of visual analogue scale (VAS) pain scores, tolerability and acceptability questionnaire results, and injection-site leakage. Secondary objectives were to investigate the tolerability of SC infusion of saline to participants, in comparison to the existing treatment of 1 mL in 10s (based on VAS pain scores and tolerability and acceptability questionnaire results), and to assess safety at the infusion site as a result of SC infusion of saline (based on assessment of the infusion site and adverse events [AEs]).

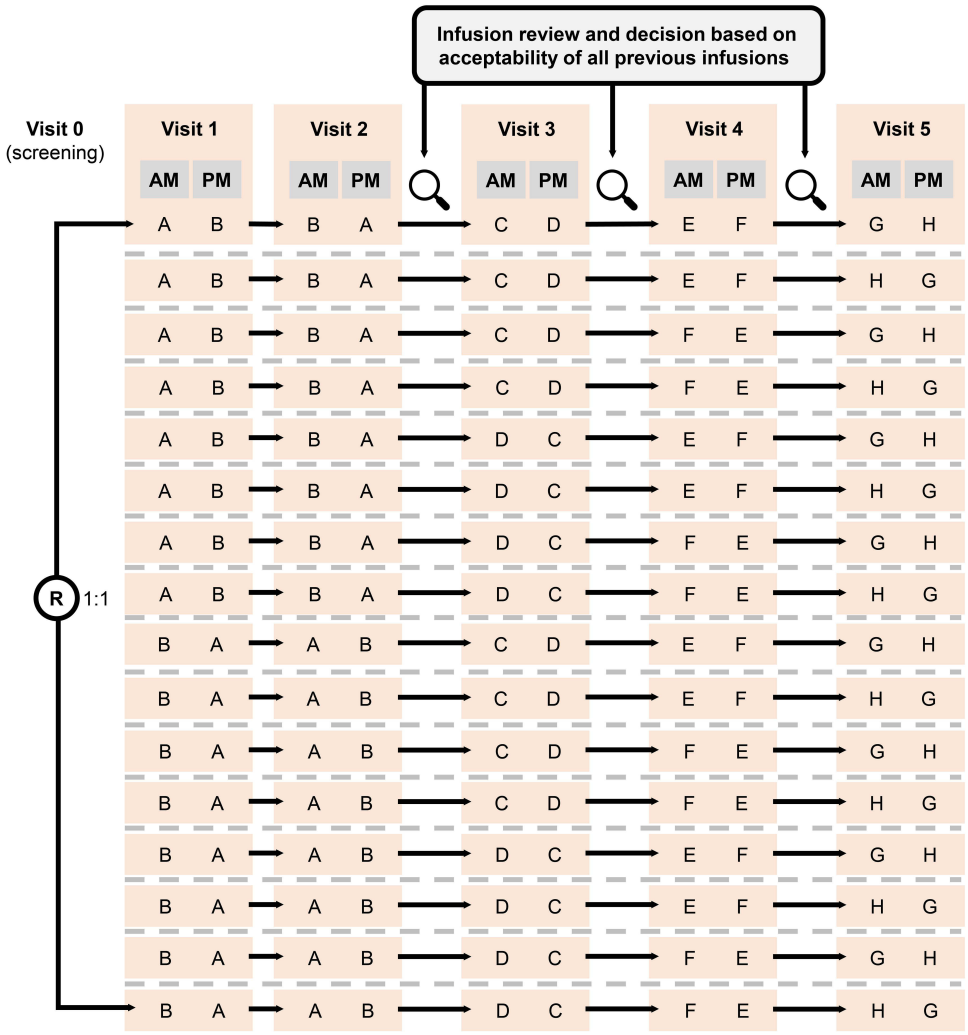
Participant pain perception was measured on a scale from 0 (no pain) to 100 (unbearable pain) using a VAS; participants graded their pain by choosing a point at or between 0 and 100 on a 100 mm line and scores were attributed accordingly. Scores were interpreted as follows: ≤4, no pain; 5–44, mild pain; 45–74, moderate pain; and ≥75, severe pain.[21] For comparison of infusions, 13 mm was the minimum clinically significant difference.[22] VAS scores were recorded for each study treatment at the following time points: prior to treatment; immediately after needle insertion; 0 min post-treatment; 10 min post-treatment; and 1 h post-treatment.

Participants completed a tolerability and acceptability questionnaire (Supplementary Figure 1) after each infusion. Questions related to the acceptability of the infusion, comfortable frequency for the infusion as treatment for a debilitating condition, and possible adjustments to improve acceptability.

Infusion sites were assessed for leakage, local oedema/wheal formation, erythema, and bruising prior to treatment, 0 min post-treatment, and 1 h post-treatment. Leakage at the infusion site after SC infusion was quantified by placing a TearFlo strip on the infusion site and categorizing the leakage, according to the liquid absorption distance, as either 0–6 mm (not considered a significant leakage) or >6 mm (considered a significant leakage). Local oedema/wheal formation at the site of infusion was quantified by measurement of the height of the local oedema/wheal as none, mild (up to 5 mm high), moderate (5–10 mm high), or severe (>10 mm high). Erythema and bruising were categorized as none, mild (up to 2 cm diameter), moderate (2–4 cm diameter), and severe (>4 cm diameter).[20]

The primary endpoint of acceptability was achieved for any given treatment if the following predefined criteria were fulfilled: mean VAS score <45 (none to mild pain) at 0, 10 min, and 1h post-treatment time points; <50% of responses in the tolerability and acceptability questionnaire "not acceptable"; and ≥90% of leakage assessments at the 0 min post-treatment time point were not considered significant. Mean VAS scores were calculated after exclusion of corresponding infusion timepoint data for participants with a VAS score >45 immediately after needle insertion for the respective infusion visit, and "not acceptable" responses were excluded if the only reason was "takes too long".

AEs and serious AEs were monitored at all study visits and during the seven-day follow-up period after the last visit.



Infusion	Volume (mL)	Time	Rate (mL/min)	Hold (s)
A	1	10 s	6.00	62
B	5	1.2 min	4.17	0
C	4	58 s	4.14	62
D	5	2 min	2.50	0
E	5	3 min	1.67	0
F	5	2 min 5 s	2.40	55
G	4	2 min	2.00	30
H	3	2 min	1.50	30

Figure 1 Study design.
Note: Infusions A and B were predetermined at the start of the study. Infusions C to H were determined iteratively according to the acceptability of infusions already administered. The hold times were used to blind the participants to the delivery volume/time/rate.
Abbreviations: Min, minute; s, second.

Randomization and Blinding

The randomization schedule was generated by the study Sponsor prior to the study using a validated internal software (RandAll). On Day 1, each participant was assigned a unique randomization number in ascending numerical order encoding their assignment to a particular treatment sequence.

Participants were blinded to the volume and rate of every infusion; achieved by having a second infusion pump activated, which ran for the length of time corresponding to the alternate infusion scheduled within the study visit. This

was done to prevent the noise of their infusion pump from giving an indication of the start and end time for a given infusion. Hold time was also added such that the needle was not removed until the longest infusion time was complete for that study visit.

Equipment

Saline solution was delivered through an infusion pump and pre-infusion skin preparation, performed as per standard clinical practice.[23] Materials included a 50 mL saline infusion bag, Infusomat Spaceline (B Braun type IV standard luer lock 250–145 cm), HighFlo infusion needle set (24G 12 mm), one small Tegaderm dressing, two sachets of 2% chlorhexidine skin wipes, and two TearFlo strips per participant. An Infusomat Space infusion pump (B Braun, Sheffield, United Kingdom) was used.

Procedure and Assessments

Participants were placed in a semi-supine position, and a thorough inspection of the abdomen was conducted to assess the suitability of the site for infusion. The injection site was cleaned with a 2% chlorhexidine skin wipe and allowed to dry for 10–15 s before the SC needle was inserted. The needle was inserted at an approximate 90-degree angle and secured with a Tegaderm dressing before the infusion was started. Upon completion of the infusion and holding period, the needle was removed and a TearFlo strip was placed over the infusion site to assess leakage. After each infusion, participants completed a tolerability and acceptability questionnaire. VAS scores were recorded prior to treatment, immediately after needle insertion, 0 min post-treatment, 10 min post-treatment, and 1 h post-treatment. Per the protocol, in cases where the VAS score on needle insertion exceeded 45 mm (mild), the associated post-treatment VAS scores were excluded from the acceptability criteria and VAS summaries (where noted). The infusion site was assessed for leakage, local oedema/wheal formation, erythema, and bruising prior to treatment, 0 min post-treatment, and 1 h post-treatment. The assessment also included a standardized medical photograph of the infusion site.

Data Analysis

All participants who passed screening and entered the study were included in the enrolled population, which was used for the acceptability/tolerability analyses. All participants who received ≥1 infusion were included in the safety population, which was used for safety analyses. All data were summarized descriptively.

Results

Participants

Screening took place between September 10 (first subject first visit) and September 27, 2018, and the study was completed as planned on December 6, 2018 (last subject, last visit). Overall, 44 participants were screened, of whom 13 (30%) did not meet the eligibility criteria and seven participants (16%) were not enrolled at the discretion of the investigator; they were kept in reserve and were not used (Supplementary Figure 2). The remaining 24 were enrolled, randomized, and received ≥1 infusion, and therefore were included in both the enrolled population and the safety population. Twenty-one participants completed the study and three were withdrawn early per protocol-defined stopping criteria as they received prohibited medication, which could have influenced their perception of pain. One participant did not attend during Visit 2 and hence received infusions A and B once rather than twice as scheduled. Of the participants, 92% were white, 58% were male, and the mean BMI was 25.4 kg/m^2. Baseline demographics of the enrolled population are given in Table 1.

Acceptability and Tolerability

Treatments that met the predefined acceptability criteria were infusions A, C, and H (Table 2). The remaining infusions (B, D, E, F, and G) did not meet the predefined acceptability criterion for leakage at the infusion site post administration.

All treatments assessed in the study demonstrated acceptable VAS scores at 0 min, 10 min, and 1 h post-treatment. Similarly, all treatments met the acceptability and tolerability criterion as assessed by the questionnaire.

Table 1 Baseline Demographics

	Enrolled population (N = 24)
Mean Age, Years (SD)	45.1 (10.6)
Sex, n (%)	
Female	10 (42)
Male	14 (58)
Mean BMI, kg/m^2 (SD)	25.4 (3.2)
Mean Height, cm (SD)	172.8 (8.7)
Mean Weight, kg (SD)	76.4 (14.3)
Race, n (%)	
Black or African American	2 (8)
White – White/Caucasian/European Heritage	22 (92)

Abbreviations: BMI, body mass index; SD, standard deviation.

The VAS score data were not normally distributed; hence, the median (range) scores are reported in addition to the mean scores. At the needle insertion time point, median VAS scores were similar across treatments (median scores ranged from 1.0 to 2.0 mm); however, a large range of VAS scores was observed (range 0.0–77.0 mm across treatments). Per the protocol, in cases where the VAS score on needle insertion exceeds 45 mm (mild), the associated post-treatment VAS scores were excluded from subsequent summaries for all treatments, median VAS scores were highest at 0 min post-treatment (median scores ranged from 2.0 to 11.0 mm; minimum and maximum values observed over all treatments ranged from 0.0 to 73.0 mm) (Figure 2a). At 10 min post-treatment (Figure 2b), the median VAS scores subsided to the category of no pain (median [range] 0.0 mm [0.0–20.0 mm] across treatments) and, by 1 h post-treatment, the VAS scores subsided further (median [range] 0.0 mm [0.0–3.0 mm] across all treatments) (Figure 2c).

At 0 min post-treatment, infusion B (5 mL, 4.17 mL/min) produced the highest median VAS score (11.0 mm) (Table 2). Median VAS scores ranging from 5.0 to 5.5 mm were observed at 0 min post-treatment for infusions C (4 mL, 4.14 mL/min), F (5 mL, 2.40 mL/min), and G (4 mL, 2.00 mL/min). Infusions D (5 mL, 2.50 mL/min), E (5 mL, 1.67 mL/min), and H (3 mL, 1.50 mL/min) had similar observed median VAS scores ranging from 3.0 to 4.0 mm at 0 min post-treatment. The smallest median VAS score at 0 min post-treatment was observed with infusion A (1 mL, 6.00 mL/min) (median VAS score 2.0 mm). The observed difference between the highest and lowest median VAS scores was not clinically significant according to predefined criteria (>13 mm).

All the infusions were acceptable to the participants (Figure 3) as assessed via the tolerability and acceptability questionnaire. One participant reported infusion B (5 mL, 4.17 mL/min) as "not acceptable" (too painful/sore) during Visit 1; the same infusion was reported as "unpleasant, but acceptable" when it was re-administered to the same participant during Visit 2. Larger volumes and faster rates of infusion were associated with higher rates of "unpleasant, but acceptable" responses. In general, infusions A (1 mL, 6.00 mL/min), G (4 mL, 2.00 mL/min), and H (3 mL, 1.50 mL/min) were the most acceptable to participants (per the tolerability and acceptability questionnaire), with an "acceptable" response of 81–90% (Figure 3).

When asked how often they would be comfortable taking a particular infusion as a treatment for a debilitating condition, considering how well or badly they tolerated the infusion, 100% of participants across all infusion groups indicated they would be comfortable with administration of the infusions monthly. Over 80% of participants would also be comfortable with administrations being weekly and daily. Specifically, for infusions A (1 mL, 6.00 mL/min), C (4 mL, 4.14 mL/min), D (5 mL, 2.50 mL/min), and G (4 mL, 2.00 mL/min) 100% of participants indicated they would be

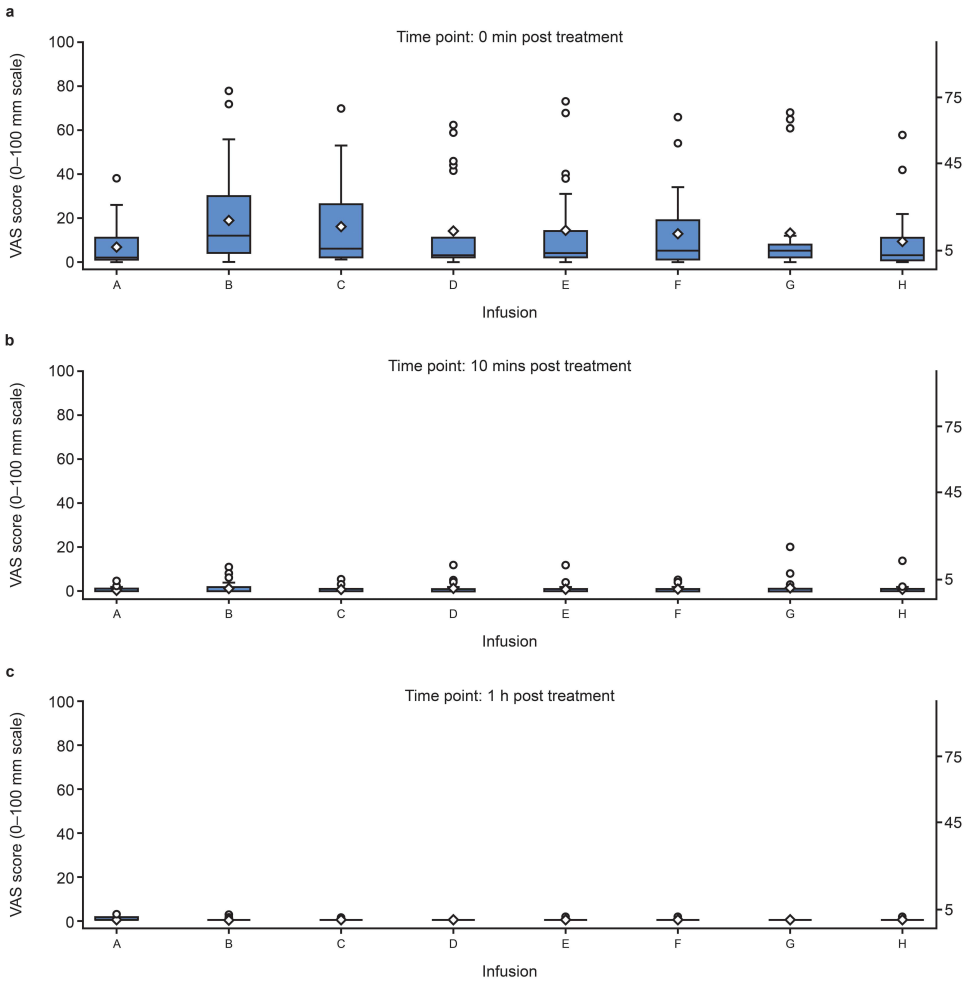
Table 2 Summary of Acceptability Criteria (Enrolled Population)

Infusion	Volume (mL)	Time	Rate (mL/min)	Hold(s)	Acceptable VAS score at (post-treatment), mm			Acceptable Tolerability and Acceptability Questionnaire Y or N (n/N1 [%])	Acceptable Assessment of Infusion Site Y or N (n/N1 [%])	Acceptability Criteria met Y or N
					0 minn Y or N (mean) Median [range]	10 minn Y or N (mean) Median [range]	1 h n Y or N (mean) Median [range]			
A (N = 24)	1	10 s	6.00	62	n = 46 **Y** (6.3) 2.0 [0–38]	n = 46 **Y** (0.5) 0.0 [0–3]	n = 46 **Y** (0.4) 0.0 [0–3]	**Y** (47/47 [100%])	**Y** (45/47 [96%])	**Y**
B (N = 24)	5	1.2 min	4.17	0	n = 46 **Y** (17.7) 11.0 [0–72]	n = 46 **Y** (1.1) 0.0 [0–8]	n = 46 **Y** (0.3) 0.0 [0–3]	**Y** (46/47 [98%])	**N** (38/47 [81%])	**N**
C (N = 24)	4	58 s	4.14	62	n = 22 **Y** (14.5) 5.5 [1–70]	n = 22 **Y** (0.6) 0.0 [0–5]	n = 22 **Y** (0.1) 0.0 [0–1]	**Y** (23/23 [100%])	**Y** (22/23 [96%])	**Y**
D (N = 24)	5	2 min	2.50	0	n = 23 **Y** (14.1) 3.0 [0–62]	n = 23 **Y** (1.3) 0.0 [0–12]	n = 23 **Y** (0.0) 0.0 [0–0]	**Y** (23/23 [100%])	**N** (16/23 [70%])	**N**
E (N = 24)	5	3 min	1.67	0	n = 23 **Y** (14.3) 4.0 [0–73]	n = 23 **Y** (1.0) 0.0 [0–12]	n = 23 **Y** (0.2) 0.0 [0–1]	**Y** (23/23 [100%])	**N** (20/23 [87%])	**N**
F (N = 24)	5	2 min 5 s	2.40	55	n = 22 **Y** (11.7) 5.0 [0–66]	n = 22 **Y** (0.7) 0.0 [0–5]	n = 22 **Y** (0.1) 0.0 [0–1]	**Y** (23/23 [100%])	**N** (20/23 [87%])	**N**
G (N = 24)	4	2 min	2.00	30	n = 21 **Y** (13.0) 5.0 [0–68]	n = 21 **Y** (1.6) 0.0 [0–20]	n = 21 **Y** (0.0) 0.0 [0–0]	**Y** (21/21 [100%])	**N** (15/21 [71%])	**N**
H (N = 24)	3	2 min	1.50	30	n = 21 **Y** (9.2) 3.0 [0–58]	n = 21 **Y** (1.1) 0.0 [0–14]	n = 21 **Y** (0.2) 0.0 [0–1]	**Y** (21/21 [100%])	**Y** (20/21 [95%])	**Y**

Note: The VAS acceptability criteria were met if the mean VAS score was less than 45 mm (mild pain) calculated for each time point (in cases where the VAS score on needle insertion exceeded 45, the associated VAS scores for that visit were to be excluded from the calculation of this mean). The Tolerability and Acceptability Questionnaire acceptability criterion was met if fewer than 50% of responses were "not acceptable" (excluding any responses for which the only reason for being "not acceptable" was "takes too long"). Percentages are of responses meeting criteria. The Assessment of Infusion Site acceptability criterion was met if leakage from infusion site was scored as 1 (no to minimal leakage) for at least 90% of infusions at the 0 min post-treatment time point.

Abbreviations: Min, minute; **N**, no; n, subgroup number; N, total number; N1, total number of responses; s, second; VAS, visual analogue scale; **Y**, yes.

https://doi.org/10.2147/MDER.S479507 DovePress



Infusion	Volume (mL)	Time	Rate (mL/min)	Hold (s)
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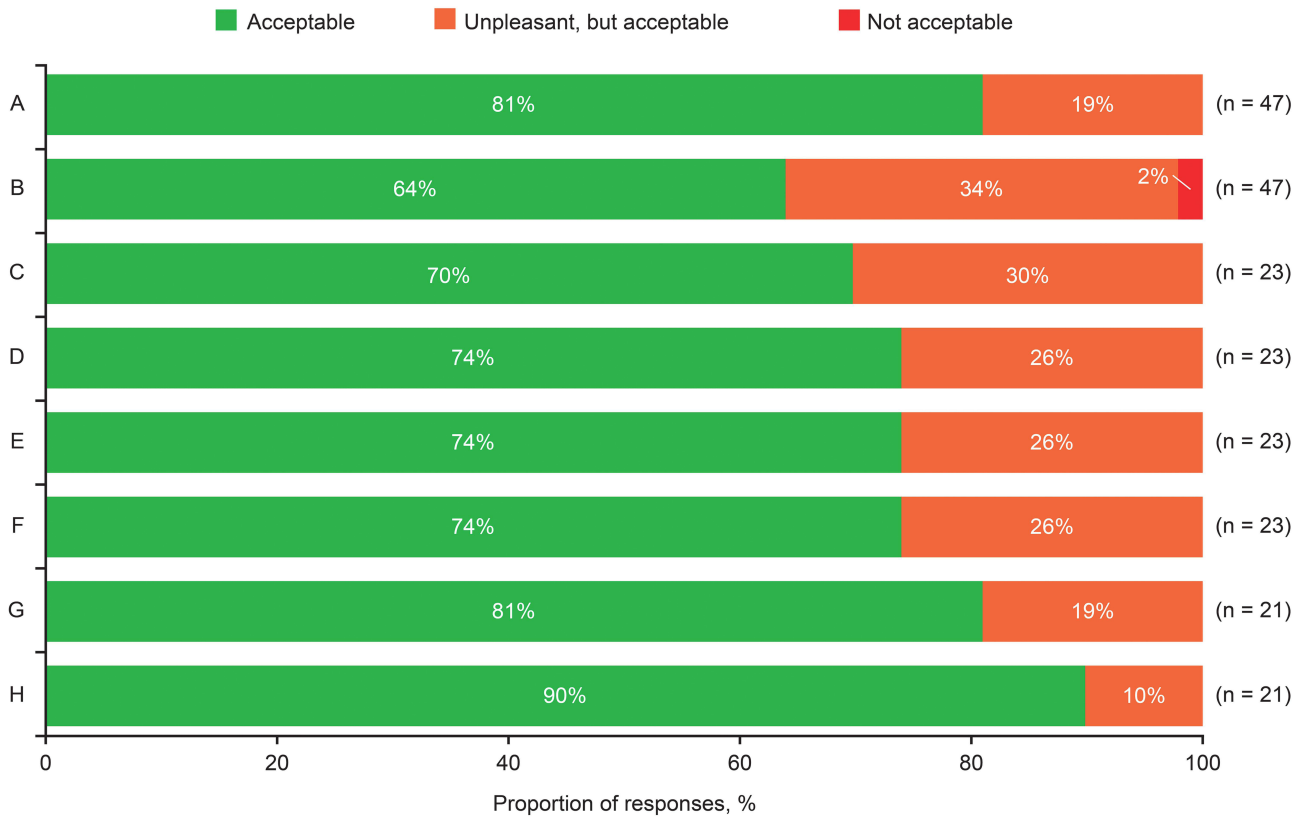
B	5	1.2 min	4.17	0
C	4	58s	4.14	62
D	5	2 min	2.50	0
E	5	3 min	1.67	0
F	5	2 min 5 s	2.40	55
G	4	2 min	2.00	30
H	3	2 min	1.50	30

Figure 2 Pain assessment (VAS) scores (0–100 mm scale) at (**a**) 0 min post-treatment, (**b**) 10 min post-treatment and (**c**) 1 h post-treatment.
Note: On this scale, scores of up to 4 can be considered as no pain; 5–44, mild pain; 45–74, moderate pain; and >75 as severe pain. The box denotes the IQR with lines for the 25th percentile, median and 75th percentile. The whiskers denote the maximum/minimum observation below the upper/lower fence defined as 1.5 IQR above/below the 75th/25th percentile. The diamond symbol denotes the mean and the circle symbols outside the whiskers denote outliers.
Abbreviations: IQR, interquartile range; min, minute; s, second; VAS, visual analogue scale.

comfortable taking these infusions on a weekly basis, further to this, for infusion A 100% of participants indicated they were comfortable receiving the infusion on a daily basis (Figure 4).

Adverse Events and Infusion Site Assessments

The number of participants experiencing AEs is shown in Table 3. A numerically higher number of participants experienced AEs with infusions F (5 mL, 2.40 mL/min; 7 participants) and B (5 mL, 4.17 mL/min; 6 participants) compared with the other treatments (range 1–4 participants). All AEs were of mild or moderate intensity, and none were serious. Across all treatments, the most common AEs reported were injection site bruising (11 participants) and



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E	5	3 min	1.67	0
F	5	2 min 5 s	2.40	55
G	4	2 min	2.00	30
H	3	2 min	1.50	30

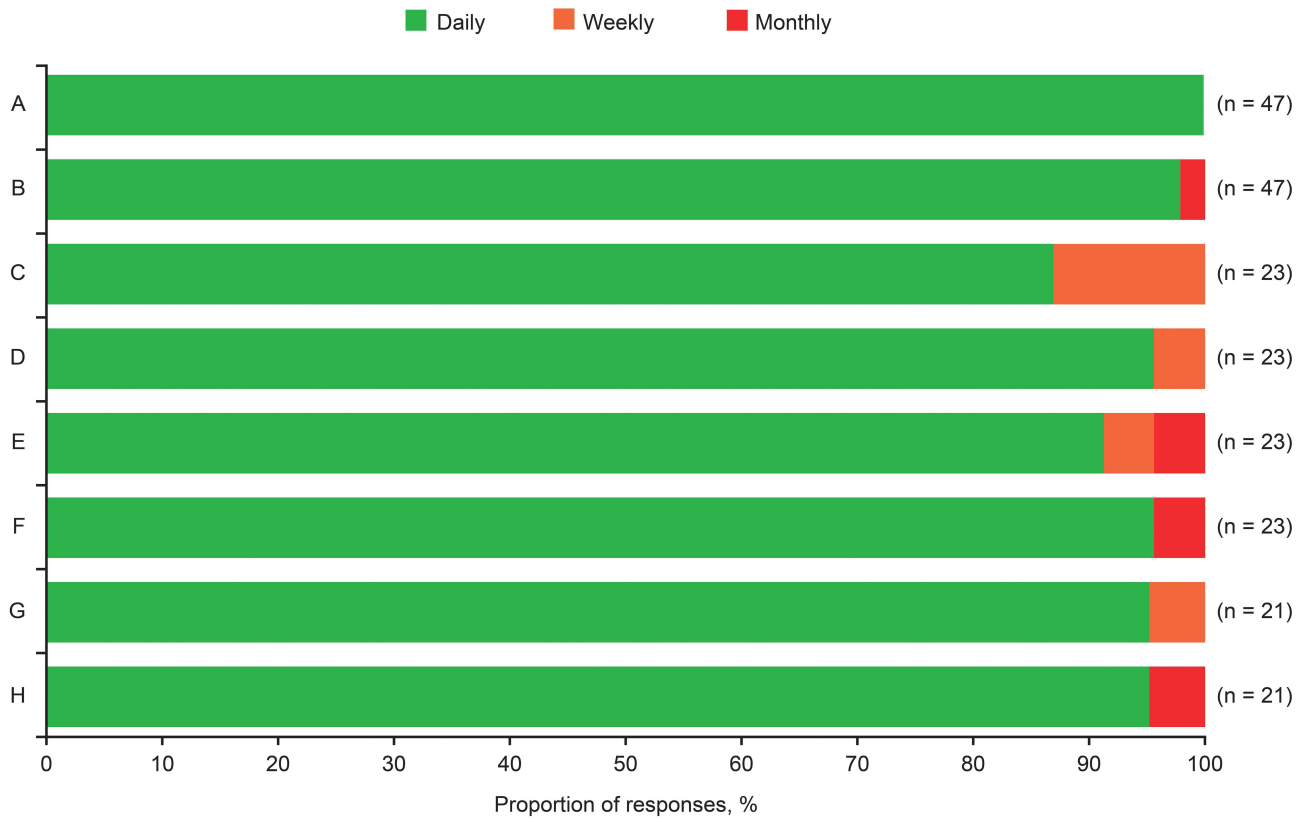
Figure 3 Tolerability and acceptability questionnaire.
Note: The participant who reported "not acceptable" for treatment B reported it as too painful and sore during Visit 1, and "unpleasant, but acceptable" during Visit 2.
Abbreviations: Min, minute; s, second.

nasopharyngitis (5 participants). Injection site bruising and nasopharyngitis were resolved within 10 h to 23 days, and 2 days to 27 days, respectively, in all participants.

Mild local oedema/wheal formation was reported with infusions B and E at 0 min post-infusion (Supplementary Table 1), and with infusions C, D, E, F, G, and H at 1 h post-infusion (Supplementary Table 2). There were no reports of local oedema/wheal formation with infusion A. Erythema of severe intensity was reported with infusions E and G, mild or moderate intensity was reported with all treatments at 0 min post-infusion (Supplementary Table 1). At 1 h post-infusion, erythema was of mild or moderate intensity, if present (Supplementary Table 2).

Discussion

This single-center, randomized, crossover study with adaptive design evaluated the tolerability and acceptability of varying volumes (up to 5 mL) and delivery rates (between 1.5 and 6 mL/min) of SC infusions of saline solution in



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C	4	58s	4.14	62
D	5	2 min	2.50	0
E	5	3 min	1.67	0
F	5	2 min 5 s	2.40	55
G	4	2 min	2.00	30
H	3	2 min	1.50	30

Figure 4 Proportion of responses indicating how often they would be comfortable taking the infusion to treat a debilitating condition.
Note: Percentages for the Daily, Weekly, and Monthly categories could each sum to 100% as participants could select multiple responses. For infusion B, 100% of responses were comfortable taking the infusion monthly; however, only 98% of responses indicated they were comfortable taking the infusion daily or weekly (but are comfortable taking the infusion monthly).
Abbreviations: Min, minute; s, second.

24 healthy volunteers. Participants found bolus injections of 5 mL in 2–3 min to be acceptable and generally well tolerated, with median VAS pain scores immediately post-injection ranging between 3.0 and 5.0.

Of eight infusions evaluated in the study, three (including an injection of 4 mL in 58s) met the predefined acceptability criterion based on VAS pain scores, tolerability and acceptability questionnaire responses, and leakage from the infusion. Failure to meet the acceptability criterion for other volumes and delivery rates was due to leakage at the injection site. Fluid leakage in this study was attributed to removal of the needle post-infusion and might, therefore, be mitigated by increasing the hold time between infusion and needle removal. For infusions A and B, hold time was included purely for blinding purposes, whereas for infusions G and H the hold time was introduced to assess whether it reduced leakage. This leakage was not considered to be of clinical concern because the amount of leakage observed was similar to that encountered in usual clinical practice.[24]

Table 3 Adverse Events

System Organ Class Preferred Term, n (%)	Safety Population (N = 24)							
	Infusion A 1 mL in 10s, rate = 6.00 mL/min, hold = 62s	**Infusion B 5 mL in 1.2 min, rate = 4.17 mL/min, hold = 0s**	**Infusion C 4 mL in 58s, rate = 4.14 mL/min, hold = 62s**	**Infusion D 5 mL in 2 min, rate = 2.50 mL/min, hold = 0s**	**Infusion E 5 mL in 3 min, rate = 1.67 mL/min, hold = 0s**	**Infusion F 5 mL in 2 min 5s, rate = 2.40 mL/min, hold = 55s**	**Infusion G 4 mL in 2 min, rate = 2.00 mL/min, hold = 30s**	**Infusion H 3 mL in 2 min, rate = 1.50 mL/min, hold = 30s**
n	24	24	23	23	23	23	21	21
Any AE	4 (17)	6 (25)	2 (9)	1 (4)	2 (9)	7 (30)	3 (14)	2 (10)
General Disorder and Administration Site Conditions								
Any Event	2 (8)	3 (13)	1 (4)	1 (4)	1 (4)	4 (17)	1 (5)	0
Injection Site Bruising	2 (8)	3 (13)	1 (4)	1 (4)	1 (4)	4 (17)	1 (5)	0
Infections and Infestations								
Any Event	0	0	0	0	0	2 (9)	1 (5)	2 (10)
Nasopharyngitis	0	0	0	0	0	2 (9)	1 (5)	2 (10)
Injury, Poisoning, and Procedural Complications								
Any Event	1 (4)	0	0	0	0	1 (4)	0	0
Chest Injury	1 (4)	0	0	0	0	0	0	0
Tendon Injury	0	0	0	0	0	1 (4)	0	0
Nervous System Disorders								
Any Event	0	1 (4)	0	0	0	0	1 (5)	0
Drug Withdrawal Headache	0	0	0	0	0	0	1 (5)	0
Headache	0	1 (4)	0	0	0	0	0	0

(*Continued*)

https://doi.org/10.2147/MDER.S479507

Table 3 (Continued).

System Organ Class Preferred Term, n (%)	Safety Population (N = 24)							
	Infusion A 1 mL in 10s, rate = 6.00 mL/min, hold = 62s	**Infusion B 5 mL in 1.2 min, rate = 4.17 mL/min, hold = 0s**	**Infusion C 4 mL in 58s, rate = 4.14 mL/min, hold = 62s**	**Infusion D 5 mL in 2 min, rate = 2.50 mL/min, hold = 0s**	**Infusion E 5 mL in 3 min, rate = 1.67 mL/min, hold = 0s**	**Infusion F 5 mL in 2 min 5s, rate = 2.40 mL/min, hold = 55s**	**Infusion G 4 mL in 2 min, rate = 2.00 mL/min, hold = 30s**	**Infusion H 3 mL in 2 min, rate = 1.50 mL/min, hold = 30s**
Skin and Subcutaneous Tissue Disorders								
Any Event	1 (4)	1 (4)	1 (4)	0	0	0	0	0
Rash	0	1 (4)	1 (4)	0	0	0	0	0
Pseudofolliculitis	1 (4)	0	0	0	0	0	0	0
Gastrointestinal Disorders								
Any Event	0	0	0	0	1 (4)	0	0	0
Toothache	0	0	0	0	1 (4)	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders								
Any Event	0	1 (4)	0	0	0	0	0	0
Nasal Congestion	0	1 (4)	0	0	0	0	0	0

Note: n is defined as the number of participants who received the infusion. However, it should be noted that they may have received an infusion more than once. In particular, the infusion sequences were defined such that the 1 mL in 10s and 5 mL in 1.2 min infusions were assigned twice for each participant, whereas all other infusions were assigned only once for each participant.
Abbreviations: AE, adverse event; min, minute; s, second.

While infusions with larger volumes and faster delivery rates were associated with higher VAS scores, indicating greater pain at the injection site, VAS scores were largely in the category of no pain within 10 min of injection and all the infusions evaluated in the study were shown to meet the VAS pain score acceptability criteria. In addition, all the infusions met the acceptability and tolerability criteria assessed by the questionnaire. No participants considered that any of the injection procedures would be unacceptable for a once-monthly injection to treat a debilitating disease. Indeed, some infusions, including volumes of up to 5 mL, were considered acceptable for weekly injections. As assessed by the tolerability and acceptability questionnaire, the 3–4 mL in 2 min infusions was comparable to the 1 mL infusion and rated more acceptable than other treatments.

SC injections were associated with mild infusion site bruising, which resolved in all cases within 10 h to 23 days as consistent with findings from previous studies.[25] No participants in the study experienced serious AEs or AEs that were severe in intensity. Clinical assessment of oedema/wheal formation and erythema at the infusion site also indicated that the infusions were generally well tolerated, in line with the findings from the tolerability and acceptability questionnaire.

Our findings are consistent with those from previous studies that have investigated the acceptance and tolerability of SC injection volumes exceeding 1 mL.[17,18] Injection of 3.5 mL of viscous placebo buffer over 1 min was well tolerated in a single-center study of 48 healthy adults, with a mean VAS pain score 19 mm (ie, mild pain) immediately after injection.[17] In line with our findings, a slower delivery rate of 3.5 mL over 10 min was associated with lower VAS pain scores; however, in that study the difference in pain scores between delivery rates was not considered to be clinically significant by the authors.[17] A single-center study in 24 healthy adults showed that an injection volume of 3 mL and a fast delivery rate (0.30 mL/s) did not significantly impact participant-perceived pain compared with a 2 mL injection and a slow delivery rate of 0.02 mL/s.[18] Similarly, a study of different saline injection volumes and rates in patients with diabetes demonstrated higher pain sensation with a larger injection volume (2.25 mL) compared to other injection volumes (range 4.3–5.1 mm) and abdomen injections (2.1 mm), but without a clinically meaningful difference based on low pain intensity and high rates of patient acceptance.[12]

Patient acceptance of self-administered medicines and willingness to adhere to and persist with treatment are influenced by multiple factors, including the convenience of the dosing schedule, ease and speed of administration, and level of discomfort experienced.[10,26,27] Despite progress in the development of devices for self-administration of therapies such as monoclonal antibodies,[28–30] a need has been identified for devices that facilitate high volume SC delivery while meeting patient preferences for faster injection time and greater convenience.[19,31] Large-volume SC injection provides a means of achieving therapeutic concentrations of biotherapeutics, avoiding the need for multiple injections and enabling faster delivery rates, which may be preferred by patients.[10] In the current study, large-volume SC injections were administered via an infusion pump, and it will be important to reconsider the tolerability of large-volume SC injections when used with self-administration devices.

Understanding of the relationship between large-volume SC injections and subject tolerability is required to develop effective and safe delivery devices, however, published studies around clinical feasibility of large-volume SC injections remain limited. The findings from this study contribute to existing data to help inform the patient-centered design of larger-volume injectors for self-administration of future medicines.

A limitation of this study is that the 0.9% saline solution used may not fully reflect the formulation of future injectable medicines. The viscosity of 0.9% saline (approximately 1 cP at room temperature) is likely lower than that of high-concentration monoclonal antibody solutions, which can reach up to 20 cP.[32] However, previous research suggests that SC injection tolerance increases with viscosity; therefore, injection regimens that were found to be tolerable with saline in this study are also likely to be tolerable with a formulation that has a viscosity more representative of a monoclonal antibody solution.[8] Osmolarity and pH are also known to impact the tolerability of SC injections. The 0.9% saline solution used in this study is unbuffered and has physiological osmolarity so that the impact of these parameters on tolerability is minimized. This is not always achievable in the formulation of injectable medicines, in which case, reduced tolerability compared to what was reported in this study would be expected. Another possible limitation of this study is that the infusions were only administered to the SC tissue of the abdomen and so this does not address potential variations in pain relating to the location of injection and the relative thickness of adipose tissue at other sites. Further limitations of this study include the single-center, single-blind design, and the small number of participants enrolled. In

addition, the study was conducted in healthy individuals, and it is unclear if these findings translate to patients with chronic or debilitating conditions. Patients with such conditions may be more experienced in the use of self-administered medicines and may have different preferences or pain sensitivity thresholds.

Conclusions

In conclusion, this study showed that SC delivery volumes of 1, 3, and 4 mL in 10s, 2 min, and 58s, respectively, was acceptable to healthy participants, according to predefined criteria. Larger injection volumes and faster rates of infusion increased the participants' pain, making those infusions unpleasant yet still acceptable. Moreover, this study showed that the largest volume (5 mL) of infusion tested was considered broadly acceptable for weekly treatment of a debilitating condition among participants. These findings may facilitate the development of larger-volume autoinjectors for self-administration of injectable medicines.

Data Sharing Statement

Information on GSK's data sharing commitments and requesting access to anonymized individual participant data and associated data can be found at www.clinicalstudydatarequest.com.

Acknowledgments

Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Suzan Maboane, MSc, of Ashfield MedComms, an Inizio company, and was funded by GSK.

Trademarks are the property of their respective owners (HIgH-Flo Subcutaneous Safety Needle Sets [KORU Medical Systems], Infusomat Spaceline and Infusomat Space infusion pump [Braun B], TearFlo [HUB Pharmaceuticals, LLC], Tegaderm [3M]).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was sponsored by GSK (209488).

Disclosure

Chika Akinseye was an employee of, and shareholder in, GSK at the time of the study. Andrew Fiorini was an employee of GSK at the time of the study, and a shareholder in GSK. Emily Jarvis is an employee of, and shareholder in, GSK. Michelle Fry is an employee of, and shareholder in, GSK. Abid Raza was a complementary worker for GSK at the time of the study. Sara Soleman was an employee of, and shareholder in, GSK at the time of the study. Stephanie Igwe is an employee of, and shareholder in, GSK. Mark Palmer is an employee of, and shareholder in, GSK. The authors report no other conflicts of interest in this work.

References

1. Jiskoot W, Hawe A, Menzen T, Volkin DB, Crommelin DJA. Ongoing challenges to develop high concentration monoclonal antibody-based formulations for subcutaneous administration: quo Vadis? *J Pharm Sci*. 2022;111(4):861–867. doi:10.1016/j.xphs.2021.11.008
2. Shire SJ, Shahrokh Z, Liu J. Challenges in the development of high protein concentration formulations. *J Pharm Sci*. 2004;93(6):1390–1402. doi:10.1002/jps.20079
3. Proj M, Zidar M, Lebar B, et al. Discovery of compounds with viscosity-reducing effects on biopharmaceutical formulations with monoclonal antibodies. *Comput Struct Biotechnol J*. 2022;20:5420–5429. doi:10.1016/j.csbj.2022.09.035
4. McDonald TA, Zepeda ML, Tomlinson MJ, Bee WH, Ivens IA. Subcutaneous administration of biotherapeutics: current experience in animal models. *Curr Opin Mol Ther*. 2010;12(4):461–470.

5. Jonaitis L, Marković S, Farkas K, et al. Intravenous versus subcutaneous delivery of biotherapeutics in IBD: an expert's and patient's perspective. *BMC Proc*. 2021;15(Suppl 17):25. doi:10.1186/s12919-021-00230-7
6. O'Shaughnessy J, Sousa S, Cruz J, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): a randomised, open-label Phase II study. *Eur J Cancer*. 2021;152:223–232. doi:10.1016/j.ejca.2021.03.047
7. Pivot X, Gligorov J, Müller V, et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. *Lancet Oncol*. 2013;14(10):962–970. doi:10.1016/S1470-2045(13)70383-8
8. Pivot X, Spano JP, Espie M, et al. Patients' preference of trastuzumab administration (subcutaneous versus intravenous) in HER2-positive metastatic breast cancer: results of the randomised MetaspHer study. *Eur J Cancer*. 2017;82:230–236. doi:10.1016/j.ejca.2017.05.009
9. Rummel M, Kim TM, Aversa F, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). *Ann Oncol*. 2017;28(4):836–842. doi:10.1093/annonc/mdw685
10. Badkar AV, Gandhi RB, Davis SP, LaBarre MJ. Subcutaneous delivery of high-dose/volume biologics: current status and prospect for future advancements. *Drug Des Dev Ther*. 2021;15:159–170. doi:10.2147/DDDT.S287323
11. Schneider A, Mueller P, Jordi C, et al. Hold the device against the skin: the impact of injection duration on user's force for handheld autoinjectors. *Expert Opin Drug Deliv*. 2020;17(2):225–236. doi:10.1080/17425247.2020.1704730
12. Zijlstra E, Jahnke J, Fischer A, Kapitza C, Forst T. Impact of injection speed, volume, and site on pain sensation. *J Diabetes Sci Technol*. 2018;12 (1):163–168. doi:10.1177/1932296817735121
13. Heise T, Nosek L, Dellweg S, et al. Impact of injection speed and volume on perceived pain during subcutaneous injections into the abdomen and thigh: a single-centre, randomized controlled trial. *Diabetes Obes Metab*. 2014;16(10):971–976. doi:10.1111/dom.12304
14. Rochon PA, Gill SS, Litner J, Fischbach M, Goodison AJ, Gordon M. A systematic review of the evidence for hypodermoclysis to treat dehydration in older people. *J Gerontol a Biol Sci Med Sci*. 1997;52(3):M169–176. doi:10.1093/gerona/52A.3.M169
15. Zaloga GP, Pontes-Arruda A, Dardaine-Giraud V, Constans T; Clinimix Subcutaneous Study Group. Safety and efficacy of subcutaneous parenteral nutrition in older patients: a prospective randomized multicenter clinical trial. *JPEN J Parenter Enteral Nutr*. 2017;41(7):1222–1227. doi:10.1177/0148607116629790
16. Caccialanza R, Constans T, Cotogni P, Zaloga GP, Pontes-Arruda A. Subcutaneous infusion of fluids for hydration or nutrition: a review. *JPEN J Parenter Enteral Nutr*. 2018;42(2):296–307. doi:10.1177/0148607116676593
17. Dias C, Abosaleem B, Crispino C, Gao B, Shaywitz A. Tolerability of high-volume subcutaneous injections of a viscous placebo buffer: a randomized, crossover study in healthy subjects. *AAPS Pharm Sci Tech*. 2015;16:1101–1107. doi:10.1208/s12249-015-0288-y
18. Berteau C, Filipe-Santos O, Wang T, Rojas HE, Granger C, Schwarzenbach F. Evaluation of the impact of viscosity, injection volume, and injection flow rate on subcutaneous injection tolerance. *Med Devices*. 2015;11:473–484.
19. Mathaes R, Koulov A, Joerg S, Mahler HC. Subcutaneous injection volume of biopharmaceuticals-pushing the boundaries. *J Pharm Sci*. 2016;105 (8):2255–2259. doi:10.1016/j.xphs.2016.05.029
20. Woodley WD, Yue W, Morel DR, Lainesse A, Pettis RJ, Bolick NG. Clinical evaluation of an investigational 5 mL wearable injector in healthy human subjects. *Clin Transl Sci*. 2021;14(3):859–869. doi:10.1111/cts.12946
21. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *J Pain*. 2003;4(7):407–414. doi:10.1016/S1526-5900(03)00716-8
22. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Ann Emerg Med*. 2001;38(6):633–638. doi:10.1067/mem.2001.118863
23. Pardeshi NN, Qi W, Dahl K, Caplan L, Carpenter JF. Microparticles and nanoparticles delivered in intravenous saline and in an intravenous solution of a therapeutic antibody product. *J Pharm Sci*. 2017;106(2):511–520. doi:10.1016/j.xphs.2016.09.028
24. Laurent PE, Pettis R, Easterbrook W, Berube J. Evaluating new hypodermic and intradermal injection devices. *Med Device Technol*. 2006;17 (2):16–19.
25. Mohammady M, Radmehr M, Janani L. Slow versus fast subcutaneous heparin injections for prevention of bruising and site pain intensity. *Cochrane Database Syst Rev*. 2021(6):CD008077.
26. Ridyard CH, Dawoud DMM, Tuersley LV, Hughes DA. A systematic review of patients' perspectives on the subcutaneous route of medication administration. *Patient*. 2016;9(4):281–292. doi:10.1007/s40271-015-0160-x
27. Schwarzenbach F, Dao Trong M, Grange L, et al. Results of a human factors experiment of the usability and patient acceptance of a new autoinjector in patients with rheumatoid arthritis. *Patient Prefer Adher*. 2014:199–209. doi:10.2147/PPA.S50583
28. Dashiell-Aje E, Harding G, Pascoe K, DeVries J, Berry P, Ramachandran S. Patient evaluation of satisfaction and outcomes with an autoinjector for self-administration of subcutaneous belimumab in patients with systemic lupus erythematosus. *Patient*. 2018;11(1):119–129. doi:10.1007/s40271-017-0276-2
29. Jones GB, Collins DS, Harrison MW, Thyagarajapuram NR, Wright JM. Subcutaneous drug delivery: an evolving enterprise. *Sci Transl Med*. 2017;9(405):eaaf9166. doi:10.1126/scitranslmed.aaf9166
30. Viola M, Sequeira J, Seiça R, et al. Subcutaneous delivery of monoclonal antibodies: how do we get there? *J Control Rele*. 2018;286:301–314. doi:10.1016/j.jconrel.2018.08.001
31. Collins DS, Sánchez-Félix M, Badkar AV, Mrsny R. Accelerating the development of novel technologies and tools for the subcutaneous delivery of biotherapeutics. *J Control Release*. 2020;321:475–482. doi:10.1016/j.jconrel.2020.02.036
32. Leng Y, Wang H, de Lucio M, Gomez H. Mixed-dimensional multi-scale poroelastic modeling of adipose tissue for subcutaneous injection. *Biomech Model Mechano*. 2022;21(6):1825–1840. doi:10.1007/s10237-022-01622-0