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ARTICLE

Clinical Evaluation of an Investigational 5 mL Wearable Injector in Healthy Human Subjects

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An investigational wearable injector (WI), the BD Libertas Wearable Injector (BD Libertas is a trademark of Becton, Dickinson and Company), was evaluated in an early feasibility clinical study for functional performance, tissue effects, subject tolerability, and acceptability of 5 mL, non-Newtonian ~ 8 cP subcutaneous placebo injections in 52 healthy adult subjects of 2 age groups (18–64 years and ≥ 65 years). Randomized WI subcutaneous injections (*n* = 208, 4/subject) were delivered to the right and left abdomen and thigh of each subject, 50% (1 thigh and 1 abdomen) with a defined movement sequence during injection. Injector functional performance was documented. Deposition was qualified and quantified with ultrasound. Tissue effects and tolerability (pain) were monitored through 24 hours with corresponding acceptability questionnaires administered through 72 hours. WI (*n* = 205) automatically inserted the needle, delivered 5 mL ± 5% in 5.42 minutes (SD 0.74) and retracted. Depots were entirely (93.2%) or predominantly (5.4%) localized within the target subcutaneous tissue. Slight to moderate wheals (63.9%) and erythema (75.1%) were observed with ≥ 50% resolution within 30–60 minutes. Subject pain (100 mm Visual Analog Scale) peaked mid-injection (mean 9.1 mm, SD 13.4) and rapidly resolved within 30 minutes (mean 0.4 mm, SD 2.6). Subjects' peak pain (≥ 90.2%), injection site appearance (≥ 92.2%) and injector wear, size, and removal (≥ 92.1%) were acceptable (Likert responses) with 100% likely to use the injector if prescribed. Injection site preference was divided between none (46%), abdomen (25%), or thigh (26.9%). The investigational WI successfully delivered 5 mL viscous subcutaneous injections. Tissue effects and pain were transient, well-tolerated and acceptable. Neither injection site, movement or subject age affected injector functional performance or subject pain and acceptability.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Transitioning chronic disease therapies from intravenous infusion to large volume subcutaneous injection requires reliable and accurate delivery devices that may enable intuitive self or care-giver administration. Limited options are commercially available.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ An investigational wearable injector's functionality and tolerability for 5 mL, ~ 8 cP subcutaneous placebo injections to the thigh and abdomen with and without movement in healthy adults of 2 age groups (18–64 years and ≥ 65 years) is described. Depot location, corresponding local tissue effects, and acceptability are documented.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The investigational injector performed as designed, consistently delivering 5 mL ± 5% to the target subcutaneous tissue in ~ 5.5 minutes with transient, well-tolerated tissue effects and pain. Neither injection site, movement or subject age affected injector functional performance or subject pain and acceptability.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The investigational injector demonstrated equivalent functional performance with broad acceptability across subject genders, body mass index categories, and age range with and without movement. Results indicate promising potential of device design and delivery boundaries.

Chronic disease biological therapies are transitioning from traditional intravenous to subcutaneous administration. Adapting intravenous therapies to subcutaneous administration creates delivery challenges, such as larger than traditional volumes and viscosities.[1–6] Intuitive and reliable subcutaneous injection system design will help navigate the complexity of these new delivery challenges while ensuring patient ease of wear and use. Effective subcutaneous injection system design requires a strong understanding of the biomechanical and physiological impact to subcutaneous tissue of delivery at increased volumes and viscosities with corresponding subject tolerability and acceptability.[1,7–11]

Subcutaneous administration conveys many benefits, such as reduced cost and treatment time and increased patient autonomy, convenience, and tolerance/acceptance.[3,12–21] Multiple comparative studies report that both patients and

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health care providers (HCPs) prefer subcutaneous to intravenous administration, citing improved clinical management, efficiency, and convenience with decreased pain and adverse systemic effects.[12,18–25]

Historically, literature has identified multiple thresholds for the subcutaneous bolus limit between 1.5 and 3 mL due to subject pain and tissue feasibility.[1–3,7,15,26] Observation that injection volumes > 2 mL may create site wheals (surface tissue displacement) or induration (hardening of the soft tissue) likely contributed to the anticipated low tolerability of these injections despite the absence of relevant clinical evidence linking wheal formation or induration to pain.[2] Multiple studies using pump-driven injection systems as surrogates for functional subcutaneous injection devices document the feasibility and tolerability of 3 to 20 mL single subcutaneous bolus injections in human clinical subjects.[1,10,12,27,28]

Subcutaneous administration is both feasible and convenient with the introduction of combination products, such as wearable or on-body injectors, autoinjectors, and prefilled syringes that use fixed dosing to reduce dosing errors and enable patient choice in injection provider, device type, and setting.[2,12] Wearable injectors (WIs) complement and may exceed the volume and viscosity capacities currently available in prefilled syringes or autoinjectors; however, there are currently limited commercial on-body or WI options available.[3,10,29]

The current study is a first-in-human clinical assessment of an investigational WI for functional performance and corresponding tissue effects, depot location, subject tolerability, and acceptability for 5 mL, ~ 8 cP injections of a viscous non-Newtonian placebo, hyaluronic acid (HA) diluted in saline. The study included 52 healthy adult subjects of both genders and 2 age groups (18–64 years and ≥ 65 years). Each subject received four injections (2 abdominal and 2 thigh) with and without movement for each location. WI functional performance (injection duration, delivered volume, adherence, and status indicator) was documented from application through removal. Depot location was qualified and quantified via ultrasound. Site tissue effects (wheal and erythema) and subject pain tolerance (100 mm Visual Analog Scale, VAS) were monitored through 24 hours with corresponding acceptability documented via questionnaires through 72 hours postinjection.

METHODS

Study design

The early feasibility, clinical study described here is a single center (Eurofins Optimed, Gières, France), open label, randomized evaluation of an investigational WI in 52 healthy adults of both genders and 2 age groups (18–64 years and ≥ 65 years). Trial subjects were seen three times in-clinic (**Figure 1**), visit one for screening (informed consent, medical examination, and confirmation of inclusion/exclusion criteria), visit two for in-clinic injections and assessments, and visit three for final in-clinic assessment of all injection sites. Subjects received 4 randomized, sequential injections delivered one at a time at least 1 hour apart to each of their right and left abdomens and anterolateral thighs during visit 2. Trained HCPs applied, actuated, and removed the WIs and performed all in-clinic assessments. During half of the injections (1 thigh and 1 abdominal), a defined movement sequence had subjects walk 60 feet (18.3 meters; **Figure 2**), reach overhead (extension), bend forward (flexion), rotate side-to-side (trunk rotation), and lean side to side (lateral flexion) while standing. The movement sequence was complete within 3 minutes of WI actuation. Subjects were instructed not to apply lotions or oils to the injection sites the day of visit two. Injection sites were shaved at the start of visit two if deemed necessary by the HCPs.

The protocol was approved by the Ethics Committee, CPP Sud-Ouest et Outre-Mer IV (CPP 18-026b), and French health agency, Agence nationale de sécurité du medicament (trial registration number 2017-A03158-45) and conducted in accordance with the Declaration of Helsinki (October 2013) and Good Clinical Practice guidelines.

Sample size determination

Based on internal preclinical data, the test for paired means (software PASS13, 80% power, alpha = 0.05) determined a minimum of 48 subjects were needed to detect a wheal volume mean difference of 1 cm^3 (SD 2.4) between injection conditions. When using the confidence intervals (CIs) for one mean routine (software PASS13), the same internal preclinical data determined that a minimum of 28 subjects would ensure a 2-sided 95% CI width of 1 cm^3 assuming a 1.9 cm^3 SD. Internal data also gives a 2-sided 95% CI of 4.96 mL and 5.10 mL for 50 subjects and 4.93 mL and 5.13 mL for 25 subjects with an assumed mean delivered volume of 5.03 mL (SD 0.25).

Using historic clinical human pain Visual Analog Scale (100 mm VAS) scores,[27] a two sample paired *t*-test (assumed correlation of 0.6, alpha = 0.05) determined clinically significant differences of 10 mm could be detected with 50 subjects with a power of 97%.

Fifty-two subjects were enrolled to ensure a minimum of 50 injections per injection condition (site and movement combination; **Table 1**). Subjects were compensated for participation.

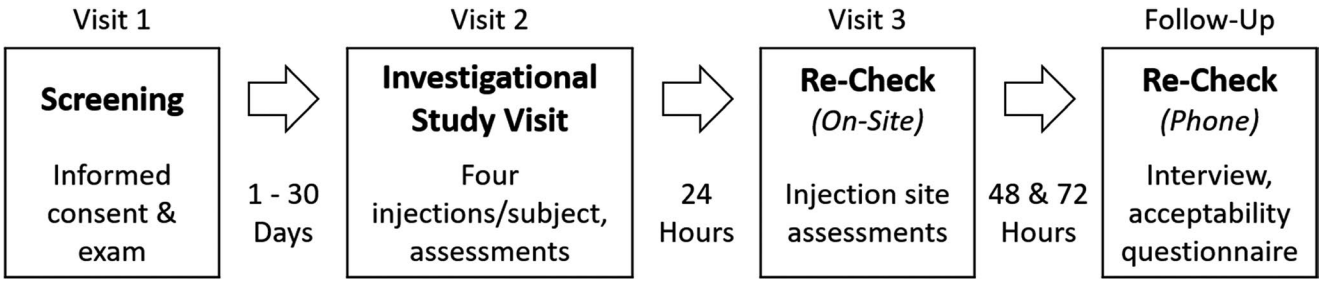

Figure 1 Clinical visit and data collection schedule.

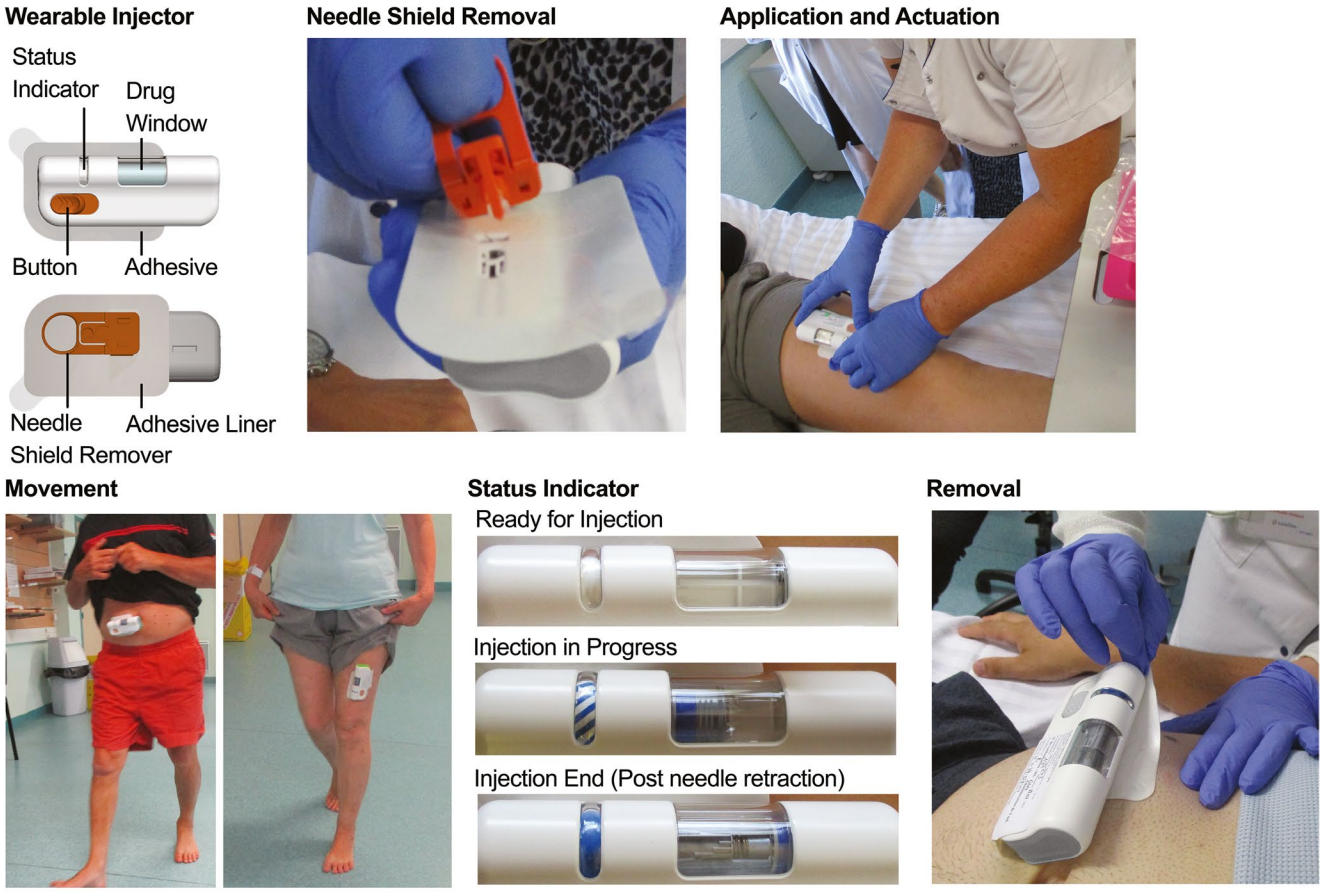

Figure 2 Representative clinical images of investigational WIs. Coloring and texture of oval button and peripheral stripe on devices shown modified to remove identifying marking. EU CE, European Union Conformité Européenne; FDA, US Food and Drug Administration; WI, wearable injector.

Delivery system

The investigational BD Libertas Wearable Injector is designed as a spring-driven, prefilled, pre-assembled, disposable, single-use bolus drug delivery injector intended for self or care-giver administration of 2–5 mL subcutaneous injections at viscosities up to 50 cP.[30] BD Libertas is a trademark of Becton, Dickinson and Company. The BD Libertas Wearable Injector is a product in development; some statements are forward looking and are subject to a variety of risks and uncertainties. The BD Libertas Wearable Injector is a device component intended for drug-device combination products and not subject to US Food and Drug Administration (FDA) 510(k) clearance or separate European Union Conformité Européenne (EU CE) mark certification. WI body dimensions are 11.8 cm long × 4.7 cm wide × 2.6 cm tall with an approximate mass of 84 g when filled and prepped for application. WIs were adhered to the injection site and button-actuated to initiate automatic needle insertion, injection, needle retraction, needle shielding, and delivery status indication. Injection delivery progression and completion were monitored by a visible injection status indicator and audible clicks at actuation (needle insertion) and completion (needle retraction). Application orientation of the WIs was horizontal on the abdomen and vertical on the thigh (**Figure 2**). The time of needle retraction (injection end) was defined as 0 hours with all postinjection data collection scheduled from that point.

Injection solutions

Although the WI is designed as a prefilled system, for purposes of this study, injection solutions were prepared and injectors filled and assembled daily per a qualified aseptic process in the on-site clinic pharmacy. The injection solution was a noncrosslinked commercial HA (Vivacy Laboratories, Paris, France) diluted to 10% volume by volume in sterile 0.9% weight per volume physiological saline to reach a nominal viscosity of ~ 8cP (shear rate ~ 1000 s^{-1} at 20°C). The HA is CE-marked, nonanimal in origin, and exhibits non-Newtonian shear thinning behavior at increasing shear rates. Samples from each daily solution preparation were measured for density and viscosity at 2 shear rates, ~ 25 s^{-1} and ~ 1000 s^{-1} at 20°C, to reflect in-vial and underflow viscosity estimates (**Table 1**).

Table 1 Injection number per injection condition and delivered volume data

Device	Injection solution	Injection volume	Viscosity,[a] cP	Site	Movement, yes/no	No. total injections	No. injections delivering 5 mL ± 5%	Mean delivered volume, mL ± SD
5 mL WI	10% HA	5 mL	17, 8	Abdomen	Yes	52	51	5.09 ± 0.04
					No	54	52	5.08 ± 0.06
				Thigh	Yes	57	51	5.07 ± 0.04
					No	53	51	5.07 ± 0.04

HA, hyaluronic acid; WI, wearable injector.
[a]Two viscosity values are displayed. The first value or range is an estimate of in-vial viscosity, measured at a low shear rate of 20–25 s^{-1}. The second value or range is the viscosity measured at ~ 1,000 s^{-1}. HA is a non-Newtonian fluid.

Injector functional performance assessment

Injector functional performance was assessed from application through retraction and removal. Actuation, delivery, and retraction were confirmed by noting audible clicks at actuation and retraction, the phase of delivery indicated by the visible status indicator (ready for injection/injection in progress/postretraction) and delivered volume. Status indicator accuracy per delivery phase was assessed from application through retraction.

Delivered volume was assessed by gravimetric analysis of the injectors pre-injection and postinjection. Fluid loss during or postinjection was also collected and weighed.[31,32] Delivered volume was confirmed using the formula: (Pre-injection WI weight – postinjection WI weight – fluid collection)/solution density.

Injector adherence integrity was graded on a 5 point observational scale as ≥ 90% adhered,[33] 89% to ≥ 75% adhered, 74% to ≥ 50% adhered, 49 to ≥ 1% adhered, or completely detached at application, 3 minutes postactuation and immediately prior to removal.

Tissue effects assessments

All injection sites were confirmed to have no visible tissue effects prior to device application. Tissue effects were evaluated following injector removal (~ 5 minutes postretraction) and at 0.5, 1, 2, and 24 hours postinjection. Injections 1 to 3 per subject also had a final additional assessment 4–7 hours postinjection (end of visit) when the fourth injection had its 2-hour assessment. The fourth randomized injection was not assessed between the 2 and 24-hour timepoints. Subjects were also asked to report injection site swelling/nodules, redness, or bruising during 48 and 72-hour follow-up telephone calls (**Figure 1**).

Wheal formation, if observed, was measured with calipers for wheal length (major axis), width (minor axis), and depth (vertical rise from skin surface).[1,15,34] Wheal dimensions were used to calculate wheal area and volume based on theoretical optimum elliptical geometry.

Wheals and erythema were assigned a grade of none, very slight, well-defined, moderate, or severe to characterize the visible observations; the grading scale was adapted from prior guidelines for grading skin reactions.[23,35] For purposes of the study, observed wheals were likely due to tissue distension from large volume subcutaneous (LVSC) injection deposition. Erythema is likely due to composite causes, including injection condition.

A similar five-point observational scale qualified observed bleeding as none, tinge of red, drop of red, oozing blood, or significant bleeding. The frequency of bruising and induration was also noted (yes/no).

Subject tolerability, acceptability, and preference

Subject pain (tolerability) was quantified using a standard 100 mm VAS (0 mm no pain to 100 mm worst pain)[36] at actuation, 3 minutes postactuation, retraction (0 hours), removal, and 0.5, 1, 2, and 24 hours postinjection. For purposes of this study, the minimum clinically significant difference between VAS scores was defined as 10 mm.[11,27,36–40]

Subjects completed acceptability and preference questionnaires (**Table 2**) at 3 minutes postactuation, retraction

Table 2 Percentage of favorable subject questionnaire responses after needle retraction, WI removal, and completion of all four injections

	Abdomen		Thigh	
Question	**Movement**	**No movement**	**Movement**	**No movement**
Percent favorable (agree + strongly agree) responses at needle retraction (0 hours, injection end)				
I feel no pain at the injection site.	72.6	77.0	78.4	72.6
The pain is acceptable.	96.1	96.1	96.1	94.1
I feel no itching at the injection site.	94.1	96.2	94.1	92.2
I feel no burning at the injection site.	92.1	84.6	96.0	92.1
I feel no pressure at the injection site.	86.3	92.3	90.1	78.4
The appearance of the injection site is acceptable.	96.1	98.1	100.0	98.1
Percent favorable (agree + strongly agree or yes) responses at WI removal				
The pain of injector removal was acceptable.	96.1	98.1	100.0	98.1
The injector was comfortable to wear during injection.	92.2	94.2	94.1	92.1
The skin at injection site does not seem irritated.	90.2	86.5	98.1	96.1
I do not notice residual adhesive at the injection site.	94.1	94.2	94.1	98.0
Overall, adhesive removal was acceptable.	98.0	98.0	100.0	100.0
The appearance of the injection site is acceptable.	92.2	96.1	96.0	98.1
Do you find the size of the injector acceptable?			98.0% yes	
Do you find the weight of the injector acceptable			99.0% yes	
Percent favorable (yes or likely + highly likely) responses after all 4 injections				
The appearance of the delivery site acceptable?			96.2% yes	
If prescribed, would you use injector monthly?			100% likely or highly likely	

WI, wearable injector.
Favorable responses denote a yes, likely/high likely or agree/strongly agree on a 5-point Likert scale response.

(0 hours), and 0.5, 1, 2, and 24 hours postinjection during visits 2 and 3 in-clinic and via follow-up telephone interviews at 48 and 72 hours. Subjects also completed a wear and removal acceptability questionnaire (**Table 2**) at injector removal. Acceptability responses were answered yes/no or with a five-point Likert scale: strongly agree, agree, neutral, disagree, or strongly disagree.[41]

Depot localization

Ultrasound imaging was performed pre-injection and post-injection by an experienced technician using a DERMCUP portable ultrasound with linear probe (Atys Medical, Jarrest, France) and MicrUs EXT-1H with linear probe (TELEMED Medical Systems, Milan, Italy). The pre-injection ultrasound scans qualified the injection site and quantified the thickness of the intradermal and subcutaneous tissue layers. Depot location postinjection was qualitatively classified as intradermal, subcutaneous, intramuscular, or some combination thereof. The postinjection depth to the perceived depot top and bottom from skin surface were measured. Depot widths exceeded the field of view of any single ultrasound image; therefore, depot widths were measured across multiple images. *In situ* depot height (difference between depot top and bottom) and surface area (elliptical geometry) were calculated from these measurements.

Adverse events

All adverse events (AEs) observed in subjects were documented. Normally expected LVSC injection effects documented as study end points through visit two, such as transient local pain during injection or tissue effects, were not documented as AEs unless judged as severe and exceeding expectation by the principal investigator or those events which persisted or manifested beyond visit two.

Statistical methods

All enrolled subjects completed the study. All WIs were included in functional assessments and related analysis. Only injectors with a confirmed delivery of 5 mL ± 5% were included for tissue effect, depot location, tolerability (pain), and acceptability analysis to ensure injection volume equivalency. Statistical software was R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Comparisons of injection conditions (combinations of site with or without movement; **Table 1**) were performed for the different end points of interest using linear mixed effect models for continuous variables, cumulative link logit mixed effect models for categorical variables, and binomial logistic mixed effect models for binary variables. A linear mixed effect model with log transformation of the wheal measurement data was performed in order to improve model adequacy. Injection condition, time, and their interactions were fixed effects, and subject was a random effect. Additional models were run with injection site and movement as the fixed effects if injection condition proved a significant contributing factor in the original model and data trends indicated a delineation between the influence of site and/or movement. The effect of covariates, such as

gender, age category, body mass index (BMI) category, and their interactions were also investigated. Correlations were assessed by either Pearson's (continuous) or Spearman's (categorical) rho.

RESULTS

Demographics

Large volume subcutaneous injection therapy is potentially broadly applicable to multiple chronic conditions representing large demographic segments; therefore, a balanced recruitment across genders, BMIs, and ages was attempted. Sixty-three subjects were screened. Subjects provided consent for trial inclusion; 52 healthy adult subjects, 27 females (52%) and 25 males (48%), were enrolled and included in the study analysis. The mean subject age was 54.5 years (SD 16) with a minimum age of 18 and a maximum of 76. Subjects were divided into 2 age categories with 27 subjects of 18–64 years (mean 42.2 years, SD 13) and 25 subjects of ≥ 65 years (mean 67.9 years, SD 3); the gender balance remained constant within the 2 age groups (52% females and 48% males). The mean subject BMI was 27.3 kg/m^2 (SD 4.53) with a minimum of 19.8 kg/m^2 and a maximum of 41.9 kg/m^2. Subjects were distributed across three standard World Health Organization BMI categories[42]: 38.5% normal (18.5–24.9 kg/m^2), 32.7% overweight (25.0–29.9 kg/m^2), and 28.8% obese (≥ 30.0 kg/m^2). An even distribution per age category and gender subgroup (i.e., males, ≥ 65 years, etc.) was attempted across the three BMI categories with a final distribution of three to six subjects per subgroup (**Table S1**). Subjects were 98.1% Caucasian.

Injector functional performance

Two hundred sixteen investigational WIs were included in the study; eight were excluded from analysis due to injector issues preventing injection. The remaining 208 WIs injected, but 3 were further excluded due to an unconfirmed delivered volume. Injection status indicators were 100% accurate throughout assessment for all injectors. Ninety-nine percent of injectors were completely adhered (≥ 90%) at all timepoints; 1% of injectors, all on the abdomen with movement, were 75–89% adhered after movement (n = 3) through removal (n = 2) with no effect on WI function.

All 205 (100%) remaining injectors actuated, delivered the 5 mL ± 5% target (mean 5.08 mL, SD 0.04) and retracted as intended in 5.42 minutes (SD 0.74). Minor leakage at the injector/skin interface was observed at removal for 68.8% of injectors, all ≤ 130 µL except one device that leaked 220 µL. Neither movement, injection site nor subject age, gender nor BMI were significant contributing factors for injector performance across all injections and subjects.

Tissue effects

Wheal formation was observed postinjection at 63.9% of injection sites; 36.1% had none. The postinjection measurable wheals were graded as 24.9% very slight (volume mean 0.23 cm^3, SD 0.31), 28.3% well-defined (volume mean 1.60 cm^3, SD 0.95), or 10.7% moderate (volume mean 6.33 cm^3, SD 2.70). Data trends per injection condition (**Figure 3**) indicate wheal formation was more common in the thigh (84% with movement and 80% without) than the abdomen (41% with movement and 50% without). Within 1 hour of injection, the majority of sites had no measurable wheals (69.3%) with 20% very slight (volume mean 0.24 cm^3, SD 0.17) or 10.7% well-defined (volume mean 1.17 cm^3, SD 0.72) wheals remaining. Wheals from the first three injections were resolved completely at the end of visit assessment (EOV, 4–7 hours postinjection). The fourth injection was not assessed between 2 and 24 hours; resolution was complete at 24 hours.

Wheals were more frequent, larger, and had a longer time to resolution for thigh injections (P value ≤ 0.016) and male subjects (P value ≤ 0.049) through 1–2 hours postinjection. Movement and BMI category were not significant contributing factors except immediately postinjection (0 hours only) when wheal volume and depth (vertical rise) were significantly larger for injections without movement (P value ≤ 0.045). Abdominal wheal volume and area were larger in subjects 18–64 years (P value ≤ 0.032).

Erythema was not observed postinjection at 24.9% of injection sites; 75.1% of sites had very slight (46.8%), well-defined (26.3%), or moderate (2.0%) erythema with significantly more intensity in the abdominal sites (P value ≤ 0.002). Erythema reduced rapidly and significantly with each incremental timepoint, 0 hours > 30 minutes > 1 hour (P value ≤ 0.003), improving to 62.0% of sites without erythema within 30 minutes postinjection and 97.1% by 2 hours. Erythema was completely resolved at all sites within 24 hours of injection except for 1 very slight erythema occurrence that persisted through 120 hours, as reported by the subject during follow-up telephone calls.

Minor bleeding observed postinjection ranged from a tinge of red (14.1%) to a drop of blood (15.6%). Bruising was observed at a single injection site through 30 minutes; no other bruising was observed. Induration (hardening of the soft tissue) was not observed. No swelling/ nodules or bruising were reported during telephone follow-up.

Injection pain (tolerability), acceptability, and adverse events

VAS pain scores (**Figure 4** scale 0 mm no pain to 100 mm worst pain) were at a mean 0 mm (SD 0.2) baseline prior to injector application. Pain scores increased after WI actuation and needle insertion (mean 4.4 mm, SD 8.3) to peak at the 3-minute injection midpoint (mean 9.1 mm, SD 13.4) before rapidly diminishing within 2–3 minutes at needle retraction (6.7 mm, SD 10.7) and returning to baseline at 30 minutes (mean 0.4 mm, SD 2.6). There were no clinically significant differences (≥ 10 mm) between injection conditions or subject factors. Subjects reported that the pain was acceptable (agree or strongly agree Likert responses) at the 3-minute injection midpoint (≥ 90.2%) and at retraction (≥ 94.1%; **Table 2**) across all injections. The VAS pain score correlations (Pearson's or Spearman's rho) to tissue effects, depot location, and injection duration are weak (rho ± 0.2–0.4) to very weak (rho 0 ± 0.2), indicating no relationship.

Subject responses across all injection conditions (**Table 2**) were ≥ 78.4% favorable (Likert agree or strongly agree) that their injection site did not itch, burn, or have

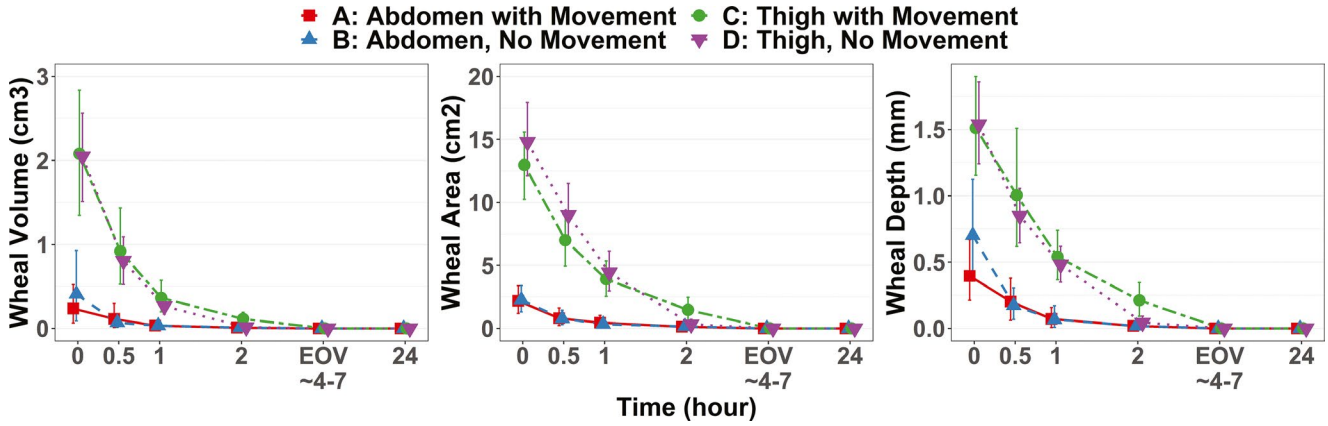

Figure 3 Wheal volume (cm^3, left), area (cm^2, middle), and depth (mm, vertical rise, right) mean data with 2-sided 95% CIs per injection condition and timepoint. Parameters were calculated from caliper measurements. EOV is for injections 1–3 only and was taken as an additional assessment 4–7 hours postinjection when the fourth injection had its 2-hour assessment. The fourth injections were not evaluated between 2 and 24 hours postinjection. 95% CI around the means were calculated using bootstrap (R, version 3.5.1). CI, confidence interval; EOV, end of visit.

the sensation of pressure at needle retraction (0 hours, injection end); responses increased to ≥ 98.5% favorable at 30 minutes postinjection and 100% at 48 hours (data not shown). Subjects found the appearance of the injection site ≥ 96.1% favorable at needle retraction prior to injector removal, ≥ 92.2% favorable after injector removal when tissue effects were first visible and 96.2% favorable at the end of the day after receiving all 4 injections. All subjects (100%) indicated they were likely to use the injector if prescribed.

Subjects either had no preference (46.2%) for injection site location or were evenly divided between a preference for the abdomen (25%) or thigh (26.9%), indicating the viability of both sites. Subject reasons for site preference included less pain, ease of movement, or discretion for both sites.

Seven trial AEs were recorded, all qualified as mild. Five of the seven AEs were procedure related, all from two subjects who had dual intradermal/subcutaneous depots and reported feeling itching or prickling at the injection site. Two of the seven AEs (headache and mosquito bite) were classified as not related to the device or protocol. No serious AEs were reported.

Depot localization

Pre-injection intradermal thickness (**Table 3**; overall mean 1.7 mm, SD 0.4) was significantly larger in the abdomen and male subjects (*P* value ≤ 0.006). Pre-injection subcutaneous thickness (**Table 3**; overall mean 22.8 mm, SD 12.8) is significantly larger in the abdomen, females, and higher BMI subjects (*P* value ≤ 0.003). The correlation between pre-injection subcutaneous thickness and injection duration is very weak (Pearson's rho 0 ± 0.2), indicating no relationship.

Based on examination of ultrasound images (representative images **Figure S1**), depots were localized within the target subcutaneous tissue for 93.2% of all injections. Subcutaneous depots with some infiltration of the injection solution into the intradermal tissue (intradermal/subcutaneous) were observed in 5.4% of depots. Two intramuscular injections (1%) occurred in the thigh of a single subject with a thin (< 1.5 mm) subcutaneous tissue layer. Ultrasound visibility was insufficient to qualify one depot (0.5%), but the injector was confirmed to have injected 5.05 mL to the site.

The depth to the depot top (**Table 3**; overall mean 2.0 mm, SD 0.6) is equivalent between injection conditions but deeper in males than females (*P* value 0.007). The correlation between the depth to the depot top and tissue effects is very weak (Pearson's rho 0 ± 0.2), indicating no relationship.

Depth to the depot bottom (**Table 3**; overall mean 14.2 mm, SD 3.4) was significantly deeper and depot heights (**Table 3**; overall mean 12.2 mm, SD 3.6) and surface areas (**Table 3**; overall mean 3.1 cm^2, SD 1.1) were significantly larger in the abdomen, females, and higher BMI subjects (*P* value ≤ 0.038). Depot widths (**Table 3**; overall mean 32.5 mm, SD 7.9) were not statistically distinct between injection conditions or factors.

DISCUSSION

The advantages of treating chronic conditions with subcutaneous administration are well-documented in literature and include reduced treatment time, cost, and systemic effects with increased patient preference, autonomy, and convenience.[1,3,12] WIs should be intuitive, straightforward, and easy to use by patients and care-givers. Such LVSC delivery systems would ideally also accommodate activities of daily living and have broad applicability to multiple chronic conditions across a wide range of patient demographics. However, commercialized LVSC ambulatory device options are limited.[3,10,29] This discussion examines the WI performance against these needs and within the limitations of the current study.

The investigational WI demonstrated equivalent functional performance across all subject genders, ages, BMIs, and injection sites. Broad favorable subject acceptability

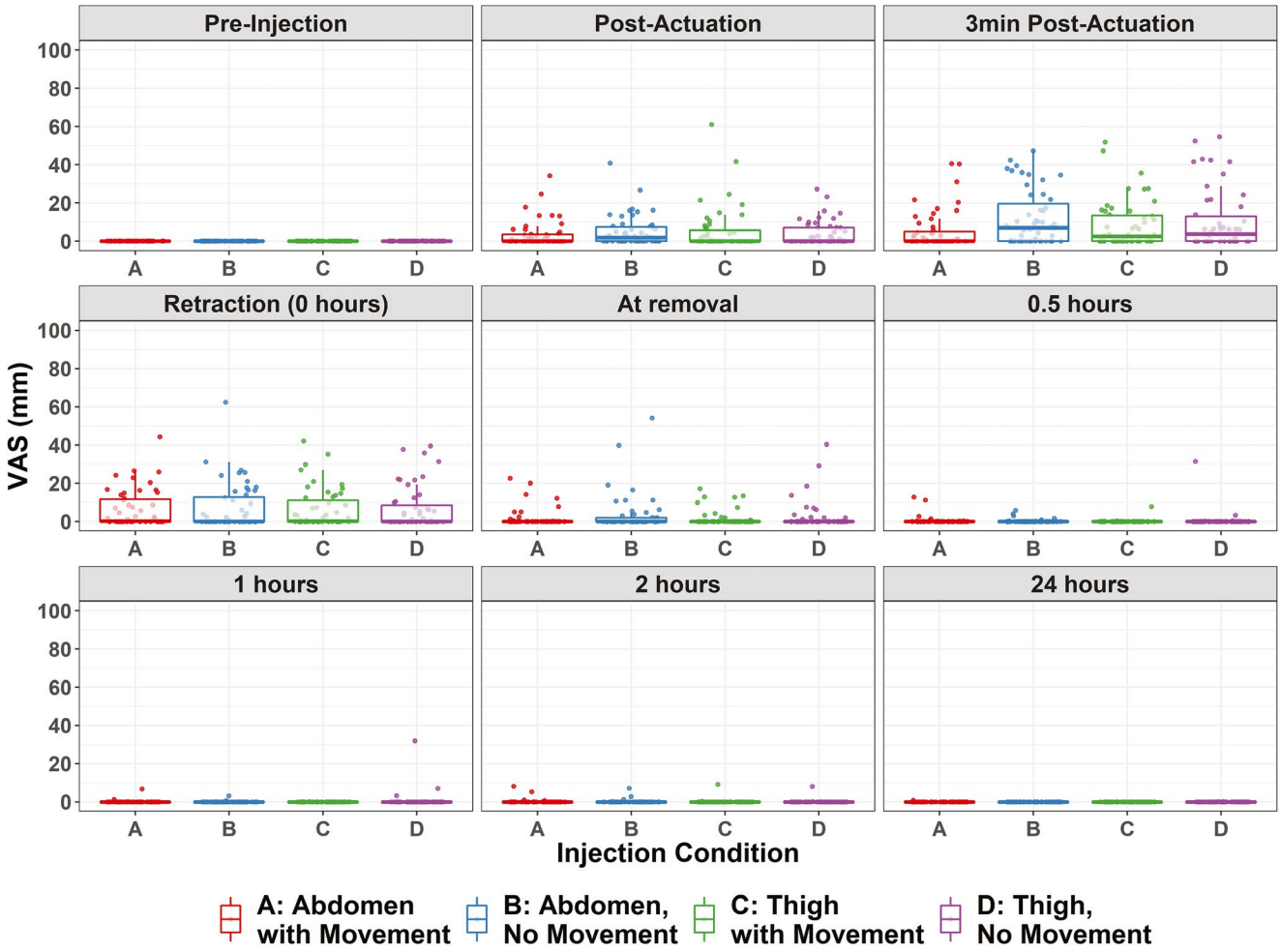

Figure 4 Pain scores (VAS mm) over time per injection condition. Actuation = needle insertion and injection start. Removal was ~ 5 minutes post-needle retraction. Mean injection duration was 5.42 minutes (SD 0.74) across injection conditions. Boxplot displays median within first and third quartiles; the whiskers are 1.5 times the interquartile range (IQR). Dots are the individual data points. VAS, Visual Analog Scale.

and willingness to use if prescribed combined with transient, rapidly resolving injection tissue effects, and pain are promising indicators of the injector's potential. However, study recruitment was limited to healthy adult subjects with limited ethnic diversity. Future broader ethnic recruitment and inclusion of subjects with relevant chronic conditions could better inform WI performance in intended real-world scenarios.

The majority of WIs performed all delivery functions as intended, including automatic needle insertion, delivery of 5 mL ± 5% of the ~ 8cP non-Newtonian placebo in ~ 5.5 minutes, and automatic retraction with needle shielding. The investigational WI is targeted for both self or care-giver administration. The multiple integrated functions, prefilled nature, visual and audible injection progress indictors, and basic use steps of adhesion application and removal with single button-push activation address needs for simplicity of use and potential utilization by nonclinicians. Standardized movements simulating potential routine activities of daily living with no impact on performance outcomes was also notable. In the present feasibility study, trained HCPs performed all placements, actuations, and removals to standardize preparation and application procedures across injections. Additional human factors and usability studies, including self-administration, are warranted to ensure function under broader real-use scenarios.

Adhesive performance during delivery was very good with the majority of WIs fully or mostly adhered. The use of skin lotions or oils on the day of injection and subjects predisposed to adhesive sensitivities were excluded. Site hair trimming was performed when investigators deemed necessary. Further assessment of adhesive performance could benefit from inclusion of these potential real-use scenarios.

The injector's spring-based drive mechanism must overcome both system fluid path flow resistance and tissue resistance to displacement by the injected bolus while accommodating solution properties, such as increased viscosity that alter injection duration according to basic fluid

Table 3 Summary per injection site (abdomen or thigh), gender (female or male), and BMI category (normal, overweight, or obese) of mean pre-injection intradermal and subcutaneous tissue thicknesses (mm) and postinjection mean depth to depot top (mm), bottom (mm) width (mm), height (mm, bottom of depot – top of depot), and depot surface area (cm^2, calculated using width, height, and elliptical geometry)

Injection site	Abdomen					Thigh					
	Gender		BMI category			Gender		BMI category			
Factor	Female	Male	Normal	Overweight	Obese	Female	Male	Normal	Overweight	Obese	Overall
Pre-injection (mean, SD)											
Intradermal thickness, mm	1.8 (0.3)	2.0 (0.4)	1.8 (0.3)	2.0 (0.4)	1.9 (0.4)	1.4 (0.3)	1.6 (0.2)	1.4 (0.2)	1.6 (0.3)	1.6 (0.3)	1.7 (0.4)
Subcutaneous thickness, mm	33.8 (9.3)	28.8 (11.9)	22.7 (9.6)	34.5 (8.1)	39.4 (6.2)	19.0 (6.7)	9.0 (5.0)	10.9 (5.9)	13.5 (5.6)	19.4 (9.3)	22.8 (12.8)
Post-injection (mean, SD)											
Depth to top of depot, mm	1.9 (0.5)	2.1 (0.4)	2.0 (0.5)	2.0 (0.4)	1.9 (0.5)	1.7 (0.4)	2.1 (0.8)	2.1 (0.9)	1.9 (0.6)	1.8 (0.3)	2.0 (0.6)
Depth to bottom of depot, mm	17.2 (3.0)	13.8 (2.9)	14.5 (2.6)	15.3 (2.6)	17.2 (4.4)	13.9 (3.1)	11.6 (2.0)	12.0 (2.3)	12.5 (2.1)	14.1 (3.7)	14.2 (3.4)
Depot height, mm	15.4 (3.1)	11.7 (2.9)	12.5 (2.7)	13.3 (2.8)	15.3 (4.5)	12.2 (3.1)	9.5 (2.1)	9.9 (2.3)	10.6 (2.4)	12.3 (3.8)	12.2 (3.6)
Depot width, mm	30.4 (5.7)	33.4 (9.2)	30.3 (5.7)	34.4 (9.4)	31.1 (7.4)	32.2 (7.6)	33.9 (8.5)	32.1 (7.7)	33.8 (9.2)	33.5 (7.3)	32.5 (7.9)
Depot surface area, cm^2	3.7 (1.0)	3.1 (1.1)	3.0 (0.9)	3.6 (1.0)	3.7 (1.4)	3.1 (1.1)	2.5 (0.9)	2.5 (0.9)	2.9 (1.0)	3.2 (1.0)	3.1 (1.1)

BMI, body mass index.
Measurements taken from ultrasound images.

dynamic principles.[15,43,44] The spring-based system mechanics of the current WI may allow fluctuations in flow rate relative to tissue counter pressure over the course of injection, potentially reducing patient pain perception. Injection rate (duration) and/or solution viscosity have been shown to influence subject tolerability and tissue effects.[1,7,11,27] A limitation of this study is use of a single non-Newtonian injection fluid. Similar studies across an extended range of viscosities would further probe WI design efficacy and extend the characterization of injector performance, tolerability, and acceptability.

Ultrasound imaging qualified depot location as entirely (93.2%) or predominantly (5.4%) localized within the target subcutaneous tissue. Rare instances of minor infiltration of the injection solution into the more superficial intradermal tissue (5.4%) or complete localization within the deeper intramuscular tissue (1%) were also observed. The ultrasound imaging utilized could not quantify the percent distribution between the intradermal and subcutaneous tissue types for the 5.4% of dual depots but could qualify the depots as predominantly within the subcutaneous tissue. The effect, if any, of depot location on postinjection pharmacokinetics was not explored in this study; similar studies of active therapeutic formulations and pharmacokinetic characterization are warranted. Additionally, prior large volume injection studies have indicated a link between subject tolerability and injection solution characteristics, such as viscosity, preservatives, diluent, pH, and osmolality.[7,11,27,45] The current study subjects gave high favorable Likert acceptability responses to questions of postinjection site comfort, but responses may change with formulation differences.

CONCLUSIONS

The investigational WI performed as intended, delivering well-tolerated ~ 8 cP, 5 mL ± 5% injections to the abdomen and thigh, both with and without movement, in ~ 5.5 minutes for all injections regardless of subject age, gender, or BMI. Subjects found injector wear, delivery, and removal and the corresponding transient pain and tissue effects acceptable and were 100% likely to use the injector if prescribed. Similar injection studies assessing the same end points at additional, higher viscosities and human factor assessments with subject self-administration would further inform injector efficacy, usability, functionality, and subject acceptability. However, all clinical data in the present study indicate promising potential for therapeutic applications of the spring-based investigational WI.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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