January 23, 2023

Tidepool Project
Howard Look
CEO
3340 Hillview Ave
Palo Alto, California 94304

Re: K203689
Trade/Device Name: Tidepool Loop
Regulation Number: 21 CFR 862.1356
Regulation Name: Interoperable Automated Glycemic Controller
Regulatory Class: Class II
Product Code: QJI
Dated: May 26, 2022
Received: May 26, 2022

Dear Howard Look:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

FDA's substantial equivalence determination also included the review of your specific procedures, validation strategies, and pre-specified acceptance criteria for software, cybersecurity, device interoperability, human factors, labeling, and training materials for modifications as described in SOP-0016, "Tidepool Loop Connected Device Integration and Validation Process and Plan," and SOP-0018, "Tidepool Loop Regulatory Determination Process." Under 21 CFR 807.81(a)(3), a new premarket submission is required if there is a major change or modification in the intended use of a device, or if there is a change or modification in a device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process. Changes made that are inconsistent with the modifications described in SOP-0016 and SOP-0018 that were reviewed in this submission could be significant modifications that could significantly affect the safety and/or effectiveness of this device (e.g., such changes could compromise the clinical functionality or performance specifications that are directly associated with the intended use of the device), in which case a new premarket submission would be required (see 21 CFR 807.81(a)(3)). Additional information about changes to software that may require a new premarket submission is provided in FDA's guidance, Deciding When to Submit a 510(k) for a Change to an Existing Device, and Deciding When to Submit a 510(k) for a Software Change to an Existing Device.

Failure to submit a new premarket submission for the changes described above would constitute adulteration and misbranding under sections 501(f)(1)(B) and 502(o) of the Act, respectively. Your device is also subject to, among other requirements, the quality systems (QS) regulation (21 CFR 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 820.90 Nonconforming product; and 820.100 Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the QS regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn

(https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Marianela Perez-torres -S

Marianela Perez-Torres, Ph.D.
Acting Director
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Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K203689

Device Name

Tidepool Loop

Indications for Use *(Describe)*

Tidepool Loop, a mobile application with algorithm technology, is intended for use with compatible integrated continuous glucose monitors (iCGM) and alternate controller enabled (ACE) insulin infusion pumps to automatically increase, decrease, and suspend delivery of basal insulin based on iCGM readings and predicted glucose values. It can also recommend, and with the user's confirmation, control the delivery of correction boluses when glucose values are predicted to exceed user configurable thresholds.

Tidepool Loop is intended for the management of type 1 diabetes mellitus in persons six years of age and greater.

Tidepool Loop is intended for single patient use.

Tidepool Loop is Rx - For Prescription Use Only.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

I. Sponsor Information:

Sponsor:	Mailing address: Tidepool Project 555 Bryant St. #429 Palo Alto CA 94301 Registration facility address: Tidepool Project 3340 Hillview Ave. Palo Alto, CA 94304
Contact Person:	Howard Look, CEO
Email:	regulatory@tidepool.org
Phone:	650-353-2352

II. Device Name

Device Classification Name:	Interoperable Automated Glycemic Controller (iAGC)
Device Classification	Class II, 21 CFR 862.1356
Product Code:	QJI
Device Proprietary Name:	Tidepool Loop

III. Predicate Device Information

Device Name	Control – IQ Technology
Manufacturer:	Tandem Diabetes Care, Inc.
Premarket Notification #:	K200467
Classification Name:	Interoperable Automated Glycemic Controller (iAGC)
Classification:	Class II, 21 CFR 862.1356
Product Code:	QJI

IV. Date Summary Prepared: January 23, 2023

V. Description of Device

Tidepool Loop is a mobile application with algorithm technology that works to control an ACE (Alternate Controller Enabled) insulin pump to automatically increase, decrease, and suspend delivery of basal insulin based on readings from an iCGM (integrated continuous glucose monitor) and glucose values predicted by Tidepool Loop. Tidepool Loop can also recommend, and with the user's confirmation, control the delivery of correction boluses when glucose values are predicted to exceed user configurable thresholds.

Tidepool Loop predicts glucose levels up to 6 hours in the future (the approximate duration of insulin action for U-100 rapid-acting insulin) based on prior iCGM readings, insulin delivery history, and user input (e.g., carbohydrate intake and exercise, and in some cases fingerstick glucose) and uses that prediction to adjust insulin delivery. Tidepool Loop can be used to adjust or suspend basal insulin delivery every 5 minutes based on actual CGM sensor and predicted glucose readings. iCGM values are automatically used by the Tidepool Loop Bolus Recommendation Tool (TLBRT) when the Tidepool Loop Algorithm technology is active, i.e. when the device is operating in closed-loop mode with an active iCGM sensor session. When closed-loop mode is off, such as when it is manually disabled or when there is no active iCGM sensor session, the Tidepool Loop Bolus Recommendation Tool (TLBRT) is disabled. The user will use Tidepool Loop's simple bolus calculator, into which iCGM values are not automatically populated into the glucose field.

Users must manually enter information about carbohydrates to initiate a meal bolus. When closed-loop mode is on, recommended bolus delivery is calculated using the Tidepool Loop Bolus Recommendation Tool (TLBRT) and can be manually adjusted.

The Tidepool Loop app requires that specific, initial therapy settings are established by a health care provider as part of creating the prescription order. These settings include:

- Target Correction Ranges for normal operation, Pre-Meal and Workout Presets
- Carb to Insulin Ratios
- Insulin Sensitivity Factors
- Basal Rates
- Max Basal Rate
- Max Bolus

Tidepool Loop uses two glucose-specific settings that may be different from the user's experience with traditional glucose monitoring or CGM therapy. These are **Correction Range** and **Glucose Safety Limit**.

Correction Range is the range of glucose values that the user wants Tidepool Loop to work to bring their glucose to. Correction Range can be set as low as 87 mg/dL and as high as 180 mg/dL. Tidepool Loop will warn the user if values outside the recommended bounds of 100-115 mg/dL are selected. The user can add different Correction Ranges for different times of day. Tidepool Loop supports up to 48 Correction Range segments in a 24-hour period.

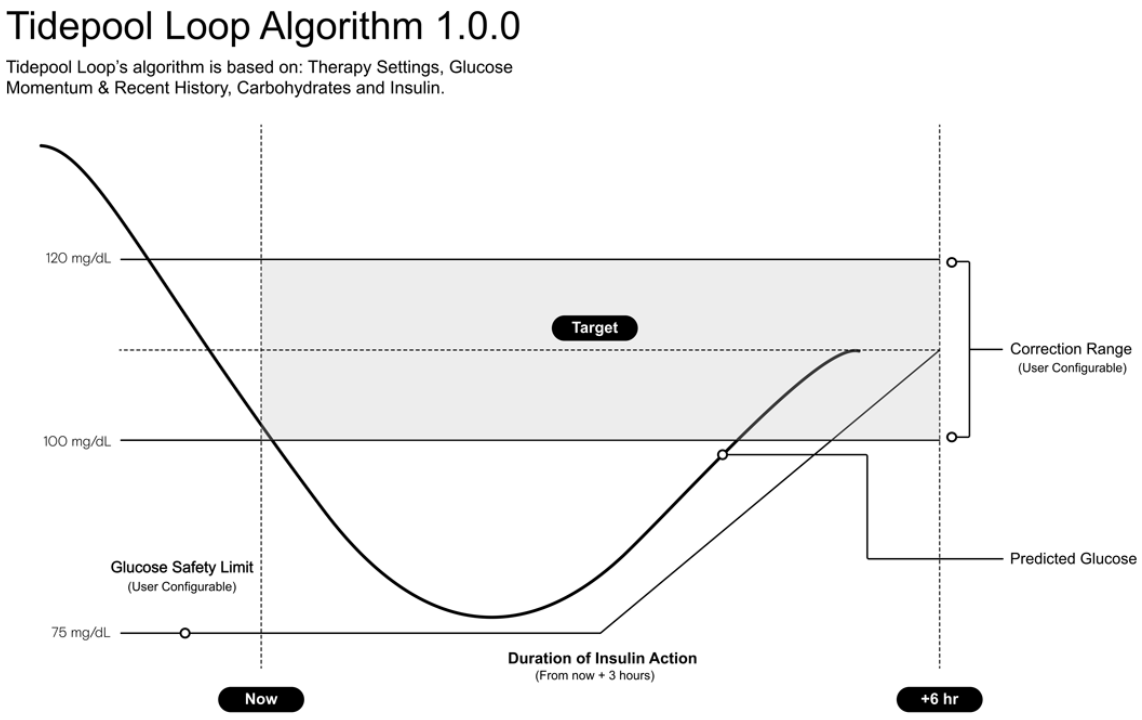
Tidepool Loop allows these user-customizable target Correction Ranges:

- Normal operation
- Pre-meal Preset
- Workout Preset

Glucose Safety Limit (mg/dL) is a safety feature of the Tidepool Loop algorithm. If the current CGM value or any future predicted glucose value is below this safety limit, Tidepool Loop will suspend insulin delivery in an effort to prevent low glucose. The algorithm will also not recommend a bolus.

Glucose Safety Limit can be set as low as 67 mg/dL. It can be set as high as 110 mg/dL or to the Correction Range minimum, whichever glucose value is lower. Tidepool Loop will warn the user if values outside Tidepool's recommended bounds of 74 to 80 mg/dL are selected.

The Glucose Safety Limit is also part of the Dosing Safety Threshold, which is part of the Tidepool Loop insulin delivery algorithm. The Dosing Safety Threshold is a period of time that has the same duration as the insulin activity duration (i.e., 6 hours). The Dosing Safety Threshold is equal to the user's Glucose Safety Limit for the first half of the insulin activity duration (i.e., 3 hours), and then increases until it is at the midpoint of the Correction Range at the end of the insulin activity duration (i.e., 6 hours). The graph below summarizes the operation of the Tidepool Loop algorithm.



Principle of Operation of Tidepool Loop Algorithm

Tidepool Loop is designed to be installed on an iPhone running iOS operating systems (version 15 or higher). The Tidepool Loop application includes an optional extension for Apple Watch devices running watchOS operating system (version 6.1 or higher).

VI. Indications for Use

Tidepool Loop, a mobile application with algorithm technology, is intended for use with compatible integrated continuous glucose monitors (iCGM) and alternate controller enabled (ACE) insulin infusion pumps to automatically increase, decrease, and suspend delivery of basal insulin based on iCGM readings and predicted glucose values. It can also recommend, and with the user's confirmation, control the delivery of correction boluses when glucose values are predicted to exceed user configurable thresholds.

- Tidepool Loop is intended for the management of type 1 diabetes mellitus in persons six years of age and greater.
- Tidepool Loop is intended for single patient use.
- Tidepool Loop is Rx - For Prescription Use Only.

Contraindications

- Tidepool Loop should not be used by anyone who is unable to notice alerts, alarms and reminders because of physical limitations.
- Tidepool Loop should not be used by anyone that is unable to monitor glucose as recommended by their healthcare provider.
- Tidepool Loop should not be used by anyone that is unable to maintain contact with their healthcare provider.
- Tidepool Loop should not be used by anyone who is unwilling or unable to follow the instructions for use and intended uses of compatible insulin pumps and continuous glucose monitor devices.
- **MR Unsafe** 

- Tidepool Loop should not be used during Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, Positron Emission Tomography (PET) scan, or high-frequency electrical heat (diathermy) treatment. Components of the Tidepool Loop system may not have been tested in magnetic fields and heat could damage the CGM or insulin pump being used with Tidepool Loop and prevent accurate sensor glucose readings or accurate insulin delivery. This could result in overdelivery or under-delivery of insulin, which can lead to low or high blood glucose. Please follow Healthcare Provider instructions and refer to the individual component manuals for more information.

VII. Comparison to Predicate Device

Tidepool Loop is substantially equivalent to the predicate device, Control-IQ Technology, currently legally marketed under K200467.
Tidepool Loop and Control-IQ are similar in that they have:

- the same general intended use,
- the same indications for use,
- the same or similar technological characteristics,
- the same principle of operation.

The devices primarily differ in that:

- Control-IQ currently operates only on Tandem's t:slim X2 insulin pump, while Tidepool Loop operates on iPhone devices;
- Control-IQ automatically delivers correction boluses, while Tidepool Loop only recommends correction boluses if a user elects to open the Bolus Entry screen;
- Tidepool Loop predicts glucose values farther into the future than Control-IQ;
- Tidepool Loop allows for more user-configurable correction ranges and other settings than Control-IQ.

Specific differences between Tidepool Loop and its predicate device are detailed in the table below.

Comparison Table, Tidepool Loop vs. Tandem Control-IQ

Differences with the predicate device are shown in bold italic.

Characteristic	Control-IQ Technology (K200467)	Tidepool Loop (this submission, K203689)
Regulatory Information		
Product Code	QJI	QJI
Regulation Name	21 CFR 862.1356, Interoperable Automated Glycemic Controller	21 CFR 862.1356, Interoperable Automated Glycemic Controller
Indications for Use, User Population		
Indication For Use	Control-IQ ***technology*** is intended for use with compatible integrated continuous glucose monitors (iCGM) and alternate controller enabled (ACE) pumps to automatically increase, decrease, and suspend delivery of basal insulin based on iCGM readings and predicted glucose values. It can also deliver correction boluses when the	Tidepool Loop is a ***mobile application and algorithm technology*** that is intended for use with compatible integrated continuous glucose monitors (iCGM) and alternate controller enabled (ACE) pumps to automatically increase, decrease, and suspend delivery of basal insulin based on iCGM readings and predicted glucose values. It can also

	glucose value is predicted to exceed a predefined threshold. Control-IQ technology is intended for the management of Type 1 diabetes mellitus in persons 6 years of age and greater. Control-IQ technology is intended for single patient use and requires a prescription. Control-IQ technology is indicated for use with NovoLog or Humalog U-100 insulin.	***recommend and*** deliver correction boluses when glucose values are predicted to exceed ***user configurable*** thresholds. Tidepool Loop is intended for the management of Type 1 diabetes mellitus in persons six years of age and greater. Tidepool Loop is intended for single patient use. Tidepool Loop is Rx - For Prescription Use Only.
Target Patient Population	Type 1 diabetes mellitus in persons six years of age and greater.	Type 1 diabetes mellitus in persons six years of age and greater.
Principal Operator	Prescription only device with the patient or caregiver as the principal operator	Prescription only device with the patient or caregiver as the principal operator
Use Location	At home	At home
Number of Users	Single user only	Single user only
Technological Characteristics		
Principle of Operation	Control-IQ technology predicts glucose levels ***30 minutes in the future*** based on prior iCGM readings, insulin delivery history, and user input (e.g., carbohydrate intake, exercise, ***and sleep schedule***) and uses that prediction to adjust insulin delivery. Control-IQ technology can be used to adjust or suspend basal insulin delivery every 5 minutes and ***automatically*** deliver correction boluses of insulin based on actual and predicted CGM sensor readings. Users must manually deliver meal boluses they can calculate using the integrated bolus calculator and can manually adjust insulin delivery (change basal rates and deliver insulin boluses)	Tidepool Loop predicts glucose levels ***up to 6 hours in the future (the approximate duration of insulin action for U-100 rapid-acting insulin)*** based on prior iCGM readings, insulin delivery history, and user input (e.g., carbohydrate intake and exercise) and uses that prediction to adjust insulin delivery. Tidepool Loop can be used to adjust or suspend basal insulin delivery every 5 minutes and deliver correction boluses of insulin based on actual and predicted CGM sensor readings. Users must manually deliver meal boluses they can calculate using **the Tidepool Loop Bolus Recommendation Tool (TLBRT)** and can manually adjust insulin delivery (change basal rates and deliver

	when the Control-IQ technology is active	insulin boluses) when Tidepool Loop is active.
Type of Algorithm	Hybrid Closed Loop - predictive control	Hybrid Closed Loop - predictive control
Compatible iCGM	Dexcom G6	Dexcom G6
Compatible ACE Pump	Tandem X2 Pump	An ACE pump that has the specifications and meets the pre-specified acceptance criteria for software, cybersecurity, device interoperability, human factors, labeling, and training materials as described in SOP-0016, "Tidepool Loop Connected Device Integration and Validation Process and Plan," and SOP-0018, "Tidepool Loop Regulatory Determination Process." Tidepool Loop must not be distributed until the pre-specified acceptance criteria in the SOPs are met.
Device Design or Material	Control-IQ Technology is software in a medical (SiMD) device, installed on a Tandem t:slim X2 pump	Tidepool Loop is ***a mobile application and a Software as Medical Device (SaMD) installed on a host mobile device***
Algorithm Platform	Tandem X2 Pump	***iPhone***
User Experience Platform	Tandem X2 Pump	***iPhone and Apple Watch***
Insulin Compatibility	Novolog or Humalog U-100	Same
Functional Characteristics		
User-controlled Target Range Settings	Not customizable. Default: 112.5 - 160 mg/dL Sleep Mode 112.5 - 120 mg/dL Exercise Mode 140 - 160 mg/dL	Customizable settings Correction Range: 87 - 180 mg/dL Pre-Meal Range: Glucose Safety Limit (which can be set from 67-110 mg/dL) - 130 mg/dL Workout Range:

		the higher of 85 mg/dL or the Glucose Safety Limit (which can be set from 67-110 mg/dL) - 250 mg/dL
Auto-populating bolus recommendation based on iCGM value:		
In closed loop mode **In open loop mode**	Yes No	Yes No
Data List & Logging	Yes	Yes
Daily Activity Records	Yes	Yes
Average Data Display	Yes	Yes
Changing Pump Settings	Yes	Yes
Invite others to view data through authorization	Yes	Yes
Password required	Yes	Yes
Performance Characteristics		
Bench Performance	Control-IQ performance was verified and validated through software verification testing including special controls, cybersecurity, wireless, and connected devices compatibility testing.	Tidepool Loop performance was verified and validated through software verification testing including special controls, cybersecurity, wireless, and connected devices compatibility testing.
Clinical Performance	Control-IQ clinical performance was supported by 1) 168 participants in a 6-month randomized trial, with 112 in the intervention arm and 56 in the control arm. 2) 101 pediatric participants in a 4-month randomized trial, with 78 in the	Tidepool Loop clinical performance is supported by representative ***1,250 participants in a 15 months duration real-world, observational, single arm study of DIY Loop*** including both pediatric and adult participants.

	intervention arm and 23 in the control arm.	
Patient Preference	Control-IQ assessed Patient Preferences through written statements and also obtained through discussion with patients and patient advocacy groups at public forums regarding patient experiences with automated insulin dosing systems and digitally connected diabetes devices.	Tidepool Loop assessed Patient Preference through written or video testimonials.
Risk Assessment	Control-IQ performed Risk Assessment including detailed hazard analysis based on ISO 14971.	Tidepool Loop performed Risk Assessment including detailed hazard analysis based on ISO 14971.
Labeling		
Training	Control-IQ provides mandatory user training before the user can use their device.	Tidepool Loop includes mandatory in-app learning and setup (user training) before the user can use Tidepool Loop.
User Guide	Control-IQ electronic User Guide includes all special controls, clinical performance information and other information needed per cybersecurity and interoperability requirements.	Tidepool Loop electronic User Guide also includes all special controls, clinical performance information and other information needed per cybersecurity and interoperability requirements.

VIII. Standards Compliance

Tidepool Loop complies with the the following standards as documented in the applicable test reports provided in this 510(k) submission:

- Special controls established under 21 CFR 862.1356.
- ISO 14971:2019: Medical Devices - Application of Risk Management to Medical Devices FDA Recognition No: 5-125
- ANSI/AAMI/IEC 62366-1:2015: Medical Devices - Part 1: Application Of Usability Engineering To Medical Devices, FDA Recognition No: 5-114
- ANSI/AAMI/IEC HE75:2009: Human factors engineering, design of medical devices FDA Recognition No:5-57
- IEEE 802.15.1-2005, IEEE Standard for Information technology-- Local and metropolitan area networks-- Specific requirements-- Part 15.1a: Wireless Medium Access Control (MAC) and Physical Layer (PHY) specifications for Wireless Personal Area Networks (WPAN)
- Bluetooth Core Specification (Bluetooth SIG)

- ISO/IEEE 11073, Health informatics - Medical / health device communication standards
- ANSI IEEE C63.27, American National Standard For Evaluation Of Wireless Coexistence
- AAMI TIR69, Risk Management Of Radio-Frequency Wireless Coexistence For Medical Devices And Systems

In addition, the following standard was used in the design and development of Tidepool Loop:

- ANSI/AAMI/UL 2800-1: 2019, Standard for Safety for Medical Device Interoperability, FDA Recognition No: 13-109

IX. Non-Clinical Performance Testing

The information presented in this 510(k) submission demonstrates the safety and effectiveness of Tidepool Loop with compatible ACE pump and iCGM devices. Non-clinical performance testing included the following:

- **Risk Management**: Risk management was performed and documented in accordance with ISO 14971:2019. A comprehensive hazard analysis was provided for this device, in which design inputs and outputs, risks, and risk mitigations for software and interoperable hardware components associated with the safe and effective functioning of the device were reviewed. The hazard analysis provided in this submission accounted for the unique design elements, intended use, and risks of the Tidepool Loop iAGC. In particular, this hazard analysis accounted for the risks associated with interoperability between the software device and the third-party digital devices it communicates with which met predefined criteria. This analysis identified hazards which could reasonably be anticipated to impact the proper use of the device, traced all identified risks to adequate design controls, and demonstrated that design features were appropriately implemented and validated.

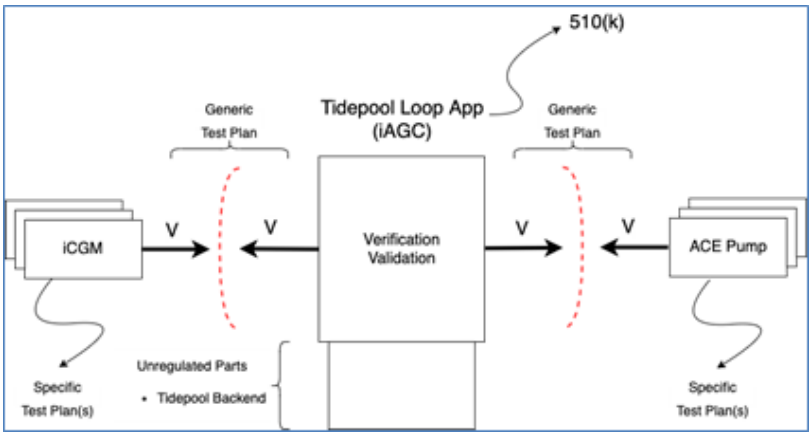
- **Human Factors Validation**: A human factors (HF) validation study was conducted in accordance with ANSI/AAMI/IEC 62366-1:2015 and ANSI/AAMI/IEC HE75:2009. The study was conducted to confirm that intended users can safely and effectively use the Tidepool Loop Mobile Application. The final device design was evaluated in a summative study performed with 51 representative participants interacting with the device in a simulated use environment. All study participants received training that was consistent with the training that patients would receive with the commercial product. Usability evaluations assessed comprehension and usability of the device for critical device tasks including those tasks that involved information from a connected device with representative interoperable technology. Results of the study demonstrated that the device could be used safely by intended users in the intended use environment.

- **Patient Perspective Data:** Patient Perspective data collected by Tidepool included summarized information provided by the patients in written statements and also obtained through discussion with patients and patient advocacy groups at public forums regarding

patient experiences with Tidepool Loop and digitally connected diabetes devices. Patients value that Tidepool Loop will allow them, in conjunction with their healthcare providers, to have more choice in the automated insulin dosing algorithm that integrates with other elements of their diabetes management strategy and works best for their body and their care.

- **Software Verification and Validation**: Software verification and validation testing was performed in accordance with IEC 62304:2014 and with FDA guidance, *General Principles of Software Validation*, issued January 11, 2002. Software testing focused on the iAGC functionality described by the iAGC special controls as defined at 21 CFR 862.1356 including interaction with iCGM and ACE insulin pump devices. Tidepool Loop was installed on compatible iPhone devices (black box testing), and was also tested extensively using automated simulation and emulation environments (white box automated testing). Testing was also performed to ensure that Tidepool Loop's functions through compatible host devices incorporating wireless technologies IEEE 802.15 (Bluetooth) and IEEE 802.11 (WiFi) performed as designed and intended.

  Given the modular nature of iAGC, ACE pumps, and iCGM devices, Tidepool isolated the implementation of an ACE pump or iCGM from the iAGC implementation using a plug-in model. This allowed Tidepool to verify the iAGC functionality of Tidepool Loop independent of a specific connected diabetes device. Therefore, the approach to verification was divided into two stages for each interoperable device type as shown in the figure below, a Generic Test Plan and Specific Test Plan(s).



Tidepool Loop Interoperability Verification Approach

A generic test plan for iCGM was defined and executed using a software simulator implementation of an iCGM. The simulator is a test fixture that enables the tester to generate different types of CGM data and error conditions without using a physical iCGM device. The iCGM simulator was used to verify the correct glucose-related functionality of Tidepool Loop for the purposes of this submission. A plan for ensuring that connected devices meet Tidepool's specifications, and that appropriate risk management, verification, and validation activities for each connected iCGM device are conducted appropriately was provided.

A generic test plan for ACE pumps was defined and executed using a software simulator that allowed the tester to manipulate the simulated pump state including initiating, suspending and resuming insulin delivery, adjusting reservoir levels and battery power, and triggering error conditions. A plan for ensuring that connected devices meet Tidepool's specifications, and that appropriate risk management, verification, and validation activities for each connected ACE pump device are conducted appropriately was provided.

Finally, Tidepool relied heavily on automated testing to catch errors and regressions. Automated tests are run with every software change and with every software build and include confirmation that hazard mitigations were effectively implemented. Verification testing was comprised of the following:

- Automated functional tests: These tests used simulated iCGM and ACE pump devices, as described above, on simulated iPhone devices. These tests were executed automatically and continuously every time Tidepool Loop was built from source code. The full suite of automated tests leverages multiple continuous integration and testing platforms, including CircleCI and Detox. At the time of this premarket submission, over 2,900 automated test cases covering varying aspects of every software build were conducted.
- Manual functional tests: These per-feature tests used real or simulated iCGM and ACE pump devices on a subset of supported iPhone devices and Apple Watch devices. These tests were developed and executed as part of the development of each feature.
- Final manual functional test: This test included the overall iAGC functionality with focus on the following areas:
    - Features that were identified by risk assessment as requiring mitigations to reduce risk to acceptable level .
    - User interface areas or features that cannot be adequately covered by automated tests due to complexity and/or time constraints

- **Data Logging**: Software verification testing demonstrated that Tidepool Loop records timestamped critical events, including information related to its state, user inputs, and device settings, as required by the iAGC special controls.

- **Interoperability:** A plan and approach for interoperability were provided according to the FDA Guidance *"Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices - Guidance for Industry and Food and Drug Administration Staff.* The plan specified expectations, requirements, and interface specifications for potential interoperable devices. In addition, the plan covered Tidepool's approach to working with connected device companies regarding contractual issues, interfaces for data communication and exchange, and post-market reporting procedures and responsibilities (e.g., who is responsible for investigating and reporting complaints, malfunctions, and adverse events). Validated software protocols were submitted, intended to ensure secure, accurate,

and reliable communication with digital interfacing devices, as well as failsafe design features to mitigate the risks associated with interruption of communication with digitally connected devices. These protocols documented testing of Tidepool Loop with a manufacturer-provided protype pump using IEEE 11073-10419 and Bluetooth SIG and a commercial, cleared iCGM with a manufacturer-provided SDK. Testing coverage is summarized in the table below.

Testing	**Interoperability with ACE Pump**	**Interoperability with iCGM**	**Tidepool Loop iAGC**
Verification (bench testing)	Tidepool-developed ACE pump software simulator. Tidepool-developed PumpManager for IEEE 11073-10419 and Bluetooth SIG compliant insulin pump. Manufacturer-provided pump hardware emulator boards (IEEE 11073-10419 and Bluetooth SIG compliant interface).	Tidepool-developed iCGM software simulator. Manufacturer-provided iCGM hardware emulator board (proprietary communication interface). Manufacturer-provided iCGM SDK (proprietary communication interface).	Tidepool Loop software verification bench testing.
Validation (simulated conditions of use)	Manufacturer-provided prototype pump, communicating with iAGC via IEEE 11073-10419 and Bluetooth SIG compliant interface.	Manufacturer-provided cleared iCGM devices, communicating with iAGC via Manufacturer-provided SDK with proprietary communication interface.	Tidepool Loop software installed on representative iOS devices, capable of communicating using BluetoothLE to: Manufacturer-provided: a) prototype pump b) hardware emulation environment Manufacturer-provided: a) cleared iCGM b) hardware emulation environment

- **Cybersecurity**:A cybersecurity analysis was performed for Tidepool Loop using FDA

guidance, *Content of Premarket Submissions for Management of Cybersecurity in Medical Devices*, issued October 18, 2020, and the principles outlined in FDA guidance, *Postmarket Management of Cybersecurity in Medical Devices*, issued December 28, 2020. Tidepool performed threat modeling of the interactions between Tidepool Loop app and the Tidepool Platform and applied mitigations as detailed in the hazard analysis and V&V report.

Tidepool provided a software bill of materials, which provided details on all software used in the device. This included all manufacturer-developed, commercially licensed, open source, and off-the- shelf software components, along with an identification of the hardware runtime environment in which each resides, with relevant version and/or model information, as well as details on whether each component was actively supported by its manufacturer or legacy licensed.

In addition, results of internal and third-party penetration testing, using existing devices and configurations, were provided.

X. Clinical Testing

Study Overview and Design: The Jaeb Center for Health Research, in collaboration with clinical research centers and Tidepool, conducted an observational study to collect data on the do-it-yourself (DIY) Loop system (ClinicalTrials.gov Identifier: NCT03838900). This study collected and analyzed data on the efficacy, safety, usability, and quality of life/psychosocial effects of the DIY Loop System. The study enrolled subjects diagnosed with type 1 diabetes (T1D) who were using insulin (either pump therapy or multiple daily injections [MDI]) and currently using DIY Loop or had plans to begin using DIY Loop for insulin delivery.

Subjects/Enrollment: The protocol allowed enrollment of up to 1,250 participants of any age with Type 1 diabetes with a target of at least 300 participants and a minimum of 150 as new DIY Loop users. Study participants were divided into two cohorts:

- Cohort A – individuals *new* to using DIY Loop (had not started Loop or had used it for <7 days prior to enrollment)
- Cohort B – *existing* DIY Loop users

A total of 1,127 participants were enrolled into the study with 799 in Cohort A, defined as new DIY Loop users, and 328 in Cohort B, defined as existing DIY Loop users. Of the enrolled participants, 255 were determined to be ineligible resulting in 872 initiating the study with 606 participants in Cohort A and 266 in Cohort B.

There was no required length of follow-up for study participants, however minimum exposure targets were exceeded. Due to the rolling nature of enrollment, not all participants were eligible to meet the 9 month and/or 12 month follow-ups. In Cohort A, 88% of participants (n=535/606) reached the 6-month observational time point. In Cohort B, 83% of participants (n=222/266) reached the 9-month observational time point.

A total of 483 person-years of DIY Loop exposure (over 175,000 person-days) were collected in 872 participants.

Investigational Device: This observational study examined DIY Loop in real-world, unsupervised, patient-driven use. Tidepool Loop is based on the same algorithm as DIY Loop, with specific design changes to enhance safety, such as adding settings guardrails.

Data Collection: CGM and insulin dosing data were collected continuously and uploaded automatically from a user's own iPhone. The Tidepool Mobile app securely sent this data to Tidepool's cloud, from where it was retrieved by the Jaeb Center for Health Research and replicated in the Jaeb Center's database.

Users completed weekly web-based surveys about Adverse Events (severe hypoglycemia, DKA, hospitalization) and device issues. Participants were followed for up to 12 months with general updates obtained after 3, 6, and 12 months. Blood samples were collected for HbA1c measurement after 3 months for Cohort A and after 6 and 12 months for both cohorts; results were self-reported by the participant. At 3 and 6 months, more extensive web-based surveys collected patient-reported outcomes and psychosocial/quality of life aspects related to DIY Loop use. Focus groups were also completed.

Data Analysis: The primary effectiveness analysis consisted of A1C and sensor glucose time in range (70-180 mg/dL) results. The primary safety analysis included the incidence of severe hypoglycemia and diabetic ketoacidosis (DKA). A summary of the primary effectiveness and safety results is presented in the table below.

Subject Demographics and Key Outcomes: The observational study included participants that may not be part of the intended user population, which is defined as $\geq$ 6 years old, using Humalog or Novolog insulin only, and making use of the Tidepool Loop guardrails (Correction Range 87-180 mg/dL and Glucose Safety Limit 67-110 mg/dL) at least 90% of the time. Cohorts A and B included participants who used DIY Loop settings that are not possible in Tidepool Loop. The table below summarizes these different populations. The results are discussed in detail following the table.

	Study population *not* limited to intended user population		**Study population limited to intended user population** *(Ages 6 and up, settings within allowable Tidepool Loop ranges at least 90% of the time during study follow-up)*
	New Users (Cohort A)	*Existing Users (Cohort B)*	
N	606	266	175
Demographics			
Age	16 Years (median) 1-72 Years (range)	34 Years (median) 13-76 Years (range)	23 years (mean) 6-71 (range)
Sex	56% Female	52% Female	56% Female

Race	91% White, 4% Hispanic/Latinx, 2% Multiracial, 2% Asian, <1% Black	94% White, 2% Hispanic/Latinx, 2% Asian, 1% Multiracial, <1% Black	91% White, 5% Hispanic/Latinx, 2% Multiracial, 1% Asian, <1% Black
Education	85% - Bachelor's Degree or Beyond	89% - Bachelor's Degree or Beyond	88% - Bachelor's Degree or Beyond
Household Income ≥ $100,000	71%	78%	68%
Summary Diabetes Outcomes			
HbA1c at baseline (mean)	6.8%	6.3%	7.1%
HbA1c after 6 months of using DIY Loop (mean)	6.6%	6.4%	6.7%
Time in Range (70-180 mg/dL) at baseline (mean)	67%	78%	62%
Time in Range (70-180 mg/dL) 1-6 months of using DIY Loop (mean)	74%	79%	70%
Summary Safety Outcomes			
All Adverse Events	No DKA events 71 SH events	No DKA events 24 SH events	No DKA events 23 SH events
Severe Hypoglycemia (SH) during study	92% no SH from baseline to 12 months. 22.6 SH events per 100 person years compared to 181.5 events per 100 person years prior to using Loop.	95% no SH from baseline to 12 months. 14.2 SH events per 100 person years.	92% no SH from baseline to 6 months. 42.3 SH events per 100 person years compared to 192.0 events per 100 person years prior to using Loop.

Results/Cohort A (New Users): A total of 314 person-years of DIY Loop exposure were collected in 606 participants. Participants had a median age of 16 years, with a range from 1-72 Years.

- ***Primary Safety Analysis***: 92% of Cohort A participants reported no severe hypoglycemia (SH) from baseline-12 months. In the remaining 8% of participants, 71 SH

events occurred in 47 participants. The overall incidence rate of SH was 22.6 events per 100 person-years, a substantially lower rate than what was reported at baseline before using DIY Loop (181.5 events per 100 person-years). No SH events were adjudicated as "Related to Loop" in Cohort A. Eleven SH events resulted in seizure or loss of consciousness, translating to an incidence rate of 3.5 events per 100 person-years. One DKA event occurred in Cohort A from baseline-12 months, resulting in a total incidence rate of 0.3 DKA events per 100 person-years; this was also a substantially lower rate than what was reported at baseline before using DIY Loop (17.2 events per 100 person-years).

- ***Primary Glycemic Outcomes:*** Mean time-in-range 70-180 mg/dL (TIR) increased from 67% at baseline to 73% from 1-6 months ($p<0.001$). TIR increased in both adults and children, across the full range of baseline HbA1c levels, and with both high and moderate income levels. Time <54 mg/dL and <70 mg/dL were both low at baseline (medians of 0.40% and 2.9%, respectively), but still improved during the study ($p<0.001$). Mean HbA1c was 6.8% at baseline and decreased to 6.6% after 6 months ($P<0.001$) of using DIY Loop. Multiple sensitivity analyses suggested that the results were robust and not impacted by missing data.
- ***Quality of Life Outcomes:*** Study participants took eight validated questionnaires throughout the study, capturing important psychosocial and quality of life outcomes. The Insulin Dosing Systems: Perceptions, Ideas, Reflections and Expectations (INSPIRE) measures were completed by adults, parents, and children; results in Cohort A showed composite scores of 4.3 and higher out of a possible 5.0 – indicating highly positive psychosocial and quality of life outcomes associated with the use of DIY Loop. The INSPIRE questionnaires were recently qualified by the FDA through the Medical Device Development Tool program (Submission Number: Q191073).

  In Cohort A, statistically significant improvements were also seen with DIY Loop in the Diabetes Distress Scale – Management Burden; Fear of Hypoglycemia (Worry Scale); Hypoglycemia Confidence; and the Pittsburgh Sleep Quality Index. These validated questionnaires appear to corroborate the CGM and HbA1c metrics discussed earlier. No significant changes were observed in the Diabetes Technology Attitudes; Technology Use for Problem Solving; and the Risk Taking Survey. In Cohort A, 75% of participants said they were "very likely" (a "5" on a 1-5 scale) to recommend Loop to another person with type 1 diabetes.

Results/Cohort B (Existing Users), a total of 169 person-years of DIY Loop exposure were collected in 266 participants. Participants had a median age of 34 years, with a range from 3-76 Years. Outcomes for Cohort B are descriptive and do not include p-values, as users were already on DIY Loop at baseline.

- ***Primary Safety Analysis***: 95% of Cohort B participants reported no severe hypoglycemia (SH) from baseline-12 months. In the remaining 5% of participants, 24 SH events occurred over the study, resulting in an overall incidence rate 14.2 SH events per 100 person-years. Four SH events were adjudicated as "related to Loop" in Cohort B. Seven SH events resulted in seizure or loss of consciousness, translating to an

incidence rate of 4.1 events per 100 person-years. No DKA events occurred in Cohort B, resulting in a total incidence rate of 0.0.

- ***Primary Glycemic Outcomes:*** Mean time-in-range 70-180 mg/dL (TIR) was 78% at baseline (already using Loop) and maintained at 78%-79% from 1-12 months. Time <54 mg/dL and <70 mg/dL were both low at baseline (medians of 0.34% and 2.6%, respectively) and remained at similar levels during the study. Mean HbA1c was 6.3% at baseline and was maintained at 6.4% at six months and 6.2% at 12 months.
- ***Quality of Life Outcomes***: INSPIRE results in Cohort B showed composite scores of 4.3 and higher out of a possible 5.0 – indicating highly positive psychosocial and quality of life outcomes associated with the use of DIY Loop. Other measures of Cohort B's quality of life remained consistent from Baseline-12 months; these data were also consistent with Cohort A's results while on DIY Loop. In Cohort B, 79% of participants said they were "very likely" (a "5" on a 1-5 scale) to recommend Loop to another person with type 1 diabetes

Results (Intended User Population): A total of 175 patients met the definition of 'intended user population'. Participants had a median age of 23 years, with a range from 6-71 years.

- **Primary Safety Analysis:** 92% of the intended use population participants reported no severe hypoglycemia (SH) from baseline-6 months. In the remaining 8% of participants, 23 SH events occurred over the study, resulting in an overall incidence rate of 42.3 SH events per 100 person-years compared to 192.0 events per 100 person-years prior to using Loop. 1 SH event was adjudicated as "related to Loop" in this population. No SH events resulted in seizure or loss of consciousness, translating to an incidence rate of 0 events per 100 person-years. No DKA events occurred in this population, resulting in a total incidence rate of 0.0.
- **Primary Glycemic Outcomes:** Mean time-in-range 70-180 mg/dL (TIR) was 62% at baseline and improved to 70% from 1-6 months. Time <54 mg/dL and <70 mg/dL were both low at baseline (medians of 0.23% and 1.8%, respectively) and were largely unchanged during the study (0.23% and 1.9% at 6 months). Mean HbA1c was 7.1% at baseline and improved to 6.7% at six months.

Adverse Events (AE): Users completed weekly web-based surveys about Adverse Events (severe hypoglycemia, DKA, hospitalization) and device issues. Participants were followed for up to 12 months with general updates obtained after 3, 6 and 12 months.

No DKA events were attributed to the use of DIY Loop in any of the study groups, as shown in the summary table above.

Adverse Events (Cohorts A and B): The data suggest that the use of DIY Loop was associated with a lower reported rate of severe hypoglycemia (SH) in Cohort A – over both 6-Month and 12-Month study time points – as compared to the baseline report of SH in the 3 months prior to starting Loop. The percentage of Loop users experiencing a severe hypoglycemia event within the first 3 months of the study (5%) was similar to the 6% 3-month frequency reported in the real-world T1D Exchange clinic registry.

It is difficult to compare AE rates between DIY Loop Study and recent controlled studies due to different study designs, methodology, data collection process and sample size. Regardless, a comparison was done for illustrative purposes only. Although the overall incidence rate of severe hypoglycemia was higher than in recent controlled studies of existing AID, this study had no exclusion criteria, whereas most previous AID studies excluded individuals with recent severe hypoglycemia or gave investigators discretion to exclude individuals if, in the opinion of the investigator, the individual's participation would put the individual or the study at risk. The difference could also reflect this study's frequent ascertainment of severe hypoglycemia through a weekly text prompt or differences in study design: the Loop study was real-world and virtual compared with other studies that had structured protocols with close clinical oversight of closed-loop system use by study staff (including system setup and maintenance). The difference is also possibly reflective of the high pre-study risk of this cohort for severe hypoglycemia, possibly driven by a more hyperglycemia-avoidant approach to diabetes management.

Adverse Events/Severe Hypoglycemia (Intended Use Population): Severe hypoglycemic event data were specifically analyzed for the "intended use" sub-population. That population is defined as individuals in the study from both cohorts that are ≥6 years old, using Humalog or Novolog insulin only, and making use of the Tidepool Loop guardrails at least 90% of the time during study follow-up.

The table below summarizes the incidence of severe hypoglycemic events at baseline and follow-up by age group in the intended use population. Given the small sample sizes and potential lack of statistical significance for these cohorts, the Tidepool team individually analyzed each adverse event from the Observational Study of Loop in detail. Each event was reviewed both by the Jaeb Center for Health Research and by Tidepool staff, including review with Tidepool's Chief Medical Advisor. These data show that:

(1) the majority of severe adverse events observed during the study were experienced by the minority of participants who also had at least one severe hypoglycemic event in the three months before using DIY Loop; and,

(2) for those participants who reported at least one severe adverse event in the three months prior to using DIY Loop, their incident rates of severe hypoglycemic events were reduced from baseline; and,

(3) across the intended use population, the incidence rate of Severe Hypoglycemia events was reduced from 192 events per 100 person-years in the 3 months prior to using DIY Loop, to 42 events per 100 person-years for the 6 months after starting on DIY Loop.

In other words, those participants who had severe hypoglycemic events before using Loop were more likely to continue to have SH events, but to have fewer of them.

Severe Hypoglycemia for Participants ≥6 Years Old

	Overall	6-13 Years	14-17 Years	≥18 Years
Overall	**N=175**	**N=76**	**N=19**	**N=80**
Severe Hypoglycemia (Baseline – 6 Months)				
Total # of events	23	11	5	7
# Events per participant				
0	161 (92%)	69 (91%)	17 (89%)	75 (94%)
1	6 (3%)	3 (4%)	0 (0%)	3 (4%)
2	7 (4%)	4 (5%)	1 (5%)	2 (3%)
≥3	1 (<1%)	0 (0%)	1 (5%)	0 (0%)
Incidence rate (per 100 person-years)	42.3	44.7	88.8	29.0
Severe Hypoglycemia (3 Months Prior to Baseline)				
Total # of events	84	50	2	32
# Events per participant				
0	149 (85%)	63 (83%)	17 (89%)	69 (86%)
1	12 (7%)	6 (8%)	2 (11%)	4 (5%)
2	4 (2%)	1 (1%)	0 (0%)	3 (4%)
≥3	10 (6%)	6 (8%)	0 (0%)	4 (5%)
Incidence rate (per 100 person-years)	192.0	263.2	42.1	160.0
Participants with 0 Event in the 3 Months Prior to Enrollment	**N=149**	**N=63**	**N=17**	**N=69**
Severe Hypoglycemia (Baseline – 6 Months)				
Total # of events	10	5	3	2
# Events per participant				
0	143 (96%)	60 (95%)	16 (94%)	67 (97%)
1	3 (2%)	1 (2%)	0 (0%)	2 (3%)
2	2 (1%)	2 (3%)	0 (0%)	0 (0%)
≥3	1 (<1%)	0 (0%)	1 (6%)	0 (0%)
Incidence rate (per 100 person-years)	21.7	23.9	63.6	9.8
Participants with ≥1 Events in the 3 Months Prior to Enrollment	**N=26**	**N=13**	**N=2**	**N=11**
Severe Hypoglycemia (Baseline – 6 Months)				
Total # of events	13	6	2	5
# Events per participant				
0	18 (69%)	9 (69%)	1 (50%)	8 (73%)
1	3 (12%)	2 (15%)	0 (0%)	1 (9%)
2	5 (19%)	2 (15%)	1 (50%)	2 (18%)
≥3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Incidence rate (per 100 person-years)	154.7	163.9	218.3	130.6

Applicability to Tidepool Loop: Tidepool Loop's design considered all identified DIY Loop known use problems, Tidepool adapted its design as necessary to mitigate those known use problems, and the design was tested as part of detailed Verification and Validation Testing. The changes in Tidepool Loop were made specifically to enhance Tidepool Loop's safety profile and to comply with US FDA's iAGC (interoperable Automated Glycemic Controller) requirements.

Therefore, Tidepool believes that the DIY Loop clinical data adequately addresses the safety and benefit/risk profile of Tidepool Loop, and is further supported by robust nonclinical data.

XI. Conclusions

Tidepool Loop has the same intended use and similar indications for use as the predicate device and is intended to be used in the same environment as the predicate Device, Control-IQ Technology (K200467). While there are minor differences in technological characteristics between the subject and predicate devices, these differences do not raise different questions about safety and effectiveness.

Tidepool believes that the non-clinical and clinical performance data described above supports the determination of substantial equivalence. This data demonstrates implementation of design considerations relative to data logging, interoperability, and cybersecurity design as required by the Special Controls for this device (21 CFR 862.1356). Human factors and clinical validation demonstrated that Tidepool Loop performed as designed and intended for the intended users, uses, and use environments.