`Comparison of Insulin Degludec U100 with Insulin Glargine U100 for adults with type 1 diabetes travelling across multiple time zones. A pilot study.

INVESTIGATOR-SPONSORED STUDY PROPOSAL
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BACKGROUND AND SIGNIFICANCE

According to the latest estimates published by the International Diabetes Federation, 415 million adults were living with diabetes in 2015 and this number is expected to rise to 642 million (or 1 adult in 10) by 2040 (1). This makes it likely that a good proportion of the 8 million people who board an aircraft each day (www.iata.org) are flying with an established diagnosis of diabetes. In the United States and based on diabetes prevalence data, approximately 17 million leisure and 5.6 million business travelers travel with diabetes and at least a quarter will be using insulin on a daily basis (2).

For insulin treated individuals planning long-haul travel (defined as a flight lasting more than 6hours), consideration needs to be given to every stage of a journey from deciding what to pack, choosing appropriate travel insurance, dealing with airport security, anticipating consequences of late or delayed flights, preparing for the potential impact of flying in a pressurized cabin on the performance of medical devices and choosing a meal on board through to assessing the impact of crossing multiple times zones and jet lag on insulin action and the perception of low blood glucose levels at altitude (3). Once a traveler with diabetes arrives at their destination, it is advisable to plan in the event their diabetes supplies are lost or stolen, as well as dealing with unfamiliar foods, unaccustomed exercise, or even riding roller coasters (4). In one survey more than half of travelers with diabetes reported difficulties in glucose management during their journey compared to the month prior to leaving (5). In general, for insulin-treated individuals around 10% of travelers on short as well as long-haul journeys experienced problems, most commonly hypoglycemia during the journey or in the first 24 hours after arriving at their destination (6). For long-haul travel in particular, there is evidence that most physicians, including diabetes specialists, are uncertain about how to adjust insulin doses for patients who travel across several time zones and some of the information provided is described as “potentially harmful” (7). Furthermore, recent testimony from on-line bloggers and patient forums continues to highlight specific problems related to diabetes and travel (8).

We sought to determine the real-life experiences of individuals traveling long distance (across five or more time-zones) with type 1 diabetes (T1D). Members of the T1D Exchange (n=503) online community (www.myglu.org) completed a 45-question survey about their travel experiences flying long distance (9). The cohort was stratified by duration of T1D and whether or not participants used continuous subcutaneous insulin infusion (CSII) therapy and/or a continuous glucose monitor (CGM). In the last 5 years, 71% of participants had flown long distance. When asked about their perceived ‘‘fear of flying,’’ CSII users (with and without a CGM) reported their primary anxiety was ‘‘losing supplies,’’ while non-CSII users described concerns over ‘‘unstable blood glucose (highs and lows)’’ ($P < 0.05$). In addition, 74% of participants reported more hypoglycemia and/or hyperglycemia while traveling overseas and 9% had avoided international travel altogether because of problems related to diabetes management. Furthermore, 22% of participants had run out of insulin at some point during a trip and 37% reported inadequate attention in current sources of information to the unpredictability of self-management needs while traveling. Especially problematic for

individuals traveling with T1D are a lack of resources adequately addressing: (a) protocols for emergencies while abroad, (b) how to navigate airport security, and (c) managing basal insulin rates when crossing time zones. A strong need exists for easily accessible, free resources for traveling with T1D that is tailored to both device use and duration of the disease

Currently, there is a lack of patient-centered research evaluating the practical and psychosocial aspects of travel and T1D. Few resources offer practical and easy to understand travel guidance to individuals with T1D. Available sources of information include publications targeting physicians and scientific researchers, online articles providing generalized tips (transportation and storage of supplies, suggested immunizations, diet regimens to follow, optimizing insulin dose modification across time zones) and free electronic dosage calculators (10-14). For the most part these articles are well written and offer sound counsel, but many guidelines are overly complicated with medical jargon and complex tables describing insulin dosing adjustments. This poses a problem for both patients and providers looking for simple travel advice (15). Diabetes also contributes to medical emergencies that affect 1 in every 614 flights (16).

On August 6th 2015 we launched www.DiabetesTravel.org, a free on-line resource focusing exclusively on long-haul travel and diabetes. As well as providing information, we have also offered a "travel calculator" to provide guidance on planning changes in the timing and frequency of insulin therapy to aid discussions with diabetes teams caring for individuals with T1D. Since launch almost 25,000 users have logged on with 52% coming from the US (source Google Analytics, accessed 12/15/2017). We have also received multiple, favorable comments on social media, and this has been achieved without marketing the site or the use of search engine optimization techniques.

RATIONALE FOR THE STUDY

The purpose of the proposed study is to compare insulin **Degludec U100** with insulin **Glargine U100** to determine the basal insulin of choice for adults with type 1 diabetes who fly non-stop across multiple time zones. With the introduction of **Degludec** as basal insulin for T1D and the opportunity to vary time of injection between 8 and 40 hours, the use of **Degludec** as a basal insulin may make it easier for both people living with T1D and diabetologists to plan long-haul travel compared to the use of existing basal insulins when crossing multiple time zones (insulin degludec injection) (Label – FDA https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203314s003lbl.pdf. Accessed March 6, 2018.)

SPECIFIC OBJECTIVES

To compare glycemic control end points between **Degludec** U100 versus **Glargine U100** as the basal insulin in a pilot study of adults with type 1 diabetes who are established on multiple daily injections (MDI) of insulin and flying long-haul.

RESEARCH DESIGN AND METHODS

Study Hypothesis: Once daily **Degludec U100** as the basal insulin will provide better glycemic control for people with type 1 diabetes on multiple daily injections who are traveling non-stop across multiple time zones than once daily **Glargine U100**.

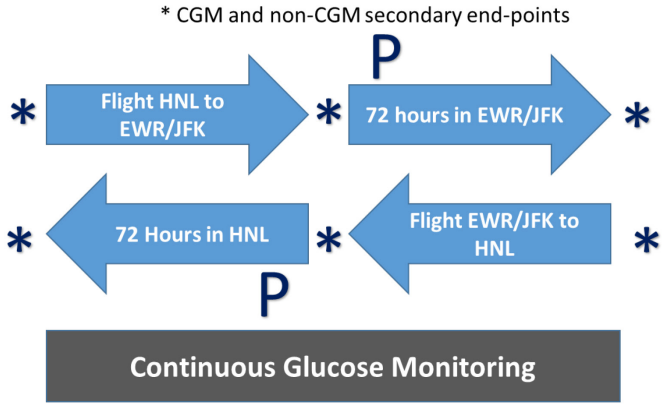
Endpoints:

The **Primary endpoint** will be, using continuous interstitial glucose monitoring (CGM), achieved glycemic control defined as time in range (**70-140 mg/dl**) during the **initial 24 hours local time** (starting within 2 hours after arriving) in Newark, NJ or JFK, NY after flying 9-10 hours West to East (from Honolulu, HI) and after the return journey from Newark to Honolulu (flying East to West) comparing **Glargine U100** versus **DegludecU100** as the basal insulin.

Participants will begin in Honolulu, HI (HNL), fly to Newark (EWR) or New York (JFK) where they will stay for up to 72 hours followed by a return long-haul flight back to Honolulu with up to 72 hours at this destination. This journey will be repeated after a 2 week period when subjects return to their original insulin treatment regimen and then switch to the alternative basal insulin. When traveling east, the day gets shorter, so the basal insulin dose given during travel needs to be adjusted (see below).

Figure 1. Overview of protocol with Primary and Secondary endpoint timelines for assessment. This journey will be undertaken twice - once using Glargine U100 and once using Degludec as the basal insulin.

P = Primary End Point : Time in range (70-140 mg/dl) during the **initial 24 hours local** time (starting within 2 hours after arriving in Newark (EWR)/ New York (JFK) from Honolulu (HNL) and after the return journey from EWR/JFK to HNL).



Secondary CGM End-Points comparing **Glargine U100** and **Degludec** as the basal insulin are based on recent consensus related to reporting of trials for artificial pancreas development (17):

- Time in range (70-180 mg/dl) within the first 24 hours after arriving in HNL and EWR or JFK (starting within 2 hours after arrival).
- For the inflight period of time and for the 72 hours in each destination:
  - Mean ±SD CGM glucose (mg/dl)

    - % CGM time <50 mg/dl
    - % CGM time <60 mg/dl
    - % CGM time <70 mg/dl
    - % CGM time 70–180 mg/dl
    - % CGM time >180 mg/dl
    - % CGM time >250 mg/dl
    - % CGM time >300 mg/dl
    - SD and coefficient of variation of CGM values
- Fasting BG at 0600 local time, using CGM
- Additionally, new CGM BG ranges will be included as consensus guidelines emerge, including but not limited to those from the 2019 Advanced Technologies and Treatments for Diabetes International Consensus on Time in Range (29):
    - % CGM time 54–69 mg/dl
    - % CGM time <54 mg/dl

Secondary non-CGM derived endpoints will be (a) Fear of hypoglycemia (HFS II) (18) and Hypoglycemic Confidence Scale (28), (b) Liverpool Jet-Lag Questionnaire (19), (c) Salivary cortisol and melatonin and (d) Sleep duration and quality and (e) Activity (ActiGraph, LLC, Florida) (20).

STUDY DESIGN

This study will be an open-label, single center, pilot study randomized to either **Glargine** or **Degludec** as the basal insulin, and then a 2 week break, followed by a cross-over to the other insulin. The study will begin in Honolulu (airport code HNL) with each non-stop flight to Newark, NJ (EWR) or New York (JFK) lasting approximately 10 hours with a 5/6 hour time difference between destinations. After up to 72 hours in EWR or JFK, they will return to Honolulu and spend up to 72 hours at that destination.

Subjects will continue to use their regular meal-time fast-acting insulin. Based on our experience with open and closed loop studies in T1D, subjects will have basal insulin optimized using CGM profiles for up to 4 weeks prior to travel (21). One month of CGM use for CGM naïve subjects is also a valid time for familiarity with this glucose monitoring system.

This is a single center pilot study based in the United States for which we are planning to recruit adults with established T1D currently being treated with multiple daily injections of insulin (MDI). Subjects for this trial will consist of individuals based on inclusion and exclusion criteria (see below). The subjects must be willing to participate in the clinical trial as per protocol and randomized to the use of **Glargine** or **Degludec** as their basal insulin with a 2 week break period between insulins and flights.

Potential subjects will be selected from the available subject database at the Sansum Diabetes Research Institute (SDRI). Every effort will be made to establish eligibility of

the participants prior to enrollment. Only participants who meet all eligibility criteria will be enrolled in the study.

We anticipate to screen up to 40 in order to obtain at least 22 evaluable subjects (see below). If an enrolled subject must withdraw or fails to complete the study, the subject will be replaced to ensure at least 25 evaluable subjects. Subjects who have been diagnosed with T1D for at least 1 year and are under current treatment with any basal insulin analogue will be considered for the trial. However, to minimize bias we plan to balance the number of subjects using either **Degludec** or **Glargine** at enrollment. Subject eligibility will be confirmed by study staff during a screening visit. Blood draws will be collected as required to demonstrate study eligibility as noted below.

INCLUSION CRITERIA

1. Males or females ≥18 and ≤65 years of age.
2. Type 1 diabetes mellitus (diagnosed clinically) for ≥12 months.
3. HbA1c <10% within 30 days of being enrolled in the study
4. Current treatment with any basal insulin analogue as the once daily basal insulin given in the evening (22) and no fewer than three injections with rapid acting bolus insulin (e.g. insulin aspart, insulin lispro, or insulin glulisine) as mealtime bolus insulin therapy. Must have been using this treatment for at least one month prior to starting basal optimization.
5. No contraindication to long-haul travel.
6. No recurrent severe hypoglycemia (more than 1 severe hypoglycemic event requiring hospitalization during the last 12 months), or hypoglycemia unawareness as judged by a score of >4 on the Gold score (23), or hospitalization for diabetic ketoacidosis during the previous 6 months.
7. Willing and able to use a continuous glucose monitoring (CGM) device (e.g. Abbott Libre and/or Dexcom G4 or G6 system).
8. Ability to self-manage insulin therapy (verbal confirmation at screening visit) of a changed bolus insulin dose the preceding 2 months prior to screening.
9. Ability and willingness to adhere to the protocol, including performance of self-monitored blood glucose (SMBG) readings and self-adjustment of insulin doses according to protocol.
10. Subject must be willing to perform 8 BG Fingersticks during flights.
11. Subject must be able to read and understand English.
12. In the Investigator's opinion, the subject must be able to follow the instructions provided to him/her by the study staff and perform all study tasks as specified by the protocol.
13. At the time of enrollment subject must be available and willing to travel on the specified dates set up per protocol.
14. Subject must be willing and able to provide written signed and dated informed consent.

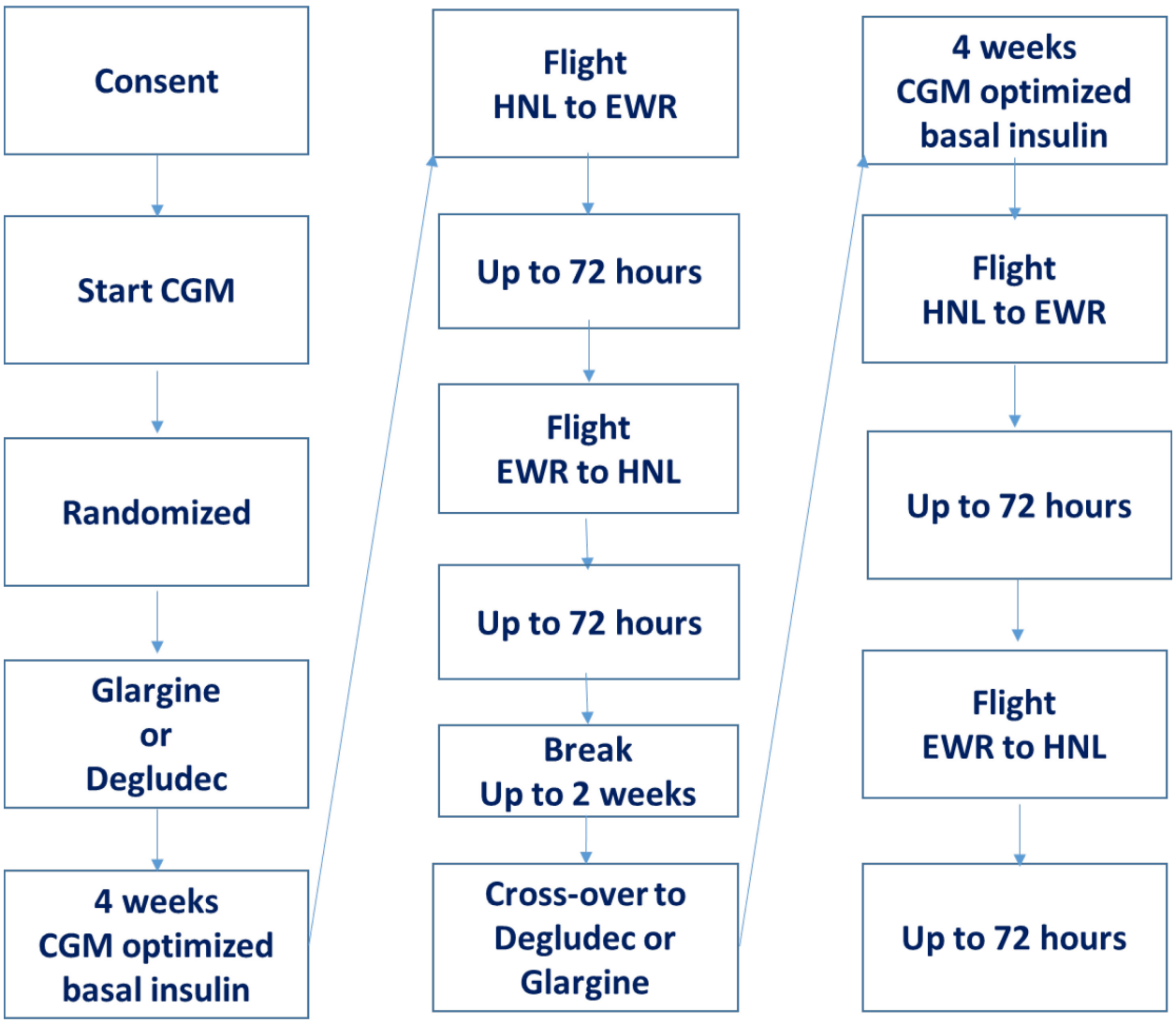
EXCLUSION CRITERIA

1. Current use of an insulin pump.
2. Use within the last 3 months prior to enrollment visit 1 of any glucose-lowering drug other than insulin.
3. Initiation or significant change of any systemic treatment which, in the investigator's opinion, could interfere with glucose metabolism, such as systemic corticosteroids, beta-blockers or monoamine oxidase inhibitors (inhaled corticosteroids allowed).
4. Proliferative retinopathy or maculopathy requiring treatment, according to the investigator.
5. Pregnancy, breast-feeding, the intention of becoming pregnant or not using adequate contraceptive measures.
6. Any clinically significant disease or disorder, which in the investigator's opinion could interfere with the results of the trial.
7. Mental incapacity, psychiatric disorder, unwillingness or language barriers precluding adequate understanding or cooperation, including subjects not able to read or write, and known or suspected abuse of alcohol, narcotics, or illicit drugs.
8. Known or suspected allergy to any of the trial products or related products.
9. Receipt of any investigational drug or participation in other trials within 1 month prior to Visit 1.
10. Use of melatonin or sleeping aids for sleep during the travel portion of the study.
11. Subject is currently participating in another clinical trial.
12. Subject is unsuitable for participation due to any other cause as determined by the Investigator.

WITHDRAWAL CRITERIA

Pregnancy or intention of becoming pregnant
Unable to participate in the flights
Unable to wear the continuous glucose monitoring device
New onset of serious inter-current illness as assessed by the investigator
Subjects will be replaced if they withdraw or become ineligible by the research staff from the database of eligible participants.

SUMMARY PROTOCOL



*East coast city can be EWR (Newark) or JFK (John F. Kennedy)

Randomization will be to begin with either **Glargine or Degludec**. Subsequently participants will switch basal insulin (i.e. from **Glargine** to **Degludec** or from **Degludec** to **Glargine**). The direction of travel will be the same direction each time.

OVERVIEW OF VISIT PROCEDURES

Screen	Visit #1	Visit #2	Visit #3	Visit #4	Visit #5	Visit #6	Visit #7
SDRI	SDRI	SDRI or Phone	SDRI or Phone	**Travel West to East**	EWR/JFK post-flight	**Travel East to West**	HNL Post-Flight
Consent	Randomize	Optimize Basal	Optimize Basal Completion	**HNL to EWR/JFK**	Primary End Point Data Collection	**EWR/JFK to HNL**	Primary End Point Data Collection
	Time = 0	Wk 2 ±3 days	Wk 2-Wk 4 ±3 days	Wk 4 ±7 days	Up to 72 hours	Wk 5 ±3 days	Up to 72 hours
Break	**Visit #8**	**Visit #9**	**Visit #10**	**Visit #11**	**Visit #12**	**Visit #13**	**Visit #14**
	SDRI	SDRI or Phone	SDRI or Phone	**Travel West to East**	EWR/JFK post-flight	**Travel East to West**	HNL post-flight
2 weeks	Cross-over Basal insulin	Optimize Basal	Optimize Basal Completion	**HNL to EWR/JFK**	Primary End Point Data Collection	**EWR/JFK to HNL**	Primary End Point Data Collection
	Wk 8 ±3 days	Wk 10 ±3 days	Wk 10-Wk 12 ±3 days	Wk 12 ±7 days	Up to 72 hours	Wk 13 ±3 days	Up to 72 hours

***East coast city can be EWR (Newark) or JFK (John F. Kennedy)**

Screening Visit: Subjects that meet the eligibility criteria and have signed the informed consent will continue to the screening visit which will be performed at SDRI (www.sansum.org). The following screening assessments will be completed at baseline (pre-randomization):

- Signed and dated informed consent
- HbA_{1c} assessment either via fingerstick and DCA2000 or equivalent NGSP-certified point-of-care method, or by local laboratory
- Inclusion and exclusion criteria
- Demographics (date of birth, gender, race and ethnicity)
- Medical history
- Substance use history (drinking, smoking, and drug habits)
- Concomitant medications
- Physical examination
- Weight and height
- Vital signs will be tested including oral temperature, blood pressure and pulse
- Urine pregnancy test for all premenopausal women who are not surgically sterile
- Blood draw for routine blood count, HbA1c, and chemistry panel (values within 3 months prior to enrollment acceptable).
- Hypoglycemia unawareness Gold score (23).
- Fear of hypoglycemia scale (HFS II) (18).
- Hypoglycemic Confidence Scale (28).

Subject randomization - Visit #1. Subjects who meet all eligibility criteria, have signed the informed consent and completed all screening assessments will continue to randomization. Screening and Visit #1 may occur on the same day. A subject will be

considered enrolled in the study after signing the informed consent.. After the study team confirms enrollment, the subject will be assigned a unique subject identification number which will be used to identify the subject throughout the study and will be used for all source documents., At this visit travel plans will be also discussed and booked including ground transportation, flights, hotels and meals.

If for any reason a subject is determined to no longer be eligible for the study after enrollment but prior to the start of the travel phase of the study, the subject will be considered ineligible to continue and will be exited from the study. No additional study assessments will be required to be completed. The reason for study exit will be clearly documented on the corresponding (eCRF). If an enrolled subject must withdraw or fails to complete the study, the subject will be replaced to ensure at least 25 evaluable subjects.

Randomization - Visit #1. In Visit 1, subjects will be randomized to either starting Degludec or Glargine insulin and begin using this insulin according to the label insert and full prescribing information (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203314lbl.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021081s034lbl.pdf). For the purpose of basal insulin optimization we will use CGM data. Subjects who do not currently use CGM will be fitted with a blinded CGM system, the Abbott FreeStyle Libre Pro (Abbott Laboratories, Abbott Park, IL). Subjects who are current CGM users may continue to use their personal CGM systems for the duration of the study. When necessary, clinical study staff will train subjects on inserting and using the study CGM devices. The investigator will use clinical judgment to confirm that subjects are suitably trained on the safe use of CGMs. Subjects will also be given a study glucometer and strips. Study staff will ensure that the study meters and strips pass quality control testing and the subject is adequately trained on the use of the study meters as per the manufacturer's instructions.

Visits for Basal Optimization – Visits #2 and #3. Once the randomization phase has been initiated, the subject will be sent home and CGM data collection will be ongoing for the purpose of basal and meal-time insulin optimization. Over the next (up to 4) weeks clinical staff will review the dose of basal insulin and make necessary adjustments based on the CGM values at least once a week. Subjects will perform up to 4 fingerstick (FS) blood glucose (BG) measurements with the study meter. The investigator will use clinical judgment to adjust the basal rate, insulin to carbohydrate ratio, and correction factor to ensure subject safety prior to continuing the study. The next visits for basal optimization visits may be conducted remotely via telephone at the subject's preference and investigator's discretion. If any visits are planned to be conducted via telephone, the subject will need to be able to upload their CGM data for the investigator to review remotely. At each visit the investigator will re-assess glycemic control. If the investigator determines that it is unsafe for the subject to continue into the travel phase of the study, the subject will not be allowed to continue in the study, and the reason for study exit will be documented on the corresponding source document.

Travel to Newark (EWR) or New York (JFK) from Honolulu (HNL) (Visit #4), up to 72 hours in Newark or New York (Visit #5), return flight from EWR (or JFK) to HNL (visit #6) and 48 hours in Honolulu (visit #7). Subjects originating in Santa Barbara will travel to Honolulu and spend up to 2 days adjusting. At this point subjects will begin their trip to the New York area. Subjects will base their travel plans at this stage according to routine advice from their clinicians and from **www.diabetestravel.org** . During travel U100 Glargine and Degludec and rapid acting insulin will be maintained in cool storage (36°F – 46°F [2°C – 8°C]) until first use using a proprietary travel storage pack (e.g. Frio Cooling Pack). Once open for use insulins can be used for up to 28 days. During this time they can be safely kept at room temperature up to 86°F (30°C). The sponsor-investigator will ensure the availability of proper storage conditions. During each flight, blood glucose meters and strips and continuous glucose monitoring devices will be taken in hand luggage. All doses of insulin (basal and rapid acting) and time of insulin injections will be recorded in the subject's travel diary as well as sleep and meals. Subjects will perform at least 8 FS BGs during the flight. Subjects who regularly use CGMs may continue their personal CGM systems.

For each flight the relevant basal insulin will be adjusted as described below. The following secondary end-point measurements will be taken starting immediately before a flight, during the flight, immediately after the flight, and after 48 hours at the destination and immediately before the beginning of each flight:

Salivary cortisol and melatonin
Liverpool Jet-Lag Questionnaire.
Sleep and Activity (ActiGraph wGT3X-BT activity monitor) (ActiGraph, Pensacola, FL)
Interstitial glucose (CGM) Abbott FreeStyle Libre Pro.
Fingerstick blood sugar readings, approximately 8 times a day

Crossover. The return to home will be followed by a 2 week period where the subject will return to their original insulin regimen and recover from long-haul travel. Study insulin will not be provided during this time.

Visits #8 to #14. After 2 weeks, subjects will start the alternative basal insulin (**Glargine U100** to **Degludec** or **Degludec** to **Glargine U100**) and the protocol outlined above repeated with the same direction of travel on the new basal insulin (**Figure 3**). The above measurements will be repeated as before.

Visit #15 will be a final visit to return equipment and complete documentation. At time of study completion, the corresponding source document will be completed with the date of study exit. Any new or ongoing adverse events will also be documented. A summary letter will be provided for each subject to inform their usual health care provider.

BASAL INSULIN ADJUSTMENTS FOR TRAVEL

For subjects taking long acting basal insulin by injection, travel requires a 4% adjustment to the insulin dose for each time zone traversed (1 hour is 4% of the 24 hour day) (24). To avoid any confounding from the direction of travel, both journeys will be identical for each basal insulin, i.e. beginning in Honolulu. With **Degludec** as the basal insulin, subjects will take this the next day after arriving at their destination taking into consideration the change in time at the destination. As shown in clinical trials in T1 and T2 diabetes, **Degludec** allows for flexibility in the timing of dose administration provided a minimum of 8 h and maximum of 40 hours between injections is ensured (www.ncbi.nlm.nih.gov/pubmed/23393185).

With **Glargine** as the basal insulin, subjects will adjust their basal insulin based on discussion with their specialist diabetes team and with information provided at www.DiabetesTravel.org.

Westward travel from Newark (EWR)/or New York (JFK) to Honolulu (HNL)

This example uses a current dose of **Glargine** 20 units at 8 PM. The flight departs at 10 AM Eastern Standard Time (EST) and arrives at 3 PM the same day local (Honolulu time -HST). Total travel time is 11 hours.

Using the Westward Travel Algorithm (Appendix 1), information on the starting time at departure is recorded along with the last time **Glargine** should be given - 20 units at 8 PM the prior evening. As a rule, if **Glargine** is due during a flight, only half the usual dose (10 units) should be taken.

The subject's watch/clock should still be on departure time (EST) and the half of the normal dose (10 units) is given at 8 PM EST. Immediately after this, the watch/clock should be reset to the destination time. Upon landing in Honolulu, the day is now 'longer' despite 11 hours having passed, as it is 3 PM HST. Since only half the basal insulin was given earlier in the day, the subject should give the remaining 50% dose (10 units) at 8 PM HST after landing in Hawaii. The next night, the normal insulin dose (20 units) is given at 8PM HST at the new location. By giving half the dose at 2 different times, the **Glargine** dose is extended out to cover the longer day to prevent hypoglycemia. Use of a time zone map (http://www.worldtimezone.com/wtz-pacific24.php) can help to determine how many time zones are traversed.

Eastward travel from Honolulu (HNL) to Newark (EWR)/or New York (JFK)

This example uses a current dose of **Glargine** 20 units at 8 PM. The flight departs at 3 PM HST from Honolulu and arrives at 7 AM EST in Newark the next day. Total travel time is 10 hours. When traveling east, the day gets shorter, so the basal insulin dose given during travel can be adjusted one time using the formula (25) (Appendix 2):

$$Travel\,Dose = Normal\,Dose \times \left(0.9 - \frac{\#of\ Time\ Zones\ Crossed}{Hours\ Between\ Basal\ Insulin\ Doses}\right)$$

For this journey only a single dosage reduction is needed. After the reduced travel dose is given, the subject should resume their normal dosing. For other journeys the number of time zones to be crossed can be found at http://www.timeanddate.com/time/map/.

Here the normal dose (20 units) of **Glargine** is given at 8 PM local time the evening before departure. During the flight at 8 PM HST, 13 units of **Glargine** are given per the formula. After this dose is given, the subject needs to change his/her watch to EST. The next full dose of **Glargine** is due 8 PM EST after arrival, which turns out to be 18 hours after the last dose. This reduced time between doses is why less **Glargine** is given on the flight.

During each flight subjects will be provided with prepared food containing 15g snacks to be eaten every 3 hours until the appropriate time for a main meal at the destination. These snacks and all meals at each destination will be logged. Larger meals will be covered using the subject's usual insulin: carbohydrate ratio and correction factor relevant to the carbohydrate content of the meal. If the subject's glucose falls outside of the required ranges during this time period, the CGM sensor will alert and prompt the subject to perform a confirmatory finger stick. If the BG value is confirmed to be outside of the acceptable range, the subject will self-treat according to usual practice, printed information and with the help of study staff traveling with them.

Assessments for Safety: As both **Degludec** and **Glargine** are approved for use for type 1 diabetes in the United States no additional safety requirements are required beyond usual clinical care. All subjects will be provided with oral glucose for the prevention of hypoglycaemia. In addition, subjects may have an experienced staff person with them during travel and will be in contact with SDRI physicians for any advice or problems that may arise.

STATISTICAL CONSIDERATIONS

Sample Size Calculation and statistical analyses

The study will have an open label, randomised cross-over design. Randomisation will be for basal insulin alone. This is a pilot study as no previous studies have been performed comparing basal insulins during long-haul travel. Given the novelty and practical relevance of the study and our recent information about the challenges face by individuals with T1D undertaking travel (see above) we believe that this project will have a very high chance of publication in a high impact peer-reviewed journal.

The aim is to compare the impact of long-haul travel on glycemic control (CGM derived data for time in range (**70-140 mg/dl**) as the primary end point with the assessment during the **initial 24 hours** after arriving at EWR or JFK and HNL (starting within 2 hours after arrival) comparing **Glargine U100** versus **Degludec U100** as the basal insulin.

Primary Endpoint: time in **70 to 140 mg/dl** after a long-haul flight from HNL to EWR or JFK and from EWR or JFK to HNL during the **initial 24 hours** after arriving at EWR or JFK and HNL (starting within 2 hours after arrival).

Secondary CGM End-Points comparing **Glargine** and **Degludec** as the basal insulin):

- Time in range (70-180 mg/dl) within the first 24 hours after arriving in HNL and EWR or JFK (starting within 2 hours after arrival).
- Mean $\pm$SD CGM glucose (mg/dl)
- % CGM time <50 mg/dl
- % CGM time <60 mg/dl
- % CGM time <70 mg/dl
- % CGM time 70–180 mg/dl
- % CGM time >180 mg/dl
- % CGM time >250 mg/dl
- % CGM time >300 mg/dl
- SD and coefficient of variation of CGM values
- Fasting BG at 0600 local time, using CGM
- Additionally, new CGM BG ranges will be included as consensus guidelines emerge, including but not limited to those from the 2019 Advanced Technologies and Treatments for Diabetes International Consensus on Time in Range (29):
    - % CGM time 54–69 mg/dl
    - % CGM time <54 mg/dl

Comparisons will be made for

- Total travel
- Total East to West travel and West to East travel
- 24 hours prior to each flight
- During each flight (total time, from take-off to meal and from meal to landing)
- 24, 48 and 72 hours at the destination

In addition the secondary end–points will be compared for **Glargine** and **Degludec** for specific time blocks to assess the contribution from each basal insulin:

A. Between 2200 and 0700 hours the night before each flight
B. Between 2200 and 0700 hours for Days 2 and 3 at each destination

For the purpose of our primary outcome data CGM data will primarily be obtained from the Abbott FreeStyle Libre Pro system, but in the case of missing data, we will also evaluate any secondary personal CGM data.

Sample size for this pilot study is based on recent data indicating that individuals with type 1 diabetes spend approximately 669$\pm$208 minutes between 70-180 mg/dl (26). With the criterion for significance set at 0.05, and using a paired t-test analysis, a sample size of 22 subjects will achieve a power of at least 80% to detect a difference of 10% between basal insulins assuming the standard deviation of the difference is $\leq$106 minutes (Table 1). Although Battelino et al (26) reported the standard deviation of the target measurement, it did not report the standard deviation of the difference in the

measurements. Since this is unknown, yet needed for the power calculation, an estimate was derived using the two treatment groups reported by the Battelino et al (26) using Altman (27). This derivation yielded a value of 25.7. It is acknowledged that the two treatment groups reported by Battelino et al (26) are different than those investigated in this protocol (and the groups were independent rather than paired), but since similarities exist the derived estimate is sufficient for preliminary power calculations. Table 1 reports that when the standard deviation of the difference is 25, this investigation will have over 99% power to detect a difference between the two insulin groups. Since 25 is a low estimate, Table 1 also reports standard deviation estimates up to 110, and reports that >80% power is achieved up to 106 but <80% when the standard deviation of the difference is >106. Assuming that the standard deviation of the difference in this investigation will be $\leq$106 minutes is justified given that the value of this standard deviation in a previous study (26) is 25.7 which is well below the 106 threshold. In anticipation of potential drop-outs 25 subjects will be recruited.

Table 1: Power obtained under a range of various assumptions for the Standard Deviation of the Difference

Alpha	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sample Size	22	22	22	22	22	22	22
Effect Size	2.680	0.893	0.670	0.638	0.632	0.626	0.609
Mean Difference	67	67	67	67	67	67	67
SD of Difference	25	75	100	105	106	107	110
Power	>99%	97.89	84.99	81.42	80.69	79.96	77.76

Comparisons will be made using Student's paired *t*-tests (two-sided) for normative and log-transformed data, Wilcoxon signed rank testing for non-parametric data, and N1 chi-square tests for proportions (30). Data will be expressed wherever possible as mean difference with 95% confidence limits for the difference or as mean $\pm$ standard error or deviation for the difference. For non-parametric data, these will be presented as median differences with inter-quartile ranges. All data will be analysed on an intention to treat basis. No interim analysis is anticipated. Furthermore, to gain as much information as possible from this pilot study, all hypotheses will be tested at 0.05 and no adjustments for multiplicity will be made.

DATA HANDLING AND RECORD KEEPING

All records and data will be held by staff employed by SDRI which has a long and established track record of exemplary recruitment and execution of clinical research studies with varying degrees of complexity. Staff are experienced and trained in HIPAA regulations and ICH GCP guidelines. All staff have signed agreements related to all appropriate regulatory and legal requirements and oversight is provided by a dedicated Objectivity and Integrity in Science Committee consisting of staff and independent members.

This trial will utilize Source documents to collect subject data.. The research team will be responsible for the accuracy and completeness of data reported. The investigator also agrees to maintain accurate source documentation as part of the subject's medical records. These source documents may include chart notes, laboratory reports, images, etc.

Subject Identifiers

All data used in the analysis and reporting of the study will be without identifiable reference to the subject. Only the unique subject number will be used to identify subject data submitted to the sponsor, and only the investigating site will be able to link the unique subject ID to the subject's name. All records and data will be held by staff employed by the Institute. SDRI has a long and established track record of exemplary recruitment and execution of clinical research studies with varying degrees of complexity. Staff are experienced and trained in HIPPA regulations and ICH GCP guidelines. All staff have signed agreements related to all appropriate regulatory and legal requirements and oversight is provided by a dedicated Objectivity and Integrity in Science Committee consisting of staff and independent members.

Study Record Retention

Investigators will maintain all study-related documentation for a period of fourteen (14) years following completion of the study, or as per the local regulatory authority's guidelines and practices, whichever is longer.

ETHICS

Ethical Conduct of the Study

The investigator agrees that the study will be conducted according to the applicable FDA regulations (21CFR 812, 56, 54, 50), ISO 14155: 2011 and the principles of the World Medical Association Declaration of Helsinki 2008. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. As the investigator of this clinical trial, the Institute has the overall responsibility for the conduct of the study, including assurance that the study meets the requirements of the appropriate regulatory bodies. In this study, the investigator will have certain direct responsibilities and may delegate certain study tasks to the clinical study staff.

Institutional Review Board (IRB)

Federal regulations, ISO 14155 and 21 CFR 812 require that approval be obtained from an IRB prior to participation of subjects in research studies. This study will require approval by the QuorumIRB and will be undertaken in accordance with the Declaration of Helsinki. Prior to subject enrolment, a signed copy of the IRB approval letter will be submitted to the sponsor. In addition, the protocol, informed consent, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to the subject will be approved by the IRB. Documentation of all IRB approvals will be maintained by the Institute and will be available for review by the Sponsor or its designee. All IRB approvals will be signed by the IRB chairperson or designee and we will identify the IRB by name and address, the clinical protocol by title and/or protocol number, and the date approval was granted.

The Investigator will be responsible for submitting and obtaining initial and continuing review of the trial at intervals not exceeding 1 year or as otherwise directed by the IRB. Sansum Diabetes Research Institute will supply Novo Nordisk or its designee written documentation of continued review of the study.

Informed consent

Subjects that appear to meet the eligibility criteria will be consented for participation in the trial. The subject will be asked to sign an informed consent form (ICF) prior to performance of any study-specific procedures. The ICF will have prior approval from the Quorum IRB.

STUDY DRUGS AND MATERIALS

U100 Insulin Glargine is manufactured by Sanofi and approved for use for type 1 diabetes by the United States Food and Drug Administration Packaging, Storage and Prescribing information is available at http://products.sanofi.us/lantus/lantus.html.

Degludec U100 is manufactured by Novo Nordisk and prescribing information is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203314lbl.pdf

Abbott FreeStyle Libre Pro is a blinded CGM system manufactured by Abbott Laboratories, Abbott Park, IL. Information is available at: https://provider.myfreestyle.com/freestyle-libre-pro-product.html

Storage and Drug Accountability of Study Medication(s)

During travel **Glargine** and **Degludec** will be maintained in cool storage (36°F – 46°F [2°C – 8°C]) until first use using a proprietary travel storage pack (e.g. Frio Cooling Pack). Once open for use both insulins can be used for up to 28 days. During this time they can be safely kept at room temperature up to 86°F (30°C). The sponsor-investigator will ensure the availability of proper storage conditions. Also and during each flight, blood glucose meters and strips and continuous glucose monitoring devices will be taken in hand luggage. The investigator/study team will ensure the availability of proper storage conditions

Auxiliary Supply

All supplies will be purchased by the Institute. These include

- Blood glucose meters and strips for the duration of the study
- Insulin, pens and/or syringes based on participant preference
- Dexcom G4 or G6 and Abbott FreeStyle Libre CGM systems for the duration of the study
- Snacks for travel
- Flight, accommodation and meal expenses – these will be arranged by research staff

RANDOMIZATION AND BLINDING

The study is open label so no blinding is required. At randomisation the subjects will be randomised to **Degludec** or **Glargine** as their basal insulin with the direction of travel identical for both basal insulin periods. Randomization will be performed using a computer generated sequence system. There will be a 2 week wash-out period between each set of trips.

CONCOMITANT ILLNESSES AND MEDICATIONS

Definitions:
Concomitant illness is defined as any illness that is present at the start of the trial *(i.e. at the first visit).* Concomitant medication are any medications (including over-the-counter) other than **Degludec** or **Glargine** that are taken during the trial. At the screening visit the research team will base inclusion or exclusion of each subject according the criteria listed above. Details of all concomitant illnesses and medication will be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication will be recorded at each visit. The information collected for each concomitant medication includes, at a minimum, start date, stop date or continuing, and indication. For each concomitant illness, date of onset, date of resolution or continuing, at a minimum, will be recorded.

ADVERSE EVENTS

An **adverse event (AE)** is defined as any untoward medical occurrence in a patient or clinical investigation subject administered/using a Product that affect the risk/benefit ratio of the study; the rights, safety, or welfare of the participants or others; or the integrity of data of the study. An Adverse Event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a Product, whether or not considered related to the Product. This includes events reported from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures

Serious Adverse Drug Reaction (SADR):
An adverse drug reaction (ADR) is an adverse event (AE) for which a causal relationship to the trial product is at least possible i.e. causal relationship is conceivable and cannot be

dismissed. Serious adverse reaction (SAR): Adverse event which fulfils both the criteria for a Serious Adverse Event and the criteria for an Adverse Reaction.

Serious Adverse Events

A serious adverse event (SAE) is defined as any event that results in the following:

- Death
- A life-threatening* experience
- In-patient hospitalisation or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening*, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Suspicion of transmission of infectious agents

*The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

Adverse Event Reporting

The sponsor-investigator will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification (e.g. initials, sex, age)
3. Event (preferably a diagnosis)
4. Trial Drug
5. Reporter identification (e.g. Name, or initials)
6. Causality
7. Outcome

All adverse events will be reported by the investigator and reviewed by Novo Nordisk in compliance with applicable regulations. Adverse events may be volunteered by subjects, elicited by the investigator or designee, or collected via observation by the investigator.

All AEs will be assessed by the investigator who will determine whether or not the event is related to the study procedures or related to the study device, and whether or not the event meets serious criteria. If it is determined that an AE has occurred, the investigator will be responsible for reporting of all adverse events, including serious adverse events (SAE) and serious adverse drug reactions (SADRs), to the competent authority and independent ethics committee/institutional review boards based upon federal regulations and local/IRB policies.

Adverse events will be assessed on an ongoing basis throughout the study. Adverse event reporting will begin at the start time of the study (i.e., insertion of the CGM sensor during Visit #1) and continue through until subject participation has ended (i.e., either time of the post-discharge telephone follow- up, or time of study exit if the subject was

discontinued early from the study). All adverse events will be followed until resolution, or until the AE has stabilized, or until the study has been completed.

Pre-existing medical conditions or symptoms observed prior to the start time of the study will not be recorded as an AE and will be collected in the subject's medical history. In the event there is a change (i.e., worsening) in the pre-existing medical condition or symptoms after the start of the open loop phase, then an AE will be reported. Typical events such as a mild cold, stomach flu, headache, etc, that are self-limiting and do not meet any aforementioned reporting requirements, will not be reported to the IRB.

Serious Adverse Event Reporting

All SAEs and SADRs will be reported to Novo Nordisk at the same time such events are reported to regulatory authorities or within 15 days from the sponsor-investigator becoming aware of such adverse events, whichever comes first.. All events will be documented on the corresponding eCRF. SDRI will also be responsible for submitting relevant source documentation for the SAE. If the subject is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary will also be included with the SAE source documentation. In case of death, the investigator will make every effort to obtain a copy of the death certificate to submit to Novo Nordisk. When submitting copies of source documentation, all subject identifying information will be redacted and only the unique subject number will be used to label the forms for identification purposes.

Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator. All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the subject to be stable.

For any event where there is suspicion that the study device is involved, the investigator will return the device to Novo Nordisk for evaluation. The investigator will provide procedures for cleaning and preparation of contaminated product as well as shipping materials for the return of used and potentially biohazardous materials.

MANAGEMENT OF HYPOGLYCEMIA

Fast acting oral carbohydrates will be used to treat hypoglycaemia. Staff will have Glucagon available as needed for the treatment of severe hypoglycemia. All treatment for hypoglycemia will be recorded on study forms.

A SMBG with the glucose meter should be tested anytime there is:

- A low threshold alert (set at 70 mg/dL) on the CGM
- Anytime the participant has symptoms of hypoglycemia
- Anytime staff has concern about the potential for hypoglycemia
- Following treatment for hypoglycemia as indicated

Hypoglycemia/Hyperglycemia Event Reporting

For the purpose of this protocol, mild symptoms of hypoglycemia and hyperglycemia (i.e., clinically non-significant) or blood glucose values out of the normal range (whether or not they resulted in delayed meals or correction boluses) will not be reported as SAEs unless determined to meet the criteria below for SAE reporting.

Hypoglycemic events are recorded as SAEs if the event required assistance of another person due to altered consciousness and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that they were unable to treat themselves, they were unable to verbalize their needs, they were incoherent, disoriented, and/or combative, or they experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Adverse Event Relatedness

The investigator will be responsible for making a determination on the causal relationship of the AE. Specifically, the investigator will report whether the AE was related to the study procedure, study drug, and/or related to the study device (malfunction of any component of the Dexcom System).

The causal relationship to the study procedure and the study device for each adverse event will be rated as follows:

- Unrelated: The event is not related to the study drug.
- Possibly Related: The temporal sequence is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the subject's condition. There is a possibility of any relation between the event and the study drug.
- Related: The event is related or most likely associated with the study drug.

Full prescribing information can be found at http://www.novo-pi.com/tresiba.pdf
For Patient Counseling and FDA approved labelling see Tresiba [package insert]. Plainsboro, NJ: Novo Nordisk Inc; March 2018.

Adverse Event Severity

The severity of the AE will be rated based upon the following grades:

- Mild – asymptomatic or mild symptoms; usually transient, requires no special treatments, and does not interfere with the subject's daily activities
- Moderate – minimal, local or non-invasive intervention indicated; usually causes a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures
- Severe – medically significant, life-threatening; hospitalization or prolongation of hospitalization indicated; interrupts a subject's usual daily activities and generally requires system drug therapy or other treatment.

Pregnancy:

The study subjects will be instructed to notify the sponsor-investigator immediately if they become pregnant.
The sponsor-investigator will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of the pregnancy by the sponsor-investigator will occur within the same timelines described above for reporting of Adverse Events.
Pregnancy complications will be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

Liability and subject insurance:
For this study, the Sansum Diabetes Research Institute will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. Medical care for study subjects will be provided regardless of their insurance status. Sansum Diabetes Research Institute agrees to indemnify Novo Nordisk in accordance with the written contract executed between the parties for this study.

Publication plan:
It is the expectation that data from this study will be presented at meeting(s) of learned societies and submitted for publication in appropriate and high impact journals within the timelines outlined above. It is our intent to register the study with a publicly assessable database such as clinicaltrials.gov.

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WESTWARD travel
Basal Insulin Adjustment

STEP 1

Departure Info	Arrival Info
City: **New York**	City: **Honolulu**
Time Zone: **EST**	Time Zone: **HST**
Date / Time: **10 AM on May 15**	Date / Time: **3 PM on May 15**

STEP 2

DAY BEFORE TRAVEL (*date* May 14)

- Be sure to pack adequate supplies in your CARRY-ON bag -

Last dose of basal insulin: 20 units @ 8 am/pm

STEP 3

DURING TRAVEL

- Start travel with your watch set to your Departure Time Zone -
- Take your bolus insulin as needed for meals -
- Check your blood sugar frequently and watch for hypoglycemia! -

At 8 am/pm DEPARTURE TIME ZONE

take ½ of your "usual" basal insulin dose = 10 units

- Then set your watch to 2 am/pm (*Arrival Time Zone*) -

At 8 am/pm ARRIVAL TIME ZONE

take ½ of your "usual" basal insulin dose = 10 units

(This may be while still traveling or after arrival depending on the time)

STEP 4

AFTER ARRIVING (*date* May 16)

- Resume normal basal insulin dosing in the Arrival Time Zone -

Next dose of basal insulin: 20 units @ 8 am/pm

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EASTWARD travel
Basal Insulin Adjustment

STEP 1

Departure Info	Arrival Info	
City: Honolulu	City: New York	Number of time
Time Zone: HST	Time Zone: EST	zones crossed: 6
Date / Time: 3 PM-May 15	Date / Time: 7 AM-May 16	Travel time: 10 hrs

STEP 2

DAY BEFORE TRAVEL (*date* May 14)

- Be sure to pack adequate supplies in your CARRY-ON bag -

Last dose of basal insulin: 20 units @ 8 am/pm

STEP 3

DURING TRAVEL

- Start travel with your watch set to your Departure Time Zone -
- Take your bolus insulin as needed for meals -
- Check your blood sugar frequently and watch for hypoglycemia! -

$$\text{Travel Dose} = \left(\frac{\text{Normal}}{\text{Basal Dose}}\right) \times \left(0.9 - \frac{\#\text{ of time zones crossed}}{\text{hrs between basal insulin doses}}\right)$$

$$13 \text{ units} = (20) \times \left(0.9 - \frac{6}{24}\right)$$

Give travel dose @ 8 am/pm DEPARTURE TIME ZONE

- Then set your watch to 2 am/pm (*Arrival Time Zone*) -

STEP 4

AFTER ARRIVING (*date* May 16)

- Resume normal basal insulin dosing in the Arrival Time Zone -

(This may be while still traveling or after)

Next dose of basal insulin: 20 units @ 8 am/pm