Protocol H9X-MC-B021(b)

Crossover Study Comparing Dulaglutide (Trulicity) Pen and the Semaglutide (Ozempic) Pen

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Protocol H9X-MC-B021(b): Crossover Study Comparing the Dulaglutide (Trulicity) Pen and the Semaglutide (Ozempic) Pen

Dulaglutide (LY2189265)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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1. Synopsis

Title of Study:

Protocol H9X-MC-B021: Crossover Study Comparing the Dulaglutide (Trulicity) Pen and the Semaglutide (Ozempic) Pen

Rationale:

Positive perceptions of injection devices could lead to better treatment adherence, which has been shown to have an impact on treatment outcomes in patients with type 2 diabetes mellitus (T2DM) (Khunti et al. 2017, 2018). Therefore, it may be useful for clinicians to consider not only the efficacy, safety, and cardiovascular effects of glucagon-like peptide-1 (GLP-1) receptor agonists (RA) but also patient preferences of injection devices when selecting the most appropriate treatment for patients with T2DM. The primary purpose of this study is to determine patient preferences between the injection devices used for the GLP-1 RAs dulaglutide versus semaglutide. The dulaglutide single-dose pen is a single-dose autoinjector pen that does not require handling of the needle, which is hidden and automatically retracts after use (Eli Lilly IFU 2017). The semaglutide single-patient-use pen can be used more than once and does require handling of the needle (Novo Nordisk IFU 2017).

This study will also evaluate the time-to-train (TTT) on using both the dulaglutide and semaglutide devices. One recent study conducted in Japan found that the dulaglutide pen was associated with a significantly shorter mean TTT compared to the insulin degludec single-patient-use pen (7.4 minutes versus 19.7 minutes; $p<.001$) (Asakura et al. 2018). The FlexTouch pen used for the insulin degludec (Asakura et al. 2018) is functionally similar to the one being evaluated in this study with semaglutide. These results suggest that it is less burdensome for health care providers to train patients to correctly use the dulaglutide device compared to other devices and easier for patients to learn self-injection with this device. The study will examine whether differences in patient preferences and TTT follow the same pattern in this comparison crossover trial between the dulaglutide and semaglutide devices in a US sample.

Summary of Study Design:

Study H9X-MC-B021 is an open-label, multicenter, randomized, crossover study assessing patient preference (and training time) with the dulaglutide single-dose pen versus the semaglutide single-patient-use pen. Study H9X-MC-B021 consists of a single study visit for approximately 290 self-injection naïve adults to all injectable treatment diagnosed with T2DM and taking oral medication to treat their condition. Self-injection naïve patients will be recruited from approximately 14 clinical sites in the US. The TTT assessment will be conducted in a subset of 75 to 80 patients from approximately 5 of the selected US clinical sites. All participants will receive training and perform mock injections on a practice pad using both devices. However, the order in which the participants are exposed to the devices will be randomized. Fifty percent (50%) of patients will be randomized to use the dulaglutide device first, while the other half will use the semaglutide device first. Participants will be under the

direct supervision of a study interviewer when handling the injection devices. Participants will also complete a series of questionnaires to determine their device preference.

Prior to commencing the study, a pilot phase will be conducted with approximately 10 to 20 patients with T2DM. The purpose of the pilot phase is to create a clear and streamlined training procedure for each device in order to finalize the steps of the training approach to use in the main phase of the study. The pilot phase data will not be included in the final sample of approximately 290 patients with T2DM for the analyses.

Treatment Arms and Duration:

Patients will be randomized into 2 study arms to control for order effects based on device administration. Fifty percent of patients will be randomized to use the dulaglutide device first, while the other half will use the semaglutide device first. All patients will be exposed to both devices under investigation in this study in a 1-time interview.

Number of Patients:

Participating patients will be randomized to ensure that there are approximately 290 completers for the main phase of this study. Prior to the main phase, approximately 10 to 20 patients will be included in the pilot phase of this study. All patients with T2DM included in the study must be self-injection naïve to all injectable treatment, in efforts to minimize potential bias based on any previous experience. Glucagon-like peptide-1 RAs are often the first injectable medication prescribed to patients with T2DM, thus the reason for targeting self-injection naïve participants.

Statistical Analyses: Refer to the third column below in Table 1.1.

Table 1.1. Objectives/Endpoints/Statistical Analyses

Objectives	Endpoints	Statistical Analyses
Primary: Determine patient preference between the 2 injection devices	The Global Preference Item: "Overall, which device do you prefer?"	The Prescott test will be run to examine whether there is a statistically significant difference in preference between the devices, while controlling for order effects (significance level at $p<.05$).
Gated Secondary: Compare devices with regard to ease of use (To be tested if a significant difference is found in the primary objective.)	Item 9 of the Diabetes Injection Device – Preference Questionnaire (DID-PQ)	If the primary objective is statistically significant, responses to the 5-point response scale of DID-PQ Item 9 (ease of use) will be collapsed into 3 categories. The "strongly prefer" and "prefer" response options will be combined for each device, resulting in 3 categories: prefer dulaglutide, prefer semaglutide, and no preference. The Prescott test will be run to examine whether there is a statistically significant difference in preference for ease of use between the devices, while controlling for order effects (significance level at $p<.05$).
Exploratory 1: Collect data to support the preference question in the primary objective	Results from the DID-PQ Items 1 to 8 and 10	Exploratory analyses of Items 1 to 8 and 10 of the DID-PQ will follow the same procedures as those for the gated secondary objective described above.

Objectives	Endpoints	Statistical Analyses
Exploratory 2: Compare time-to-train (TTT) on the dulaglutide and semaglutide devices	Results from the Observer Recording Sheet	Carryover effects will be examined. If there are no significant carryover effects, then TTT for both the first and second trainings will be used in this analysis. If there is a significant carryover effect, then this analysis will use data for whichever device is trained first. The average duration required to train and successfully inject each device will be assessed using the linear model appropriate for a crossover design.
Exploratory 3: Examine patients' willingness to use each of the devices after being trained on both	Results from the 3 Supplemental Questions	Using the data from the 3 Supplemental Questions, descriptive analyses will be run to examine willingness to use each of the devices after being trained on both.
Exploratory 4: Validation of the DID-PQ	Questionnaire validation analyses (i.e., known-groups and construct validity)	The primary validation approach will be to examine known-groups validity by comparing DID-PQ responses of patients categorized based on the responses to the Global Preference Item. Construct validity will be assessed by comparing DID-PQ responses to responses on 4 items selected from the Medication Delivery Device Assessment Battery (Yu et al. 2017). Cross-tabulation tables of these 4 items by response options for each of the DID-PQ items will be presented. In addition, the DID-PQ exploratory approach for comparing devices will be examined relative to the ancillary measures.

2. Schedule of Activities

Table 2.1. Schedule of Activities

Procedure	Pilot Phase: Conducted at 1 US Location[1] Approximately n ≈ 10 to 20		Main Phase: Conducted at Approximately 14 Clinical Sites across US[2] Approximately n ≈ 290	
	Screening	Study Visit	Screening	Study Visit
Conduct study screening; if eligible, schedule visit	X		X	
Main Phase: Inclusion/Exclusion Form			X	
Pilot Phase: Inclusion/Exclusion Form		X		
Completion of written informed consent		X		X
Randomization		X		X
Participant completes Supplemental Question S1		X		X
Participant completes training and performs mock injections with randomized Device 1		X		X
If TTT, the assigned study team observer completes Observer Recording Sheet for Device 1[3]		X		X
INTERVIEW BREAK 1: Participant will be offered a restroom and water break		X		X
Participant completes Demographic Form		X		X
Participant completes training and performs mock injections with randomized Device 2		X		X
If TTT, the assigned study team observer completes Observer Recording Sheet for Device 2[3]		X		X
Study team interviewer administers pilot phase interview questions		X		
Study team interviewer completes Interviewer Recording Sheet		X		X
OPTIONAL INTERVIEW BREAK 2		X		

Procedure	Pilot Phase: Conducted at 1 US Location[1] Approximately n ≈ 10 to 20		Main Phase: Conducted at Approximately 14 Clinical Sites across US[2] Approximately n ≈ 290	
	Screening	Study Visit	Screening	Study Visit
Participant completes Global Preference Item		X		X
Participant completes DID-PQ		X		X
Participant completes 4 items selected from the MDDAB about each of the devices under investigation		X		X
Participant completes Supplemental Questions S2 and S3		X		X
Clinical site completes Clinical Information Form				X

Abbreviations: DID-PQ = Diabetes Injection Device – Preference Questionnaire; TTT = time-to-train; MDDAB = Medication Delivery Device Assessment Battery.

[1]Pilot Phase: Recruiting, screening/scheduling, and the in-person interviews will be conducted by Evidera.

[2]Main Phase: Recruiting and screening/scheduling will be done by the clinical sites. The in-person interviews will be conducted by Evidera.

[3]TTT interviews: All pilot phase interviews will involve the TTT assessment. However, for the main phase, the TTT assessment will only be conducted in a subset of the main phase participants with approximately 75 to 80 patients across an estimated 5 clinical sites.

3. Introduction

3.1. Study Rationale

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are often recommended as part of combination therapy for type 2 diabetes mellitus (T2DM) when oral medication alone does not provide sufficient glycemic control (Inzucchi et al. 2012; NICE 2014). These injectable treatments have been shown to be effective in lowering glycated hemoglobin A1c (HbA1c) with a low risk of hypoglycemia and a potential benefit of weight loss (Aroda et al. 2012; Trujillo et al. 2015; Htike et al. 2017).

Dulaglutide is a GLP-1 RA that was approved by the FDA and EMA in 2014 (Edwards and Minze 2015). The safety and efficacy for HbA1c control were demonstrated in several clinical trials involving over 5000 patients (Dungan et al. 2014; Nauck et al. 2014; Umpierrez et al. 2014; Wysham et al. 2014; Blonde et al. 2015; Giorgino et al. 2015; Dungan et al. 2016; Ludvik et al. 2018; Pozzilli et al. 2017; Tuttle et al. 2018). The dulaglutide device is a single-dose autoinjector pen that does not require handling of the needle, which is hidden and automatically retracts after use (Eli Lilly IFU 2017). The dulaglutide device is notably different from devices used with the other medications in this class. In this study, the dulaglutide device will be compared to the semaglutide device, which is a newer weekly GLP-1 RA, administered via a single-patient-use pen. The semaglutide device can be used more than once and does require handling of the needle (Novo Nordisk IFU 2017).

Positive perceptions of injection devices could lead to better treatment adherence, which has been shown to have an impact on treatment outcomes in patients with T2DM (Khunti et al. 2017, 2018). Therefore, it may be useful for clinicians to consider not only the efficacy, safety, and cardiovascular effects of GLP-1 RAs but also patient preferences of injection devices when selecting the most appropriate treatment for patients with T2DM. The primary purpose of this study is to determine patient preferences between the injection devices used for the GLP-1 RAs dulaglutide versus semaglutide. This study will also evaluate the time-to-train (TTT) on using both the dulaglutide and semaglutide devices. One recent study conducted in Japan found that the dulaglutide device was associated with a significantly shorter mean TTT than the single-patient use-pen used for insulin degludec (7.4 minutes versus 19.7 minutes; $p<.001$) (Asakura et al. 2018). The FlexTouch pen used for the insulin degludec (Asakura et al. 2018) is functionally similar to the one being evaluated in this study with semaglutide. These findings and other results suggest that it may be less burdensome for health care providers (HCPs) to train patients to correctly use the dulaglutide device compared to other devices and easier for patients to learn self-injection with this device. The study will examine whether differences in patient preferences and TTT follow the same pattern in this comparison crossover trial between the dulaglutide and semaglutide devices in a US sample of patients with T2DM. All patients with T2DM included in the study must be self-injection naïve to all injectable treatment, in efforts to minimize potential bias based on any previous experience. GLP-1 RAs are often the first injectable medication prescribed to patients with T2DM, thus the reason for targeting self-injection naïve participants.

Please note: The protocol language will use the generic names of the medication in the devices (i.e., semaglutide and dulaglutide). However, to provide a naturalistic experience that most closely mirrors real-world treatment process, the study participants will be trained to use the branded injection devices that are used by patients who are actually treated with these medications. These pens feature the brand names (i.e., Ozempic and Trulicity) more prominently than the generic names. Therefore, to minimize confusion and ensure that study materials are clear for the respondents, the patient-completed questionnaires will use the brand names that are clearly presented on each pen. These names will always be presented in alphabetical order (i.e., Ozempic followed by Trulicity). Importantly, the use of the branded devices is not intended to be promotional in nature.

Appendix 1 ***contains the protocol abbreviations and definitions.***

3.2. Background

Several previous studies have found that patients seem to prefer the dulaglutide single-dose pen over the devices used to inject other medications in the GLP-1 RA class. For example, 2 discrete choice experiments (1 in the UK and the other in Japan) found that patients preferred the type of delivery system used for dulaglutide over the delivery system used for liraglutide (Gelhorn et al. 2015, 2016). Similarly, health state utility studies conducted in the UK and Italy found that patients preferred the dulaglutide pen attributes over the attributes of devices used with comparator treatments (Matza et al. 2017a; Matza et al. 2018b).

Research on perceptions of these injection devices has also been conducted among patients who have personal experience with the devices. For example, a recent naturalistic study conducted in over 400 patients with T2DM in the US found that the dulaglutide pen was associated with perceptions of greater ease-of-use and convenience than the liraglutide device (Matza et al. 2018a). Furthermore, the subset of 58 patients who had tried both treatments preferred the dulaglutide pen over the liraglutide device, as indicated across all 10 items of the Diabetes Injection Device – Preference Questionnaire (DID-PQ), which was designed to assess preferences between non-insulin injection devices. The dulaglutide device was also preferred over the single-patient-use pen device (used with insulin degludec) in a recent crossover study conducted among self-injection naïve patients with T2DM in Japan (Asakura et al. 2018). In addition, the dulaglutide pen was associated with greater ease-of-use and less time required for training. The dulaglutide device was also found to be a safe and effective device for use by injection-naïve patients with T2DM in a 4-week Phase 3b usability trial (Matfin et al. 2015).

3.2.1. Dulaglutide Pen

The dulaglutide single-dose pen (Figure 3.1) is a single-use autoinjector designed for a once-weekly subcutaneous (SC) injection of dulaglutide in either a 0.75 mg or 1.5 mg dose for adult patients with T2DM (Eli Lilly IFU 2017). Dulaglutide may be self-administered or administered by patients' caregivers or HCPs.

The dulaglutide pen is designed to deliver a SC injection without the need for management of the injection site such as needle insertion into a skin fold. The needle in the dulaglutide pen is 29

gauge. The dulaglutide pen is approximately 16 cm in length and is constructed of polymer molded components, metal springs, and the pen label.

Figure 3.1. Dulaglutide pen external view.

The pen is prepared for use by removing the base cap (which also removes a rigid needle shield from the syringe), placing it at the injection site, and rotating the lock ring to unlock. The pen is then used by depressing the Injection Button (green button in Figure 3.1). This action releases a spring-enabled plunger rod that inserts the needle to a predetermined depth and then delivers the contents of the syringe into SC tissue. The plunger rod initiates a second spring-enabled mechanism to automatically retract the needle after the dose is completely delivered. The retracted syringe and needle is permanently contained within the structure of the pen after the injection cycle is complete. The entire pen is disposed after each use.

3.2.2. Semaglutide Pen

Ozempic is a registered trademark of Novo Nordisk A/S. All other trademarks are the property of their respective owners.

The semaglutide single-patient-use pen (Figure 3.2) is a multi-use, disposable injection device designed for once-weekly SC injection of semaglutide (Novo Nordisk IFU 2017). Adult patients with T2DM are prescribed semaglutide in an escalating dose regimen of 0.25 mg starting dose for 4 weeks, followed by 0.5 mg, and a possible dose escalation after 4 weeks to 1.0 mg. The 0.25 mg and 0.5 mg doses are administered by 1 pen, with patients requiring 1.0 mg switching to the respective 1.0 mg pen device. Semaglutide may be self-administered or administered by patients' caregivers or HCPs.

The semaglutide pen is designed to deliver a SC injection in a manner similar to an insulin pen. The exposed needle length is variable, using NovoFine® needles ranging from 4 to 8 mm. The needles used with the semaglutide pen will have a 32 gauge.

Figure 3.2. Semaglutide single-patient-use pen external view.

According to the instructions for use (IFU), the semaglutide pen is prepared by attaching a new needle via a push-on retention mechanism, priming the pen by dialing the flow check symbol and depressing the dose knob, turning the dose selection knob to the appropriate dose, inserting the needle under the skin, and pushing the dose knob to the end of travel. The patient is then instructed to count to 6, remove the needle from the skin, and safely discard the used needle.

3.3. Benefit/Risk Assessment

While there are no direct therapeutic benefits to patients participating in the study, the results from this study will offer valuable insights into the patient preference and TTT of different injection devices in the same drug class. Injection inertia is a documented and valid concern in the T2DM treatment paradigm, and this study will provide a further understanding of T2DM patients' preferences for injection devices themselves (Khunti et al. 2013, 2016; Norrbacka et al. 2018). The risk of this study will be minimized because the mock injections will be performed in practice pads and participants will be under the direct supervision of a study interviewer when handling the injection devices. Participants are not injecting themselves in this study.

3.4. Risks and Foreseeable Adverse Events/Device Effects

The following is a list of potential risks associated with participation in this clinical study:

- Accidental needlestick injury
- Accidental exposure to drug product (accidental self-injection)

The following is a list of potential risks associated with the study devices:

- Improper functioning and/or mechanical failure of the device or its components (for example, no injection, slow injection into practice pad, partial injection into practice pad, cracked syringes, high force to operate device, damaged needle)
- Skin reaction (for example, after accidental needlestick)
- Nausea, gastrointestinal event, or low blood sugar potentially associated with exposure to drug product

3.5. Methods to Minimize Risks

Training on both study devices will be provided by Evidera study staff based on the approved IFUs (Eli Lilly IFU 2017; Novo Nordisk IFU 2017). Training for correct sharps handling/disposal is part of the study training, and no cross contamination is expected due to each participant receiving their own device, as well as injecting drug into a practice pad instead

of themselves. In order to minimize risk of accidental needle sticks, participants will not recap the semaglutide needle. A sharps container will be available to permit participants to remove the semaglutide needle and dispose of it immediately, rather than recapping the needle for later disposal. Participants will be instructed to place the outer needle cap in the sharps container once it is removed from the device so they do not have the temptation to recap, which was found to be a potential opportunity for accidental needle sticks during the pilot study. Study staff will monitor the participant at all times in the room and intervene should a dangerous situation occur. Participants will be under direct supervision of the study interviewer when handling the devices.

If a needlestick injury occurs or if a patient is exposed to drug, medical personnel will always be available to address any potential medical issues or concerns. With patients recruited from 10 of the 14 sites, the interviews will be conducted at the sites where there will be nurses and physicians on staff ready to assist if necessary. These clinical staff members will follow (monitor) the patient as per clinical judgment for a potential adverse event (AE) and follow the appropriate device-reporting procedures. With patients recruited from the other four sites, the interviews will be conducted at interview facilities where medical professionals (e.g., nurses) hired specifically for this study will be ready to assist if necessary in case of AEs such as unanticipated needlesticks or self-injection.

It is very unlikely that a participant will receive an accidental dose of medication for several reasons:

1. The participants will only handle the devices under direct supervision of a study interviewer after the interviewer has demonstrated how to use the device on a mock injection pad.
2. Patients will be told that they should not inject themselves, and these devices will only be used for mock injections into an injection pad.
3. If a participant appears to begin injecting themselves rather than the injection pad, the interviewer would immediately interrupt the process and stop the participant from completing this self-injection.
4. In the unlikely circumstance that a patient does have an accidental "needle stick," no medication would be injected unless the patient continues with the injection procedure. It is not possible for a patient to accidentally deliver a full dose of medication without intending to do so because a series of steps needs to be followed to inject a medication dose. These steps for dulaglutide and semaglutide are described below:
    a. Dulaglutide: The participant would need to place the device over their skin, unlock the device by turning a lock ring, press the injection button, and hold the device in place for approximately 5 – 10 seconds.
    b. Semaglutide: The participant would need to turn the dose selector to a dose, insert the needle into their skin, press the injection button, and wait approximately 6 seconds.

Even if a participant completes this highly unlikely series of events and does receive an injection of medication, a single dose of either drug is likely to have minimal clinical impact. These two medications are GLP-1 receptor agonists, not insulin. Therefore, the risk of hypoglycemia after

a single dose is low, and steady state therapeutic medication concentration is not achieved for approximately 25 days with dulaglutide and 4 – 5 weeks with semaglutide. However, medical personnel available for the study will be aware of this risk and ready to give oral sugar preparations. Medical personnel would also be informed of the potential for transient GI side effects of a single dose which would be easily manageable with antiemetics.

More detailed information about the known and expected benefits and risks of dulaglutide and semaglutide may be found in the following: Protocol Sections 3.3 and 3.4.

4. Objectives and Endpoints

Table 4.1 shows the objectives and endpoints of the study.

Table 4.1. Objectives and Endpoints

Objectives	Endpoints
Primary: Determine patient preference between the 2 injection devices	The Global Preference Item: "Overall, which device do you prefer?"
Gated Secondary: Compare devices with regard to ease of use (to be tested if a significant difference is found in the primary objective.)	Item 9 of the Diabetes Injection Device – Preference Questionnaire (DID-PQ)
Exploratory 1: Collect data to support the preference question in the primary objective	Results from the DID-PQ Items 1 to 8 and 10
Exploratory 2: Compare time-to-train on the dulaglutide and semaglutide devices	Results from the Observer Recording Sheet
Exploratory 3: Examine patients' willingness to use each of the devices after being trained on both	Results from the 3 Supplemental Questions
Exploratory 4: Validation of the DID-PQ	Questionnaire validation analyses (i.e., known-groups and construct validity)

5. Study Design

5.1. Overall Design

Study H9X-MC-B021 is an open-label, multicenter, randomized, crossover study assessing patient preference (and training time) for the dulaglutide pen versus the semaglutide pen (Figure 5.1). Approximately 290 self-injection naïve patients with T2DM and taking oral medication to treat their condition will be recruited from approximately 14 clinical sites in the US. The TTT assessment will be conducted in a subset of 75 to 80 self-injection naïve patients from approximately 5 of the selected US clinical sites. All participants will receive training and perform mock injections on a practice pad using both devices. The order of device training and administration will be randomized. Participants will also complete a series of questionnaires to determine their device preference. All participants will attend a single in-person study visit.

Prior to commencing the study, a pilot phase will be conducted with approximately 10 to 20 self-injection naïve patients with T2DM. The purpose of the pilot phase is to create a clear and streamlined training procedure for each device in order to finalize the steps of the training approach to use in the main phase of the study. The pilot phase data will not be included in the final sample of approximately 290 self-injection naïve patients with T2DM for the analyses.

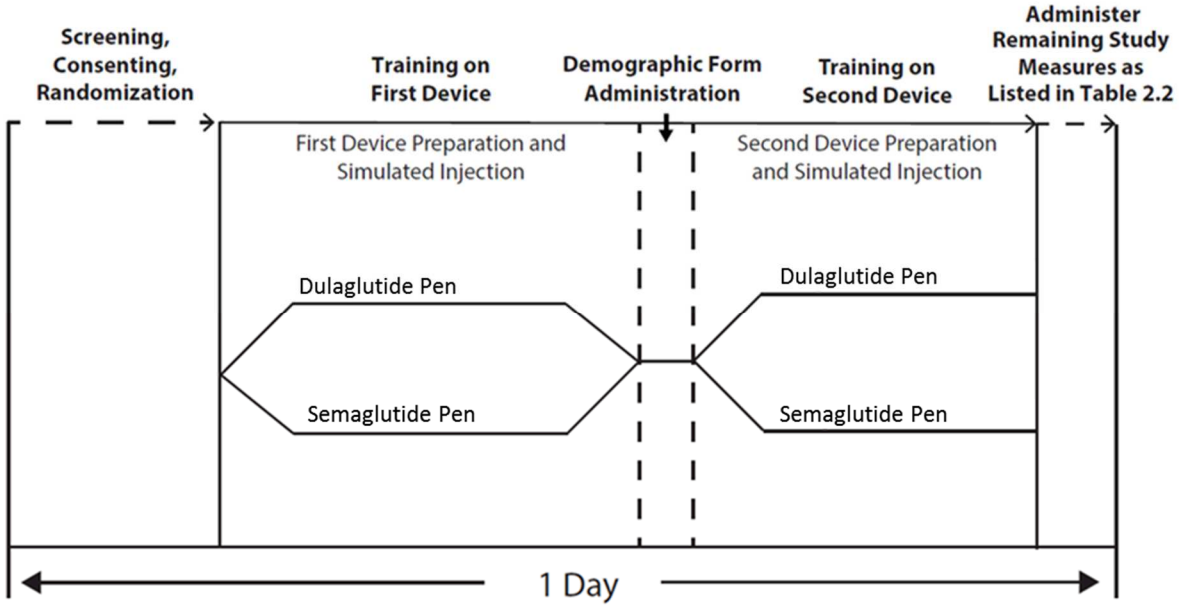

Figure 5.1. Study diagram for the patient preference study.

The devices for this study will be the commercialized injection pens containing non-modified commercial product with stickers on the devices indicating that the devices are intended for use in clinical trial. However, no active drug will be administered as patients will not be injecting themselves. Instead, patients will perform mock injections into a practice pad after being trained in the use of each device. Fifty percent of patients will be randomized to use the dulaglutide device first, while the other half will use the semaglutide device first. Lilly will provide all

injection devices that will be used in this study because commercial devices are being used during the interviews and mock injections. The drug names will be visible to patients and the device names will not be blinded to the participants. The devices are physically different from one another, thus even if the participants were blinded to the pens they could discern the name of each device. More details about blinding are provided in Section 7.3.

5.2. Number of Participants

It is expected that approximately double the estimated total sample will be screened (i.e., an estimated 580 participants across all clinical sites, 48 to 50 participants per site will be screened) to achieve 290 evaluable participants who are eligible and interested to participate in the main phase. Patients will not be randomized to device training order, until they have signed consent.

Similarly, for the preceding pilot phase, approximately 20 to 40 participants will be screened to reach 10 to 20 evaluable participants who are eligible and interested to participate.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

The multicenter crossover study design was selected to control for order effects while allowing patients to directly compare 2 devices. The order in which the participants are exposed to the devices will be randomized. Fifty percent of patients will be randomized to use the dulaglutide device first, while the other half will use the semaglutide device first. All participants will attend a single in-person study visit. Table 2.1 displays the schedule of activities for this crossover study. Ethical Review Board (ERB) approval will be obtained before study implementation. More details about the regulatory and ethical considerations for this study, including the informed consent process, are provided in Appendix 2.

5.5. Data Collection Process

An overview of the study data collection procedures is presented in this section. Subsections are presented separately for the pilot and the main phase. For the pilot phase, recruitment and data collection efforts will be conducted by Evidera (a business unit within Pharmaceutical Product Development, LLC [PPD]). For the main phase, approximately 14 clinical sites across the US will be identified. These clinical sites will recruit, confirm patient eligibility, and schedule all study interviews. The interviews that do not include the TTT assessment will take place at the actual clinical sites. Approximately 5 clinical sites will be selected for the subset of TTT interviews. The TTT interviews will occur at interview facilities with a 1-way mirror near to the clinical sites selected for recruitment. Evidera study staff will travel to all main phase interview locations to conduct the study interviews in-person.

Any study interviews conducted at non-clinical facilities will require a medical professional (for example, nurse or paramedic) to be on site in case of AEs such as unanticipated needlesticks.

5.5.1. Pilot Phase: Participant Recruitment and Screening Procedures

Approximately 10 to 20 participants will be recruited for the pilot phase via ERB-approved newspaper advertisements, internet classified advertisements, and/or other advertisements in social media outlets (Appendix 3). For advertisements, study staff from Evidera will arrange toll-free phone numbers for interested participants to call and leave messages. Study staff will also arrange a study-specific e-mail address that participants can use to respond to advertisements and provide their contact information via e-mail. Study staff will regularly check the voicemail box and e-mail inbox to promptly respond to interested participants. The voicemail box will be password protected, and only assigned study team members will have access to the password to obtain participants' contact information. For the study e-mail account, only the necessary study team members will be granted permission to the e-mail account by Evidera IT staff.

Type 2 diabetes mellitus diagnosis will be verified through proof of oral antidiabetic medication use. Study staff will screen potential participants who respond to the advertisement to ensure that they meet study inclusion criteria (Appendix 4). In addition to the inclusion/exclusion criteria, several demographic questions such as age, gender, and employment status will be asked to monitor eligibility and sample diversity throughout the recruitment process. If any inclusion/exclusion criteria cannot be confirmed via phone screening (for example, participant's cognitive ability to understand the device trainings), the final eligibility determination will be established at the time of the interview (Appendix 5 for Inclusion/Exclusion Form will be completed at the beginning of the interview).

Those participants considered eligible based on screening will be scheduled for an interview by study staff. All pilot phase participants will participate in the TTT assessment. Any identifying information (for example, names, addresses, telephone numbers) that is recorded on the screening/scheduling scripts will be kept in a limited access, locked filing cabinet. Prior to the interviews, project staff will send participant's confirmation (and directions to the interview location) by e-mail or mail according to participant's preference (Appendix 6). Reminder phone calls will be made to participants 1 day before the interview. During previous studies, it has been found that these reminder phone calls reduce the likelihood that participants will fail to attend their appointment (Appendix 7). However, it might not be possible to speak to all participants 1 day before the interviews (for example, no answer), if so, e-mail reminders will be sent (Appendix 7). At least 1 reminder will be sent to all pilot phase participants about their study interview when possible from the assigned study team member.

5.5.2. Main Phase: Participant Recruitment and Screening Procedures

The Evidera clinical site database will be used to identify the appropriate US clinical sites for inclusion in the study. Sites in a variety of geographical locations with diverse patient populations will be recruited to ensure sample diversity. Approximately 14 sites will be targeted for recruitment for the total estimated sample size of 290 injection naïve patients with T2DM.

The TTT assessment will be conducted in a subset of 75 to 80 patients from approximately 5 of the US clinical sites in the main phase. Evidera will identify interview facilities in the same city as the selected clinical sites participating in the TTT interviews. Study staff will determine facilities that are conveniently located for participants. Facilities will provide a private interview room with a closed door and a 1-way mirror for the second staff member to time the training. The non-TTT study interviews will be conducted at the actual clinical sites the T2DM participants are recruited from throughout the US.

Clinical site staff will identify and verify the initial eligibility of participants through a records review. A clinical site staff member will approach the potential participant in person (at the clinic or by phone) and briefly introduce the study using a standard screening script (Appendix 8). If the patient is interested, the study will be explained in full detail, and a full screening will be conducted to ensure eligibility (Appendix 9). Clinical staff will schedule all study interviews during the specified timeframe when Evidera staff will be conducting the study interviews for their site. Clinical staff will track recruitment efforts using the participant recruitment tracking log (Appendix 10). Any identifying information (for example, names, addresses, telephone numbers) that is recorded on the screening/scheduling scripts will be kept in a limited access, locked filing cabinet.

Prior to the interviews, clinical site staff will send participants confirmation (and directions to the interview location) by e-mail or post according to participant's preference (Appendix 6). Reminder phone calls will be made to participants 1 day before the interview. During previous studies, it has been found that these reminder phone calls reduce the likelihood that participants will fail to attend their appointment (Appendix 7). However, it might not be possible to speak to all participants 1 day before the interviews (for example, no answer), if so, e-mail reminders will be sent (Appendix 7). At least 1 reminder will be sent to all participants about their study interview when possible from the clinical sites.

5.5.3. Overview of Study Visit Procedures for the Pilot Phase

Table 2.1 provides an overview of the study schedule of activities. During the study visit, participants will begin with the completion of the informed consent. The order in which self-injection naïve participants are trained on using each device will then be randomized using a validated software system. More details about the randomization process are described in Section 7.2. Half the participants will be randomized to be trained and perform mock injections on the dulaglutide device first followed by the semaglutide device and the other half of the participants will use the devices in the reverse order. All participants will complete a Supplemental Question (Appendix 11) at the beginning of the study to determine their baseline willingness to use a diabetes injectable medication prior to being exposed to either the dulaglutide or semaglutide devices.

Trained interviewers will follow the study Interview and Device Training Guide (Appendix 12), in order to standardize the presentation of devices to participants and ensure that the training is clear and not biased in favor of either device. For the pilot phase, the trained interviewers will try several training options for each device to determine the finalized steps of the training

approach to use in the main phase of the study. Various approaches will include detailed demonstration by the interviewer, presentation of video demonstrations on tablets or laptops, independent reading of the IFU, and combinations of these 3 approaches. Participants will perform mock injections on a practice pad after being trained in the use of each device.

During the interview, if the participant does not complete one of the critical steps or if the steps are completed out of order, the Interview and Device Training Guide (Appendix 12) provides interviewers instructions for handling these situations. The participant will be allowed 5 attempts to follow the instructions and perform the mock injection(s) for each device. If after 5 attempts the participant is unable to successfully perform the mock injection on the practice pad for either device, the interviewer will instruct the participant to stop using the device and proceed ahead with the interview.

The TTT assessment for each device will also be tested in the pilot phase after the near-final methods are determined. The appropriate staff member will discreetly record the necessary training times using the TTT Observer Recording Sheet for each device (Appendix 13). In between the trainings on each device, all participants will be given a restroom and water break. During this break, participants will also complete the Demographic Form (Appendix 14).

Once participants have attempted each device training and mock injection(s) on the practice pad, interviewers will complete the Interviewer Recording Sheet to document randomization order and if the patient was able to complete both device trainings (Appendix 15). Pilot phase participants will also be administered a series of interview questions about the training procedures (Appendix 16). Based on interviewer experiences and patient feedback during these estimated 10 to 20 pilot phase interviews, the training approach and interview procedures will be finalized prior to beginning the main phase with approximately 290 patients.

After the interview questions, pilot phase participants will be given an optional second break. Participants will then be asked to complete questionnaires to report their preferences between the 2 devices. Specifically, participants will complete a Global Preference Item (Appendix 17) and the DID-PQ (Appendix 18). Four items selected from the Medication Delivery Device Assessment Battery (MDDAB) (Matfin et al. 2015; Yu et al. 2017) will be asked of participants about each of the devices under investigation to use in the validation of the DID-PQ (Ozempic device-specific questions: Appendix 19; Trulicity device-specific questions: Appendix 20). These additional questions will be completed in the order the participants were randomized to use the devices. Participants will also complete Supplemental Questions S2 and S3 to determine their end of study willingness to use each of the study injection devices (Appendix 21).

Pilot phase interview will last approximately 90 to 120 minutes including consenting and training in device procedures. All pilot phase participants will be remunerated an amount slightly more than the main phase participants (i.e., a specified amount between $100 and $150 via Greenphire ClinCard) because they will be participating in debriefing procedures and possibly multiple training approaches. The pilot phase interviews are expected to be longer than the main phase interviews.

5.5.4. Overview of Study Visit Procedures for the Main Phase

Table 2.1 provides an overview of the study schedule of activities. During the study visit, participants will begin with the completion of the informed consent. The order in which participants are trained on using each device will then be randomized. More details about the randomization process are described in Section 7.2. Half the participants will be randomized to be trained and perform mock injections on the dulaglutide device first followed by the semaglutide device and the other half of the participants will use the devices in the reverse order. All participants will complete a Supplemental Question (Appendix 11) at the very beginning of the study to determine their baseline willingness to use a diabetes injectable medication prior to being exposed to either the dulaglutide or semaglutide devices.

Trained study interviewers will follow the study Interview and Device Training Guide (Appendix 12) to standardize the presentation of devices to participants and ensure that the training is clear and not biased in favor of either device. Based on findings from the pilot phase, the finalized main phase training approach will be conducted with the patients for each device including a detailed demonstration by the interviewer. The same standardized interview approach will be used for all the main phase patients. For each device, patients will be given the IFU and asked to read it. Then the interviewer will demonstrate how to use the device. Participants will perform mock injections on a practice pad after being trained in the use of each device. Patients will have access to the IFU during the entire training and injection process. If the participant does not complete one of the critical steps or if the steps are completed out of order, the Interview and Device Training Guide (Appendix 12) provides interviewers instructions for handling these situations. The participant will be allowed 5 attempts to follow the instructions and perform the mock injection(s) for each device. If after 5 attempts the participant is unable to successfully perform the mock injection on the practice pad for either device, the interviewer will instruct the participant to stop using the device and proceed ahead with the interview.

For those participants selected for the TTT assessment (i.e., a subset of approximately 75 to 80 patients across an estimated 5 clinical sites), the assessments will be done in an off-site facility to allow for the discreet timing of the training event (for example, 1-way mirror). The appropriate staff member will discreetly record the necessary training times using the TTT Observer Recording Sheet for each device (Appendix 13). In between the trainings on each device, all participants will complete the Demographic Form (Appendix 14).

Once participants have attempted each device training and mock injection(s) on the practice pad, interviewers will complete the Interviewer Recording Sheet to document randomization order and if the patient was able to complete both device trainings (Appendix 15). Participants will then be asked to complete questionnaires to report their preferences between the 2 devices. Specifically, participants will complete a Global Preference Item (Appendix 17) and the DID-PQ (Appendix 18). Four items selected from the MDDAB (Matfin et al. 2015; Yu et al. 2017) will be asked of participants about each of the devices under investigation to use in the validation of the DID-PQ (Ozempic device-specific questions: Appendix 19; Trulicity device-specific questions: Appendix 20). These additional questions will be completed in the order the

participants were randomized to use the devices. Participants will also complete Supplemental Questions S2 and S3 to determine their end of study willingness to use each of the study injection devices (Appendix 21). A Clinical Information Form (Appendix 22) will also be completed by the site clinical staff for each patient in the main phase.

Main phase interview will last approximately 60 to 90 minutes including consenting and training in device procedures. The maximum time for all study procedures is 90 minutes as specified in the consent form. All main phase participants will be remunerated a specified amount between $100 and $150 (via Greenphire ClinCard) for their time and travel time to the study interview.

5.6. Justification for Dose

The devices used for this study will be commercialized injection pens containing non-modified commercial product with stickers on the devices indicating for use in clinical trial. However, no active drug will be administered because patients will not be injecting themselves. Instead, patients will perform mock injections into a practice pad after being trained in the use of each device by a study team member. Specifically, the patients will be trained on devices that contain the lowest dose (i.e., dulaglutide = 0.75mg; semaglutide = 0.25mg) for both treatments for safety concerns (for example, accidental needle stick) and because these are the typical starting and training doses for these 2 products in the US. However, it is critical to acknowledge that the devices are very similar across all drug strengths. Therefore, the study findings could be applicable to other dulaglutide and semaglutide device doses, as well as other antidiabetic drugs using the same devices.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study if they meet all the following criteria at screening:

Participant Characteristics

[1] are at least aged ≥18 years at the time of screening

[2] diagnosed with type 2 diabetes

[3] self-injection naïve to all injectable treatment (for example, diabetes therapies and other medical conditions)

[4] injection naïve to performing all injectable treatment (for example, diabetes therapies and other medical conditions) to others

[5] must **currently receive oral** treatment for their type 2 diabetes

[5a] **pilot phase participants only:** must be able to **bring proof of their oral treatment prescription for type 2 diabetes to the interview** (for example, the medication itself, the medication packaging, a prescription note, or a letter from their doctor). This criterion does not apply to the main phase because main phase participants will have diagnoses confirmed by the clinical sites with awareness of the patients' diabetes and treatment.

[6] willing and able to attend an in-person interview session

[7] able to read, speak, write, and understand the English language

[8] able and willing to give signed informed consent prior to study entry

[9] able to complete the protocol requirements

6.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

[1] currently diagnosed with gestational diabetes and/or type 1 diabetes

[2] cognitive or physical difficulties that could interfere with ability to understand the training, perform the injection tasks, or complete the study questionnaires as judged by the investigator

Prior/Concurrent Clinical Trial Experience

[3] are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[4] have participated, within the last 30 days, in a clinical study involving an investigational product.

Other Exclusions

[5] is a health care practitioner who is trained in giving injections

[6] **for main phase participants only:** Investigator, site personnel, or immediate family member of investigator or site personnel. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[7] is an employee of any of the following companies: Eli Lilly and Company, Novo Nordisk, Evidera, or PPD

[8] currently pregnant

6.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of marketed devices, and no treatment will be administered.

The investigator or his/her designee is responsible for the following:

- Explaining the correct use of the investigational agent(s) to the patient
- Verifying that instructions are followed properly
- Maintaining accurate records of investigational product dispensing and collection
- At the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labeling

The dulaglutide and semaglutide devices will be labeled according to applicable regulatory requirements. The devices used in the study shall be securely stored until returned or destroyed according to instructions from the sponsor. Information such as lot number, quantity, and disposition of device(s) used during the clinical study shall be documented.

Refer to the device labeling/instructions for use (IFU) for the following:

- Instructions regarding storage and handling requirements, preparation for use, pre-use checks, and any precautions to be taken after use or disposal.
- Summary of necessary training and experience required.
- Description of procedures for use.

7.1.2. Medical Devices

The manufactured medical devices provided for use in the study are the dulaglutide pen and the semaglutide pen.

7.2. Method of Device Assignment

For the pilot phase, assignment to device order study groups will be randomized using a validated software system.

For the main phase, assignment to device order study groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign the first device to be used by the patient. Randomization will occur at the study level in efforts to make sure that there are a comparable number of patients who start with the dulaglutide device versus the semaglutide device across the entire study population.

7.2.1. Selection and Timing of Doses

Timing of dosing is not applicable. The patients will be trained on devices that contain the lowest dose per device (i.e., dulaglutide = 0.75mg; semaglutide = 0.25mg).

7.3. Blinding

This is an open-label study. All participants will be trained and perform mock injections on a practice pad using labeled dulaglutide and semaglutide devices with the brand names of Trulicity and Ozempic on the pens as displayed in Figure 3.1 and Figure 3.2, respectively.

7.4. Dosage Modification

Although dose modification is not an objective of this study, information on how to modify a dose will be provided in the training for each device as this information is typically provided by HCPs to patients (Appendix 12).

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- Obtaining the correct number of devices in advance of each interview. Staff performing all the trainings must have received all the necessary training for both devices.
- Storing the study devices in a secure and monitored area in accordance with the labeled storage conditions with access limited to the investigator and authorized study staff.
- Obtaining the appropriate number of practice pads to perform all the mock injections and following the required instructions to dispose of all the materials used in the device trainings and mock injections.

7.6. Treatment Compliance

Patient compliance with study procedures will be assessed at each visit. Patients will be properly trained on how to use and perform mock injections with both the dulaglutide and semaglutide devices. The patients will be allowed several attempts to follow the instructions and perform the mock injections. It will be the discretion of the study interviewer to determine if the patient is not capable of completing the study interview, including the mock injections and/or questionnaires, and should be terminated. More details about study discontinuation are provided in Section 8.

7.7. Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and can be used during the study so long as they are not self-injected (per the exclusion criteria).

7.8. Treatment after the End of the Study

Not applicable.

7.8.1. Special Treatment Considerations

Not applicable.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

This is a device preference study and investigational product is not being administered to any patients.

8.1.2. Temporary Discontinuation from Study Treatment

Not applicable.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be excluded from the study.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice
- Investigator decision
    - The investigator decides that the patient should be discontinued from the study
- Subject decision
    - The patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 9.2 (Adverse Events) and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

Not applicable because this is a 1-time interview study and no additional study visits are required.

9. Study Assessments and Procedures

Table 2.1 lists the Schedule of Activities for this crossover study for each of the study phases. All outcome assessments will be administered in both phases, except the pilot phase interview questions will only be administered during the pilot phase and the Clinical Information Form will only be completed by the clinical site for each patient in the main phase.

9.1. Outcome Assessments

9.1.1. Primary/Secondary Assessments

After participants have been trained and used both devices, they will then complete a Global Preference Item about which device they prefer (Appendix 17) to evaluate the primary objective. Specifically, participants will be asked, "Overall, which device do you prefer?" Participants will also be asked to explain why they selected their response for Ozempic, Trulicity, or no preference.

Participants will then complete the 10-item DID-PQ to evaluate the gated secondary objective, which is based on Item 9 of the DID-PQ (i.e., overall ease of using the injection device). The DID-PQ compares the dulaglutide and semaglutide devices head-to-head in terms of a variety of device characteristics (for example, ease of preparing the injection device, time it takes to prepare and inject each dose of medication, confidence that you are using the injection device correctly, and overall convenience of using the injection device) (Appendix 18).

9.1.2. Appropriateness of Assessments

9.1.2.1. Supplemental Questions

In addition to the Global Preference Item, the DID-PQ, and the 4 items selected from the MDDAB for each device, Supplemental Questions will be included in the survey to elicit patients' perceptions of T2DM treatment using injectable agents (Appendix 11). The Supplemental Questions developed for this study are based on previous items used in the article by Poon et al. (2018). The first question will be administered to participants before the device trainings and will determine the participants' "willingness to use a diabetes medication that required an injection for each dose." The second and third Supplemental Questions will be administered to the participants after all the trainings, mock injections, and other study measures have been completed. Questions S2 and S3 will ask participants specifically about their willingness to use the Ozempic and Trulicity devices, respectively (Appendix 21). Responses to these questions will be used to determine patients' willingness to use each of the devices after being trained on both.

9.1.2.2. Time-to-Train Observer Recording Sheet

For the TTT interviews, the study staff member observing and timing behind the 1-way mirror at the interview facilities will record the start and end times of the key training steps for each device (Appendix 13).

9.1.2.3. Demographic Form

A Demographic Form will be completed by participants in between the device trainings. This form includes questions on age, sex, ethnicity, living situation, employment, education level, and other health conditions (Appendix 14).

9.1.2.4. Interviewer Recording Sheet

The trained interviewer will use the Interviewer Recording Sheet to document each participant's randomization order and whether or not the participant was able to complete each of the device trainings. If the participant was shown the device, but did not complete the actual device training, the interviewer should explain what happened on this sheet (Appendix 15).

9.1.2.5. Pilot Phase Interview Questions

During the pilot phase, once the participants have completed both trainings and mock injections on the practice pad, the participants will be administered a series of interview questions about the training procedures (Appendix 16). These interview questions will guide the discussion with the participants to determine the final training approach to use during the main phase.

9.1.2.6. Global Preference Item

All participants will complete the Global Preference Item after being trained and using both devices (Appendix 17). Participants will be asked, "Overall, which device do you prefer?" Interviewers will then ask participants to explain why they selected their response for Ozempic, Trulicity, or no preference. The interviewer will transcribe the participant's response using quotation marks to capture the respondent's exact words. The Global Preference Item was developed specifically for use in this device preference multicenter crossover study. To help participants remember the devices more accurately, colored images of the devices have been inserted into the questionnaire.

9.1.2.7. Diabetes Injection Device – Preference Questionnaire

The Diabetes Injection Device – Preference Questionnaire (DID-PQ) was designed for the purpose of assessing patient preferences between 2 non-insulin injection devices (Appendix 18) (Matza et al. 2018a). On the DID-PQ, each item is rated on a 5-point scale allowing patients to indicate whether they prefer or strongly prefer one of the devices over the other. For each item, patients may also respond by selecting the "no preference" (i.e., neutral) response option, indicating that they have no preference between the 2 devices. Specifically, for this study, the DID-PQ response options will be: Strongly Prefer Ozempic Device, Prefer Ozempic Device, Strongly Prefer Trulicity Device, Prefer Trulicity Device, or have No Preference. To help participants remember the devices more accurately, colored images of the devices have been inserted into the questionnaire.

9.1.2.8. Four Items from the Medication Delivery Device Assessment

The original MDDAB was adapted from insulin-specific questionnaires and has been modified for use in both injection-naïve and non-insulin requiring participants (Matfin et al. 2015). Four items selected from the MDDAB (Matfin et al. 2015; Yu et al. 2017) will be asked of the participants about each of the devices under investigation in this study (Ozempic device-specific questions: Appendix 19; Trulicity device-specific questions: Appendix 20). These additional

questions will be completed in the order the participants were randomized to use the devices. The first 3 questions ask participants how easy or difficult it was to: (1) learn to use the device, (2) to follow the instructions when using the device, and (3) overall, how difficult or easy was the device to use? The last question asks participants to "Please check the number that best indicates how willing you are to continue using the device" on a scale from 1 ("Definitely Unwilling") to 5 ("Definitely Willing"). These items will be used in the validation of the DID-PQ, specifically to assess construct validity of the DID-PQ by comparing responses.

9.1.2.9. Clinical Information Form

A Clinical Information Form will be completed by the site personnel for each participant completing the study visit (Appendix 22). This form includes a question to document the patients' T2DM diagnosis date, the current oral medications the patient is taking to treat their T2DM, and the patients' most recent HbA1c value and date this value was measured.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the informed consent form is signed, study site personnel will record via designated data transmission methods the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational device, via designated data transmission methods.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure, and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and non-surgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational device is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via designated data transmission methods, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

The appropriate AE reporting procedures will be followed for each device under investigation in this study.

9.2.1. Serious Adverse Events

A serious adverse event (SAE) is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (i.e., immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- When a condition related to the injection pens necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the designated data transmission methods.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition case report form) has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Event Monitoring with a Systematic Questionnaire

Not applicable because this is a device preference study, and no active drug will be administered as patients will not be injecting themselves.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he/she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

The appropriate product complaint reporting procedures will be followed for each device under investigation in this study.

9.3. Treatment of Overdose

Not applicable.

9.4. Safety

Refer to Section 10.3.4.

9.4.1. Electrocardiograms

Not applicable.

9.4.2. Vital Signs

Not applicable.

9.4.3. Laboratory Tests

Laboratory tests are not required and will not be taken for this study as this is a device preference study. The protocol template language for this section is not applicable for this study.

9.4.4. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.4.1. Hepatic Safety Monitoring

Not applicable.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics or Genetics

9.7.1. Samples for Pharmacogenetic Research

Samples of whole blood and/or saliva are not required and will not be taken for this study as this is a device preference study. The protocol template language for this section is not applicable for this study.

9.8. Biomarkers and Other Analyses

Samples of serum, plasma, urine, cerebral spinal fluid, whole blood RNA, whole blood for epigenetics, etc. are not required and will not be taken for this study as this is a device preference study. The protocol template language for this section is not applicable for this study.

9.9. Health Economics or Medical Resource Utilization and Health Economics

Not applicable.

10. Statistical Considerations

10.1. Sample Size Determination

To test the null hypothesis that patients have equal preference for either dulaglutide or semaglutide pen (50% of patients prefer dulaglutide pen and 50% prefer semaglutide pen), a sample size of 260 patients will provide 90% power against alternative hypothesis that there is a preference with 60% of the patients choosing the dulaglutide pen over the semaglutide pen. Calculation is carried out using 2-sided chi-square test (normal approximation) at 0.05 level of significance. Software used is Nquery + nTerim 4.0. Assuming that approximately 10% will not provide any preference information by choosing the "no preference" option on the Global Preference Item, 290 patients will be needed to have at least 260 patients with preference information. The Prescott test which takes into account the order the device is used as well as the choice of "no preference" provides approximately 90% power against the alternative hypothesis of 54% choosing dulaglutide pen, 10% indicating no preference, and the remaining 36% choosing semaglutide pen. This is based on simulation of 1000 runs and assumes that there is no order effect.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Randomized	Participants determined to be eligible and then assigned to one of 2 device order groups (50% will be randomized to use the dulaglutide device first, while the other half will use the semaglutide device first). More details about randomization for this study are provided in Section 7.2.
Evaluable	Participants for whom device preference can be evaluated: Randomized participants who are exposed to both devices (i.e., participant was shown both devices via demonstration, regardless of whether they successfully complete the training) and complete the Global Preference Item.
Withdrawn	Participants who withdraw from the study before being exposed to both devices and completing the Global Preference item. Details on study withdrawal are provided in Section 8.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Evidera. The statistical analyses are summarized by study objective and endpoint(s) in Table 1.1.

Statistical analyses will be conducted on the evaluable patient population (i.e., patients who provide a response to the Global Preference Item).

The significance level for all statistical tests will be $p<.05$. Gatekeeping strategy will be used to control for type 1 error for the primary and gated secondary objective.

Any change to the statistical analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the statistical analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). A more detailed description of this statistical analysis will be provided in a statistical analysis plan (SAP), and additional exploratory analyses of the data may be conducted as deemed appropriate.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study.

10.3.2.2. Patient Characteristics

Descriptive statistics will summarize demographics, clinical characteristics, and patient-reported outcome (PRO) measures. Continuous variables will be summarized with means, standard deviations, ranges, and minimum and maximum values. Categorical variables such as gender and race will be presented in terms of frequencies and percentages. Demographics, clinical characteristics, and PRO data will be presented by assigned randomization group.

10.3.2.3. Concomitant Therapy

Not applicable.

10.3.2.4. Treatment Compliance

Not applicable.

10.3.3. Statistical Analyses

10.3.3.1. Primary Analyses

The primary analysis of this study will evaluate the results of the Global Preference Item (i.e., Overall, which device do you prefer?) to examine whether there is a difference in preference between the dulaglutide device and the semaglutide device. The Prescott test will be run to determine whether there is a statistically significant difference in preference between the devices, while controlling for order effects. The preference results (for example, counts, percentages and 95% confidence interval [CI]) will also be presented. The qualitative data capturing reasons for the response to the Global Preference Item will also be presented.

10.3.3.2. Gated Secondary Analyses

The gated secondary analysis of this study will be conducted if the primary objective is found statistically significant. The analysis will compare the dulaglutide and semaglutide devices with regard to ease of use. Responses to the 5-point response scale of DID-PQ Item 9 (Overall ease of use) will be collapsed into 3 categories. The “strongly prefer” and “prefer” response options will be combined for each device, resulting in 3 categories: prefer dulaglutide, prefer semaglutide, and no preference. Then, the Prescott test will be run to examine whether there is a

statistically significant difference in preference between the devices, while controlling for order effects. Data from global Item 9 on the DID-PQ will also be presented to illustrate the "ease of use" responses by device (for example, counts, percentages, and 95% CI).

The complete scoring guide for the DID-PQ will be presented in the SAP for this study.

10.3.3.3. Exploratory Analyses

10.3.3.3.1. Exploratory 1. DID-PQ Analyses of Items 1 to 8 and 10

Exploratory analyses of Items 1 to 8 and 10 of the DID-PQ will follow the same procedures as those for the gated secondary objective described above.

10.3.3.3.2. Exploratory 2. Time-to-Train Analyses

Exploratory analysis 2 of this study will focus on the TTT for each device. The average duration required to train and successfully inject each device will be assessed using the linear model appropriate for a crossover design. Carryover effects will be examined. If there are no significant carryover effects, then TTT for both the first and second trainings will be used in this analysis. If there is a significant carryover effect, then this analysis will use data for whichever device is trained first. Average duration required to train and successfully inject each device will be reported.

10.3.3.3.3. Exploratory 3. Supplemental Question Analyses

Using the data from the 3 Supplemental Questions (i.e., S1. Would you be willing to use a diabetes medication that required you to give yourself an injection for each dose?; S2. How willing would you be to use the Ozempic injection device?; and S3. How willing would you be to use the Trulicity injection device?), descriptive analyses will be run to examine willingness to use each of the devices after being trained on both. Descriptive statistics will be reported for each item (i.e., frequencies, percentages).

10.3.3.3.4. Exploratory 4. Evaluation of the DID-PQ

Exploratory analysis 4 will focus on psychometric evaluation of the DID-PQ. The DID-PQ has been administered in 2 studies thus far: the original psychometric validation study (Matza et al. 2017b) and the US study comparing the dulaglutide and liraglutide devices (Matza et al. 2018a). In both studies, the DID-PQ was administered to a relatively small subgroup of patients who had used more than 1 GLP-1 RA device. Therefore, it has not previously been possible to perform statistical analyses examining the validity of this PRO instrument.

Since all estimated 290 patients in this study will complete the DID-PQ, this study provides a unique opportunity to perform analyses evaluating the performance of this instrument. The primary validation approach will be to examine known-groups validity, which is the extent to which scores from an instrument distinguish among groups of participants that differ in terms of a relevant clinical or other indicator. By comparing DID-PQ responses of patients categorized based on the responses to the Global Preference Item, known-groups validity will be evaluated.

Additional analyses will examine construct validity, which is the degree to which a measure performs as expected in relation to other measures. Construct validity will be assessed by comparing DID-PQ responses to responses on 4 items selected from the MDDAB

(Matfin et al. 2015; Yu et al. 2017). Cross-tabulation tables of these 4 items by response options for each of the DID-PQ items will be presented. The 4 items assess (1) ease of learning how to use the device, (2) ease of following instructions when using the device, (3) overall ease-of-use, and (4) willingness to continue using the device.

Lastly, the DID-PQ exploratory approach for comparing devices will be examined relative to the ancillary measures (i.e., responses on the 4 items selected from the MDDAB for each device). This approach to analyzing data from the DID-PQ was developed as part of the original instrument development work, but it has never before been implemented and evaluated in a study. Among patients indicating a preference for one device over the other, a statistical test can be performed to determine whether a significant preference exists. This test would assess whether the proportion indicating preference for one of the 2 devices differs from 0.5. A value of 0.5 would indicate that there is equal preference for the 2 devices. The frequency of preferences for Device 1 and Device 2 may be examined using a 2-sided binomial test for each item of the DID-PQ. For each DID-PQ item, the null hypothesis would be that the probability of preferring one of the devices is 0.5. If the binomial test yields a significant p-value, then the null hypothesis can be rejected, which would mean that significantly more respondents preferred one device over the other.

10.3.3.4. Missing Data

Study team members will perform a thorough review of the participants' questionnaires prior to the completion of each interview to minimize missing data. No imputations will be performed for missing data. If a participant decides to withdraw from the study, data collected to the point of withdrawal may be used in analysis to preserve the integrity of the research project. There will be no lost to follow-up data because there is no follow-up period in this study.

10.3.4. Safety Analyses

This study focuses on preference between devices, and no medication will be administered to study participants. However, if a participant reports an AE related to the study, the appropriate reporting procedures will be followed. See Section 9.2 for more AE details.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable as no investigational drug or treatment will be administered during this study.

10.3.6. Evaluation of Immunogenicity

Not applicable.

10.3.7. Other Analyses

10.3.7.1. Health Economics

Not applicable.

10.3.7.2. Subgroup Analyses

Not applicable.

10.3.7.3. Pilot Phase Analyses

Analyses of the pilot phase data will include both descriptive statistics and a content analysis approach. The purpose of the pilot phase is to ensure that the training materials and interview procedures are clear, comprehensible, and feasible prior to the main phase.

Descriptive statistics (for example, mean, standard deviation, frequency) will be used to summarize the sample in terms of sociodemographic characteristics and on the other measures completed by the participants (i.e., Global Preference Item, DID-PQ, 4 items selected from the MDDAB for each device).

A content analysis approach will be used to analyze the responses collected on the pilot phase interview questions. This content analysis applies only to the pilot phase. Responses will be examined to determine answers to the following questions for each device:

- Are there any ways the device training could be easier or more clear? If yes, please explain.
- Would you recommend any changes to the device training procedures? If yes, please explain.
- How much additional guidance is appropriate and useful during the device training?

During the pilot phase, the principal investigator and study team will be continuously monitoring the interview and data as they are collected to determine if changes need to be implemented immediately. If major changes are required, Evidera and Lilly will determine if the pilot phase sample size needs to be increased. Upon conclusion of the pilot phase, Evidera study staff will send to Lilly a summary document of the pilot phase, which will serve as the interim analysis.

The pilot phase data for an estimated 10 to 20 participants will not be included in the final sample of approximately 290 patients with T2DM.

10.3.8. Interim Analyses

Not applicable.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
CI	confidence interval
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all study-related, good clinical practice, and applicable regulatory requirements.
DID-PQ	Diabetes Injection Device – Preference Questionnaire
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
Enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GLP-1	Glucagon-like peptide-1
HbA1c	glycosylated hemoglobin A1c
HCP	health care provider
IFU	instructions for use
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
Investigational device	The investigational devices in this study will include the 2 devices under investigation (i.e., Ozempic and Trulicity) that are being evaluated in this multicenter crossover device preference study.

Term	Definition
IWRS	interactive web-response system
MDDAB	Medication Delivery Device Assessment Battery
PPD	Pharmaceutical Product Development, LLC
PRO	patient-reported outcomes
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions
TTT	time-to-train
T2DM	type 2 diabetes mellitus

Appendix 2. Study Governance Considerations

Appendix 2.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 2.1.1. Informed Consent

The Evidera investigator and research staff are responsible for the following:

- Ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- Ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- Answering any questions the patient may have throughout the study, and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- Ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- Ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date when the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 2.1.2. Recruitment

For the pilot phase, Evidera is responsible for the central recruitment strategy for participants.

For the main phase, the clinical sites are responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 2.1.3. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Eli Lilly and Company (Lilly) before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study's ERB(s) should be provided with the following:

- The protocol and related amendments and addenda, and updates during the course of the study;
- ICF;
- Other relevant documents (for example, curricula vitae, advertisements).

Appendix 2.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable ICH GCP Guidelines;
- Applicable laws and regulations.

The sponsor (Lilly), Evidera investigator, and Evidera research staff are responsible for adhering to any regulations and/or laws pertinent to using and transferring the devices for clinical trial use.

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 2.1.5. Investigator Information

Physicians with a specialty in internal medicine, endocrinology, or primary care/family doctors will participate as investigators in this clinical trial.

Appendix 2.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 2.1.7. Final Report Signature

The sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 2.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Evidera will do the following:

- Provide instructional material to the study sites, as appropriate;
- Sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on all study recruitment procedures;
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax;

- Train Evidera staff to deliver the standardized trainings on both devices following the Interview and Device Training Guide (Appendix 12);
- Review and evaluate Case Report Form (CRF) data and use standard computer edits to detect errors in data collection;
- Conduct a quality review of the database.

Data collection will be conducted according to the protocol and will progress according to the study procedures previously outlined in Section 5.5.

At the time of enrollment, participants will be assigned unique identification numbers. The unique identifiers assigned will be used to track the participants throughout the study. Only the unique participant identification and participant initials will be entered into the database and recorded on the participant questionnaires—not participant names.

Participants will be assured of the confidential nature of the interview. If, at any time, participants become uncomfortable with a question or the process, they will be given the option of terminating the study interview. All interviews will take place in a quiet and private space to ensure confidentiality. Evidera study staff will review all forms for completeness prior to concluding the study visit.

Only Evidera staff for the pilot phase and both Evidera and the clinical site staff for the main phase involved in participant recruitment and data collection, will know the identity of the participants. Study staff will be instructed to maintain complete confidentiality of all collected data. For both study phases, trained Evidera interviewers and research support staff will observe the interviews, and have access only to de-identified data on the study CRFs. Lilly employees may also observe some of the study interviews.

Extensive procedures for the careful and complete collection of data will be implemented by the clinical sites and Evidera. At the completion of each interview, study staff will check every page of each questionnaire to ensure that no items were unintentionally skipped. Participant recruitment will be monitored on a regular basis throughout the study using tracking logs. The Evidera Principal Investigator and Quality Assurance Analyst will be available for consultation regarding study implementation, recruitment, and any other queries throughout this process.

The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 2.2.1. Data Capture System

For data collection, Evidera will use DataFax, a data management system that relies on optical character recognition software, for collecting study data. The CRFs for this study will be formatted for the DataFax system. DataFax improves data quality through quality control reports and automatic queries, while increasing speed and efficiency of data collection. When the data is

received, the system identifies any problems with the data, and queries are automatically generated. Evidera will implement this data entry process and prepare the data verification guidelines.

For both the pilot and main phase, Evidera will be responsible for the following:

- Entering and cleaning all data collection forms in DataFax;
- Storing all the original patient-completed CRFs. Retaining records for a minimum of 2 years on-site and an additional 5 years off-site in storage;
- Managing the completed data, performing quality checks, and merging all participant datasets;
- Following good research practice guidelines; and
- Adhering to all procedures outlined in the protocol.

Evidera will maintain the originals of all patient-completed CRFs and the clinical sites will maintain the originals of all site-completed CRFs. However, for the main phase, sites will provide Evidera scanned copies of the Inclusion/Exclusion Forms in advance of all study interviews to confirm patients' eligibility. Sites will also provide Evidera scanned copies of the site-completed Clinical Information Forms.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 2.3. Study and Site Closure

Appendix 2.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or Evidera, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 2.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or Evidera judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 2.4. Publication Policy

The publication policy for Study H9X-MC-B021 is described in the study proposal.

Appendix 3. Recruitment Advertisements

RESEARCH PARTICIPANTS NEEDED

If you are currently treated for type 2 diabetes with oral medication and have never used self-injected medication, you may be eligible to participate in this study.

We are looking for people to take part in a 90–120 minute interview about diabetes medication. The study does not involve treatments. We are interested in your opinions. Study visits will be held in-person in [location].

Participants will receive <$insert amount> for their time.

Please **CALL** Evidera at [to be inserted (free phone)] and leave a message with your name and telephone number **or** send an **E-MAIL** with your name and telephone number to [to be inserted].

Evidera | PPD

Ref # 23274

Appendix 4. Pilot Phase Screening Script

Screening Script (Evidera) – Pilot Phase

My name is [XXXX], and I conduct research at Evidera, an independent healthcare research company. Thank you for responding to our advertisement about the diabetes research study.

The goal of this interview study is to determine patient preferences for two type 2 diabetes treatment devices currently commercialized. Your experience with type 2 diabetes can help us in this process.

If you qualify and choose to participate, you would be asked to attend a 90–120 minute individual, in-person interview with an Evidera researcher interviewer at [location]. You will not receive treatment with any drugs during this study. During the interview, you will be trained on how to use two injection devices that are currently commercialized. You will be asked to perform mock injections using both devices on a pad, and then asked to complete a series of questionnaires related to your condition and the use of the devices. The amount of time it takes for an interviewer to train you to use each device will be recorded.

The information that you provide in the interview will be kept as confidential as possible. A study identification number will be assigned to the information you give and your name will be kept separate.

There are minimal risks to participating in the study because of being trained and performing mock injections on pads with devices. For example, you could have an accidental needle stick injury. All interviewers have been trained on how to handle any issues that may arise from using the devices. During all interviews, a medical professional (e.g., nurse or paramedic) will be on site in case of adverse events such as unanticipated needlesticks. Participation is entirely voluntary. You are free to withdraw from the study at any time.

For your time and participation, you will receive <$ insert amount>, which will be given to you in the form of a Greenphire ClinCard that is used just like a credit card.

Would you be interested in participating?

- ☐ **No -** ***Thank him/her for his/her time and consideration.***
- ☐ **Yes -** ***Continue with the script.***

That's great! To find out if you are eligible to participate, I need to ask a few questions. The information you give will be kept as confidential as possible. You do not have to answer questions you do not want to, but that may disqualify you.

ELIGIBILITY SCREENING

Note to screener: Please complete the following inclusion/exclusion criteria table for each participant. Certain inclusion/exclusion criteria may not be determined via phone screen (e.g., cognitive ability to understand the device trainings). For these criteria, the final eligibility determination will be established at the time of the interview.

ELIGIBILITY CRITERIA	Answer	Fits criteria?
1. What is your **age**?	Age: _____ ***[If less than 18 years old, not eligible.]***	☐ Yes ☐ No
2. Have you been **diagnosed with type 2 diabetes**? If yes, in **what year** were you diagnosed?	☐ Yes, record diagnosis year: _____ ☐ No ***[not eligible, terminate]***	☐ Yes ☐ No
3. Have you been **diagnosed with type 1 diabetes**?	☐ Yes ***[not eligible, terminate]*** ☐ No	☐ Yes ☐ No
4. Are you currently pregnant?	☐ Yes ***[not eligible, terminate]*** ☐ No ***[continue to 5]***	☐ Yes ☐ No
5. Have you **ever been on self-injectable therapy** (e.g., diabetes therapies such as insulin or for other medical conditions)?	☐ Yes ***[not eligible, terminate]*** ☐ No	☐ Yes ☐ No
6. Have you **ever administered injectable treatment** (e.g., diabetes therapies such as insulin or for other medical conditions) to others?	☐ Yes ***[not eligible, terminate]*** ☐ No	☐ Yes ☐ No
7. Are you a **health care practitioner** that is trained in giving injections?	☐ Yes ***[not eligible, terminate]*** ☐ No	☐ Yes ☐ No

ELIGIBILITY CRITERIA	**Answer**	**Fits criteria?**
8. Do you **currently receive oral** treatment for your type 2 diabetes?	☐ Yes, which one(s)?: _____ _____ ☐ No ***[not eligible, terminate]***	☐ Yes ☐ No
9. Are you able to **bring proof of your oral treatment prescription for type 2 diabetes to the interview**? (e.g., the medication itself, the medication packaging, a prescription note, or a letter from your doctor).	☐ Yes ☐ No ***[not eligible, terminate]***	☐ Yes ☐ No
10. Are you **willing and able to attend an in-person interview**?	☐ Yes ☐ No ***[not eligible, terminate]***	☐ Yes ☐ No
11. Do you feel that you are able to **read, speak, and understand English sufficiently** to fully participate in an interview and complete questionnaires?	☐ Yes ☐ No ***[not eligible, terminate]***	☐ Yes ☐ No
12. Are you willing and able to **provide written informed consent**?	☐ Yes ☐ No ***[not eligible, terminate]***	☐ Yes ☐ No
13. Are you **currently enrolled in any other clinical study involving an investigational product**?	☐ Yes ***[not eligible, terminate]*** ☐ No	☐ Yes ☐ No
14. Have you participated, within the last **30 days, in a clinical study** involving an investigational product?	☐ Yes ***[not eligible, terminate]*** ☐ No	☐ Yes ☐ No

ELIGIBILITY CRITERIA	**Answer**	**Fits criteria?**
15. Are you an **Eli Lilly and Company, Novo Nordisk, Evidera, or PPD** (Pharmaceutical Product Development) **employee**?	☐ Yes ***[not eligible, terminate]*** ☐ No	☐ Yes ☐ No

*Respondents must be able to attend interview and meet all the required criteria. Otherwise, the respondent is **NOT ELIGIBLE** to participate.*

ELIGIBILITY RATING

Based on the eligibility responses above, the respondent is:

☐ **Not Eligible -** I'm sorry, but based on your responses I'm not able to include you in the study. Thank you for your time. *[Terminate call]*

☐ **Eligible -** Based on what you have told me, you are eligible to participate in the study. Can I ask you some additional questions?

Proceed with gathering additional demographic information from eligible & interested participants.

ADDITIONAL DEMOGRAPHIC INFORMATION	
1. What is your gender?	☐ Male ☐ Female
2a. What is your ethnic background?	☐1 Hispanic or Latino ☐2 Not Hispanic or Latino ☐3 Not applicable
2b. What is your racial background? (check all that apply)	☐1 American Indian or Alaska Native ☐2 Asian ☐3 Black or African American ☐4 Native Hawaiian or Other Pacific Islander ☐5 White ☐6 Other: _____
3. What is your current employment status?	☐ Full-time work ☐ Part-time work ☐ Homemaker/housewife ☐ Student ☐ Unemployed ☐ Retired ☐ Disabled ☐ Other: _____
4. Where did you find out about this research study?	☐ Newspaper Ad: _____ ☐ Other: _____

Thank you for providing me with this information.

We are also being asked to pass on to the study sponsor any details of adverse events and product complaints that are mentioned during this research study. Although this is a 1-time interview and what you say will, of course, be treated in confidence, should you mention an adverse event

or product device complaint, the study team will need to report this even if it has already been reported by you directly to the company or the regulatory authorities.

Are you willing to proceed with the interview?

☐ Yes (continue)

☐ No (terminate)

Based on the answers you just gave me, you are able to participate in this study. Are you able to come [insert interview location] for an in-person interview?

☐ Yes (continue)

☐ No (terminate)

SCHEDULING INFORMATION

Thank you for your interest in participating.

We are trying to conduct these interviews over a period of [roughly two weeks in *Month*], so we are looking for dates that you may be available. If one of the dates that you are available is selected, we will contact you soon to confirm that you are still interested and available on the selected date and time. We will then send you directions to the interview location.

Schedule Interview	
Participant Name	
Potential Dates of Participation or Unavailability	
Finalized Date and Time of Study Visit	/ / _____:_____ AM/PM DD / MMM / YYYY time
Phone Numbers	*Please **check the box** with the preferred number* ☐ Home _____ ☐ Work _____ ☐ Cell _____ Best times to call: _____
Information for sending a confirmation letter with directions to the interview	We need to send your interview confirmation via e-mail or regular mail with directions to the interview. In addition, closer to the interview you will receive a reminder phone call. Please be aware that if you share an e-mail account with someone else, they may be able to read the information that we send. How would you prefer to receive your interview information? ☐ E-mail confirmation (Ask participant to provide e-mail address): _____ ☐ Regular mail confirmation (Ask participant for mailing address to send via regular mail): _____ _____

Screener Name: _____

Screener Signature: _____ Date: ____/_____/_____
DD MMM YYYY

Appendix 5. Pilot Phase Inclusion/Exclusion Criteria

INCLUSION/EXCLUSION CRITERIA FORM
(EVIDERA STUDY STAFF) – PILOT PHASE

Check YES or NO for each of the following criteria:

INCLUSION CRITERIA	YES	NO
1. Participant is ≥18 years of age	☐	☐
2. Participant has been diagnosed with type 2 diabetes	☐	☐
3. Participant is self-injection naïve to all injectable treatment (e.g., diabetes therapies and other medical conditions)	☐	☐
4. Participant is injection naïve to performing all injectable treatment (e.g., diabetes therapies and other medical conditions) to others	☐	☐
5. Participant is currently receiving oral treatment for their type 2 diabetes	☐	☐
6. Participant is willing and able to attend an in-person interview	☐	☐
7. Participant is able to read, speak, write, and understand the English language	☐	☐
8. Participant is willing and able to provide written informed consent	☐	☐

If **ANY** of the above answers are **NO**, the participant is **NOT ELIGIBLE** for participation in this study. ***Do not proceed any further with this participant***. If **ALL** of the above items are **YES**, continue.

Please assess the exclusion criteria by checking YES or NO for each of the following criteria:

EXCLUSION CRITERIA	YES	NO
Study staff should use recruitment/screening interaction to assess these questions:		
1. Currently diagnosed with gestational diabetes and/or type 1 diabetes	☐	☐
2. Currently pregnant	☐	☐
3. Cognitive or physical difficulties that could interfere with ability to understand the training, perform the injection tasks, or complete the study questionnaires as judged by the investigator	☐	☐
4. Currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study	☐	☐
5. Has participated, within the last 30 days, in a clinical study involving an investigational product	☐	☐
6. Is a health care practitioner who is trained in giving injections	☐	☐
7. Is an Eli Lilly and Company, Novo Nordisk, Evidera, or PPD employee	☐	☐

If **ANY** of the above answers to the exclusion questions are **YES;** the participant is **NOT ELIGIBLE** for participation in this study.

CONSENT	

1. Participant has provided written consent:	☐ Yes ☐ No
2. Date consent obtained:	__ __/__ __ __/__ __ __ __ DD MMM YYYY
INVESTIGATOR SIGNATURE	**DATE**
I certify that the above information is correct. **Investigator/Designee** **Signature:**_____	__ __/__ __ __/__ __ __ __ DD MMM YYYY

Appendix 6. Confirmation Letter/E-mail

PARTICIPANT CONFIRMATION LETTER/E-MAIL – PILOT & MAIN PHASE

[Date for letter]

[Participant Name and Address for letter]

Dear [Participant]:

Thank you for your interest in our research study. We appreciate you taking the time out of your schedule to participate in our interview. We have scheduled your in-person interview at <Time> on <Date> at <location name and address>. We have included driving directions and [public transport system] directions to this facility with this [letter or e-mail].

The purpose of this study is to better understand patients' preferences for diabetes treatments. For this study, we are interviewing people with type 2 diabetes, and this study is sponsored by a large pharmaceutical company. During the interview, you will be trained on how to use two different commercialized devices that dispense type 2 medications. You will also be asked to complete a brief series of questionnaires about the devices, your diabetes condition, and your general health. If you become uncomfortable with any of the interview questions, you can always completely terminate the interview at any time or prefer not to answer the questions that make you feel uncomfortable. All information you provide will be kept confidential, you have the right to withdraw at any time. Your personal information will be stored within Evidera. This is not a sales promotional activity. Aggregate study results without any of your personal information might be published.

The interview will last approximately [**pilot phase**: 1.5 to 2 hours; **main phase:** 1 to 1.5 hours]. [**For pilot phase only participants**: Please remember to bring proof of your type 2 diabetes oral medication(s) with you to the interview (e.g., the medication itself, the box the medication comes in, or a letter from your doctor).] After your interview, you will be compensated a specified amount for your time and travel to the study interview [**pilot phase:** <$ insert amount>; **main phase:** <$ insert amount>].

Upon arrival to the <location>, please <to provide instructions for checking in and proceeding to interview room>. If you have any questions or concerns, please call [**pilot phase:** Evidera contact person name and telephone number; **main phase:** Clinical site contact person name and telephone number]. Thank you again for your interest in this study. We greatly appreciate your participation.

Sincerely,

[**pilot phase:** Evidera contact person name, title]

[**main phase:** Clinical site contact person name, title]

Appendix 7. Reminder Phone Call/E-mail

PARTICIPANT REMINDER PHONE CALL – PILOT & MAIN PHASE

Hello [Insert Participant Greeting]

My name is [XXXX], from [**pilot phase**: Evidera; **main phase**: Clinical site name]. I am just calling to remind you that you are scheduled to take part in a one-on-one interview at <Time> on <Date> at <Location name and address>. *[**For pilot phase only participants**: Please remember to bring proof of your type 2 diabetes oral medication(s) with you to the interview (e.g., the medication itself, the box the medication comes in, or a letter from your doctor).]*

Full details of the study have been previously e-mailed or sent to you by post.

Will you be able to attend? [If no, please try and re-schedule the participant.]

PARTICIPANT REMINDER E-MAIL – PILOT AND MAIN PHASE

Dear [Insert Participant Greeting]:

You are scheduled to take part in a one-on-one interview at <Time> on <Date> at <Location name and address>. The interview will last approximately [**pilot phase**: 1.5 to 2 hours; **main phase:** 1 to 1.5 hours]. *[**For pilot phase only participants**: Please remember to bring proof of your type 2 diabetes oral medication(s) with you to the interview (e.g., the medication itself, the box the medication comes in, or a letter from your doctor).]*

Please respond to this e-mail with confirmation that you are still able to attend.

Full details of the study have been previously e-mailed or sent to you by post.

[**pilot phase:** Evidera contact person name, title]

[**main phase:** Clinical site contact person name, title]

Appendix 8. Main Phase Screening Script

Screening Script (Clinical Site) – Main Phase

The Inclusion/Exclusion Criteria Form is a separate form but there are criteria that can be reviewed by the clinic site prior to contacting the patient. **Before you introduce the research study to the patient please confirm using the patient's medical chart:**

1. Patient is ≥18 years of age	☐ Confirmed
2. Patient has been diagnosed with T2DM	☐ Confirmed
3. Patient is self-injection naïve to all injectable treatment (e.g., diabetes therapies and other medical conditions)	☐ Confirmed
4. Patient is currently receiving oral treatment for their type 2 diabetes	☐ Confirmed

Once all above criteria have been confirmed, please conduct recruitment with patient according to the following script. Please complete the Inclusion/Exclusion Criteria Form.

Hello, this is [name] from [clinic]. We are currently recruiting patients with type 2 diabetes to participate in a research study being conducted by Evidera, a health outcomes research organization. The goal of the interview study is to determine patient preferences for the type 2 diabetes treatment devices currently commercialized.

If you qualify and choose to participate, you would be asked to attend a 60-90 minute individual, in-person interview with an Evidera researcher at [location]. You will not receive treatment with any drugs during this study. During the interview, you will be trained on how to use two injection devices currently commercialized. You will be asked to perform mock injections using both devices on a pad, and then asked to complete a series of questionnaires related to your condition and the use of the devices.

[For Time-to-Train Participants: The amount of time it takes for an interviewer to train you to use each device will be recorded.]

The information that you provide in the interview will be kept as confidential as possible. A study identification number will be assigned to the information you give and your name will be kept separate. The information you share during the interview will not be shared with your doctor, and will have no impact on the care that you receive or your ability to participate in future studies.

There are minimal risks to participating in the study because of the use of being trained and performing mock injections on pads with devices. For example, you could have an accidental needle stick injury. All interviewers have been trained on how to handle any issues that may arise from using the devices. During all interviews, a medical professional (e.g., nurse or paramedic) will be on site in case of adverse events such as unanticipated needlesticks. Participation is entirely voluntary. You are free to withdraw from the study at any time.

For your time and participation, you will receive: <$ insert amount> (via Greenphire ClinCard).

Are you interested in participating?

☐ No – Thank them for their time and consideration.

☐ Yes – Great. Now, to find out if you are eligible for this study, I need to ask a few questions.

Confirm any inclusion/exclusion criteria with the patient that cannot be ascertained based on the chart/information using the ***Inclusion/Exclusion Criteria Form****.*

If not eligible: Thank you for your interest in the study, however you are not eligible to participate.

If eligible, continue.

We are also being asked to pass on to the study sponsor any details of adverse events and product complaints that are mentioned during this research study. Although this is a 1-time interview and what you say will, of course, be treated in confidence, should you mention an adverse event or product device complaint the study team will need to report this even if it has already been reported by you directly to the company or the regulatory authorities.

Are you happy to proceed with the interview on this basis?

☐ Yes (continue)

☐ No (terminate)

Based on the answers you just gave me, you are able to participate in this study. Are you able to come [insert interview location] for an in-person interview?

☐ Yes (continue)

☐ No (terminate)

If in-person, continue:

What is the best day and time for you to come in to complete the interview?
[Schedule for interview]

Participant Initials: _____

Name of Person Entering Initials: _____

Interview Date: _____ **Time**: _____

For all interviews, continue:

May I have your e-mail, mailing address and/or phone numbers? We will need this information to contact you in the future as we arrange the scheduling of the interviews and/or to remind you about your interview (*Please remind participant that if they share an e-mail address with someone, that individual may be able to read the information that we send*).

☐ **Yes** (proceed with asking for contact information)

☐ **No** (Skip to bottom of script and give participant [your site] contact information)

What is the best phone number to use?

Patient Name: _____ Address: _____ _____ _____	*Please check the box with the preferred number* ☐ Home _____ ☐ Work _____ ☐ Cell _____ Best times to call: _____ _____ E-mail address: _____ _____ *Please remind participant that if they share an e-mail address with someone else, this other person may be able to read the information that we send.*

If you have any questions or if you would like to cancel/reschedule your interview, please contact [*clinic staff name*] at [*clinic staff number*]. Thank you very much for your time. Have a nice day!

Screener Name: _____

Screener Signature: _____ **Date:** ____/_____/_____
DD MMM YYYY

Appendix 9. Main Phase Inclusion/Exclusion Criteria

INCLUSION/EXCLUSION CRITERIA FORM (CLINICAL SITE) – MAIN PHASE

Please review the participant's eligibility. Check YES or NO for each of the following criteria:

INCLUSION CRITERIA	YES	NO
1. Patient is ≥18 years of age	☐	☐
2. Patient has been diagnosed with type 2 diabetes	☐	☐
3. Patient is self-injection naïve to all injectable treatment (e.g., diabetes therapies and other medical conditions)	☐	☐
4. Patient is injection naïve to performing all injectable treatment (e.g., diabetes therapies and other medical conditions) to others	☐	☐
5. Patient is currently receiving oral treatment for their type 2 diabetes	☐	☐
These questions will need to be asked of the patient to see if he or she is eligible:	☐	☐
6. Are you self-injection naïve to all injectable treatment (e.g., diabetes therapies and other medical conditions)?	☐	☐
7. Are you injection naïve to performing all injectable treatment (e.g., diabetes therapies and other medical conditions) to others?	☐	☐
8. Are you willing and able to attend an in-person interview?	☐	☐
9. Do you feel that you are able to read, speak, write, and understand English sufficiently to fully participate in an interview and complete questionnaires?	☐	☐
10. Are you willing and able to provide written informed consent?	☐	☐

If **ANY** of the above answers are **NO**, the participant is **NOT ELIGIBLE** for participation in this study. ***Do not proceed any further with this participant***. If **ALL** of the above items are **YES**, continue.

Please assess the exclusion criteria by checking YES or NO for each of the following criteria:

EXCLUSION CRITERIA	YES	NO
Clinic site should use the patient's medical record and the recruitment/screening interaction to assess these questions:		
1. Currently diagnosed with gestational diabetes and/or type 1 diabetes	☐	☐
2. Currently pregnant	☐	☐
3. Cognitive or physical difficulties that could interfere with ability to understand the training, perform the injection tasks, or complete the study questionnaires as judged by the investigator	☐	☐
4. Currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study	☐	☐
5. Has participated, within the last 30 days, in a clinical study involving an investigational product	☐	☐
6. Is a health care practitioner who is trained in giving injections	☐	☐

EXCLUSION CRITERIA		YES	NO
7.	Investigator, site personnel, or immediate family member of investigator or site personnel. (Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.)	☐	☐
8.	Is an Eli Lilly and Company, Novo Nordisk, Evidera, or PPD employee	☐	☐

If **ANY** of the above answers to the exclusion questions are **YES;** the participant is **NOT ELIGIBLE** for participation in this study.

CONSENT	
1. Participant has provided written consent:	☐ Yes ☐ No
2. Date consent obtained:	__ __/__ __ __/__ __ __ __ DD MMM YYYY
INVESTIGATOR SIGNATURE	**DATE**
I certify that the above information is correct. **Investigator/Designee Signature:** _____	__ __/__ __ __/__ __ __ __ DD MMM YYYY

Appendix 10. Participant Recruitment Tracking Log

Please send the Recruitment Tracking Log to Evidera every [insert day of the week]
(Attn: XXXX at 301-654-9864 or e-mail: [insert e-mail address])

Screening ID	Initials	Eligible	Participant Age	Participant Gender	Participant ID	Interview Date and Time (DD/MON/YYYY; time)	All Reasons Ineligible or Withdraw
Example S01-001	ABC	Y ☑ N ☐	35	F	Example 101-101	01/NOV/2018; 9:30 AM EST	
Example S01-002	DEF	Y ☑ N ☐	60	M	Example 101-102	01/NOV/2018; 11:30 AM EST	
Example S01-003	GHI	Y ☐ N ☑	55	F	N/A	N/A	Ineligible (Inclusion #3)
Example S01-004	JKL	Y ☐ N ☑	17	F	N/A	N/A	Ineligible (Exclusion #1 and 3)

Appendix 11. Supplemental Question S1

Supplemental Question S1

S1. Would you be willing to use a diabetes medication that required you to give yourself an injection for each dose?

☐ Not willing

☐ Somewhat not willing

☐ Neutral

☐ Somewhat willing

☐ Very willing

Appendix 12. Interview and Device Training Guide

Interview Guide

I. MATERIALS

1. IFU for Trulicity
2. IFU for Ozempic
3. Trulicity Injection Pen
4. Trulicity Demonstration Pen
5. Two Ozempic Injection Pens (one for demonstration and one for participant use)
6. Sharps container (for disposal of Trulicity Devices and Ozempic Needles)
7. Injection pad
8. Alcohol wipes
9. Trash can (for pen cap)
10. Non-latex gloves

II. INTERVIEW STEPS

1. Confirm the in/ex form has been completed
2. Informed consent
3. Complete Supplemental Question S1
4. Randomization with IWRS system to determine which device is first
5. Explain study to the participant
6. First Device: Training and Mock Injection
7. Complete demographic form
8. Second Device: Training and Mock Injection
9. Complete Interviewer Recording Sheet
10. Complete questionnaires about device preferences and Supplemental Questions S2 and S3

STEP 1. CONFIRM IN/EX FORM HAS BEEN COMPLETED

- Review the site-completed in/ex form for the participant to confirm eligibility.
- This form should be provided to you by the site, and it should already be completed prior to the interview.

STEP 2. INFORMED CONSENT

- Review the consent form with the participant and confirm comprehension.
- Provide the participant with opportunity to answer questions before signing.
- Ask the participant to sign two copies of the consent form if they wish to participate.

- Countersign the forms and provide a copy to the participant.

STEP 3. COMPLETE SUPPLEMENTAL QUESTION S1

- Ask the participant to independently complete this question: "Please complete this question, and let me know when you are finished."

STEP 4. RANDOMIZATION WITH IWRS SYSTEM

- Complete the randomization process to determine the order of device training for the participant.
- Record the order on the Interviewer Recording Sheet.

STEP 5. EXPLAIN THE STUDY TO THE PARTICIPANT

- "You will be trained to use two devices for injecting medication for type 2 diabetes."
- "For each device, I will walk you through the steps for using each device and demonstrate the steps for you. Then, you will use the device to administer an injection into an injection pad."
- "After you have had a chance to use both devices, I will ask you to complete some questionnaires that ask about your preference between the devices."
- "**Do not inject medication into yourself. You will only be injecting into the injection pad**."
- "Please handle the devices carefully to avoid accidently sticking yourself with the needle. If you appear to be handling the device incorrectly, I will try to correct you so you do not accidently stick yourself with the needle."

STEP 6. FIRST DEVICE TRAINING

Follow the Trulicity Training Guide or the Ozempic Training Guide based on the randomization order for the participant.

STEP 7. DEMOGRAPHIC FORM

"Please complete this form."

STEP 8. SECOND DEVICE TRAINING

Follow the Trulicity Training Guide or the Ozempic Training Guide based on the randomization order for the participant.

STEP 9. COMPLETE INTERVIEWER RECORDING SHEET

The interviewer completes the interviewer recording sheet to document order of device training and completion status.

STEP 10. PARTICIPANT-COMPLETED QUESTIONNAIRES

Instruct the participant to complete questionnaires on device preference and supplemental questions S2 and S3.

Ozempic Training Guide

A. Time to Train

The observer should complete the TTT Observer Recording Sheet.

a. Start of the training (i.e., after reading the IFU)

b. The participant picks up the device to start the mock injection.

c. The participant successfully injects the medication into the injection pad and removes the needle/device from the pad.

d. The Ozempic pen is recapped with the pen cap (the inner needle cap and outer needle cap should not be placed back on the pen).

e. The participant has completed the injection and finished asking questions. Participants comments/opinions about the device after completing the injection will not be included unless the participant asks a question.

B. Safety Procedures

If the participant appears to be making an error that could lead to self-harm, the trainer should immediately intervene and stop the injection process.

C. Introduction

Introduce the device and training steps.

- "Now, you will learn to use an injection device."
- "When you feel comfortable with the procedures for using the device, you will use the device to perform a mock injection into the injection pad."
- "You should NOT use this device to inject yourself. You will only be injecting medication into this pad."
- "This is the Ozempic device. This device is used to administer medication once a week, and you would typically use it at home." (*Show the device to the participant.*)

D. Device Training

1. Open the device box and place the IFU in front of the participant.
2. Instruct the participant to "Please read the Instructions for Use and let me know when you are finished. After you are done reading, I will demonstrate all of these steps for you in detail. You can also refer back to this document throughout the interview as much as you want."

3. Demonstrate the injection process using the demo device.

    1. **"The Ozempic device is a prefilled dial-a-dose pen**. You can select doses of 0.25 mg or 0.5 mg. You will be selecting 0.25 mg for the injection today."

    2. "The needles for this device are enclosed in the package."

    3. **"Always use a new needle for each injection."**

    4. **Device parts**
        a. "This is the pen cap."

        b. "This is the pen window."

        c. "This is the dose counter and dose pointer."

        d. "This is the dose selector and the dose button."

        e. "When you turn the dose selector, you will see the flow check symbol and the dashed line to guide to your dose (*turn dose selector to show these symbols*). The flow check symbol comes right after the zero."

        f. "The needle has an outer needle cap, inner needle cap, needle, and paper tab."

    5. **Step 1: Prepare your pen with a new needle**
        a. "If you were injecting, you would begin by washing your hands with soap and water. Since you are injecting a pad today, you do not need to wash your hands this time."

        b. "The next step is to **check the name and colored label** of your pen to make sure that it contains Ozempic."

        c. "Then **pull off the cap**."

        d. **"Check that the Ozempic in your pen is clear and colorless**. Look through the pen window. If the Ozempic is cloudy, do not use the pen."

        e. **"Take a new needle**, and tear off the paper tab."

        f. **"Push the needle straight on to the pen. Turn until it is on tight**."

        g. **"Pull off the outer needle cap**. You can put it in the sharps container."

h. **"Pull off the inner needle cap**, and throw it away."

6. **Step 2: Check the Ozempic flow with each new pen**
   a. "Check the Ozempic flow before your first injection with each new pen."

   b. "Turn the dose selector **until the dose counter shows the flow check symbol**."

   c. "Hold the pen with the needle pointing up. **Press and hold in the dose button** until the dose counter shows 0. The 0 must be lined up with the dose pointer. A drop of Ozempic will appear at the needle tip. The medication may spray out a bit in some cases, so please point the tip away from your face and away from me."

   d. **"If no drop appears**, repeat these flow check steps up to six more times. **Do not use the pen** if a drop of Ozempic still does not appear."

7. **Step 3: Select your dose**
   a. **"Turn the dose selector until the dose counter shows your dose (0.25 mg)**. If you select the wrong dose, you can turn the dose selector forward or backwards to the correct dose."

8. **Step 4. Inject your dose**
   a. "Choose your injection site."

   b. **"Insert the needle into your skin [injection pad]**."

   c. **"Make sure you can see the dose counter**. Do not cover it with your fingers. This could stop the injection."

   d. **"Press and hold down the dose button until the dose counter shows 0**. The 0 must line up with the dose pointer. You may then hear or feel a click."

   e. **"Keep the needle in your skin [injection pad] after** the dose counter has returned to 0 and **count slowly to 6**."

   f. "If the needle is removed earlier, you may see a stream of Ozempic coming from the needle tip. If this happens, the full dose will not be delivered."

   g. **"Remove the needle from your skin [injection pad]**."

9. **Step 5. After your injection**
   a. **"Carefully twist the needle off of the pen.** Since we have a sharps container, please do not put the needle caps back on the needle to avoid needle sticks."

b. **"Place the needle in a sharps container** right away."

c. **"Put the pen cap on** your pen after each use to protect Ozempic from light."

4. Permit the participant to ask any questions they may have about the device or IFU.
   - "Do you have any questions about the steps involved in the injection process?"
   - "Do you feel ready to administer the mock injection? Is there anything you would like to review before trying it?"
   - *When the patient is ready:* "I will leave the instructions for use here, and you can refer to them as much as you like while you go through the injection process. Please take all the time you need."

5. Participant performs mock injection into the injection pad while trainer observes and evaluates injection success based on the critical steps listed below.

6. The mock injection will be considered complete when the patient has successfully performed all critical steps listed below and recapped the pen.

7. If the participant is struggling to remove the needle and appears to be putting themselves at risk of an accidental needle stick, the interviewer should volunteer to remove the needle for them.
   - "Would you like me to remove the needle for you?"

   If the interviewer removes the needle, this should be recorded on the Interviewer Recording Sheet.

8. If the participant does not dispose of the needle in the sharps container independently, the trainer should instruct the participant on disposal using the provided sharps container.
   - "Please place the needle in the sharps container."

9. Ask the participant if they have any questions, and answer them. The training is complete when there are no further questions.
   - "Do you have any questions?"

E. Checklist to assist interviewer in tracking critical steps

Critical Steps	First attempt	Second attempt	Third attempt	Fourth attempt	Fifth attempt
1. Pull off the pen cap	☐	☐	☐	☐	☐
2. Push the needle straight on to the pen. Turn until it is on tight.	☐	☐	☐	☐	☐
3. Pull off the outer needle cap and pull off the inner needle cap	☐	☐	☐	☐	☐
4. Turn the dose selector until the dose counter shows the flow check symbol	☐	☐	☐	☐	☐
5. Press and hold the dose button until the dose counter shows 0 and a drop of Ozempic appears at the needle tip	☐	☐	☐	☐	☐
6. If the drop does not appear on the first attempt, repeat flow check until a drop appears (up to 6 times).	☐	☐	☐	☐	☐
7. Select your dose. Continue turning the dose selector until the dose counter shows 0.25	☐	☐	☐	☐	☐
8. Insert the needle in the pad	☐	☐	☐	☐	☐
9. Press and hold down the dose button until the dose counter shows 0	☐	☐	☐	☐	☐
10. Slowly count to 6 (operationally: patient pauses after pressing injection button).	☐	☐	☐	☐	☐
11. Remove the needle from the pad	☐	☐	☐	☐	☐
12. Remove the needle from the pen (capped or uncapped)	☐	☐	☐	☐	☐

F. Retraining

If the critical steps are not performed correctly on the first attempt, the participant should be retrained on critical steps that were missed or performed incorrectly. The participant may have to repeat all or some of the injection process. The error should be explained to the participant and the participant should be asked to make the correction and continue the injection process.

If the participant is making a mistake during the injection, you can call his or her attention to the mistake so that he or she can continue the injection correctly. For example, if the participant is trying to do the flow check without removing the inner cap, tell him or her to remove the cap first. "It looks like the inner cap is still on. Could you remove the inner cap before checking the flow?"

Trulicity Training Guide

A. Time to Train

The observer should complete the TTT Observer Recording Sheet.

a. Start of training (i.e., after reading the IFU)

b. The participant picks up the device to start the mock injection.

c. The participant successfully injects the medication into the injection pad and removes the needle/device from the pad.

d. The Trulicity pen is dropped into the sharps container.

e. The participant has completed the injection and finished asking questions. Participant comments/opinions about the device after completing the injection will not be included unless the participant asks a question.

B. Safety Procedures

If the participant appears to be making an error that could lead to self-harm, the trainer should immediately intervene and stop the injection process.

C. Introduction

Introduce the device and training steps.

- "Now, you will learn to use an injection device."
- "When you feel comfortable with the procedures for using the device, you will use the device to perform a mock injection into the injection pad."
- "You should NOT use this device to inject yourself. You will only be injecting medication into this pad."
- "This is the Trulicity device. This device is used to administer medication once a week, and you would typically use it at home." (*Show the device to the participant.*)

D. Device Training

1. Open the device box and place the IFU in front of the participant.
2. Instruct the participant to "Please read the Instructions for Use and let me know when you are finished. After you are done reading, I will demonstrate all of these steps for you in detail. You can also refer back to this document throughout the interview as much as you want."
3. Demonstrate the injection process using the demo device.

1. **Before you get started**
   a. "Check the pen label to make sure you have the right medicine and it has not expired."

   b. "Inspect the pen to make sure it is not damaged"

   c. "Inspect the medicine to make sure it is not cloudy or discolored, and it should not have particles in it."

   d. "If you were injecting yourself, you would then wash your hands. Since you are injecting a pad today, you do not need to wash your hands this time."

   e. "If you were injecting yourself, you would select an injection site. Today, you will inject into this injection pad and NOT into your body."

2. **Device parts**
   a. "At the top of the device, there is a green injection button."

   b. "Beneath that is a lock ring, and an indicator which lines up with the lock and unlock symbols."

   c. "Down here you can see the medicine."

   d. "At the bottom, you can see the clear base and the base cap."

   e. "The needle is inside the device."

3. **Steps for injection**
   a. Uncapping the pen.

      i) "You would first make sure the pen is locked"

      ii) "Then pull the base cap straight off and throw it away in the trash".

      iii) "Do not put the base cap back on – this could damage the needle."

   b. Second, place the base on the injection site and unlock the device
      i) "You would place the clear base flat and firmly against your skin (or in this case, the injection pad)."

      ii) "Unlock by turning the lock ring".

c. Third, administer the injection
   i) "You would press and hold the green injection button. You will hear a loud click."

   ii) "When you press the button, the medication is injected."

   iii) "Continue to hold the clear base firmly against the pad until you hear a second click. This happens when the needle starts retracting in about 5 – 10 seconds. My demo device may be slower than the actual device you use, so listen closely for the click on your device."

   iv) "Then remove the pen from your skin [injection pad]."

   v) "You will know the injection is complete when the gray plunger is visible."

d. The final step is disposing of the pen.
   i) "Put your used pen in the sharps disposal container right away after use".

4. Permit the participant to ask any questions they may have about the device or IFU.
   - "Do you have any questions about the steps involved in the injection process?"

   - "Do you feel ready to administer the mock injection? Is there anything you would like to review before trying it?"

   - *When the patient is ready:* "I will leave the instructions for use here, and you can refer to them as much as you like while you go through the injection process. Please take all the time you need."

5. Participant performs mock injection into the injection pad while trainer observes and evaluates injection success based on the critical steps listed below.

6. The mock injection will be considered complete when the patient has successfully performed all critical steps listed below and placed the device in the sharps container.

7. If the participant does not dispose of the device in the sharps container independently, the trainer should instruct the participant on device disposal using the provided sharps container.
   - "Please place the pen in the sharps container."

8. Ask the participant if they have any questions, and answer them. The training is complete when there are no further questions.
   - "Do you have any questions?"

E. Checklist to assist interviewer in tracking critical steps

Critical Steps	First attempt	Second attempt	Third attempt	Fourth attempt	Fifth attempt
1. Take off base cap	☐	☐	☐	☐	☐
2. Place on injection site	☐	☐	☐	☐	☐
3. Unlock device	☐	☐	☐	☐	☐
4. Press button and hold the device in place until the grey plunger is visible. The participant should pause.	☐	☐	☐	☐	☐
5. Remove from injection site	☐	☐	☐	☐	☐

F. Retraining (if necessary)

If the critical steps are not performed correctly on the first attempt, the participant should be retrained on critical steps that were missed or performed incorrectly. The participant may have to repeat all or some of the injection process. The error should be explained to the participant and the participant should be asked to make the correction and continue the injection process.

If the participant is making a mistake during the injection, you can call their attention to the mistake so that he or she can continue the injection correctly. For example, if the participant is trying to press the injection button without unlocking the device, tell the participant to unlock it. "It looks like the device is still locked. Can you unlock it before injecting?"

Appendix 13. Time-to-Train (TTT) Observer Recording Sheet

TTT Observer Recording Sheet

To be completed by the TTT observer:

1. Ozempic

1a. Start time of training (i.e., after reading the IFU): 0:00
1b. Start time of participant performing mock injection(s): _____:_____
1c. End time of successfully administered mock injection (i.e., withdrawal of needle/device from injection pad): _____:_____
1d. End time of mock injection procedures (Ozempic = recapping the pen): _____:_____
1e. End time of training, including all procedures and questions: _____:_____
Number of interventions: _____

2. Trulicity

2a. Start time of training introduction (i.e., after reading the IFU): 0:00
2b. Start time of participant performing mock injection(s): _____:_____
2c. End time of successfully administered mock injection (i.e., withdrawal of needle/device from injection pad): _____:_____
2d. End time of mock injection procedures (Trulicity = disposing of the pen in the sharps container): _____:_____
2e. End time of training, including all procedures and questions: _____:_____
Number of interventions: _____

Appendix 14. Demographic Form

Demographic Form – Participant Completed

1. What is your age? _____

2. What is your gender? ☐ Male ☐ Female

3a. What is your ethnic background?

- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino
- ☐ Not applicable

3b. What is your racial background? (*Please check all that apply*)

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White
- ☐ Other: _____

4. What is your marital status?

- ☐ Single
- ☐ Married
- ☐ Divorced
- ☐ Separated
- ☐ Widowed
- ☐ Other: _____

5. How would you describe your employment status? (Please tick all boxes that apply)

- ☐ Full-time work
- ☐ Part-time work
- ☐ Homemaker/housewife
- ☐ Student
- ☐ Unemployed
- ☐ Stay-at-home parent
- ☐ Retired
- ☐ Disabled
- ☐ Other: _____

6. What is the highest level of education you have completed? (*Please check only one*)
   - ☐ Elementary/primary school
   - ☐ Secondary/high school
   - ☐ Some college
   - ☐ College degree
   - ☐ Postgraduate degree
   - ☐ Other: _____

7. Have you had any of the following health conditions? (Please tick/check all boxes that apply*)*
   - ☐ Angina
   - ☐ Arthritis
   - ☐ Cancer
   - ☐ Chronic obstructive pulmonary disease/emphysema
   - ☐ Heart attack or heart disease
   - ☐ Hypertension
   - ☐ Stroke
   - ☐ Depression
   - ☐ Other mental health conditions (please specify): _____
   - ☐ Other health conditions (please specify): _____
   - ☐ None

Appendix 15. Interviewer Recording Sheet

Interviewer Recording Sheet

To be completed by the interviewer:

1. Device Randomized to First Training: ☐ Ozempic Device ☐ Trulicity Device

☐ Participant **completed training** for first device

☐ Participant completed training, but required interviewer's assistance to remove the needle (Ozempic only)

☐ Participant was exposed to this device, but **did not complete** training. Please explain below:

_____

_____

_____

_____

_____

2. Device Randomized to Second Training: ☐ Ozempic Device ☐ Trulicity Device

☐ Participant **completes training** for second device

☐ Participant completed training, but required interviewer assistance to remove the needle (Ozempic only)

☐ Participant was exposed to this device but **did not complete** training. Please explain below:

_____

_____

_____

_____

_____

Appendix 16. Pilot Phase Interview Questions

Pilot Phase Interview Questions

Participants Randomization Order (select one):

☐ 1. Ozempic Device; 2. Trulicity Device ☐ 2. Trulicity Device; 1. Ozempic Device

Questions about Ozempic Device:

1. Are there any ways the Ozempic device training could be easier or more clear? If yes, please explain.

   ☐ **No**

   ☐ **Yes**, please explain:

   _____

   _____

   _____

2. Would you **recommend any changes** to the Ozempic device training procedures? If yes, please explain.

   ☐ **No**

   ☐ **Yes**, please explain:

   _____

   _____

   _____

3. How much additional guidance is appropriate and useful during the Ozempic training?

   ☐ **Video**

   ☐ **Interviewer uses demonstration pens to review key device steps**

   ☐ **Interviewer answers questions**

   ☐ **Other suggestions?**

   Please explain response:

   _____

   _____

   _____

Questions about Trulicity Device:

1. Are there any ways the Trulicity device training could be easier or more clear? If yes, please explain.

   ☐ **No**

   ☐ **Yes**, please explain:

   _____

   _____

   _____

2. Would you **recommend any changes** to the Trulicity device training procedures? If yes, please explain.

   ☐ **No**

   ☐ **Yes**, please explain:

   _____

   _____

   _____

3. How much additional guidance is appropriate and useful during the Trulicity training?

   ☐ **Video**

   ☐ **Interviewer uses demonstration pens to review key device steps**

   ☐ **Interviewer answers questions**

   ☐ **Other suggestions?**

   Please explain response:

   _____

   _____

   _____

Thank the participant for taking part in the study. Ask the participant to refrain from discussing the interview with anyone else who plans to take part in the study.

Appendix 17. Global Preference Item

To be completed by all participants:

1. Overall, which device do you prefer?

☐ **Ozempic** ☐ **Trulicity** ☐ **No Preference**

To be completed by interviewer:

2. Please explain your preference indicated in Item 1 on the Global Preference Questionnaire (interviewer to record reasons for device preference provided by the participant, provide quotes with quotations marks and write neatly):

_____

_____

_____

_____

_____

Appendix 18. DID-PQ

Please select **only one** response for each item to indicate which of the two injection devices you prefer.

	Ozempic Device			Trulicity Device	
					
	Strongly Prefer Ozempic Device	**Prefer Ozempic Device**	**No Preference**	**Prefer Trulicity Device**	**Strongly Prefer Trulicity Device**
1. Ease of preparing the injection device and medication for use	☐	☐	☐	☐	☐
2. Ease of fitting the injection into your routine	☐	☐	☐	☐	☐
3. Ease of bringing the injection device with you when it is necessary to inject away from home	☐	☐	☐	☐	☐
4. Confidence that the injection device provides the correct dose of medication every time	☐	☐	☐	☐	☐
5. Confidence that you are using the injection device correctly	☐	☐	☐	☐	☐
6. The size of the needle	☐	☐	☐	☐	☐
7. The time it takes to prepare and inject each dose of medication	☐	☐	☐	☐	☐
8. Overall satisfaction with the injection device	☐	☐	☐	☐	☐
9. Overall ease of using the injection device	☐	☐	☐	☐	☐
10. Overall convenience of using the injection device	☐	☐	☐	☐	☐

Appendix 19. Four Items From MDDAB – Ozempic Device

Four Items From MDDAB – Ozempic Device

Instructions: Based on your experience with the medication delivery device used in this study, please indicate how easy or difficult it was to use the device. For each question, please check the number that best represents your experience with using the device.

How difficult or easy was it to do the following?

	Very Difficult	Difficult	Neither Difficult nor Easy	Easy	Very Easy
1. To learn how to use the device	1	2	3	4	5
2. To follow the instructions when using the device	1	2	3	4	5
3. Overall, how difficult or easy was the device to use?	1	2	3	4	5

Instructions: The following question asks you to think about your confidence in continuing to use the device you used in this study. Please think about the following question as if you were prescribed this medicine and this device would be available to you after the study.

	Definitely Unwilling	Mostly Unwilling	Not Sure	Mostly Willing	Definitely Willing
1. Please check the number that best indicates ***how willing you are to continue using the device.***	1	2	3	4	5

Appendix 20. Four Items From MDDAB – Trulicity Device

Four Items from MDDAB – Trulicity Device

Instructions: Based on your experience with the medication delivery device used in this study, please indicate how easy or difficult it was to use the device. For each question, please check the number that best represents your experience with using the device.

How difficult or easy was it to do the following?

	Very Difficult	Difficult	Neither Difficult nor Easy	Easy	Very Easy
1. To learn how to use the device	1	2	3	4	5
2. To follow the instructions when using the device	1	2	3	4	5
3. Overall, how difficult or easy was the device to use?	1	2	3	4	5

Instructions: The following question asks you to think about your confidence in continuing to use the device you used in this study. Please think about the following question as if you were prescribed this medicine and this device would be available to you after the study.

	Definitely Unwilling	Mostly Unwilling	Not Sure	Mostly Willing	Definitely Willing
1. Please check the number that best indicates ***how willing you are to continue using the device.***	1	2	3	4	5

Appendix 21. Supplemental Questions S2 and S3

Supplemental Questions S2 and S3

S2. How willing would you be to use the Ozempic injection device?

- ☐ Not willing
- ☐ Somewhat not willing
- ☐ Neutral
- ☐ Somewhat willing
- ☐ Very willing

S3. How willing would you be to use the Trulicity injection device?

- ☐ Not willing
- ☐ Somewhat not willing
- ☐ Neutral
- ☐ Somewhat willing
- ☐ Very willing

Appendix 22. Clinical Information Form

Clinical Information Form – Site Completed

Instructions: Please complete the following questions for eligible patients.

1. When was the patient diagnosed with T2DM?

If the day and month are unknown, please report the year of diagnosis, and check the box "Day and Month of T2DM diagnosis unknown".

If day is unknown, please report month and year of diagnosis, and check the box "Day of T2DM diagnosis unknown".

D	D	M	M	M	Y	Y	Y	Y

☐ Day and Month of T2DM diagnosis unknown

☐ Day of T2DM diagnosis unknown

2. What type 2 diabetes <u>oral</u> medication(s) is the patient <u>currently</u> taking? Please check all that apply.

Oral Class	**Oral Medication Options (select all that apply)**	**Estimated Start Date of Oral T2DM Medication** (MMM/YYYY)
Sulfonylureas	☐ chlorpropamide	
	☐ glibenclamide or glyburide	
	☐ glibornuride	

Oral Class	Oral Medication Options (select all that apply)	Estimated Start Date of Oral T2DM Medication (MMM/YYYY)
	☐ gliclazide	
	☐ glimepiride	
	☐ glipizide	
	☐ gliquidone	
	☐ glisoxepide	
	☐ glyburide micronized	
	☐ glyclopyramide	
	☐ glycyclamide or tolhexamide	
	☐ metahexamide	
	☐ tolazamide	
	☐ other	
Meglitinides	☐ metformin	
	☐ nateglinide	
	☐ repaglinide	
	☐ other	
DPP-4 Inhibitors	☐ alogliptin benzoate	
	☐ linagliptin	
	☐ saxagliptin	
	☐ sitagliptin	
	☐ vildagliptin	

Oral Class	Oral Medication Options (select all that apply)	Estimated Start Date of Oral T2DM Medication (MMM/YYYY)
	☐ other	
SGLT2 Inhibitors	☐ canagliflozin	
	☐ dapagliflozin	
	☐ empagliflozin	
	☐ other	
Thiazolidinediones (TZDs or Glitazones)	☐ pioglitazone	
	☐ rosiglitazone	
	☐ other	
Alpha-glucosidase inhibitors	☐ acarbose	
	☐ miglitol	
	☐ other	
Combination Pills	☐ alogliptin benzoate/metformin hydrochloride	
	☐ canagliflozin/metformin hydrochloride	
	☐ dapagliflozin/metformin	
	☐ dapagliflozin propanediol/metformin hydrochloride	
	☐ empagliflozin/linagliptin	

Oral Class	Oral Medication Options (select all that apply)	Estimated Start Date of Oral T2DM Medication (MMM/YYYY)
	☐ glimepiride/pioglitazone	
	☐ glimepiride/rosiglitazone maleate	
	☐ metformin/empagliflozin	
	☐ metformin/glipizide	
	☐ metformin/glyburide	
	☐ metformin/linagliptin	
	☐ metformin/pioglitazone	
	☐ metformin/repaglinide	
	☐ metformin/rosiglitazone maleate	
	☐ metformin/saxagliptin	
	☐ metformin/sitagliptin	
	☐ metformin/vildagliptin	
	☐ simvastatin/sitagliptin phosphate	
	☐ other	

3. Does the patient <u>currently</u> have any of the following comorbidities? Please check all that apply.

☐ Congestive heart failure

☐ Dementia
☐ Chronic Pulmonary Disease
☐ Rheumatologic Disease
☐ Mild Liver Disease
☐ Diabetes with chronic complications
☐ Hemiplegia or paraplegia
☐ Renal disease
☐ Any malignancy, including leukemia and lymphoma
☐ Moderate or severe liver disease
☐ Metastatic solid tumor
☐ AIDS/HIV
☐ None

4. Please record the patient's most recent HbA1c value and the date this value was measured.

Date of HbA1c measurement	**HbA1c value**
DD/MMM/YYYY	___%

Appendix 23. Protocol Amendment H9X-MC-B021(b) Summary Crossover Study Comparing the Dulaglutide (Trulicity) Pen and the Semaglutide (Ozempic) Pen

Overview

Protocol H9X-MC-B021(a) [Crossover Study Comparing the Dulaglutide (Trulicity) Pen and the Semaglutide (Ozempic) Pen] has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

Based on the results from pilot portion of the study, some scheduling, training, and administrative protocol elements have changed to reflect learnings from the pilot study.

Changes to the protocol were made for the following reasons:

- Sponsor decision to streamline study based on participant feedback

Minor editorial changes have also been made throughout the document.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol H9X-MC-B021 Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Section 2, Synopsis Table 2.1	A break will be 'offered' to participants	Participants in the pilot study did not require a restroom or water break between device trainings. The break will be offered to participants, but it will be optional.
Section 2, Synopsis Table 2.1	Optional second interview break removed for main study	Participants in the pilot study did not need a break between device trainings and questionnaires. This second break will not be included in the main study, but participants will be permitted to take a break if they request it.

Section 3.5 Methods to Minimize Risks	Guidance was added on instructing participants to use a study-provided sharps container rather than attempt to recap the semaglutide needle.	A potential for needle stick was identified in the pilot study, as participants may have considered recapping the needle.
Section 5.5.4 Overview of study visit procedures for the main study	Video was removed	The video was removed from the main study procedures based on the results of the pilot study. The video was not necessary in addition to the interviewer demonstration.
Section 5.5.4 Overview of study visit procedures for the main study	Optional second interview break removed for main study	Participants in the pilot study did not need a break between device trainings and questionnaires. This second break will not be included in the main study, but participants will be permitted to take a break if they request it.
Section 5.5.4 Overview of study visit procedures for the main study	IFUs are provided to participants to read, and the interviewer will demonstrate how to use the device.	The participant should have the IFU available to read and review during the training, so additional text was added to help assure clarity on this point.
Section 5.5.4 Overview of study visit procedures for the main study	Maximum time for all study procedures was added.	90 minutes, as specified in the consent form
Section 9.1.2.6 Global Preference Item	The open ended response to explain reasons for device preference was changed from patient completed to interviewer completed.	The results of the pilot study indicate that many patients are not able to write a clear response to this question. Participants are better able to articulate reasons for preference when speaking with the interviewer. Therefore, in the main study, the interviewer will ask the participant for the reasons for their device preference and record the reasons for the participant using quotations marks to capture the respondent's exact words.
10.2 Populations for analysis	Video removed	Based on results of the pilot study, the video will not be used in the main study.
Appendix 12 Interview and Device Training Guides	Interview guides were updated to incorporate revisions made during the pilot study.	The interview guides were revised during the pilot study to streamline language, present training information clearly, and address issues identified during the pilot study.

Appendix 13 Time-to-Train Observer Recording Sheet	Training time points were revised and clarified, a field was added to capture the number of interventions.	The timing points for time to train were changed to capture time elapsed between start of training rather than time of day to increase accuracy by observer, time points were clarified for consistency, and number of interventions field was added based on pilot study observation that interviewers needed to intervene during mock injections.
Appendix 14 Demographic form	Subscripts removed	The subscripts are not necessary for data entry using the Evidera Datafax system. These subscripts were removed to simplify the form for participant completion.
Appendix 15 Interviewer Recording Sheet	Field added to capture interviewer assistance with Ozempic needle removal	Some participants are unable to remove the needle from the Ozempic device safely. In these cases, interviewers will offer to assist with needle removal to lower the risk of AEs.
Appendix 17 Global Preference Item	Item 2 changed from participant completed to interviewer completed.	The results of the pilot study indicate that many patients are not able to write a clear response to this question. Participants are better able to articulate reasons for preference when speaking with the interviewer. Therefore, in the main study, the interviewer will ask the participant for the reasons for their device preference and record the reasons for the participant using quotations marks to capture the respondent's exact words.
Appendix 22 Clinical Information Form	Date reporting format changed to DDMMMYYYY	Change for consistency with other date reporting fields in the study and to remove an ambiguity in day and month reporting.
Appendix 22 Clinical Information Form	None added to item 3	None was added to permit a responses if a participant does not have any of the listed conditions.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

2. Schedule of Activities

Table 2.1. Schedule of Activities

Procedure	Pilot Phase: Conducted at 1 US Location[1] Approximately n ≈ 10 to 20		Main Phase: Conducted at Approximately 14 Clinical Sites across US[2] Approximately n ≈ 290	
	Screening	Study Visit	Screening	Study Visit
INTERVIEW BREAK 1: Participant will be ~~given~~ offered a restroom and water break		X		X
OPTIONAL INTERVIEW BREAK 2		X		~~X~~

3.5. Methods to Minimize Risks

Training on both study devices will be provided by Evidera study staff based on the approved IFUs (Eli Lilly IFU 2017; Novo Nordisk IFU 2017). Training for correct sharps handling/disposal is part of the study training, and no cross contamination is expected due to each participant receiving their own device, as well as injecting drug into a practice pad instead of themselves. In order to minimize risk of accidental needle sticks, participants will not recap the semaglutide needle. A sharps container will be available to permit participants to remove the semaglutide needle and dispose of it immediately, rather than recapping the needle for later disposal. Participants will be instructed to place the outer needle cap in the sharps container once it is removed from the device so they do not have the temptation to recap, which was found to be a potential opportunity for accidental needle sticks during the pilot study. Study staff will monitor the participant at all times in the room and intervene should a dangerous situation occur. Participants will be under direct supervision of the study interviewer when handling the devices.

5.5.4. Overview of Study Visit Procedures for the Main Phase

Trained study interviewers will follow the study Interview and Device Training Guide (Appendix 12) to standardize the presentation of devices to participants and ensure that the training is clear and not biased in favor of either device. Based on findings from the pilot phase, the finalized main phase training approach will be conducted with the patients for each device including a detailed demonstration by the interviewer.~~(for example, will include a combination of the following: detailed demonstration by the interviewer, presentation of video demonstrations on tablets or laptops, and/or independent reading of the IFU).~~ The same standardized interview approach will be used for all ~~of~~ the main phase patients. For each device, patients will be given the IFU and asked to read it. Then the interviewer will demonstrate how to use the device. Participants will perform mock injections on a practice pad after being trained in the use of each device. Patients will have access to the IFU during the entire training and injection process. If the participant does not complete one of the critical steps or if the steps are completed out of order, the Interview and Device Training Guide (Appendix 12) provides interviewers instructions for handling these situations.

5.5.4 Overview of Study Visit Procedures for the Main Phase

Once participants have attempted each device training and mock injection(s) on the practice pad, interviewers will complete the Interviewer Recording Sheet to document randomization order and if the patient was able to complete both device trainings (Appendix 15). ~~Next, participants will be offered an optional second break.~~ Participants will then be asked to complete questionnaires to report their preferences between the 2 devices.

5.5.4 Overview of Study Visit Procedures for the Main Phase

Main phase interview will last approximately 60 to 90 minutes including consenting and training in device procedures. The maximum time for all study procedures is 90 minutes as specified in the consent form. All main phase participants will be remunerated a specified amount between $100 and $150 (via Greenphire ClinCard) for their time and travel time to the study interview.

9.1.2.6. Global Preference Item

All participants will complete the Global Preference Item after being trained and using both devices (Appendix 17). Participants will be asked, “Overall, which device do you prefer?” Interviewers will then ask ~~P~~participants ~~will also be asked~~ to explain why they selected their response for Ozempic, Trulicity, or no preference. The interviewer will transcribe the participant’s response using quote~~s~~ation marks to capture the respondent’s exact words. ~~This item.~~ The Global Preference Item was developed specifically for use in this device preference multicenter crossover study. To help participants remember the devices more accurately, colored images of the devices have been inserted into the questionnaire.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Randomized	Participants determined to be eligible and then assigned to one of 2 device order groups (50% will be randomized to use the dulaglutide device first, while the other half will use the semaglutide device first). More details about randomization for this study are provided in Section 7.2.
Evaluable	Participants for whom device preference can be evaluated: Randomized participants who are exposed to both devices (i.e., participant was shown both devices via ~~either video or~~ demonstration, regardless of whether they successfully complete the training) and complete the Global Preference Item.
Withdrawn	Participants who withdraw from the study before being exposed to both devices and completing the Global Preference item. Details on study withdrawal are provided in Section 8.

Appendix 12. Interview and Device Training Guide

~~EVA-23274 Interview and Device Training Guide~~

~~(Will be modified based on findings from the Pilot Phase)~~
~~Updated 12Jul2018~~

~~I. NECESSARY MATERIALS~~

~~11. IFU for Trulicity~~
~~12. IFU for Ozempic~~
~~13. Trulicity Injection Pen~~
~~14. Trulicity Demonstration Pen~~
~~15. Ozempic Injection Pen (the real Ozempic Pen will also be used for demonstrations)~~
~~16. Extra needles for Ozempic~~
~~17. Sharps container (for disposal of Trulicity Devices and Ozempic Needles)~~
~~18. Injection pad~~
~~19. Alcohol wipes~~
~~20. Trash can (for pen cap)~~
~~21. Non-latex gloves~~

~~II. INTERVIEW STEPS~~

~~11. Confirm that site has completed In/Ex form~~
~~12. Administer informed consent~~
~~13. Complete Supplemental Question S1~~
~~14. Randomization with IWRS system to determine which device is first~~
~~15. Explain study to the participant~~
~~16. Training and mock injection with the first device~~
~~17. Complete demographic form~~
~~18. Training and mock injection with the second device.~~

19. Complete Interviewer Recording Sheet
20. Complete questionnaires about device preferences and Supplemental Questions S2 and S3

III. Trulicity Pen

For time-to-train participants, the observer should begin the timer when the training introduction is started. The observer should also complete the TTT Observer Recording Sheet.

A. Device Training

1. Explain the overall training steps and introduce the device to the participant.
2. Open the device box and place the IFU in front of the participant. Explain that the video will follow along with the instructions for use and demonstrate how the device is used.
3. Show the participant the Trulicity training video, which is based on the IFU.
4. If the participant needs additional training, demonstrate the injection process using the demo device. Have the participant follow along with the steps on the IFU.
5. Permit the participant to ask any questions they may have about the device or IFU.
6. Participant performs mock injection into the injection pad while trainer observes and evaluates injection success based on the critical steps listed below.
7. The training will be considered complete when the patient has successfully performed all critical steps listed below and indicated to the trainer that they are finished (for example, by placing the device on the table). For the time-to-train patients, timing will end after successful injection completion at the time patients indicate they are finished.
8. If the participant does not dispose of the device in the sharps container independently, the trainer should instruct the participant on device disposal using the provided sharps container.

B. Checklist of Critical Steps

Critical Steps	First attempt	Second attempt	Third attempt	Fourth attempt	Fifth attempt
1. Take off base cap	☐	☐	☐	☐	☐
2. Place on injection site	☐	☐	☐	☐	☐
3. Unlock device	☐	☐	☐	☐	☐
4. Press button and hold the device in place until the grey plunger is visible. The participant should pause.	☐	☐	☐	☐	☐
5. Remove from injection site	☐	☐	☐	☐	☐

C. Retraining

If the first injection attempt is not successful, the participant should be retrained on the critical steps that they missed or performed incorrectly. The participant will have to repeat all or some of the injection process. If the participant appears to be making an error that could lead to self-harm or prevent successful injection (e.g., trying to inject with the cap on), the trainer should intervene and stop the injection process. The error should be explained to the participant and the participant should be asked to restart the injection process.

IV. Ozempic Pen

For time-to-train participants, the observer should begin the timer when the training introduction is started. The observer should also complete the TTT Observer Recording Sheet.

A. Device Training

1. Explain the overall training steps and introduce the device to the participant.
2. Open the device box and place the IFU in front of the participant. Explain that the video will follow along with the instructions for use and demonstrate how the device is used.
3. Show the participant the Ozempic training video, which is based on the IFU.
4. If the participant needs additional training, demonstrate the injection process using the demo device. Have the participant follow along with the steps on the IFU.
5. Permit the participant to ask any questions they may have about the device or IFU.
6. Participant performs mock injection into the injection pad while trainer observes and evaluates injection success based on the critical steps listed below.
7. The training will be considered complete when the patient has successfully performed all critical steps listed below and indicated to the trainer that they are finished (for example, by placing the device on the table). For the time-to-train patients, timing will end after successful injection completion at the time patients indicate they are finished.
8. If the participant does not dispose of the device in the sharps container independently, the trainer should instruct the participant on device disposal using the provided sharps container.

B. Checklist of Critical Steps

Critical Steps	First attempt	Second attempt	Third attempt	Fourth attempt	Fifth attempt
1. Pull off the pen cap	☐	☐	☐	☐	☐
2. Push the needle straight on to the pen. Turn until it is on tight.	☐	☐	☐	☐	☐

~~3. Pull off the outer needle cap and pull off the inner needle cap~~	☐	☐	☐	☐	☐
~~4. Turn the dose selector until the dose counter shows the flow check symbol~~	☐	☐	☐	☐	☐
~~5. Press and hold the dose button until the dose counter shows 0 and a drop of Ozempic appears at the needle tip~~	☐	☐	☐	☐	☐
~~6. If the drop does not appear on the first attempt, repeat flow check until a drop appears (as needed).~~	☐	☐	☐	☐	☐
~~7. Select your dose. Continue turning the dose selector until the dose counter shows 0.25~~	☐	☐	☐	☐	☐
~~8. Insert the needle in the pad~~	☐	☐	☐	☐	☐
~~9. Press and hold down the dose button until the dose counter shows 0~~	☐	☐	☐	☐	☐
~~10. Slowly count to 6 (operationally: patient pauses after pressing injection button).~~	☐	☐	☐	☐	☐
~~11. Remove the needle from the pad~~	☐	☐	☐	☐	☐
~~12. Remove the needle (capped or uncapped)~~	☐	☐	☐	☐	☐

~~C. Retraining~~

~~If the first injection attempt is not successful, the participant should be retrained on the critical steps that they missed or performed incorrectly. The participant will have to repeat all or some of the injection process. If the participant appears to be making an error that could lead to self-harm or prevent successful injection (e.g., trying to inject with the cap on), the trainer should intervene and stop the injection process. The error should be explained to the participant and the participant should be asked to restart the injection process.~~

Interview Guide

I. MATERIALS

1. IFU for Trulicity
2. IFU for Ozempic
3. Trulicity Injection Pen

4. Trulicity Demonstration Pen
5. Two Ozempic Injection Pens (one for demonstration and one for participant use)
6. Sharps container (for disposal of Trulicity Devices and Ozempic Needles)
7. Injection pad
8. Alcohol wipes
9. Trash can (for pen cap)
10. Non-latex gloves

II. INTERVIEW STEPS

1. Confirm the in/ex form has been completed
2. Informed consent
3. Complete Supplemental Question S1
4. Randomization with IWRS system to determine which device is first
5. Explain study to the participant
6. First Device: Training and Mock Injection
7. Complete demographic form
8. Second Device: Training and Mock Injection
9. Complete Interviewer Recording Sheet
10. Complete questionnaires about device preferences and Supplemental Questions S2 and S3

STEP 1. CONFIRM IN/EX FORM HAS BEEN COMPLETED

- Review the site-completed in/ex form for the participant to confirm eligibility.
- This form should be provided to you by the site, and it should already be completed prior to the interview.

STEP 2. INFORMED CONSENT

- Review the consent form with the participant and confirm comprehension.
- Provide the participant with opportunity to answer questions before signing.
- Ask the participant to sign two copies of the consent form if they wish to participate.
- Countersign the forms and provide a copy to the participant.

STEP 3. COMPLETE SUPPLEMENTAL QUESTION S1

- Ask the participant to independently complete this question: "Please complete this question, and let me know when you are finished."

STEP 4. RANDOMIZATION WITH IWRS SYSTEM

- Complete the randomization process to determine the order of device training for the participant.
- Record the order on the Interviewer Recording Sheet.

STEP 5. EXPLAIN THE STUDY TO THE PARTICIPANT

- "You will be trained to use two devices for injecting medication for type 2 diabetes."
- "For each device, I will walk you through the steps for using each device and demonstrate the steps for you. Then, you will use the device to administer an injection into an injection pad."
- "After you have had a chance to use both devices, I will ask you to complete some questionnaires that ask about your preference between the devices."
- "**Do not inject medication into yourself. You will only be injecting into the injection pad**."
- "Please handle the devices carefully to avoid accidently sticking yourself with the needle. If you appear to be handling the device incorrectly, I will try to correct you so you do not accidently stick yourself with the needle."

STEP 6. FIRST DEVICE TRAINING

Follow the Trulicity Training Guide or the Ozempic Training Guide based on the randomization order for the participant.

STEP 7. DEMOGRAPHIC FORM

"Please complete this form."

STEP 8. SECOND DEVICE TRAINING

Follow the Trulicity Training Guide or the Ozempic Training Guide based on the randomization order for the participant.

STEP 9. COMPLETE INTERVIEWER RECORDING SHEET

The interviewer completes the interviewer recording sheet to document order of device training and completion status.

STEP 10. PARTICIPANT COMPLETED-QUESTIONNAIRES

Instruct the participant to complete questionnaires on device preference and supplemental questions S2 and S3.

Ozempic Training Guide

A. Time to Train

The observer should complete the TTT Observer Recording Sheet.

a. Start of training (i.e., after reading the IFU)

b. The participant picks up the device to start the mock injection.

c. The participant successfully injects the medication into the injection pad and removes the needle/device from the pad.

d. The Ozempic pen is recapped with the pen cap (the inner needle cap and outer needle cap should not be placed back on the pen).

e. The participant has completed the injection and finished asking questions. Participants comments/opinions about the device after completing the injection will not be included unless the participant asks a question.

B. Safety Procedures

If the participant appears to be making an error that could lead to self-harm, the trainer should immediately intervene and stop the injection process.

C. Introduction

Introduce the device and training steps.

- "Now, you will learn to use an injection device."
- "When you feel comfortable with the procedures for using the device, you will use the device to perform a mock injection into the injection pad."
- "You should NOT use this device to inject yourself. You will only be injecting medication into this pad."
- "This is the Ozempic device. This device is used to administer medication once a week, and you would typically use it at home." (*Show the device to the participant.*)

D. Device Training

1. Open the device box and place the IFU in front of the participant.

2. Instruct the participant to "Please read the Instructions for Use and let me know when you are finished. After you are done reading, I will demonstrate all of these steps for you in detail. You can also refer back to this document throughout the interview as much as you want."

3. Demonstrate the injection process using the demo device.

    1. **"The Ozempic** device **is a prefilled dial-a-dose pen**. You can select doses of 0.25 mg or 0.5 mg. You will be selecting 0.25 mg for the injection today."

    2. "The needles for this device are enclosed in the package."

    3. **"Always use a new needle for each injection."**

    4. **Device parts**
        a. "This is the pen cap."

        b. "This is the pen window."

        c. "This is the dose counter and dose pointer."

        d. "This is the dose selector and the dose button."

        e. "When you turn the dose selector, you will see the flow check symbol and the dashed line to guide to your dose (*turn dose selector to show these symbols*). The flow check symbol comes right after the zero."

        f. "The needle has an outer needle cap, inner needle cap, needle, and paper tab."

    5. **Step 1: Prepare your pen with a new needle**
        a. "If you were injecting, you would begin by washing your hands with soap and water. Since you are injecting a pad today, you do not need to wash your hands this time."

        b. "The next step is to **check the name and colored label** of your pen to make sure that it contains Ozempic."

        c. "Then **pull off the cap**."

        d. **"Check that the Ozempic in your pen is clear and colorless**. Look through the pen window. If the Ozempic is cloudy, do not use the pen."

        e. **"Take a new needle**, and tear off the paper tab."

f. **"Push the needle straight on to the pen. Turn until it is on tight."**

g. **"Pull off the outer needle cap**. You can put it in the sharps container."

h. **"Pull off the inner needle cap**, and throw it away."

6. **Step 2: Check the Ozempic flow with each new pen**
   a. "Check the Ozempic flow before your first injection with each new pen."

   b. "Turn the dose selector **until the dose counter shows the flow check symbol**."

   c. "Hold the pen with the needle pointing up. **Press and hold in the dose button** until the dose counter shows 0. The 0 must be lined up with the dose pointer. A drop of Ozempic will appear at the needle tip. The medication may spray out a bit in some cases, so please point the tip away from your face and away from me."

   d. **"If no drop appears**, repeat these flow check steps up to six more times. **Do not use the pen** if a drop of Ozempic still does not appear."

7. **Step 3: Select your dose**
   a. **"Turn the dose selector until the dose counter shows your dose (0.25 mg)**. If you select the wrong dose, you can turn the dose selector forward or backwards to the correct dose."

8. **Step 4. Inject your dose**
   a. "Choose your injection site."

   b. **"Insert the needle into your skin [injection pad]**."

   c. **"Make sure you can see the dose counter**. Do not cover it with your fingers. This could stop the injection."

   d. **"Press and hold down the dose button until the dose counter shows 0**. The 0 must line up with the dose pointer. You may then hear or feel a click."

   e. **"Keep the needle in your skin [injection pad] after** the dose counter has returned to 0 and **count slowly to 6**."

   f. "If the needle is removed earlier, you may see a stream of Ozempic coming from the needle tip. If this happens, the full dose will not be delivered."

   g. **"Remove the needle from your skin [injection pad]**."

9. **Step 5. After your injection**
   a. **"Carefully twist the needle off of the pen.** Since we have a sharps container, please do not put the needle caps back on the needle to avoid needle sticks."

   b. **"Place the needle in a sharps container** right away."

   c. **"Put the pen cap on** your pen after each use to protect Ozempic from light."

4. Permit the participant to ask any questions they may have about the device or IFU.
   - "Do you have any questions about the steps involved in the injection process?"

   - "Do you feel ready to administer the mock injection? Is there anything you would like to review before trying it?"

   - *When the patient is ready:* "I will leave the instructions for use here, and you can refer to them as much as you like while you go through the injection process. Please take all the time you need."

5. Participant performs mock injection into the injection pad while trainer observes and evaluates injection success based on the critical steps listed below.

6. The mock injection will be considered complete when the patient has successfully performed all critical steps listed below and recapped the pen.

7. If the participant is struggling to remove the needle and appears to be putting themselves at risk of an accidental needle stick, the interviewer should volunteer to remove the needle for them.

   - "Would you like me to remove the needle for you?"

   If the interviewer removes the needle, this should be recorded on the Interviewer Recording Sheet.

8. If the participant does not dispose of the needle in the sharps container independently, the trainer should instruct the participant on disposal using the provided sharps container.
   - "Please place the needle in the sharps container."

9. Ask the participant if they have any questions, and answer them. The training is complete when there are no further questions.
   - "Do you have any questions?"

E. Checklist to assist interviewer in tracking critical steps

Critical Steps	First attempt	Second attempt	Third attempt	Fourth attempt	Fifth attempt
1. Pull off the pen cap	☐	☐	☐	☐	☐
2. Push the needle straight on to the pen. Turn until it is on tight.	☐	☐	☐	☐	☐
3. Pull off the outer needle cap and pull off the inner needle cap	☐	☐	☐	☐	☐
4. Turn the dose selector until the dose counter shows the flow check symbol	☐	☐	☐	☐	☐
5. Press and hold the dose button until the dose counter shows 0 and a drop of Ozempic appears at the needle tip	☐	☐	☐	☐	☐
6. 6. If the drop does not appear on the first attempt, repeat flow check until a drop appears (up to 6 times).	☐	☐	☐	☐	☐
7. Select your dose. Continue turning the dose selector until the dose counter shows 0.25	☐	☐	☐	☐	☐
8. Insert the needle in the pad	☐	☐	☐	☐	☐
9. Press and hold down the dose button until the dose counter shows 0	☐	☐	☐	☐	☐
10. Slowly count to 6 (operationally: patient pauses after pressing injection button).	☐	☐	☐	☐	☐
11. 11. Remove the needle from the pad	☐	☐	☐	☐	☐
12. Remove the needle from the pen (capped or uncapped)	☐	☐	☐	☐	☐

F. Retraining

If the critical steps are not performed correctly on the first attempt, the participant should be retrained on critical steps that were missed or performed incorrectly. The participant may have to repeat all or some of the injection process. The error should be explained to the participant and the participant should be asked to make the correction and continue the injection process.

If the participant is making a mistake during the injection, you can call his or her attention to the mistake so that he or she can continue the injection correctly. For example, if the participant is trying to do the flow check without removing the inner cap, tell him or her to remove the cap first. "It looks like the inner cap is still on. Could you remove the inner cap before checking the flow?"

Trulicity Training Guide

A. Time to Train

The observer should complete the TTT Observer Recording Sheet.

a. Start of training (i.e., after reading the IFU)

b. The participant picks up the device to start the mock injection.

c. The participant successfully injects the medication into the injection pad and removes the needle/device from the pad.

d. The Trulicity pen is dropped into the sharps container.

e. The participant has completed the injection and finished asking questions. Participants comments/opinions about the device after completing the injection will not be included unless the participant asks a question.

B. Safety Procedures

If the participant appears to be making an error that could lead to self-harm, the trainer should immediately intervene and stop the injection process.

C. Introduction

Introduce the device and training steps.

- "Now, you will learn to use an injection device."
- "When you feel comfortable with the procedures for using the device, you will use the device to perform a mock injection into the injection pad."
- "You should NOT use this device to inject yourself. You will only be injecting medication into this pad."
- "This is the Trulicity device. This device is used to administer medication once a week, and you would typically use it at home." (*Show the device to the participant.*)

D. Device Training

1. Open the device box and place the IFU in front of the participant.
2. Instruct the participant to "Please read the Instructions for Use and let me know when you are finished. After you are done reading, I will demonstrate all of these steps for you in detail. You can also refer back to this document throughout the interview as much as you want."
3. Demonstrate the injection process using the demo device.

1. Before you get started

a. "Check the pen label to make sure you have the right medicine and it has not expired."

b. "Inspect the pen to make sure it is not damaged"

c. "Inspect the medicine to make sure it is not cloudy or discolored, and it should not have particles in it."

d. "If you were injecting yourself, you would then wash your hands. Since you are injecting a pad today, you do not need to wash your hands this time."

e. "If you were injecting yourself, you would select an injection site. Today, you will inject into this injection pad and NOT into your body."

2. **Device parts**
   a. "At the top of the device, there is a green injection button."

   b. "Beneath that is a lock ring, and an indicator which lines up with the lock and unlock symbols."

   c. "Down here you can see the medicine."

   d. "At the bottom, you can see the clear base and the base cap."

   e. "The needle is inside the device."

3. **Steps for injection**
   a. Uncapping the pen.

      i) "You would first make sure the pen is locked"

      ii) "Then pull the base cap straight off and throw it away in the trash".

      iii) "Do not put the base cap back on – this could damage the needle."

   b. Second, place the base on the injection site and unlock the device
      i) "You would place the clear base flat and firmly against your skin (or in this case, the injection pad)."

      ii) "Unlock by turning the lock ring".

   c. Third, administer the injection

i) "You would press and hold the green injection button. You will hear a loud click."

ii) "When you press the button, the medication is injected."

iii) "Continue to hold the clear base firmly against the pad until you hear a second click. This happens when the needle starts retracting in about 5 – 10 seconds. My demo device may be slower than the actual device you use, so listen closely for the click on your device."

iv) "Then remove the pen from your skin [injection pad]."

v) "You will know the injection is complete when the gray plunger is visible."

d. The final step is disposing of the pen.
   i) "Put your used pen in the sharps disposal container right away after use".

4. Permit the participant to ask any questions they may have about the device or IFU.
   - "Do you have any questions about the steps involved in the injection process?"
   - "Do you feel ready to administer the mock injection? Is there anything you would like to review before trying it?"
   - *When the patient is ready:* "I will leave the instructions for use here, and you can refer to them as much as you like while you go through the injection process. Please take all the time you need."

5. Participant performs mock injection into the injection pad while trainer observes and evaluates injection success based on the critical steps listed below.

6. The mock injection will be considered complete when the patient has successfully performed all critical steps listed below and placed the device in the sharps container.

7. If the participant does not dispose of the device in the sharps container independently, the trainer should instruct the participant on device disposal using the provided sharps container.
   - "Please place the pen in the sharps container."

8. Ask the participant if they have any questions, and answer them. The training is complete when there are no further questions.
   - "Do you have any questions?"

E. Checklist to assist interviewer in tracking critical steps

Critical Steps	First attempt	Second attempt	Third attempt	Fourth attempt	Fifth attempt
1. Take off base cap	☐	☐	☐	☐	☐
2. Place on injection site	☐	☐	☐	☐	☐
3. Unlock device	☐	☐	☐	☐	☐
4. Press button and hold the device in place until the grey plunger is visible. The participant should pause.	☐	☐	☐	☐	☐
5. Remove from injection site	☐	☐	☐	☐	☐

F. Retraining (if necessary)

If the critical steps are not performed correctly on the first attempt, the participant should be retrained on critical steps that were missed or performed incorrectly. The participant may have to repeat all or some of the injection process. The error should be explained to the participant and the participant should be asked to make the correction and continue the injection process.

If the participant is making a mistake during the injection, you can call their attention to the mistake so that he or she can continue the injection correctly. For example, if the participant is trying to press the injection button without unlocking the device, tell the participant to unlock it. "It looks like the device is still locked. Can you unlock it before injecting?"

Appendix 13. Time-to-Train (TTT) Observer Recording Sheet

TTT Observer Recording Sheet
~~(Will be modified based on findings from the Pilot Phase)~~

To be completed by the TTT observer:

1. Ozempic – ☐ ~~Ozempic Device~~ ☐ ~~Trulicity Device~~

1a. Start time of training ~~introduction~~ (i.e., after reading the IFU): 0:00
1b. Start time of participant performing mock injection(s): _____:_____
1c. End time of successfully administered mock injection (i.e., withdrawal of needle/device from injection pad): _____:_____
1d. End time of mock injection procedures (Ozempic = recapping the pen): _____:_____

1e. End time of training, including all procedures and questions: _____:_____
Number of interventions: _____

~~Key Steps of Training For Device Used First~~	~~Check If Not Applicable~~
~~1a. Start time of training introduction: _____:_____:_____ am/pm~~ ~~1b. Finished time of training introduction: _____:_____:_____ am/pm~~	☐
~~1c. Start time of training video: _____:_____:_____ am/pm~~ ~~1d. Finished time of training video: _____:_____:_____ am/pm~~	☐
~~1e. Start time of training and questions after video: _____:_____:_____ am/pm~~ ~~1f. End time of training and questions after training: _____:_____:_____ am/pm~~	☐
~~1g. Start time of participant performing mock injection(s): _____:_____:_____ am/pm~~ ~~1h. End time of participant performing mock injection(s): _____:_____:_____ am/pm~~	☐
~~1i. Start time of answering remaining questions: _____:_____:_____ am/pm~~ ~~1j. End time of answering remaining questions: _____:_____:_____ am/pm~~	☐

2. Trulicity ~~☐ Ozempic Device ☐ Trulicity Device~~

2a. Start time of training ~~introduction~~ (i.e., after reading the IFU): 0:00
2b. Start time of participant performing mock injection(s): _____:_____
2c. End time of successfully administered mock injection (i.e., withdrawal of needle/device from injection pad): _____:_____
2d. End time of mock injection procedures (Trulicity = disposing of the pen in the sharps container): _____:_____
2e. End time of training, including all procedures and questions: _____:_____
Number of interventions: _____

~~Key Steps of Training For Device Used Second~~	~~Check If Not Applicable~~

~~2a. Start time of training introduction: _____:_____:_____ am/pm~~ ~~2b. Finished time of training introduction: _____:_____:_____ am/pm~~	☐
~~2c. Start time of training video: _____:_____:_____ am/pm~~ ~~2d. Finished time of training video: _____:_____:_____ am/pm~~	☐
~~2e. Start time of training and questions after video: _____:_____:_____ am/pm~~ ~~2f. End time of training and questions after training: _____:_____:_____ am/pm~~	☐
~~2g. Start time of participant performing mock injection(s): _____:_____:_____ am/pm~~ ~~2h. End time of participant performing mock injection(s): _____:_____:_____ am/pm~~	☐
~~2i. Start time of answering remaining questions: _____:_____:_____ am/pm~~ ~~2j. End time of answering remaining questions: _____:_____:_____ am/pm~~	☐

Appendix 14. Demographic Form

Demographic Form – Participant Completed

1. What is your age? _____

2. What is your gender? ☐~~1~~ Male ☐~~2~~ Female

3a. What is your ethnic background?

- ☐~~1~~ Hispanic or Latino
- ☐~~2~~ Not Hispanic or Latino
- ☐~~3~~ Not applicable

3b. What is your racial background? (*Please check all that apply*)

- ☐~~1~~ American Indian or Alaska Native
- ☐~~2~~ Asian
- ☐~~3~~ Black or African American
- ☐4 Native Hawaiian or Other Pacific Islander
- ☐~~5~~ White
- ☐~~6~~ Other: _____

4. What is your marital status?

- ☐~~1~~ Single
- ☐~~2~~ Married
- ☐~~3~~ Divorced
- ☐4 Separated

☐5 Widowed
☐6 Other: _____

5. How would you describe your employment status? (Please tick all boxes that apply)
   - ☐ Full-time work
   - ☐ Part-time work
   - ☐ Homemaker/housewife
   - ☐ Student
   - ☐ Unemployed
   - ☐ Stay-at-home parent
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other: _____

7. What is the highest level of education you have completed? (*Please check only one*)
   - ☐1 Elementary/primary school
   - ☐2 Secondary/high school
   - ☐3 Some college
   - ☐4 College degree
   - ☐5 Postgraduate degree
   - ☐6 Other: _____

7. Have you had any of the following health conditions? (Please tick/check all boxes that apply*)*
   - ☐ Angina
   - ☐ Arthritis
   - ☐ Cancer
   - ☐ Chronic obstructive pulmonary disease/emphysema
   - ☐ Heart attack or heart disease
   - ☐ Hypertension
   - ☐ Stroke
   - ☐ Depression
   - ☐ Other mental health conditions (please specify): _____
   - ☐ Other health conditions (please specify): _____
   - ☐ None

Appendix 15. Interviewer Recording Sheet

Interviewer Recording Sheet
~~(May be modified based on findings from the Pilot Phase)~~

To be completed by the interviewer:

1. Device Randomized to First Training: ☐ Ozempic Device ☐ Trulicity Device

☐ Participant **completed training** for first device

☐ Participant completed training, but required interviewer assistance to remove the needle (Ozempic only)

☐ Participant was exposed to this device but **did not complete** training. Please explain below:

_____

_____

_____

_____

_____

2. Device Randomized to Second Training: ☐ Ozempic Device ☐ Trulicity Device

☐ Participant **completes training** for second device

☐ Participant completed training, but required interviewer assistance to remove the needle (Ozempic only)

Appendix 17. Global Preference Item

To be completed by all participants:

3. Overall, which device do you prefer?

☐ **Ozempic** ☐ **Trulicity** ☐ **No Preference**

~~**4. Please explain your preference indicated above in Item 1.**~~

_____

_____

_____

_____

_____

_____

To be completed by interviewer:

5. Please explain your preference indicated in Item 1 on the Global Preference Questionnaire (interviewer to record reasons for device preference provided by the participant, provide quotes with quotations marks and write neatly):

Appendix 22. Clinical Information Form

Clinical Information Form – Site Completed

Instructions: Please complete the following questions for eligible patients.

5. When was the patient diagnosed with T2DM?

If the day and month are unknown, please report the year of diagnosis, and check the box "Day and Month of T2DM diagnosis unknown".

If day is unknown, please report month and year of diagnosis, and check the box "Day of T2DM diagnosis unknown".

MD MD DM DM M Y Y Y Y

☐ Day and Month of T2DM diagnosis unknown

☐ Day of T2DM diagnosis unknown

6. What type 2 diabetes oral medication(s) is the patient currently taking? Please check all that apply.

Oral Class	Oral Medication Options (select all that apply)	Estimated Start Date of Oral T2DM Medication (MMM/YYYY)
Sulfonylureas	☐ chlorpropamide	
	☐ glibenclamide or glyburide	
	☐ glibornuride	
	☐ gliclazide	
	☐ glimepiride	
	☐ glipizide	
	☐ gliquidone	
	☐ glisoxepide	
	☐ glyburide micronized	
	☐ glyclopyramide	
	☐ glycyclamide or tolhexamide	
	☐ metahexamide	
	☐ tolazamide	
	☐ other	
Meglitinides	☐ metformin	
	☐ nateglinide	
	☐ repaglinide	
	☐ other	
DPP-4 Inhibitors	☐ alogliptin benzoate	
	☐ linagliptin	
	☐ saxagliptin	
	☐ sitagliptin	
	☐ vildagliptin	
	☐ other	
SGLT2 Inhibitors	☐ canagliflozin	
	☐ dapagliflozin	

Oral Class	Oral Medication Options (select all that apply)	Estimated Start Date of Oral T2DM Medication (MMM/YYYY)
	☐ empagliflozin	
	☐ other	
Thiazolidinediones (TZDs or Glitazones)	☐ pioglitazone	
	☐ rosiglitazone	
	☐ other	
Alpha-glucosidase inhibitors	☐ acarbose	
	☐ miglitol	
	☐ other	
Combination Pills	☐ alogliptin benzoate/metformin hydrochloride	
	☐ canagliflozin/metformin hydrochloride	
	☐ dapagliflozin/metformin	
	☐ dapagliflozin propanediol/metformin hydrochloride	
	☐ empagliflozin/linagliptin	
	☐ glimepiride/pioglitazone	
	☐ glimepiride/rosiglitazone maleate	
	☐ metformin/empagliflozin	
	☐ metformin/glipizide	
	☐ metformin/glyburide	
	☐ metformin/linagliptin	
	☐ metformin/pioglitazone	
	☐ metformin/repaglinide	
	☐ metformin/rosiglitazone maleate	
	☐ metformin/saxagliptin	

Oral Class	**Oral Medication Options (select all that apply)**	**Estimated Start Date of Oral T2DM Medication** (MMM/YYYY)
	☐ metformin/sitagliptin	
	☐ metformin/vildagliptin	
	☐ simvastatin/sitagliptin phosphate	
	☐ other	

7. Does the patient currently have any of the following comorbidities? Please check all that apply.

☐ Congestive heart failure
☐ Dementia
☐ Chronic Pulmonary Disease
☐ Rheumatologic Disease
☐ Mild Liver Disease
☐ Diabetes with chronic complications
☐ Hemiplegia or paraplegia
☐ Renal disease
☐ Any malignancy, including leukemia and lymphoma
☐ Moderate or severe liver disease
☐ Metastatic solid tumor
☐ AIDS/HIV
☐ None

8. Please record the patient's most recent HbA1c value and the date this value was measured.

Date of HbA1c measurement	**HbA1c value**
~~MM~~DD/~~DD~~MMM/YYYY	___%