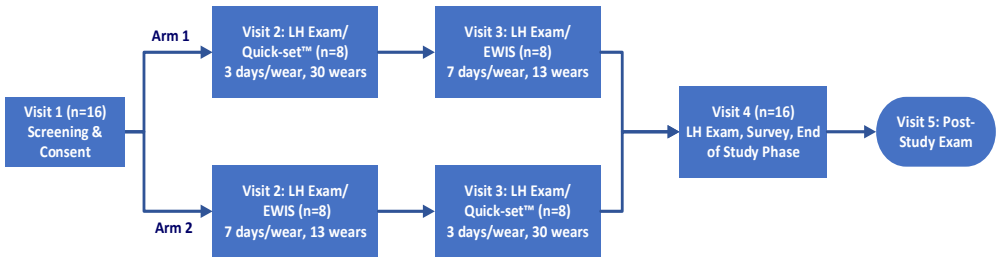
Title:	The Impact of Two Medtronic Infusion Sets (a 3-day Set & a 7-day Set) on Lipohypertrophy (LH) in Persons with Type 1 Diabetes (T1D) and Thought to Have LH
Protocol Number:	1.0
Date of Protocol:	June 9, 2021
Unique Protocol ID (NCT ID not yet assigned)	299_CELazio1_220322

Synopsis

Title	The impact of two Medtronic infusion sets (a 3-day set & a 7-day set) on lipohypertrophy (LH) in persons with Type 1 diabetes (T1D) and thought to have LH.
Study Number	ERP-2021-xxxxx
Devices	***Investigational devices:*** None ***Non-Investigational devices:*** Medtronic Extended Wear Infusion Set (EWIS) (MMT- 433 & MMT-443) Medtronic Quick-set™ Infusion Set (MMT-396 & MMT-398) MiniMed™ 670G Insulin Pump (MMT-1781) Guardian™ Sensor (3) (MMT-7020) Guardian™ Link (3) Transmitter/Recorder Guardian™ Link Charger Tester CareLink™ USB CareLink™ Clinical Therapy Management Bayer Contour ® Next (or Plus) Link 2.4 Meter Bayer Contour ® Next (or Plus) Test Strips Bayer MICROLET®2 Lancing Device (usage is optional) Bayer MICROLET® Lancets (usage is optional) Precision Xtra™* ketone meter or equivalent ketone meter MiniMed™ 3-day Reservoirs (MMT-332A/MMT-326A) MiniMed™ 7-day Reservoirs (MMT-342) AA batteries (Lithium or Alkaline) Insulin Pump accessories, including activity guard, skins kit, belt clip.
Purpose/Objective	The purpose of this study is to assess the impact of two Medtronic infusion sets (a 3-day set & a 7-day set) on lipohypertrophy (LH) in persons with Type 1 diabetes and thought to have LH. This is an observational study using ultrasound (US) and palpation to assess the impact of infusion sets on lipohypertrophy (LH) in an infusion set crossover study.

What is Lipo-hypertrophy?	Lipohypertrophy (LH) occurs in subcutaneous tissue as a result of the lipogenic effect of repeated insulin exposure. The fat cells enlarge and proliferate resulting in thickened tissue, sometimes forming lumps under the skin. LH is associated with suboptimal glycemic control.
Study Design	This is a 1-center, prospective, open label, 2-arm study of ≥16 subjects who use the insulin pumps. These subjects will be using 2 types of infusion sets for two periods of 3 months each type that will serve as an exploratory pilot study to assess the impact of infusion sets on LH (see **Figure 1** for study design). **Figure 1. Study Design**  Each subject will use their own MiniMed™ 670G insulin system as usual. Each subject will be given 2 types of infusion sets to wear and change sets per label use (3 days for Quick-set™ and 7 days for EWIS). Each type of infusion set with the longest length (43" in) will be used for this study. 7-day reservoirs will be used with the Medtronic Extended and 3-day reservoirs will be used with the Quick-set™. The infusion set(s) or reservoir(s) can be replaced independent of each other for Medtronic Extended. The subject will use either Medtronic Extended or Quick-set™ infusion set for consecutive 3 months. During the three-month period, either the right side or the left side of the abdomen will be designated for one or the other infusion set (defined randomly). For each type of infusion set, a coordinate rule for site rotation will be given to have the Set placed in a specified area (left or right side) of anterior abdominal wall (see appendix). For each placement/wear, a daily log will be given to the subject to record time and location for the infusion set placement. Patients will be instructed to recognize areas of clinical apparent LH sites and refrain from inserting in these areas. At home, the subject will be expected to inspect their infusion site on a daily basis and if they observe signs of infection (i.e. erythema > 1 cm in diameter with warmth, pain, and/ or induration) at the infusion site, they should call the investigational center. In addition to the study procedures, the subjects are to continue their standard routine care. In the end of each month, the subject should self-inspected by palpation for LH and record the findings on the daily log. At each study visit, insulin pump and CONTOUR® NEXT LINK 2.4 study meter will be uploaded into CareLink™ Personal For Clinical Research. Also, all the infusion sites will be examined ultrasonically for LH.

	At each visit the clinical team will assess the skin in a systematic using the palpation method procedure and the US evaluation procedure (see appendix). All participants will be asked to give demographic details and medical history. They will be asked to complete a series of questionnaires about their pump routine, diabetes distress, insulin treatment satisfaction and quality of life. All participants will have a baseline glycated hemoglobin (HbA1C) taken. The Total Daily Dose (TDD) will be calculated based on the CareLink™ data.
Sample Size and Investigational Center	The study will be conducted at up to 1 investigational center. It is anticipated that approximately 16 subjects will complete the study. Up to 20 subjects may be screened. As this is an exploratory study - no power assumptions are planned.
Study Duration	The study is anticipated to last up to 12 months.
Inclusion Criteria	Subjects will be considered for enrollment in the study if they meet all of the following criteria: 1. Clinical diagnosis of type 1 diabetes and has been a pump user for at least 10 years 2. Using a MiniMed™ 670G or 640G Insulin pump with Guardian sensor 3. Age 18 to 80 years 4. Hemoglobin A1c level less than or equal to 10% 5. Not currently known to be pregnant, nor planning pregnancy during the study. 6. Willingness to follow the protocol and sign the informed consent 7. Use U100 Humalog (insulin lispro) or U100 NovoRapid/Novolog (insulin aspart)
Exclusion Criteria	Subjects who meet any of the following criteria are not eligible for study participation and **these exclusion criteria are study specific**: 1. Conditions that affect the skin evaluation, e.g. scleroderma or amyloidosis 2. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol. 3. Pregnant or lactating females 4. Subject has Glycosylated hemoglobin (HbA1c) > 10 % at time of screening.
LH Detection by Palpation and Ultrasound	LH identification by palpation and Ultrasound will follow literature method, as described in Gentile et al. SpringerPlus (2016) 5:563; *A suitable palpation technique allows to identify skin lipohypertrophic lesions in insulin-treated people with diabetes*

Study Timeline

Enrolled subjects will have 5 investigational site visits.

Visit 1: Informed Consent and Screening.

Visit 2: Initial LH examination by ultrasound. Device training and Set 1 distribution (13 Medtronic Extended or 30 Quick-set™ infusion sets). A coordinate rule for site rotation will be given to have the Set 1 placed in a specified area (left side or right side) of anterior abdominal wall.

Visit 3: LH examination by ultrasound & Set 2 distribution (13 Medtronic Extended or 30 Quick-set™ infusion sets, different from Visit 1). A coordinate rule for site rotation will be given to have the Set 2 placed in opposite site of anterior abdominal wall used for Set 1.

Visit 4: End of study- 90 ±7 days

Visit 5: 6-month examination

Data Collection	VISIT 1*	VISIT 2*	VISIT 3*	VISIT 4 * End of Study	Visit 5* Post-Study
Visit number	**1**	**2**	**3**	**5**	**6**
Informed consent	X				
Enrollment screening	X				
Demographics	X				
Medical history	X				
Local HbA1c	X			X	X
CareLink Clinical upload		X	X	X	X
Infusion set training		X	X		
Diary collect and review			X	X	X
Collection of study sets			X	X	
Ultrasound examination		X	X	X	X
Pain/comfort/Infusion set questionnaire				X	X
Adverse events and device deficiencies				X	X
Study deviations				X	
*Unscheduled visit may be arranged upon patient observation of site reaction.					

Subject Stopping Rules

1. Retracting of Patients consent
2. Unanticipated Adverse Device Effects (UADEs);
3. Diabetic Ketoacidosis (DKA);
4. Severe hypoglycemia events that result in subject requiring paramedic assistance, an Emergency Room (ER) visit or subjects who experience seizure, coma or death.

Statistical Analysis for Endpoints and Hypothesis	**Primary Endpoint** The primary endpoint is the event rate of lipohypertrophy (LH). The study will be evaluated and summarized, including but not limited to the following: • Self-assessed LH by palpation using a visual analogue scale (VAS) 1 to 10, coupled with clinical examination by a physician if possible • LH (appearance, location, mass, indices of vascularization and distribution) characterized by ultrasound. Standardized semiquantitative description will be used: variations in the thickness of the subcutaneous adipose tissue; single/multiple mass; size/dimension measurement; vascularisation index, flow index and vascularisation flow index; dense, fibrotic; localized, diffused, etc. • The relationship between the observed LH and infusion set type, TDD, glycemic control, HbA1C etc. • Satisfaction of infusion sets using validated questionnaire, e.g. the diabetes treatment satisfaction questionnaire (DTSQ) Statistical analysis may be performed for relationship determination. **Exploratory Endpoints** • Descriptive of site reactions. Pain at the infusion site device related issues (leakage, occlusion in fluid path, etc.). • Descriptive of set failure cases: accidental pull out, adhesive tape issues, infection, erythema and/or induration. • Descriptive of catheter explants: • Gross examination for cannula kinking and crimping. • Pain and comfort questionnaires. • Samples of infusion set, insulin, and sensors will be stored for future analysis including microscopy and chemistry. **Descriptive Endpoints** A number of Descriptive Comparisons of Interest will be made. They include, but are not limited to, the following • Continuous Glucose Monitoring (CGM) data, Time Above Range (TAR): Duration, and Area Under the Curve (AUC) when Sensor Glucose>180, >240, and >250 mg/dL • CGM data, Time Below Range (TBR): Duration, AUC when Sensor Glucose <50, <60, and <70 mg/dL • CGM data, Time in Range (TIR): Duration, AUC when Sensor Glucose > 70 e < 180 mg/dL • Glycemic variability: Standard Deviation (SD), Coefficient of Variation (CV), Mean Amplitude Of Glycemic Excursions (MAGE) • Cohort analysis by age • Cohort analysis by duration of diabetes

APPENDIX

Site rotation of infusion set

The infusion sets should be place on the side of abdomen designed for each one type of set. The subject should choose areas with a reasonable fat pad rotating the infusion site in an organized fashion, using a 4 x 4 pattern starting from right lateral upper quadrant and going from right side to left side and numbering from 1 to 16 for abdomen left side and from 20 to 29 for abdomen left side. A site rotation tool kit of Association of Diabetes Care and Education Specialist will be provided to each patient(https://www.diabeteseducator.org/docs/default-source/living-with-diabetes/tip-sheets/insulin-injections/siterotationtoolkit.pdf).
The subject should place the new infusion set about five cm from the previous one keeping the old infusion set on the body can serve as a good reference point for placing the new infusion set. The following areas must be avoided:

- A five cm area surrounding continuous glucose sensors
- Sites that have existing lipodystrophy
- A five cm area surrounding the navel, skin folds and scars
- Places subject to prolonged restrictive pressure from sitting, sleeping and tight clothing
- Sites that have very little subcutaneous fat tissue

Lipohypertrophy (LH) identification protocol

A validated protocol previously published [*Gentile S. et al. Diabetes Ther (2020) 11:2001–2017*], will be performed to LH identification. It consists of:
1. the inspection of each area of interest using direct and tangential light against a dark background.
2. a palpation technique involving slow circular and vertical fingertip movements followed by repeated horizontal attempts on the same spot. The pressure of the fingers on the skin must be initially gentle and then gradually increase. The pinch manoeuvre will be perform when perceiving a harder skin, to comparing the thickness of the suspected spot to that of surrounding areas. The abdominal examination will be performed with the patient lying supine and standing on afterward; for thigh examination, they will be asked to seat with the legs bent and the feet on the floor.

High-Frequency Skin Ultrasound Scans

High-frequency B-mode skin ultrasound scans (USS) will be performed at all infusion sites by experienced ultrasound scan (US) operator using the linear 15 MHz probe (EsaoteMyLab Alpha, Novarium SRL, Rapallo, Italy) with the patient in the supine position.

The protocol involves measuring the thickness of the subcutaneous fat at each infusion site to determine the presence and size of lipohypertrophic lesions, and to assess their echogenicity, uniformity, acoustic solidity and vascularity. The operator will be performed USS measurements of thickness of subcutaneous fat in millimeters

in the infusion sites by positioning electronic calipers at the skin-fat (excluding skin) and fat–muscle interfaces, without pressing the underlying skin; variations in the thickness of the subcutaneous adipose tissue will be measured and recorded at each visit with respect to time zero. The mean grey value (MG1) of lipohypertrophic sites and the density of regions of normal subcutaneous fat (MG2) will be determined, and the MG1:MG2 ratio calculated. A three-dimensional (3D) Doppler study of blood flow will be also performed in 3D-angio mode, and indices of vascularisation of the lipohypertrophic sites will be measured (vascularisation index, VI; flow index, FI and vascularisation flow index, VFI).

According to US features [*Gentile S. et al. Diabetes Ther (2020) 11:2001–2017*], LH areas will be also identified as:

- hyper-type A: iso-hyperechoic with a prevailing fibrotic component.
- iso-type B: isoechoic associated with small edema-like islands bordered by fibrous strips.
- iso-hypo type C: iso-hypoechoic fiber-free.

US-based grouping depended on the individual prevailing aspect (50% of the entire nodule).