Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014;371:313-25. DOI: 10.1056/NEJMoa1314474

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Supplement to: Russell SJ, El-Khatib FH, Sinha M, *et al.* Outpatient glycemic control in type 1 diabetes with a bionic pancreas.

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METHODS

Institutional and regulatory oversight

In addition to institutional review board (IRB) oversight from both the Partners Human Research Committee (Massachusetts General Hospital IRB) and the Boston University IRB, the studies were conducted under United States Food and Drug Administration Investigational Device Exemptions #G120255 (Beacon Hill Study) and #G130065 (Summer Camp Study), which were approved by the Office of In Vitro Diagnostics and Radiological Health within the Center for Devices and Radiological Health. We received an Investigational New Drug Exemption from the FDA for the use of glucagon in a pump for up to 27 hours. Both studies were overseen by independent data safety monitoring boards at Massachusetts General Hospital. Companies providing device components and in-kind support had no role in the design, conduct, analysis, or decision to publish the studies.

Eligibility criteria

Additional exclusion criteria for the adults in the Beacon Hill Study included current participation in another diabetes-related clinical trial other than one that was primarily observational, pregnancy or sexual activity without the use of contraception, history of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, stimulated C-peptide $>$ 0.1 nmol/l at 90 minutes after liquid mixed meal by the DCCT protocol, total daily dose of insulin $>$ 1.5 units/kg/day, hypoglycemia unawareness defined as lack of symptoms with plasma glucose (PG) levels $<$ 50 mg/dl, end stage renal disease on dialysis, history of impaired gastric motility requiring treatment, anemia, abnormal thyroid function, alanine amino transferase $>$ 3-fold upper limit of normal, albumin $<$ 3 g/dl, body mass index $<$ 18 or $>$ 35, coronary artery disease, abnormal EKG suggestive of coronary artery disease or increased risk of malignant arrhythmia, heart failure, seizure disorder or history of hypoglycemic seizure in the last 5 years, history of TIA or stroke, use of medications for glycemic control other than insulin or medications that affected gastric motility, history of aspirin allergy, aspirin intolerance, active peptic ulcer disease, blood dyscrasia or bleeding diathesis, alcohol or substance abuse, untreated or inadequately treated mental illness, inadequate venous access, unwilling or unable to avoid acetaminophen during the study, history of pheochromocytoma, history of adverse reaction to glucagon other than nausea or vomiting, and inability to perform at least 30 minutes of moderate exercise.

Additional exclusion criteria for the adolescents in the Summer Camp Study included current participation in another diabetes-related clinical trial other than one that was primarily observational, pregnancy or sexual activity without the use of contraception, personal history of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, total daily dose of insulin $>$ 2.0 units/kg/day, hypoglycemia unawareness defined as lack of symptoms with PG levels $<$ 50 mg/dl, end-stage renal disease on dialysis, congenital heart disease or known cardiac disease, history of prolonged QT or other arrhythmia, seizure disorder or history of hypoglycemic seizure in the last 5 years, history of TIA or stroke, use of medications for glycemic control other than insulin, history of eating disorder such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight, and history of intentional inappropriate dosing of insulin.

There were no exclusion criteria in either study relating to hemoglobin A1c, glycemic stability, or major or minor hypoglycemia.

Bionic pancreas algorithm

The insulin and glucagon control algorithms used in both the adult and adolescent studies were identical, and similar to those used in our previous studies [1–3]. As with recent versions of our control system, the model predictive control algorithm used in the present study for determining insulin dosing, set the pharmacokinetic clearance time for insulin to be 6.5 hours [1,2]. However, the revised version of the insulin control algorithm used in these outpatient studies included a modification in the online adaptation scheme that prevents relaxation of control aggressiveness in the daytime following good glycemic control overnight [1]. In the glucagon control algorithm, we added an automatic trigger of a glucagon dose of a certain threshold magnitude (e.g. 0.05–0.10 mg) whenever the continuous glucose

monitoring (CGM) glucose level falls below a certain threshold value (e.g. $\leq$ 65 mg/dl), and periodically after that if the CGM glucose (CGMG) level remains entirely at or below that threshold value (e.g. every 30–60 minutes). These refinements were motivated by our analysis of our previous studies [1–4].

Nocturnal hypoglycemia alert system

The nocturnal hypoglycemia alert system used in the Summer Camp Study was designed to prompt for nighttime fingerstick PG checks for the purpose of averting significant nocturnal hypoglycemia. At every five-minute step taken by the bionic pancreas, the alert system would update its online projection of when a significant hypoglycemic episode is likely to occur, based on (i) the current CGMG level and the average CGMG slope over the last 30 minutes as well as (ii) the latest fingerstick PG check (these were entered into the bionic pancreas at night) and how it had related to the CGM level at the time. Note, the bionic pancreas did not utilize these entered PG values when determining insulin or glucagon doses – they were used solely to enhance the accuracy of the hypoglycemia projections of the nocturnal hypoglycemia alert system. To be effective, the alert system required a reference fingerstick PG check around the time the subject went to bed. From then on, the alert system would continually update its projection of when a hypoglycemic episode is likely to occur and would produce alerts as needed to prompt a fingerstick PG check. Whether the prompted fingerstick PG check would lead to carbohydrate treatment or a brief period of closer monitoring, or neither, it would nevertheless be taken by the alert system to update its hypoglycemia projections. There was a mandatory 03:45 fingerstick PG check, and that check served to update the nocturnal hypoglycemia alert system. The goal of the nocturnal hypoglycemia alert system was to prevent significant nocturnal hypoglycemic episodes (PG $\leq$ 50 mg/dl) without prompting too many unnecessary fingerstick PG checks.

Experimental protocol — The Beacon Hill Study

The order of the bionic pancreas and usual care arms was randomized in blocks of two subjects. Subjects were taught how to use the point-of-care fingerstick PG meter (HemoCue). The G4 Platinum CGM sensor (DexCom) was inserted in the abdominal area by 18:00 on day 0 for each subject during both the bionic pancreas and usual care arms. The CGM was initially calibrated two hours after placement and then at home by the subject before breakfast on the day the experiment started.

Bionic pancreas arm: On study start day, subjects checked in to the hotel at 16:00 and continued their normal basal insulin infusion through their own pump until 18:00.

Two infusion sets, FDA cleared for subcutaneous insulin infusion, were inserted in the abdominal area. The infusion set tubing from each infusion site was connected to its corresponding t:slim infusion pump (Tandem Diabetes Care), one for insulin and one for glucagon. The standard priming sequence was performed according to manufacturer's instructions. One pump cartridge was filled with 3 ml of U-100 insulin lispro (Humalog, Lilly) and the other with 2 ml of freshly reconstituted glucagon (Lilly). The insulin cartridge and tubing were replaced every other day and the infusion set was changed daily. The glucagon was reconstituted according the manufacturer's instructions. In accordance with our Investigational New Drug Exemption, which allows for the use of glucagon in a pump for up to 27 hours, the glucagon cartridge, tubing, and infusion sets were replaced daily during the five-day bionic pancreas arm. The commercially available formulations of glucagon are unstable in solution [5–7]. However, it has previously been shown in human experiments that the anti-hypoglycemic effect of this glucagon formulation, when given in microdoses, is retained up to 27 hours after reconstitution in a pump reservoir, without any apparent loss of efficacy [2–4,8]. In experiments performed in porcine models of diabetes, we and others have shown that the anti-hypoglycemic effects of this glucagon formulation are retained for up to seven days after reconstitution [5,9].

Just before 18:00, the subject's own insulin infusion pump was removed. The bionic pancreas was initialized with their body weight and started at 18:00.

The CGM that was integrated into the bionic pancreas was calibrated before dinner, before breakfast, and before lunch during the first 24-hr period, and then twice daily (before breakfast and before dinner), on days 2 through 5. Calibrations were postponed if carbohydrates were consumed in the last 30 minutes, glucagon was dosed in the last

15 minutes, or the slope of the CGMG trace was $> |1|$ mg/dl/min. When a fingerstick PG check performed before a meal, exercise, or for symptoms of hypoglycemia (i.e. a "for cause check, in contrast to routine checks performed for data collection purposes), an additional calibration was performed if the CGMG level was not within the ISO standard compared with the PG level (i.e. CGMG level within 20% of PG level if the PG level > 75 mg/dl or within 15 mg/dl of PG level if the PG level < 75 mg/dl) and the aforementioned conditions were met. If a calibration was delayed, it was performed at the next available opportunity. All CGM calibrations were performed using PG values obtained with the HemoCue glucose monitor.

On the bionic pancreas, CGMG levels streamed wirelessly to the bionic pancreas via a radio frequency signal every five minutes and the control algorithm commanded doses of insulin and/or glucagon wirelessly via Bluetooth Low Energy to the two infusion pumps (Fig. S3). The dose that was delivered was then plotted and taken into account during future dosing. If all or a portion of a dose failed at one time step, as occasionally happened, the control algorithm accounted for this in determining the size of the dose at the next time step. The bionic pancreas was worn by the subjects or kept close by (such as when sleeping) at all times in order to ensure good radio frequency communication was maintained between the bionic pancreas and the sensor transmitter and infusion pumps. Most plasma glucose values were manually entered into the bionic pancreas as they were performed, but these were not used by the bionic pancreas unless they were calibrations or if there was no CGMG signal. If the CGMG signal was interrupted, the bionic pancreas would continue to dose automatically determined basal insulin based on requirements learned by the system when the CGM was online. Fingerstick PG measurements were obtained as frequently as every 30 minutes until the CGM came back online. In addition to providing automatically determined basal insulin during these periods, the fingerstick PG values entered when the CGM was offline allowed the bionic pancreas to automatically administer insulin and glucagon boluses. In the event of a CGM sensor failure or loss of the CGM sensor (e.g. due to adhesive failure), a new sensor was inserted and the bionic pancreas automatically delivered insulin as described above until the sensor warmup period was completed. If the CGMG level reached its threshold at 400 mg/dl and remained there for more than one hour or if a PG measurement was > 400 mg/dl, the CGM input to the bionic pancreas was briefly interrupted to input a PG value. This allowed the system to give an automatic insulin bolus in response to the true PG level. The CGMG signal was then restored and the bionic pancreas resumed normal operation.

Because the bionic pancreas was not waterproof, the system was disconnected (for not more than one hour) for swimming and showering. During the bionic pancreas arm, a member of the study staff (nurse, nurse practitioner, or physician) was either accompanying each subject or remotely monitoring from a nearby location at all times. The study staff carried carbohydrates for hypoglycemia treatment, glucagon for hypoglycemic emergencies, spare insulin lispro in a cold pack, spare infusion sets and infusion pump supplies, and spare CGM sensors and transmitters.

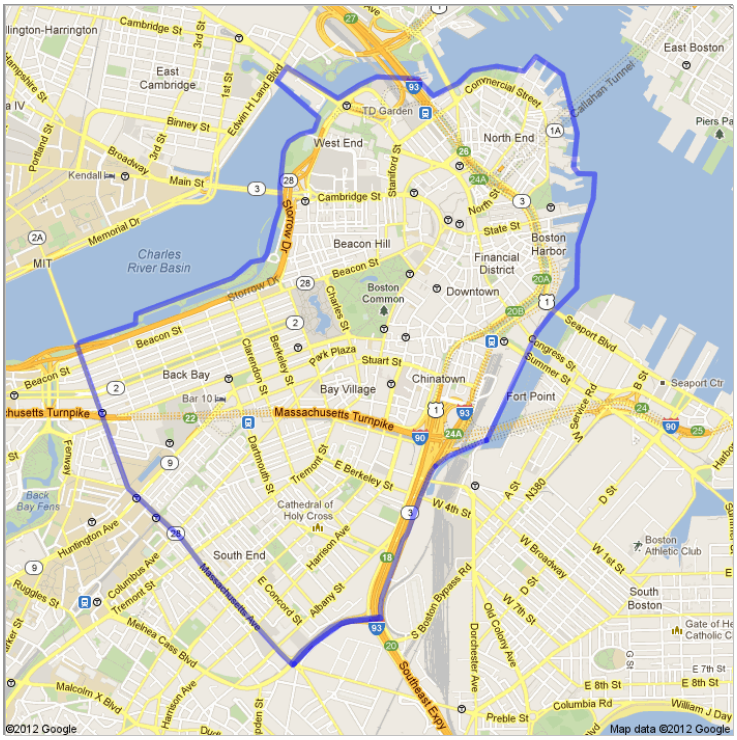
Subjects had no meal restrictions. They were given $250 to purchase food at any location they chose and could supplement this amount from their own funds.

For all meals, subjects were asked to announce meal size to the bionic pancreas as "typical", "more than usual", "less than typical", or "a small bite" and the type as "breakfast", "lunch", or "dinner". This triggered a partial meal-priming bolus, which automatically adapted towards 75% of the four-hour post-prandial insulin need for meals of that size and type. The first meal-priming bolus of each type was based solely on body mass (0.05 U/kg). Subjects were not reminded if they forgot or chose not to announce meals. Subjects were also asked to restrict they consumption of ethanol to no more than three alcoholic drinks per day for men and no more than two alcoholic drinks per day for women.

Subjects were free to walk, ride a bicycle (assuming the study staff escort was willing and able to ride a bicycle to accompany them), or take public transportation or a taxi within the designated geographic area of downtown Boston and the Back Bay between the hours of 07:00 and 23:00. The areas were bounded on the North/Northwest by the Charles River (while including the Museum of Science situated on the locks in the Charles River), on the North/Northeast by the Atlantic Ocean, on the East/Southeast by the Fort Point Channel, I-93, and Melnea Cass Blvd, on the South by I-90, and on the West/Southwest by Massachusetts Avenue (see map of study area below).

Google

3 square miles



Beacon Hill Study Boundaries
Map showing boundaries volunteers in MGH/BU Beacon Hill Study of closed-loop blood glucose control
with a bi-hormonal bionic pancreas will
Public - 0 views
Created Jan 2012 - By - Updated <1 minute ago
Land Boundary

Geographical area for the Beacon Hill Study. Map showing boundaries (blue perimeter line) of the designated three-square-mile geographical region for the Beacon Hill Study.

From 07:00 to 23:00 PG, levels were measured every two hours and before each meal and bedtime using a point-of-care PG meter (HemoCue). More measurements were performed if there were differences in meal timing, exercise, and/or hypoglycemia. Subjects were allowed to exercise at will. The only restriction was that the subjects had to stay near the nurse and could not require the nurses to make any excessive exertion (for example, any running would have to be around a field or track or on a treadmill, and any cycling would have to be on a stationary bike unless the nurse was also willing to cycle). Fingerstick PG measurements were taken at the onset of exercise as well as every 30 minutes during exercise. Subjects were allowed to treat for any episodes of hypoglycemia with oral carbohydrates at their discretion. However, they were required to take oral carbohydrates for PG $<$ 50 mg/dl.

Subjects remained in the hotel room from 23:00–07:00. They had a 20 gauge or smaller intravenous (IV) catheter placed before 23:00 on day 1. The IV was connected to the GlucoScout and serum PG values were obtained every 30 minutes. The GlucoScout device was used according to the manufacturer's instruction except that no heparin was added to the flush bag. All subjects were given an 81 mg baby aspirin to be chewed at the beginning of the study and then daily in order to help prevent occlusion of IV lines.

If an interruption in the CGMG signal occurred, study staff assisted the volunteer in recovering CGMG streaming through forced calibrations or replacement of the sensor and calibration. Once the sensor was back online, the bionic pancreas could resume responding to the CGMG signal automatically. If there was a complete failure of bionic pancreas operation, volunteers were to take over their own glycemic control using their own insulin pump until the bionic pancreas was brought back online. However, this never occurred.

If the PG level (venous or fingerstick) was $\geq$ 400 mg/dl or $>$ 250 mg/dl for 4 hours, a ketone measurement was performed on capillary blood using a Precision Xtra point-of-care meter (Abbott Diabetes Care) and the bionic pancreas was checked for any malfunction. Repeat PG and ketone measurements were performed hourly until the ketone level was negative ($<$ 0.6 mmol/l).

The experiment was ended at 18:00 on day 5 after 120 hours.

Usual care arm: Under usual care, the subjects wore a G4 Platinum CGM sensor and a G4 Platinum CGM receiver with the display masked and alarms muted. The calibration was the same as during the bionic pancreas period except that calibrations only took place before breakfast and dinner and if requested by the CGM receiver. Subjects were encouraged to wear their own CGM, unblinded, if that was their usual practice. They were given a HemoCue meter and were asked to use it for all fingerstick PG measurements and calibrations. Subjects documented meal times, estimated carbohydrate amounts, and took photos of their meals. They also documented the timing and duration of their exercise. They were asked to document any carbohydrate interventions taken for hypoglycemia along with the corresponding PG measurement at that time.

Subjects were given $250 to purchase food at any location they chose and were encouraged to eat restaurant meals to promote parity with the bionic pancreas arm.

The experiment was ended at 18:00 on day 5 after 120 hours.

Experimental protocol — The Summer Camp Study

The order of the bionic pancreas and comparator periods for each subject was randomized in blocks of two subjects. The G4 Platinum CGM sensor was inserted in the abdominal area by 13:00 on day 0 for each subject during both study periods. The CGM was initially calibrated two hours after placement at 15:00 on day 0, so that sensor streaming would initiate $\sim$ 24 hours prior to study start. The CGM was calibrated a second time, 24 hours after the first calibration, at 15:00 on day 1. Subsequent CGM calibrations were performed before dinner and before breakfast. Calibrations were postponed if carbohydrates were consumed in the last 30 minutes, glucagon was dosed in the last 15 minutes, or the slope of the CGMG trace was $> |1|$ mg/dl/min. When a fingerstick PG check performed before a meal, exercise, or for symptoms of hypoglycemia (i.e. a for cause check, in contrast to routine checks performed for data collection purposes), an additional calibration was performed if the CGMG level was not within the ISO standard compared with the PG level (i.e. CGMG level within 20% of PG level if the PG level $>$ 75 mg/dl or within 15 mg/dl of PG level if the PG level $<$ 75 mg/dl) and the aforementioned conditions were met. If a calibration was delayed, it was performed at the next available opportunity. All CGM calibrations were performed using PG values obtained with the HemoCue glucose monitor.

Bionic pancreas arm: Subjects continued usual insulin dosing through their own insulin pumps until study start at 15:00 on day 1.

Two infusion sets, FDA cleared for subcutaneous insulin infusion (in most cases the Inset 30, Animas), were inserted in the abdominal area. The infusion set tubing from each infusion site was connected to its corresponding t:slim infusion pump, one for insulin and one for glucagon. Occasionally, the infusion sets and/or CGM sensor were placed on the subject's arm or buttocks at the subject's request due to discomfort as a result of insufficient subcutaneous fat. Occasionally, the subject's own preferred insulin infusion set was used instead of the Inset 30 if the subject complained of irritation or pain. The standard priming sequence was performed according to manufacturer's instructions. One pump cartridge was filled with 3 ml of U-100 insulin lispro and the other with 2 ml of glucagon. The insulin cartridge and tubing were replaced every other day and the infusion set was changed daily. The glucagon was reconstituted according the manufacturer's instructions. In accordance with our Investigational New Drug Exemption, which allows for the use of glucagon in a pump for up to 27 hours, the glucagon cartridge, tubing, and infusion sets were replaced daily during the five-day bionic pancreas arm because the commercially available formulation of glucagon is unstable in solution[5–7].

Just before 15:00, the subject's own insulin infusion pump was removed. The bionic pancreas was initialized with their body weight and started at 15:00.

On the bionic pancreas, CGMG levels streamed wirelessly to the bionic pancreas via a radio frequency signal every five minutes and the control algorithm commanded doses of insulin and/or glucagon wirelessly via Bluetooth Low Energy to the two infusion pumps (Fig. S3). The dose that was delivered was then plotted and taken into account during future dosing. If all or a portion of a dose failed at one time step, as occasionally happened, the control

algorithm accounted for this in determining the size of the dose at the next time step. The bionic pancreas was worn by the subjects or kept close by (such as when sleeping) at all times in order to ensure good radio frequency communication was maintained between the bionic pancreas and the sensor transmitter and infusion pumps. Plasma glucose values were manually entered into the bionic pancreas as they occurred, but these were not used by the bionic pancreas unless they were calibrations or if there was no CGMG signal. If the CGMG signal was interrupted, the bionic pancreas would continue to dose automatically determined basal insulin based on requirements learned by the system when the CGM was online. Fingerstick PG measurements were obtained as frequently as every 30 minutes until the CGM came back online. In addition to providing automatically determined basal insulin during these periods, the fingerstick PG values entered when the CGM was offline allowed the bionic pancreas to automatically administer insulin and glucagon boluses. In the event of a CGM sensor failure or loss of the CGM sensor (e.g. due to adhesive failure), a new sensor was inserted and the bionic pancreas automatically delivered insulin as described above until the sensor warmup period was completed. If the CGMG level reached its threshold at 400 mg/dl and remained there for more than one hour or if a PG measurement was $>$ 400 mg/dl, the CGM input to the bionic pancreas was briefly interrupted to input a PG value. This allowed the system to give an automatic insulin bolus in response to the true PG level. The CGMG signal was then restored and the bionic pancreas resumed normal operation.

Because the bionic pancreas was not waterproof, the system was disconnected (for not more than one hour) for swimming and showering.

During the bionic pancreas period camp nurses assisted subjects $<$ 18 years of age in announcing their meal size to the bionic pancreas as "typical", "more than usual", "less than typical", or "a small bite" and the type as "breakfast", "lunch", or "dinner". This triggered a partial meal-priming bolus, which automatically adapted towards 75% of the four-hour post-prandial insulin need for meals of that size and type. The first meal-priming bolus of each type was based solely on body mass (0.05 U/kg). The size designation of each meal was based on an interview with the campers and their parents or guardians who designated what range of carbohydrates would fall into each of the four meal-size bins. These meal-size ranges were provided to camp staff who then used them to announce all meals for subjects $<$ 18 years of age. Only three meals (breakfast, lunch, and dinner) were announced during the bionic pancreas period; snacks were not announced, regardless of their size. Subjects 18 years and older announced their own meals without guidance on the bionic pancreas, and no reminder was provided if they failed to announce a meal.

Comparator arm: Subjects wore the integrated iPhone/CGM receiver unit with the displays on both the iPhone and CGM receiver blinded and all alarms muted. Subjects continued their usual insulin dosing through their own insulin infusion pumps throughout the comparator period. Insulin dosing during the comparator period could be adjusted by the camp physician during daily chart review as per normal camp practice. The study team had no role in determining insulin dosing during the comparator period. Subjects were encouraged to wear their own CGM, unmasked, if that was their usual practice at camp.

During the comparator period camp nurses assisted subjects $<$ 18 years of age in determining their meal boluses based on the orders of the camp physician. During the comparator period insulin boluses were given for snacks according to the usual camp policy. Subjects 18 years and older determined their own meal bolus sizes and administered their own meal boluses with their insulin infusion pumps.

Procedures common to both study arms: During both study periods all fingerstick PG values were obtained using the HemoCue point-of-care fingerstick PG monitor. Scheduled PG checks occurred in both study periods before meals, and at bedtime, 00:00, and 03:45. All checks were usual camp checks, except for the 03:45 check, which was done in usual camp care if the 00:00 check found hypoglycemia or if ordered by a camp physician. Additional fingerstick PG values were obtained before swimming, before disconnecting from the pump, for symptoms of hypoglycemia or hyperglycemia, and when determined by the nocturnal hypoglycemia alert system. The nocturnal hypoglycemia alert system was monitored in real-time and a study nurse was sent to perform a PG check if the system predicted a PG $<$ 60 mg/dl between 23:00 to 07:00. During the rest of the day (07:00–23:00) a nurse was sent to obtain a PG measurement if the CGMG level was $<$ 50 mg/dl. The CGMG signal was monitored remotely and real-time by telemetry around-the-clock.

Any suspected hypoglycemia was investigated with a fingerstick PG measurement. The usual camp protocol was to treat any PG level < 80 mg/dl with 15 g rapid-acting carbohydrate (typically glucose tablets or juice). The PG level was rechecked in 15–20 minutes. If the rechecked PG level was > 70 mg/dl, then 15 g of complex carbohydrates was given (typically snack crackers with peanut butter or cheese) and the treatment algorithm was complete. The complex carbohydrate was omitted if the time was within one hour of a scheduled meal or snack. If the rechecked PG level was < 70 mg/dl, then the treatment algorithm started over, with 15 g of rapid-acting carbohydrates, followed by another PG level recheck in 15–20 minutes. Management of hypoglycemia was different than the usual camp protocol during both the bionic pancreas and comparator periods in order to test the hypoglycemia prevention function of the bionic pancreas and to keep the management identical between the two study arms. For PG levels between 60 and 80 mg/dl with symptoms of hypoglycemia, and for PG levels < 60 mg/dl, 15 g of rapid-acting carbohydrate was given and then the normal camp protocol was followed from that point forward. However, for PG levels between 60 and 80 mg/dl without symptoms, the PG level was rechecked in 15–20 minutes. If the PG was > 70 mg/dl at the time of the recheck then no action was taken. If the rechecked PG level was < 70 mg/dl, then 15 g of rapid-acting carbohydrates was given and then the normal camp protocol was followed from that point forward.

If the fingerstick PG level was ≥ 400 mg/dl or > 250 mg/dl for 4 hours, a ketone measurement was performed on capillary blood using a Precision Xtra point-of-care meter and the bionic pancreas was checked for any malfunction. Repeat PG and ketone measurements were performed hourly until the ketone level was negative (< 0.6 mmol/l).

The subjects consumed meals and snacks according to the usual camp schedule: breakfast at $\sim$ 08:00, lunch at $\sim$ 12:00, dinner at $\sim$ 18:00, bedtime snack at $\sim$ 21:00. The menu for meals was the same as that used during other camp sessions. It was developed by camp staff and was assessed for balance and compliance with the USDA's nutritional requirement suggestions. A camp dietitian intern worked closely with kitchen staff to provide healthy options and accurate carbohydrate content information to all campers, which assisted subjects in the comparator arm with pre-prandial insulin dosing. The dietitian substituted meal items in cases of food allergy or dietary restrictions. All meals were served family style.

The subjects were very active in the camp setting, with multiple activity periods ("actives") daily. Subjects in both arms of the study participated in the same activities as campers not enrolled in the trial. Campers had a minimum of four 45-minute activity periods daily (two more active, two less active), in addition to an optional swimming period and an evening activity period. For any given period they were allowed to choose between activities (e.g. between basketball or softball, etc.). Each subject could choose different activities in each of multiple periods of every day.

The first experimental period ended at 15:00 on day 5 after 120 hours. After the first experimental period, there was a two-day washout period followed by the second experimental period. All subjects received usual camp care during the washout period. The CGM sensor for the second experimental period was placed at 13:00 on the second day of the washout period so that it had its first calibration 24 hours prior to the start of the second experimental period.

Study staff (two nurses and one physician or nurse practitioner) were available on site at all times during the study to assist with CGM calibrations, any needed technical assistance or troubleshooting, to assist camp staff with fingerstick PG measurements on subjects, to perform fingerstick PG measurement based on the nocturnal hypoglycemia alert system (at nighttime), and based on CGMG readings < 50 mg/dl (during daytime), to replace infusion pump cartridges and infusion sets as needed, to assist camp staff with properly following the protocol when it differed from the usual camp protocol, and to perform documentation that was not part of usual camp care. However, study staff did not interfere in the operation of the bionic pancreas. No insulin or glucagon was given during the bionic pancreas period other than that given by the bionic pancreas. Study staff had no role in decisions about treatment of subjects during the comparator period, except to ensure compliance with the protocol.

The study ended at 15:00 on day 5 of the second study period.

Adverse events — The Beacon Hill Study

Adverse events were reported to the nurses and documented during the bionic pancreas arm. No data on adverse events other than hypoglycemia were collected during the usual care arm. There were no episodes of severe hypoglycemia (requiring assistance from another person) on the bionic pancreas. Headache occurred on three occasions in two subjects on the bionic pancreas. In one subject, no glucagon had yet been dosed. In the other subject, one episode occurred approximately 100 minutes after the last glucagon dose and the other occurred approximately 5 hours after the last glucagon dose. Given the half-life of glucagon in plasma, these are unlikely to be related to glucagon dosing[3,4]. Nausea without vomiting occurred on one occasion each in four subjects on the bionic pancreas. In three of these cases, no glucagon dosing had occurred in over 2 hours, making it unlikely that these symptoms were related to glucagon. In one case the nausea was coincident with a glucagon dose of $\sim$42 μg (4.2% of the FDA approved dose for treatment of severe hypoglycemia). Nausea with vomiting occurred in one subject in the setting of an intravenous catheter removal, with the last glucagon dosed approximately 1 hour earlier. The clinical characteristics of this event were most consistent with a vasovagal episode. Three insulin infusion sets and one glucagon infusion set were removed for pain or inflammation during the bionic pancreas arm. One subject developed moderate hyperketonemia (0.8 mmol/l) on the bionic pancreas in the setting of a leaking insulin infusion set. The hyperketonemia resolved after the infusion set was changed. More details about all adverse events in the adult subjects can be found in the captions of the individual experiments (Figs. S4–S23).

Adverse events — The Summer Camp Study

Adverse events were reported to the nurses and documented during both arms of the study. There were no episodes of severe hypoglycemia (requiring assistance from another person) on the bionic pancreas. There was one episode of hypoglycemia associated with confusion (lowest PG measured 19 mg/dl) in the comparator period that was successfully treated with oral carbohydrates. All other hypoglycemia was associated with only mild symptoms. Three subjects on the bionic pancreas and three during the comparator period developed transient hyperketonemia (ketone levels 0.6–1.9 mmol/dl) that resolved after changing the insulin infusion set or, in one case, after resolving a technical problem with the bionic pancreas. One subject reported nausea on the bionic pancreas and two subjects reported vomiting on the bionic pancreas on one occasion each. In each case the last dose of glucagon had been given 2–5 hours earlier. Given the half-life of glucagon in plasma, these are unlikely to be related to glucagon dosing[3,4]. One insulin infusion set was removed for inflammation and leakage during the bionic pancreas period. More details about all adverse events in the adolescent subjects can be found in the captions of the individual experiments (Figs. S24–S55).

Beacon Hill Study CONSORT Flow Diagram

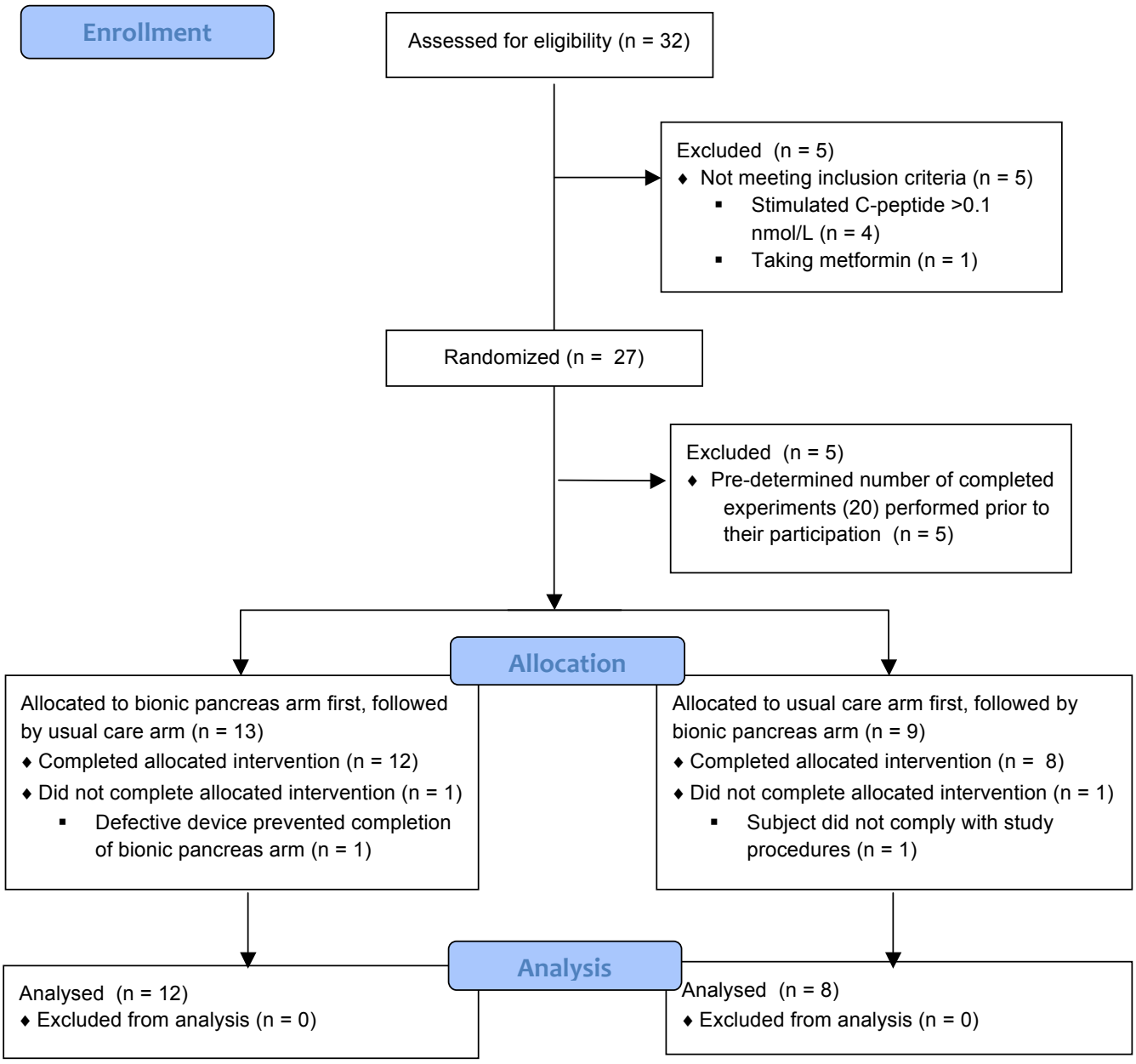


Figure S1. Beacon Hill Study consort flow diagram. Of 32 subjects assessed for eligibility, 5 were excluded. Four of these were due to low-level endogenous insulin production (stimulated C-peptide $>$ 0.1 nmol/L) and one was taking metformin. Of the remaining 27 subjects who were randomized to either the bionic pancreas or usual care arm first, 20 completed the allocated interventions. Two subjects did not complete the allocated interventions. In one case a defective device prevented completion of the bionic pancreas arm. In the other case the subject did not comply with study procedures and was removed from the study prior to completion of the bionic pancreas arm. Five randomized subjects were not asked to participate in experiments because the pre-specified number of complete experiments (20) had been reached. All of the data from the 20 subjects who completed the allocated interventions were included in the analysis, including periods associated with technical problems.

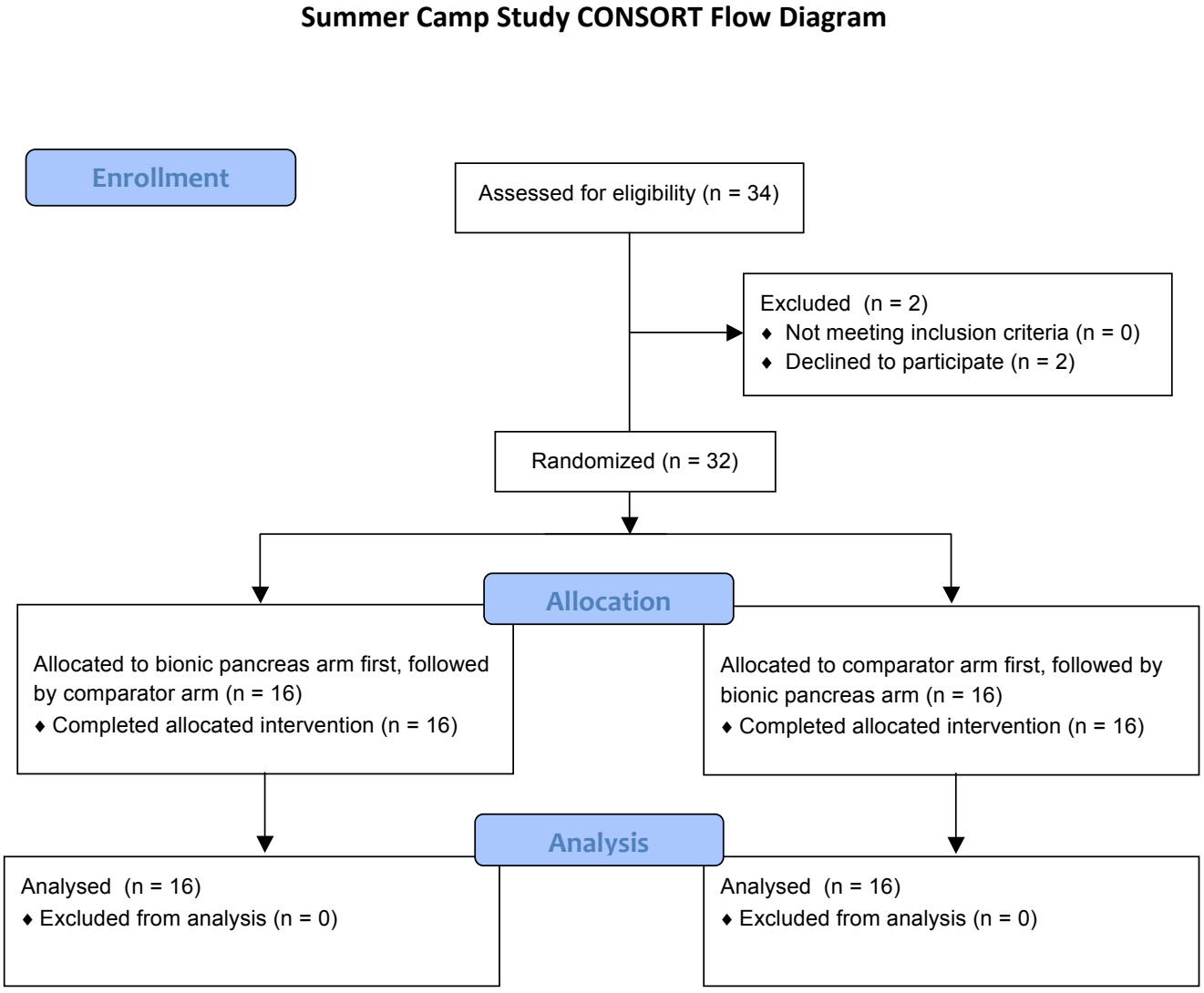


Figure S2. Summer Camp Study consort flow diagram. Of 34 subjects assessed for eligibility, all met inclusion criteria. However, two subjects declined to participate prior to the start of the study; one did not want to stay at camp and went home with their parents on the day of arrival, the other did not want to follow the study procedure that required subjects to remain on the camp grounds for the duration of the study. The remaining 32 subjects were randomized to either the bionic pancreas or comparator arm first. All 32 completed the allocated interventions. All of the data were included in the analysis, including periods associated with technical problems.

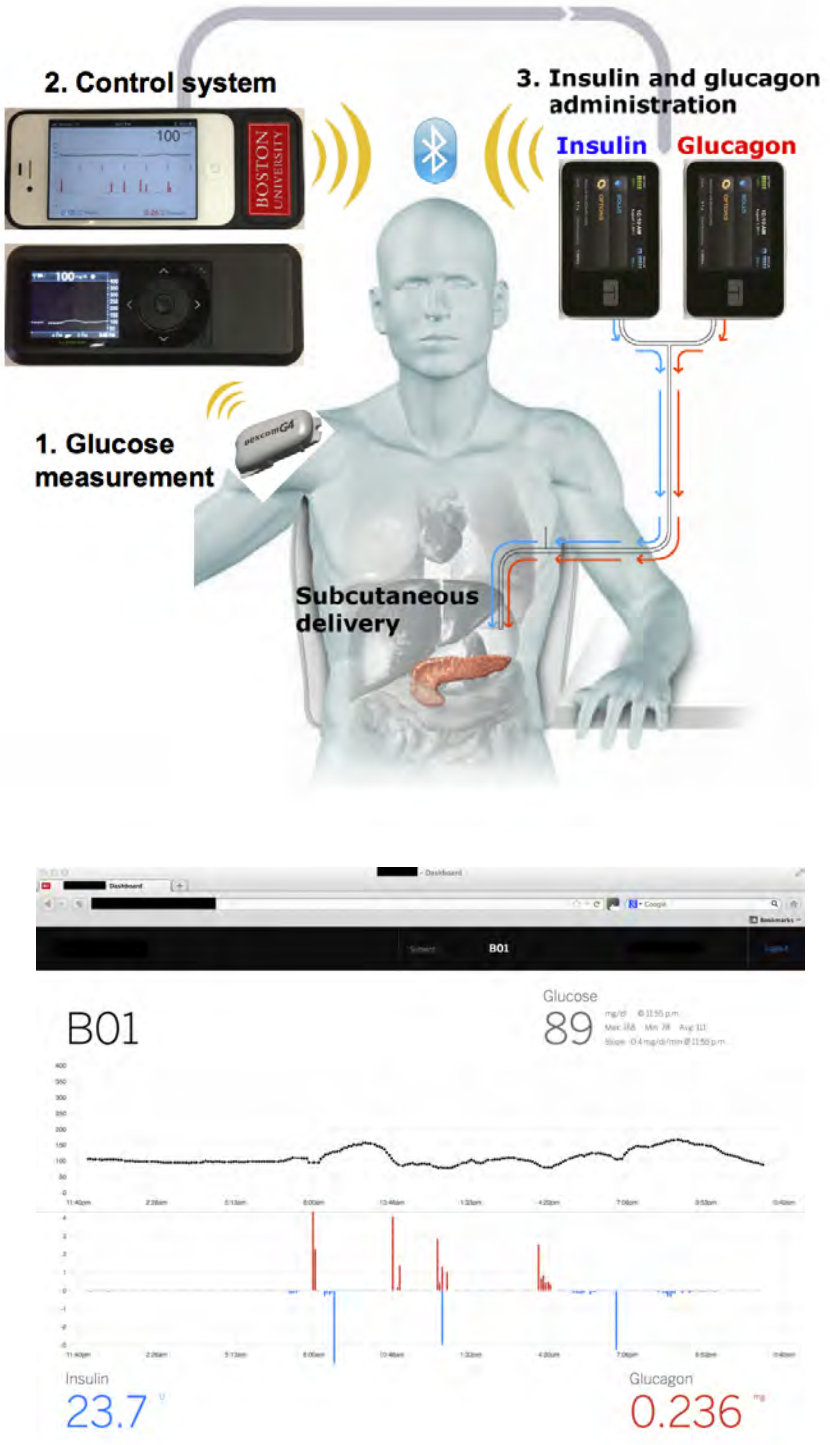


Figure S3. Schematic of the wearable bihormonal bionic pancreas system used in the outpatient studies. Top: The control algorithm, which is written in C++ in an app that runs on an Apple iPhone 4S (station 2 – Control system), responds to CGMG levels streamed online every five minutes using the integrated G4 Platinum CGM (station 1 – Glucose measurement), and commands insulin and glucagon control doses using two t:slim infusion pumps (station 3 – Insulin and glucagon administration). Bottom: A screenshot (with all subject-identifiable information redacted) from our web-based realtime remote-monitoring dashboard showing data from one of our adult outpatient experiments in the Beacon Hill Study. This dashboard included live streaming of instantaneous CGMG profiles, insulin and glucagon dosing, current CGMG and its rate-of-change, total daily insulin and glucagon doses, and all fingerstick PG values entered into the bionic pancreas.

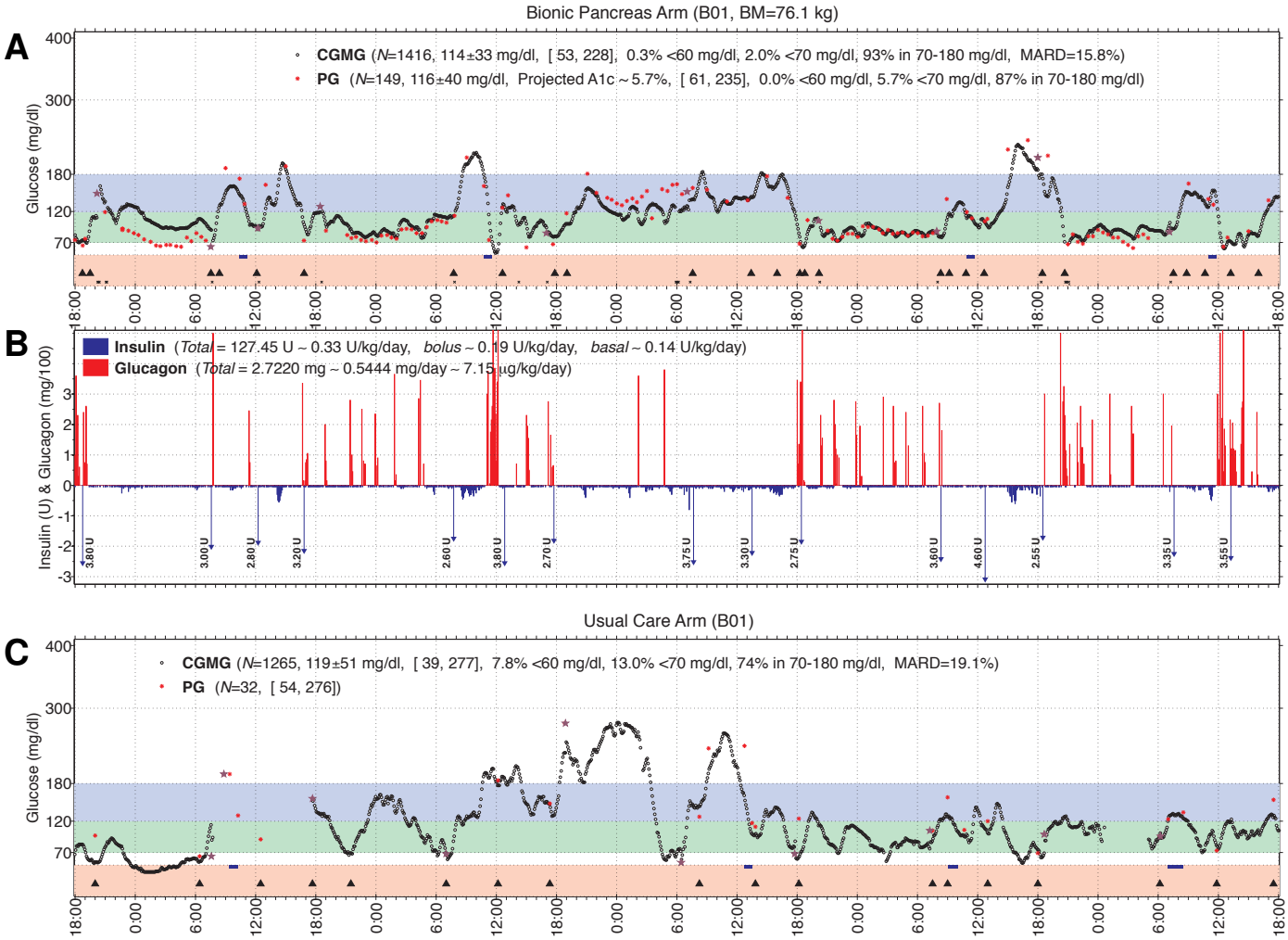


Figure S4. Outpatient experiments in adult subject #B01. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. Fingerstick and venous PG measurements (red stars) are superimposed on the CGMG trace (black circles). Calibrations of the CGM are indicated by purple stars. Along the timeline, carbohydrate treatments for hypoglycemia are indicated by black rectangles, meals and snacks by black triangles, and exercise periods by horizontal blue bars. A small black $\times$ indicates a step for which no CGMG level was captured or used by the bionic pancreas. Insulin and glucagon doses that were issued by the control algorithm are respectively indicated by downward blue and upward red bars in panel **B**. Over the entire 5-day period on the bionic pancreas, mean CGMG was 114 mg/dl (116 mg/dl for PG), and average dosing was 0.33 U/kg/day and 7.15 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 114 mg/dl (117 mg/dl for PG), average dosing was 0.33 U/kg/day and 8.09 μg/kg/day, CGMG was $<$ 60 mg/dl 0.4% of the time (0% for PG), within 70–180 mg/dl 92.3% of the time (90.3% for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 119 mg/dl, CGMG was $<$ 60 mg/dl 7.8% of the time, and within 70–180 mg/dl 74% of the time. There were no carbohydrate interventions under usual care. Insulin infusion sets were replaced during bionic pancreas arm on day 3 15:30 and day 5 at 09:58 when subject complained of discomfort. The subject exercised on 4 out of 5 days for approximately 45 min at a time during both the bionic pancreas and usual care arms with no carbohydrate interventions required.

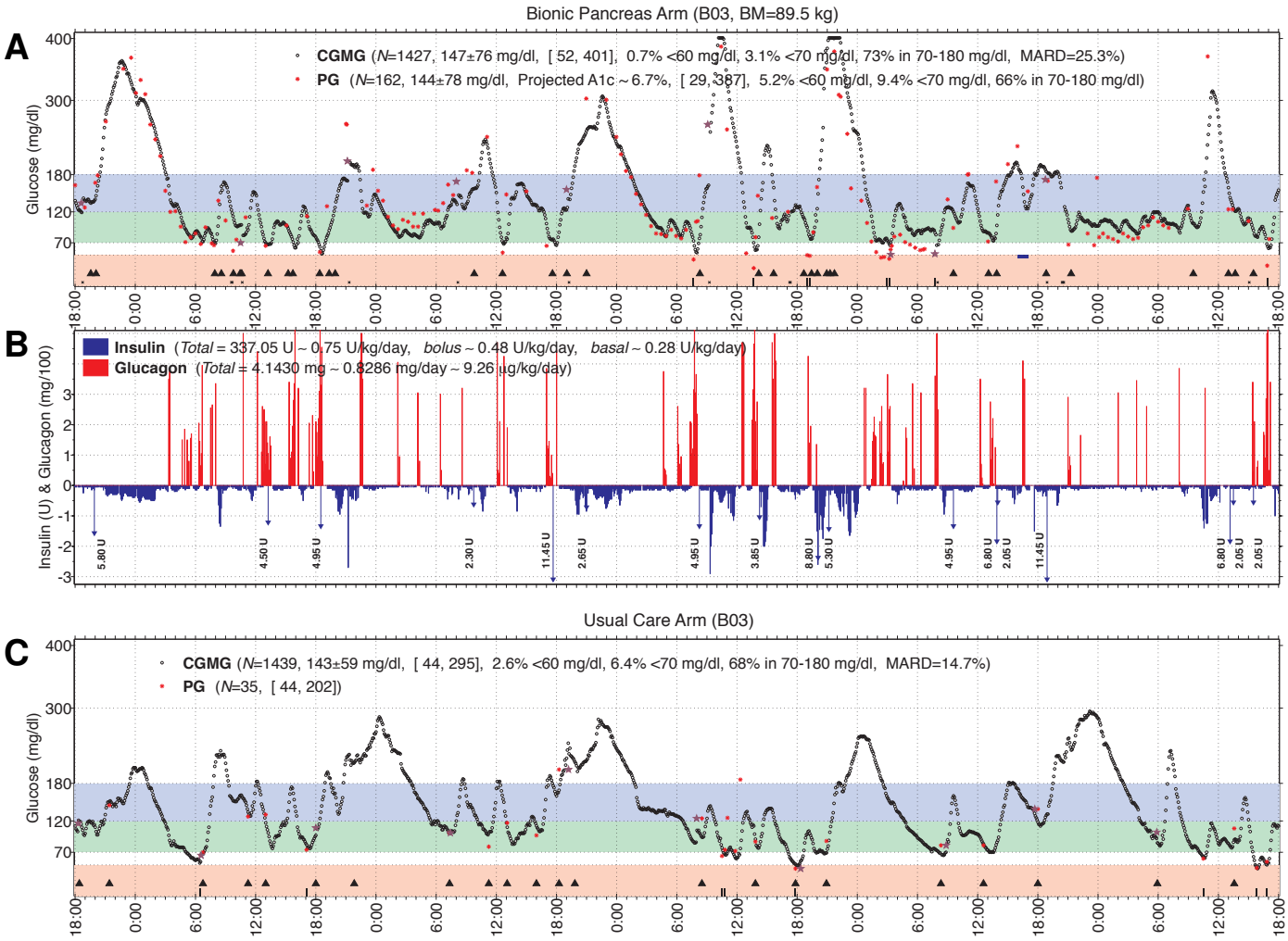


Figure S5. Outpatient experiments in adult subject #B03. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 147 mg/dl (144 mg/dl for PG), and average dosing was 0.75 U/kg/day and 9.26 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 144 mg/dl (130 mg/dl for PG), average dosing was 0.79 U/kg/day and 9.15 μg/kg/day, CGMG was $<$ 60 mg/dl 0.9% of the time (9.9% for PG), within 70–180 mg/dl 74.5% of the time (65.8% for PG), and there were 10 carbohydrate interventions (8 day, 2 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 143 mg/dl, CGMG was $<$ 60 mg/dl 2.6% of the time, and within 70–180 mg/dl 67.8% of the time. There were 6 carbohydrate interventions (5 day, 1 night) under usual care. At 08:15 on day 2 of bionic pancreas arm, the subject reported having a headache coincident with a small dose of glucagon. At 10:25 on day 3 of bionic pancreas arm, the subject reported a headache, nausea and loss of appetite (no glucagon was dosed for the preceeding 2.5 hours), which had resolved by 11:00. There were no other reports of nausea during the bionic pancreas arm. The glucagon pump cartridge and infusion set were replaced at 19:03 on the day 2 of bionic pancreas arm because of site failure following an intervention for hypoglycemia. The insulin and glucagon infusion sets were changed from a 90 degree metal set (micro orbit) to an angled teflon set (Animas Inset 30) at 22:55 on day 3 of bionic pancreas arm following another suspected glucagon site failure associated with to 2 carbohydrate interventions at 19:00 and a suspected insulin infusion set failure at 22:55. The subject exercised for approximately 60 minutes on day 5 of bionic pancreas control with no carbohydrate interventions required.

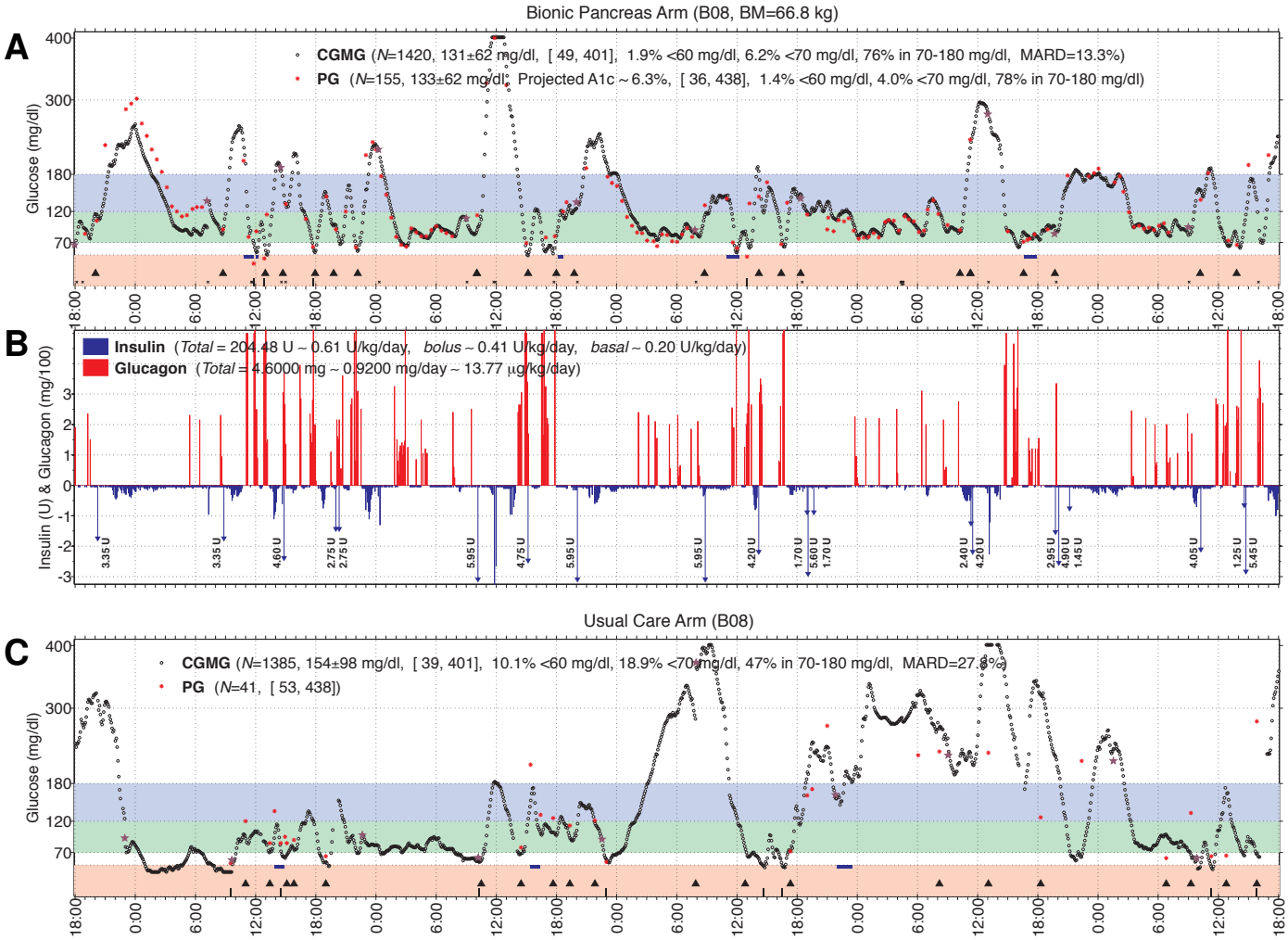


Figure S6. Outpatient experiments in adult subject #B08. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 131 mg/dl (133 mg/dl for PG), and average dosing was 0.61 U/kg/day and 13.77 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 129 mg/dl (128 mg/dl for PG), average dosing was 0.63 U/kg/day and 13.61 μg/kg/day, CGMG was $<$ 60 mg/dl 1.6% of the time (1.0% for PG), within 70–180 mg/dl 79.2% of the time (81.2% for PG), and there was 6 carbohydrate intervention (5 day, 1 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 154 mg/dl, CGMG was $<$ 60 mg/dl 10.1% of the time, and within 70–180 mg/dl 46.6% of the time. There were 5 carbohydrate interventions (4 day, 1 night) under usual care. At 11:45 on the day 2 of bionic pancreas control, an insulin infusion set failure was suspected and the CGMG reached its upper limit of 400 mg/dl. The CGM stream was briefly interrupted to allow a single PG value to be manually entered (as described above) which allowed the system to deliver a single correction bolus. Normal operation was then resumed. At 13:00 day 3 of bionic pancreas control, a hypoglycemia episode requiring carbohydrate intervention occurred while the subject was showering and disconnected from the glucagon pump. The subject exercised on four out of the five days during the bionic pancreas arm for approximately 75 minutes daily with one carbohydrate intervention on day 1. During the usual care arm, the subject exercised on three out of five days for approximately 60 minutes at a time with on carbohydrate intervention on day 1.

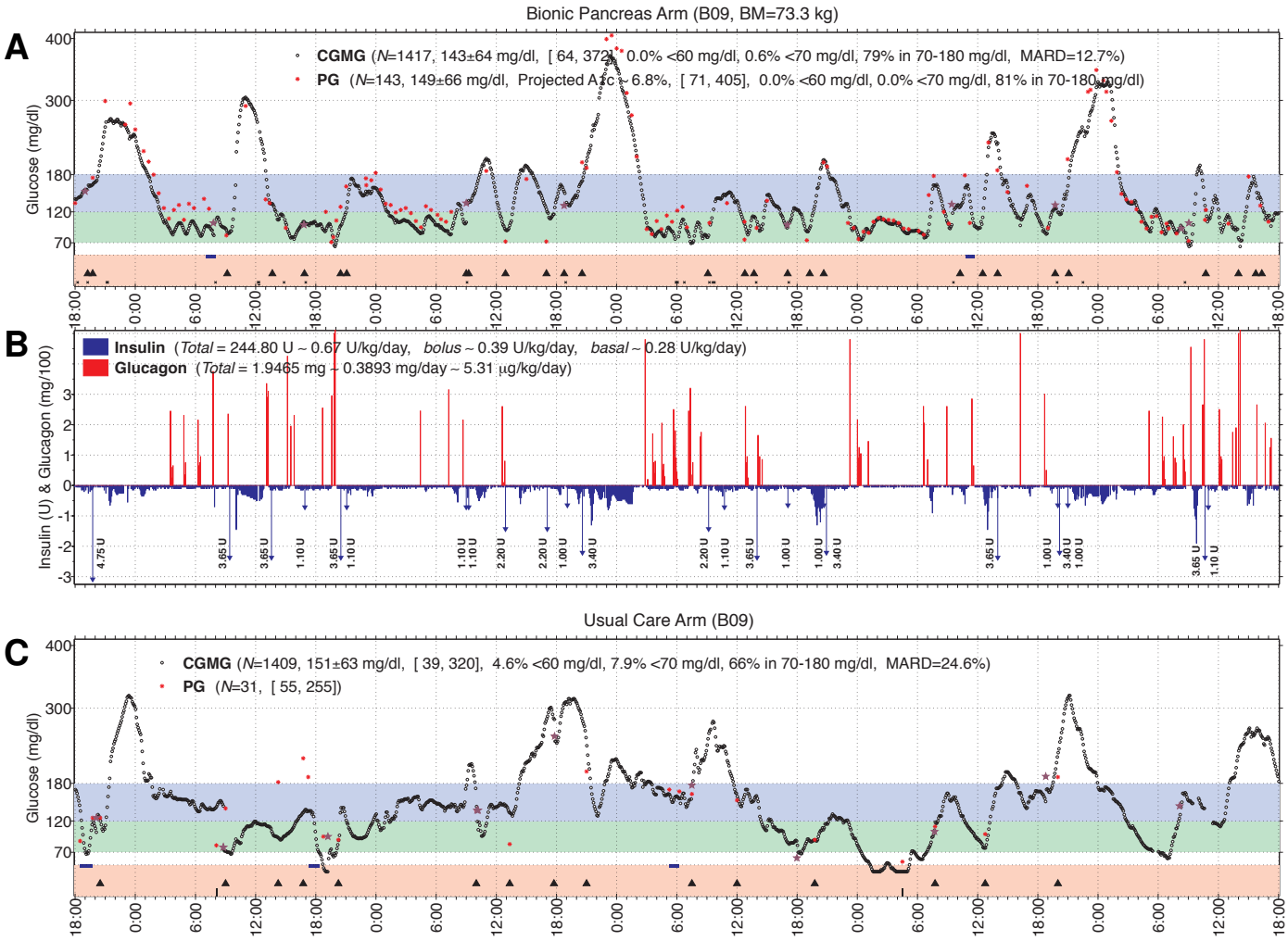


Figure S7. Outpatient experiments in adult subject #B09. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 143 mg/dl (149 mg/dl for PG), and average dosing was 0.67 U/kg/day and 5.31 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 140 mg/dl (144 mg/dl for PG), average dosing was 0.66 U/kg/day and 5.42 μg/kg/day, CGMG was $<$ 60 mg/dl 0.0% of the time (0.0% for PG), within 70–180 mg/dl 82.6% of the time (84.6 % for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 151 mg/dl, CGMG was $<$ 60 mg/dl 4.6% of the time, and within 70–180 mg/dl 66.3% of the time. There were 1 carbohydrate interventions (0 day, 1 night) under usual care. At 15:34 on day 1 of the bionic pancreas arm, the subject reported nausea during a period of glucagon dosing. There were no other reports of nausea during the bionic pancreas arm. At 22:59 on day 3 of bionic pancreas control the insulin infusion set was replaced due hyperglycemia and insulin site leakage and a ketone level of 0.8 mmol/dl. After site replacement the bionic pancreas regulated the PG excursion autonomously and the hyperketonemia resolved. On day 3 of the bionic pancreas arm, the CGM was underestimating the PG. The subject was noted to be compressing the transmitter during sleep in that time frame. At 22:55 on day 5 of the bionic pancreas arm an insulin pump infusion set was replaced because the subject reported discomfort at the site. The subject exercised for approximately 60 min on day 1 and 4 of the bionic pancreas arm with no carbohydrate interventions required. During the usual care arm, the subject exercised for approximately 65 minutes on three out of the five days with no carbohydrate interventions required.

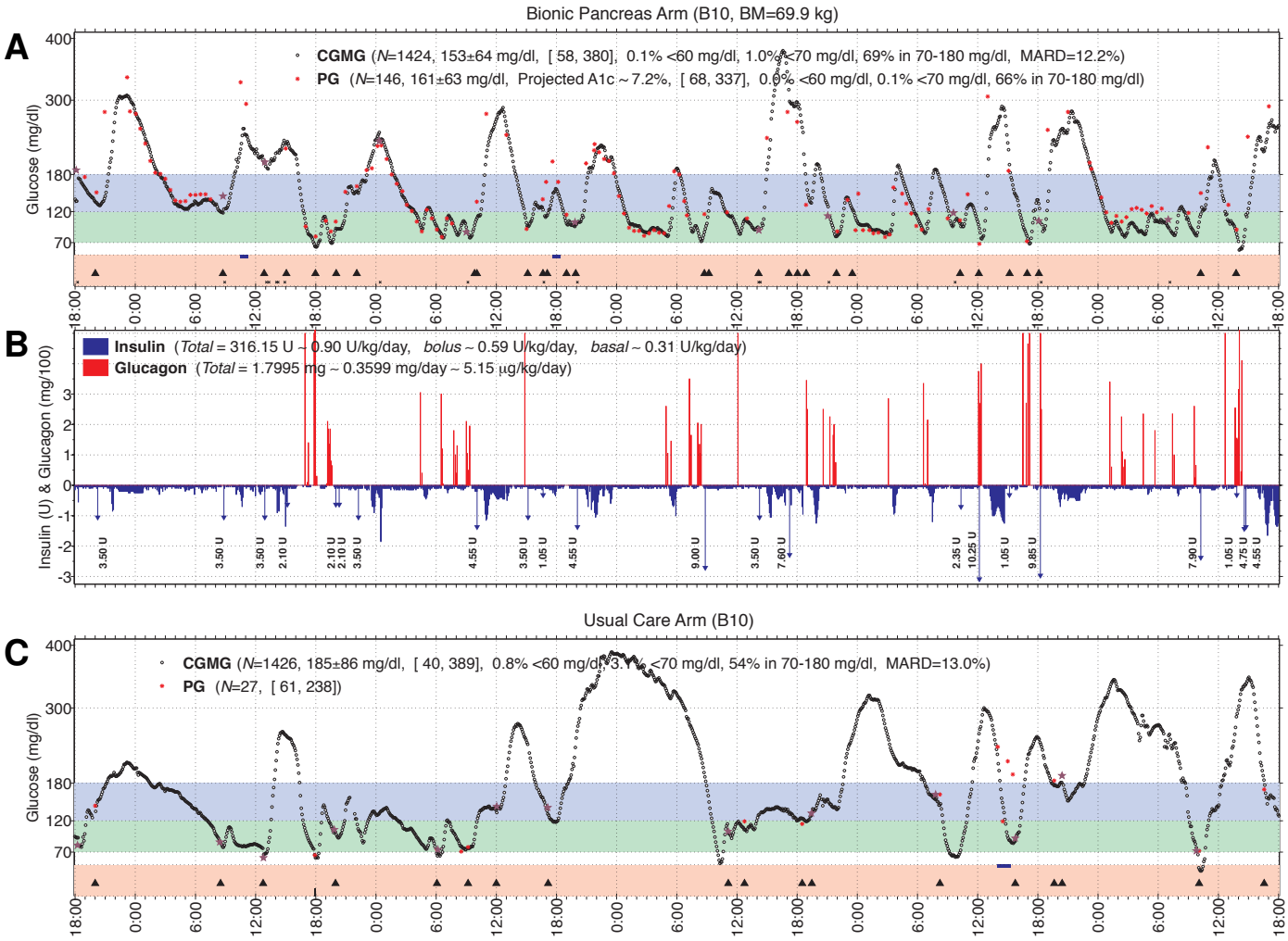


Figure S8. Outpatient experiments in adult subject #B10. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 153 mg/dl (161 mg/dl for PG), and average dosing was 0.90 U/kg/day and 5.15 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 145 mg/dl (151 mg/dl for PG), average dosing was 0.96 U/kg/day and 5.74 μg/kg/day, CGMG was $<$ 60 mg/dl 0.2% of the time (0.0% for PG), within 70–180 mg/dl 73.7% of the time (71.9 % for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 185 mg/dl, CGMG was $<$ 60 mg/dl 0.8% of the time, and within 70–180 mg/dl 53.9% of the time. There was 1 carbohydrate intervention (1 day, 0 night) under usual care. The subject exercised for approximately 45 min on day 1 and 2 of the bionic pancreas arm with no carbohydrate interventions required. During usual care, the subject exercised for approximately 90 minutes on day 4 with no carbohydrate intervention required.

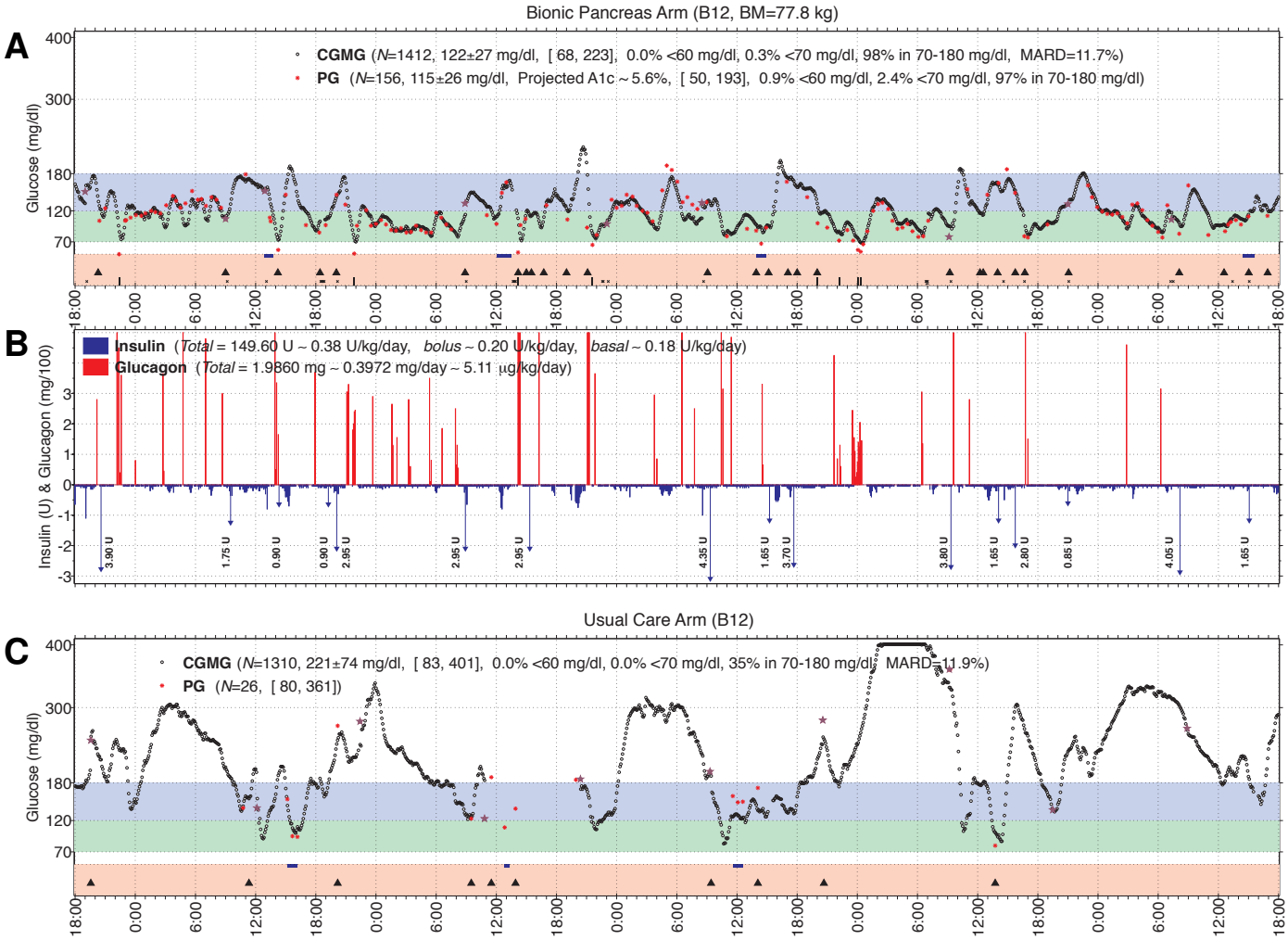


Figure S9. Outpatient experiments in adult subject #B12. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 122 mg/dl (115 mg/dl for PG), and average dosing was 0.38 U/kg/day and 5.11 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 119 mg/dl (112 mg/dl for PG), average dosing was 0.39 U/kg/day and 4.83 μg/kg/day, CGMG was $<$ 60 mg/dl 0.0% of the time (0.8% for PG), within 70–180 mg/dl 97.6% of the time (96.8% for PG), and there were 7 carbohydrate interventions (5 day, 2 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 221 mg/dl, CGMG was $<$ 60 mg/dl 0.0% of the time, and within 70–180 mg/dl 35.4% of the time. There were no carbohydrate interventions under usual care. At 08:30 on the day 4 of bionic pancreas control, the subject reported nausea and a headache with glucagon last dosed more than 1 hour previously. There were no other reports of nausea during the bionic pancreas arm. The subject exercised for approximately 65 min daily on four out of the five days of bionic pancreas control with no carbohydrate interventions required.

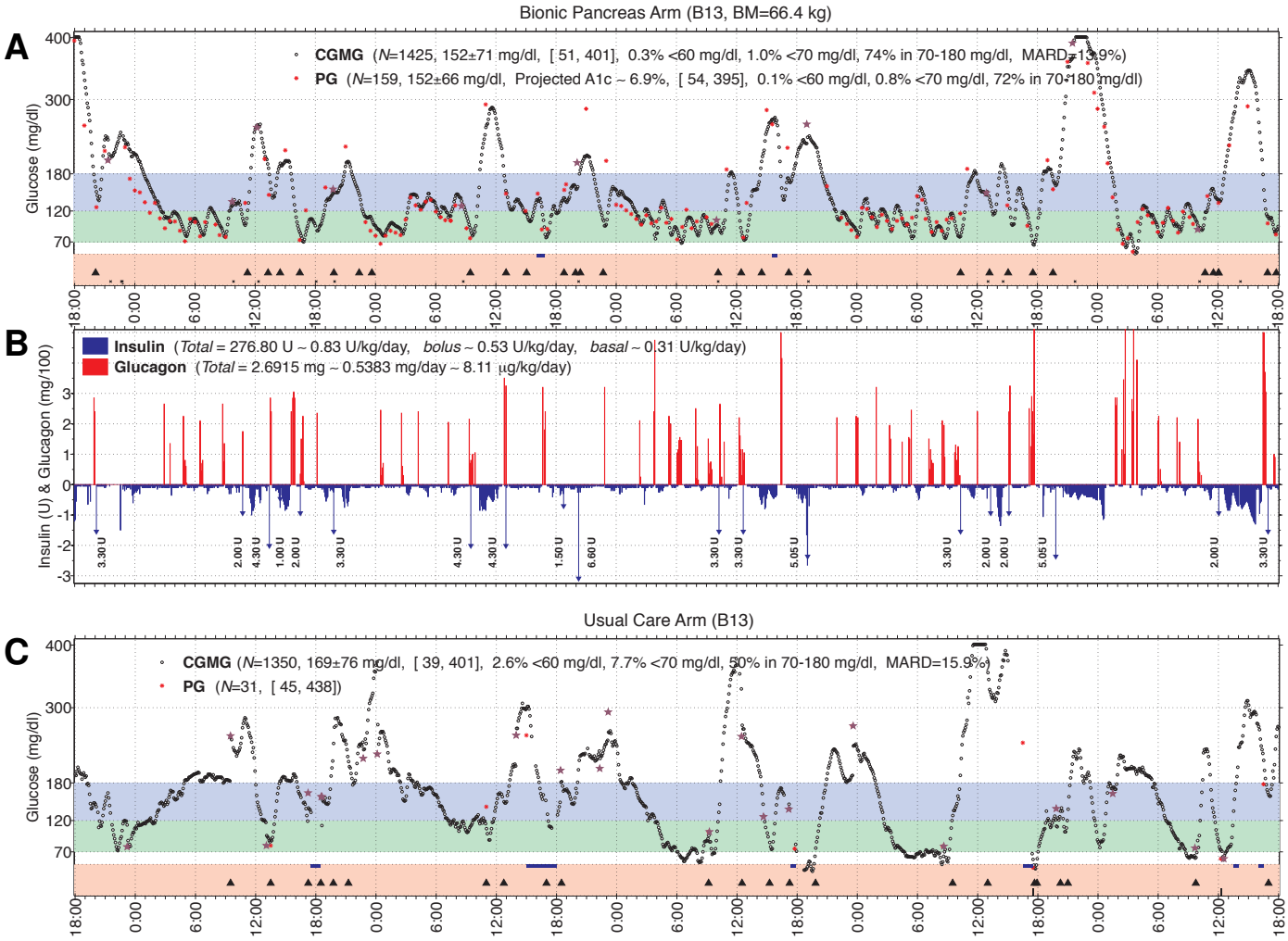


Figure S10. Outpatient experiments in adult subject #B13. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 152 mg/dl (152 mg/dl for PG), and average dosing was 0.83 U/kg/day and 8.11 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 149 mg/dl (153 mg/dl for PG), average dosing was 0.84 U/kg/day and 8.39 μg/kg/day, CGMG was $<$ 60 mg/dl 0.3% of the time (0.2% for PG), within 70–180 mg/dl 77.7% of the time (73.0% for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 169 mg/dl, CGMG was $<$ 60 mg/dl 2.6% of the time, and within 70–180 mg/dl 50.3% of the time. There were 2 carbohydrate interventions (2 day, 0 night) under usual care. At 09:45 on day 1 of the bionic pancreas arm, the subject became pale, reported nausea and lightheadedness during IV removal and vomited. Symptoms were consistent with a vasovagal episode and resolved quickly. A small amount of glucagon had been dosed within 30 minutes of the development of symptoms. There were no other reports of nausea during the bionic pancreas arm. The subject exercised for 30 and 45 minutes on day 2 and 3 of the bionic pancreas arm respectively, with no carbohydrate interventions required. During the usual care arm, the subject exercised daily for 30–180 minutes at a time, with a carbohydrate intervention required on day 4.

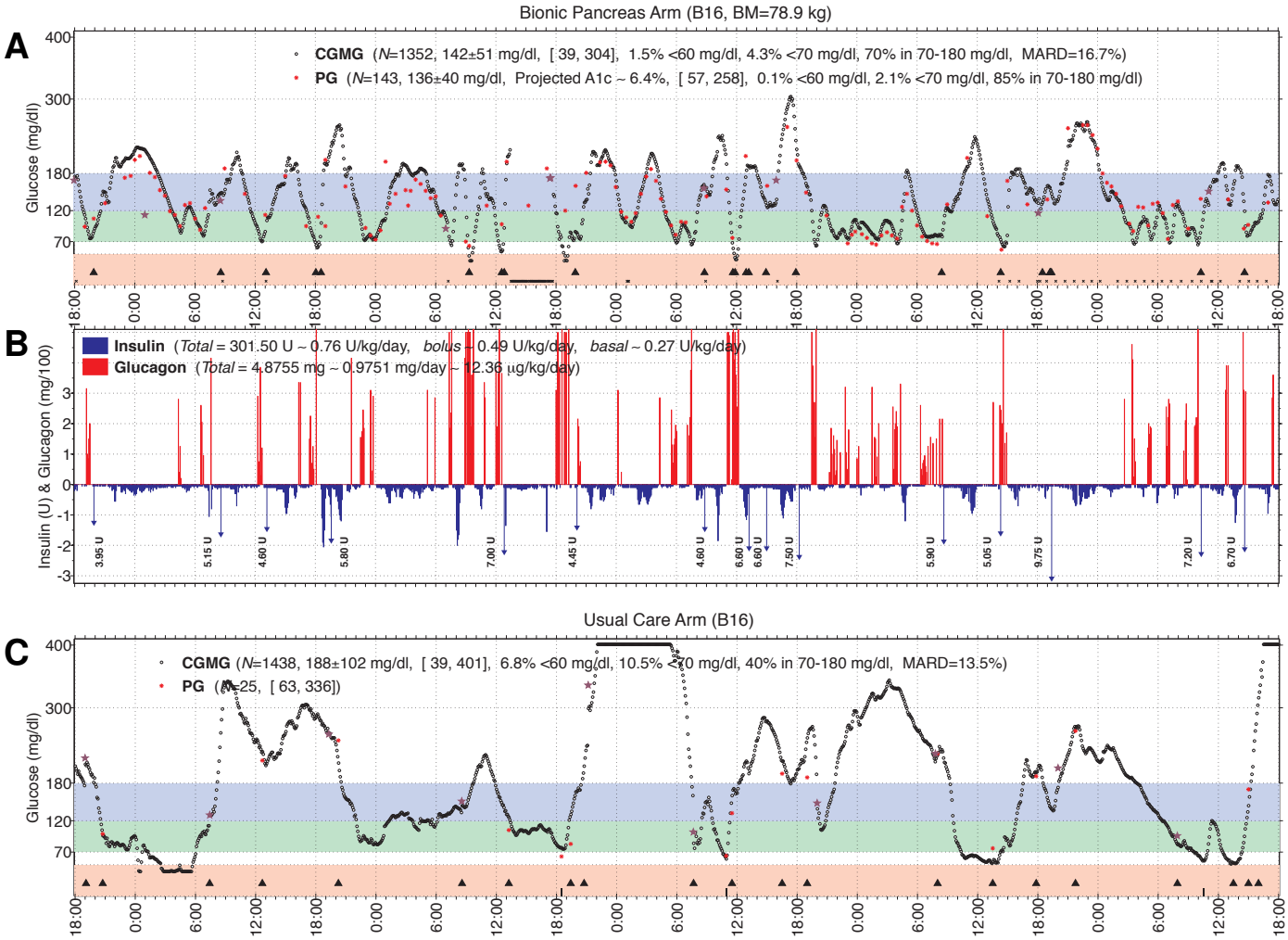


Figure S11. Outpatient experiments in adult subject #B16. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 142 mg/dl (136 mg/dl for PG), and average dosing was 0.76 U/kg/day and 12.36 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 140 mg/dl (136 mg/dl for PG), average dosing was 0.80 U/kg/day and 14.13 μg/kg/day, CGMG was $<$ 60 mg/dl 1.9% of the time (0.1% for PG), within 70–180 mg/dl 69.3% of the time (82.8% for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 188 mg/dl, CGMG was $<$ 60 mg/dl 6.8% of the time, and within 70–180 mg/dl 40.3% of the time. There were 2 carbohydrate interventions (2 day, 0 night) under usual care. A CGM sensor was replaced at 14:45 on day 2 during the bionic pancreas arm after the sensor fell off.

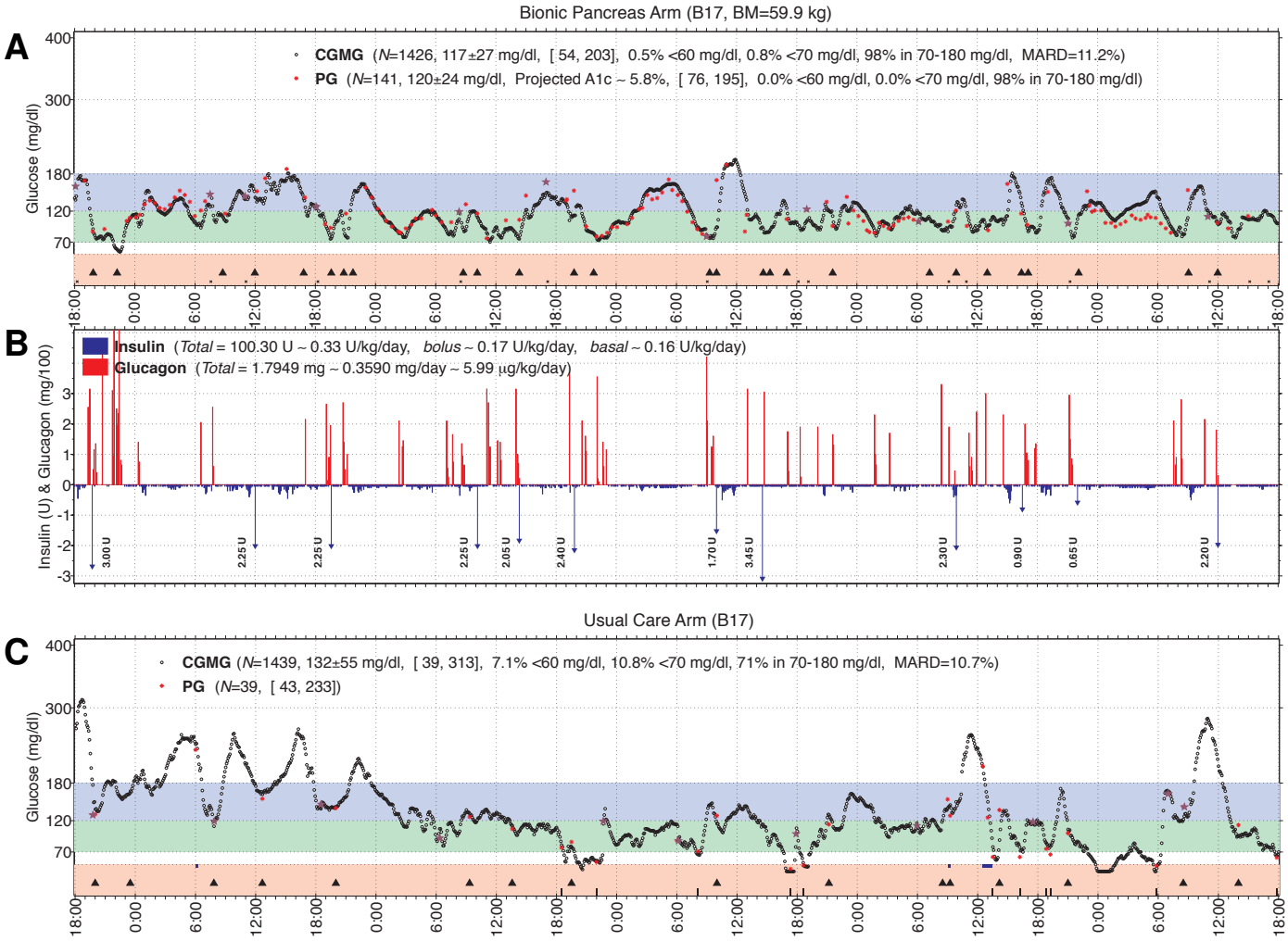


Figure S12. Outpatient experiments in adult subject #B17. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 117 mg/dl (120 mg/dl for PG), and average dosing was 0.33 U/kg/day and 5.99 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 115 mg/dl (116 mg/dl for PG), average dosing was 0.33 U/kg/day and 5.33 μg/kg/day, CGMG was $<$ 60 mg/dl 0.0% of the time (0.0% for PG), within 70–180 mg/dl 98.2% of the time (99.2% for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 132 mg/dl, CGMG was $<$ 60 mg/dl 7.1% of the time, and within 70–180 mg/dl 71.1% of the time. There were 8 carbohydrate interventions (6 day, 2 night) under usual care. The subject exercised for approximately 15 and 60 minutes on day 2 and 4 of the usual care arm respectively, with a carbohydrate intervention required for a PG of 62 mg/dl on day 4.

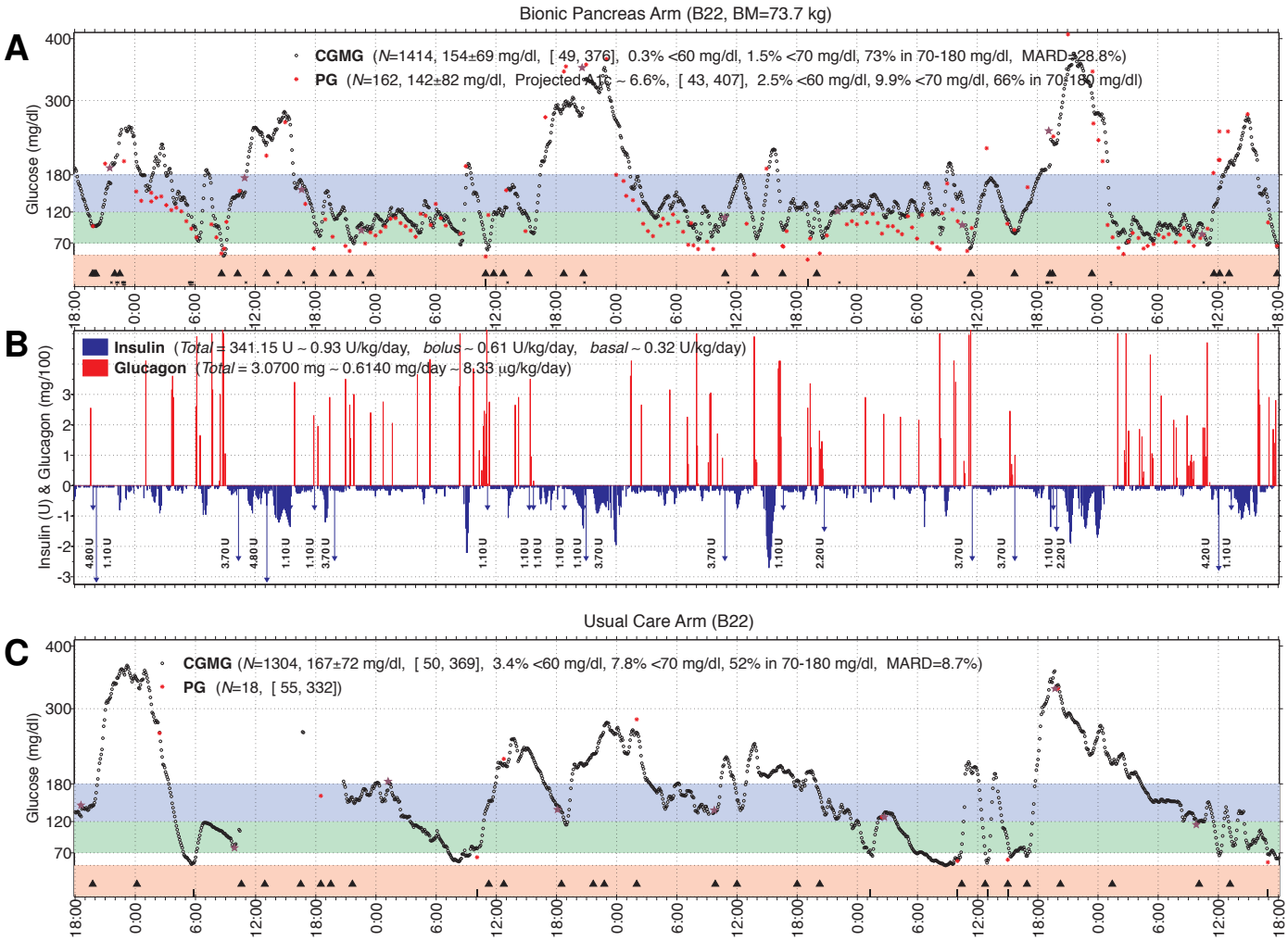


Figure S13. Outpatient experiments in adult subject #B22. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 154 mg/dl (142 mg/dl for PG), and average dosing was 0.93 U/kg/day and 8.33 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas system has undergone most of its online adaptation, mean CGMG was 150 mg/dl (141 mg/dl for PG), average dosing was 0.91 U/kg/day and 8.50 μg/kg/day, CGMG was $<$ 60 mg/dl 0.01% of the time (2.8% for PG), within 70–180 mg/dl 76.6% of the time (66.4% for PG), and there was 2 carbohydrate intervention (2 day, 0 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 167 mg/dl, CGMG was $<$ 60 mg/dl 3.4% of the time, and within 70–180 mg/dl 52.3% of the time. There were 4 carbohydrate interventions (4 day, 0 night) under usual care. A glucagon pump infusion set was replaced at 21:00 on day 2 of the bionic pancreas arm secondary to subject discomfort. At 11:25 on day 2 of the bionic pancreas arm, a hypoglycemia episode requiring carbohydrate intervention occurred while the subject was temporarily disconnected from the glucagon pump.

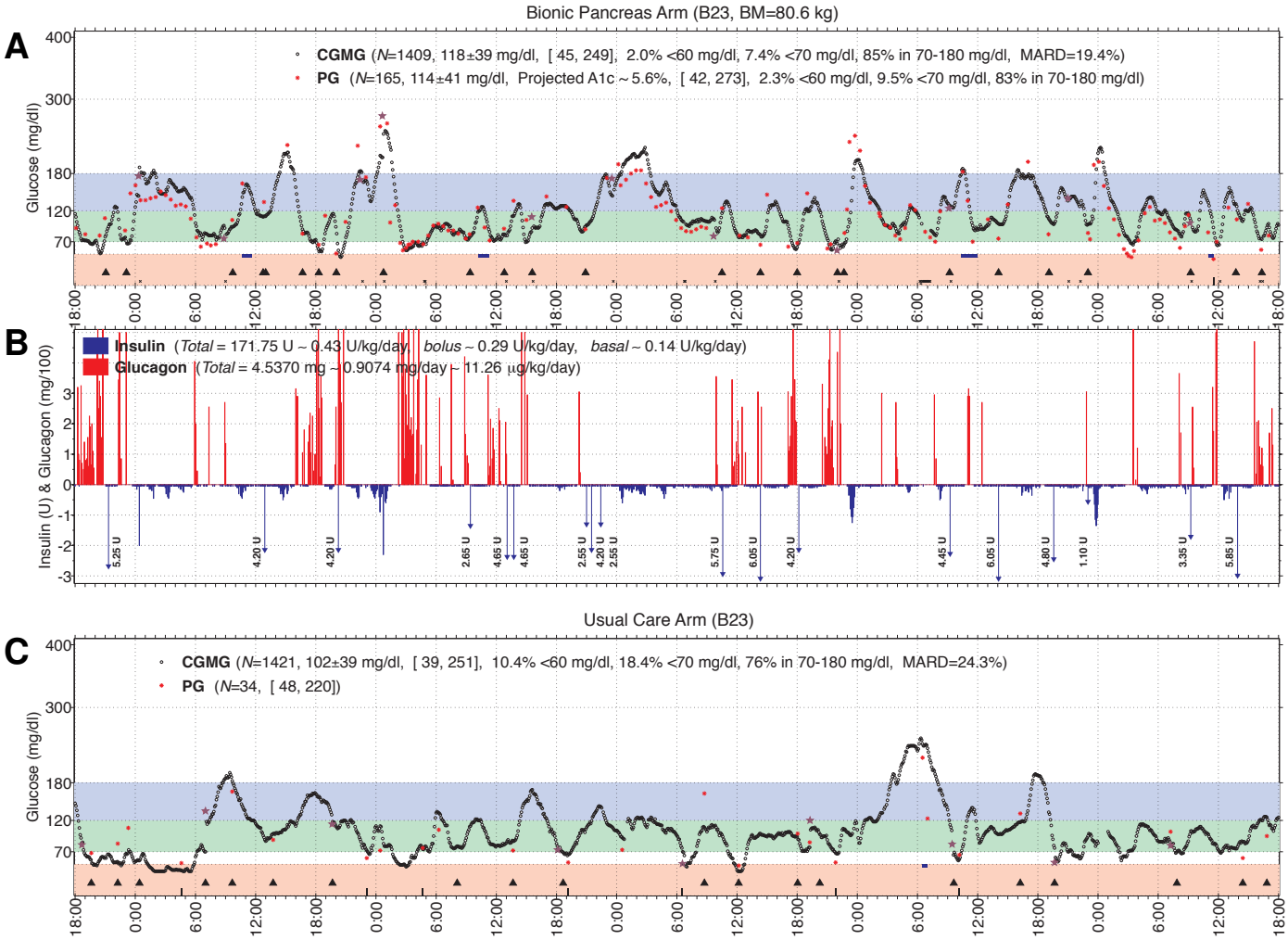


Figure S14. Outpatient experiments in adult subject #B23. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 118 mg/dl (114 mg/dl for PG), and average dosing was 0.43 U/kg/day and 11.26 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 117 mg/dl (113 mg/dl for PG), average dosing was 0.45 U/kg/day and 10.79 μg/kg/day, CGMG was $<$ 60 mg/dl 2.1% of the time (2.9% for PG), within 70–180 mg/dl 85.0% of the time (82.4% for PG), and there was 2 carbohydrate intervention (2 day, 0 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 102 mg/dl, CGMG was $<$ 60 mg/dl 10.4% of the time, and within 70–180 mg/dl 76.3% of the time. There were 6 carbohydrate interventions (3 day, 3 night) under usual care. On day 1 of the bionic pancreas arm, a glucagon infusion site was changed at 17:50 due to leakage at the site. On day five, at 02:43, the insulin pump was unpaired for 30 minutes during which time insulin was not delivered. In addition, the glucagon pump was unpaired at 03:15, at a time when the CGMG level was $<$80 mg/dl. The subject exercised on days 1–5 on the bionic pancreas for approximately 60 minutes daily with 1 carbohydrate intervention on day 5.

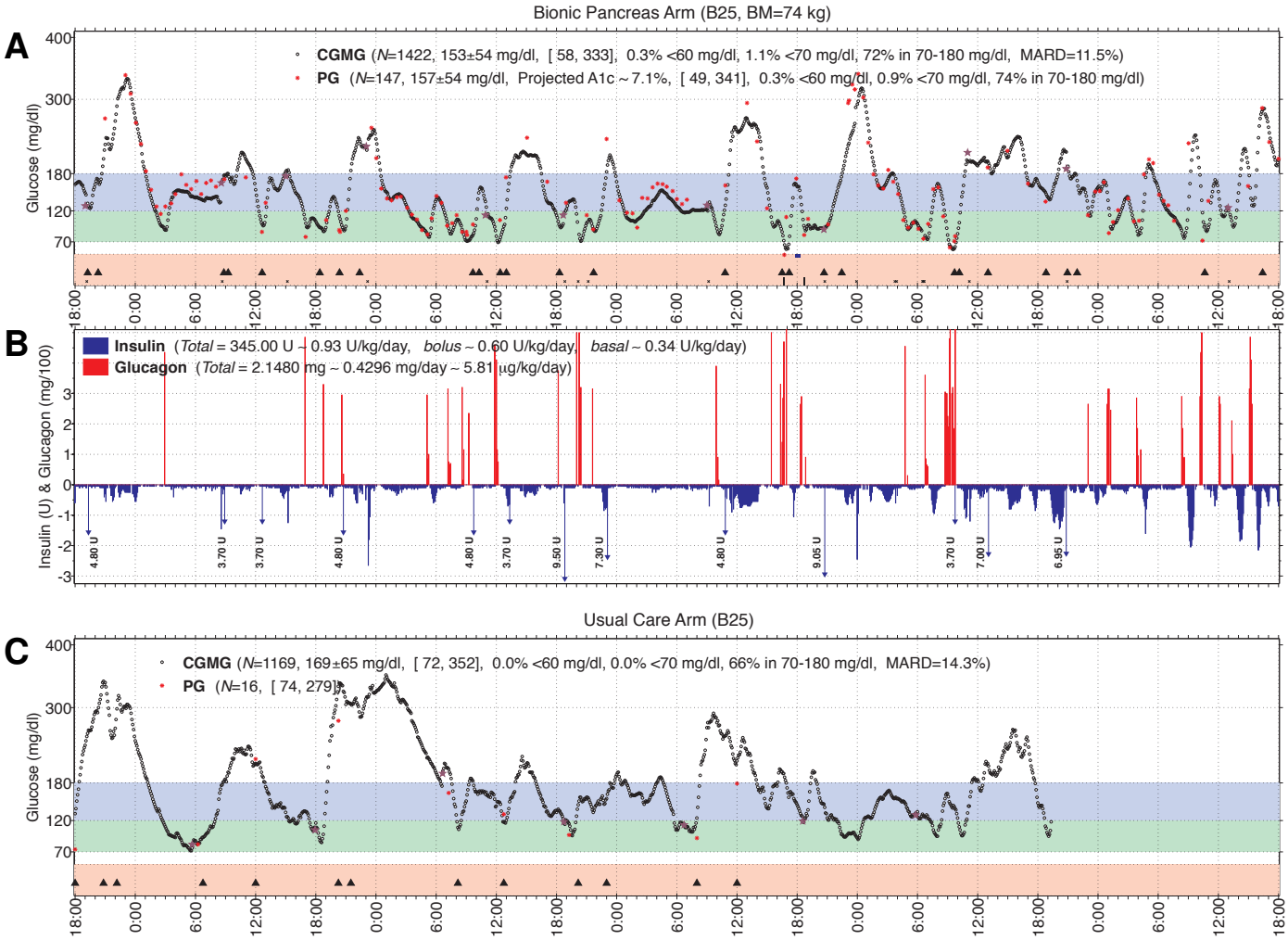


Figure S15. Outpatient experiments in adult subject #B25. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 153 mg/dl (157 mg/dl for PG), and average dosing was 0.93 U/kg/day and 5.81 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas system has undergone most of its online adaptation, mean CGMG was 149 mg/dl (153 mg/dl for PG), average dosing was 1.02 U/kg/day and 6.95 μg/kg/day, CGMG was $<$ 60 mg/dl 0.4% of the time (0.3% for PG), within 70–180 mg/dl 71.9% of the time (72.7% for PG), and there were 1 carbohydrate interventions (1 day, 0 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 169 mg/dl, CGMG was $<$ 60 mg/dl 0.0% of the time, and within 70–180 mg/dl 66.3% of the time. There were no carbohydrate interventions under usual care. On day 2 on the bionic pancreas, the glucagon pump was unpaired at 09:21 and glucagon was not dosed for 30 minutes. During the nighttime on day 3, fingerstick PG values were obtained due to GlucoScout failure. The subject exercised for approximately 30 minutes on day 3 on the bionic pancreas without any interventions needed.

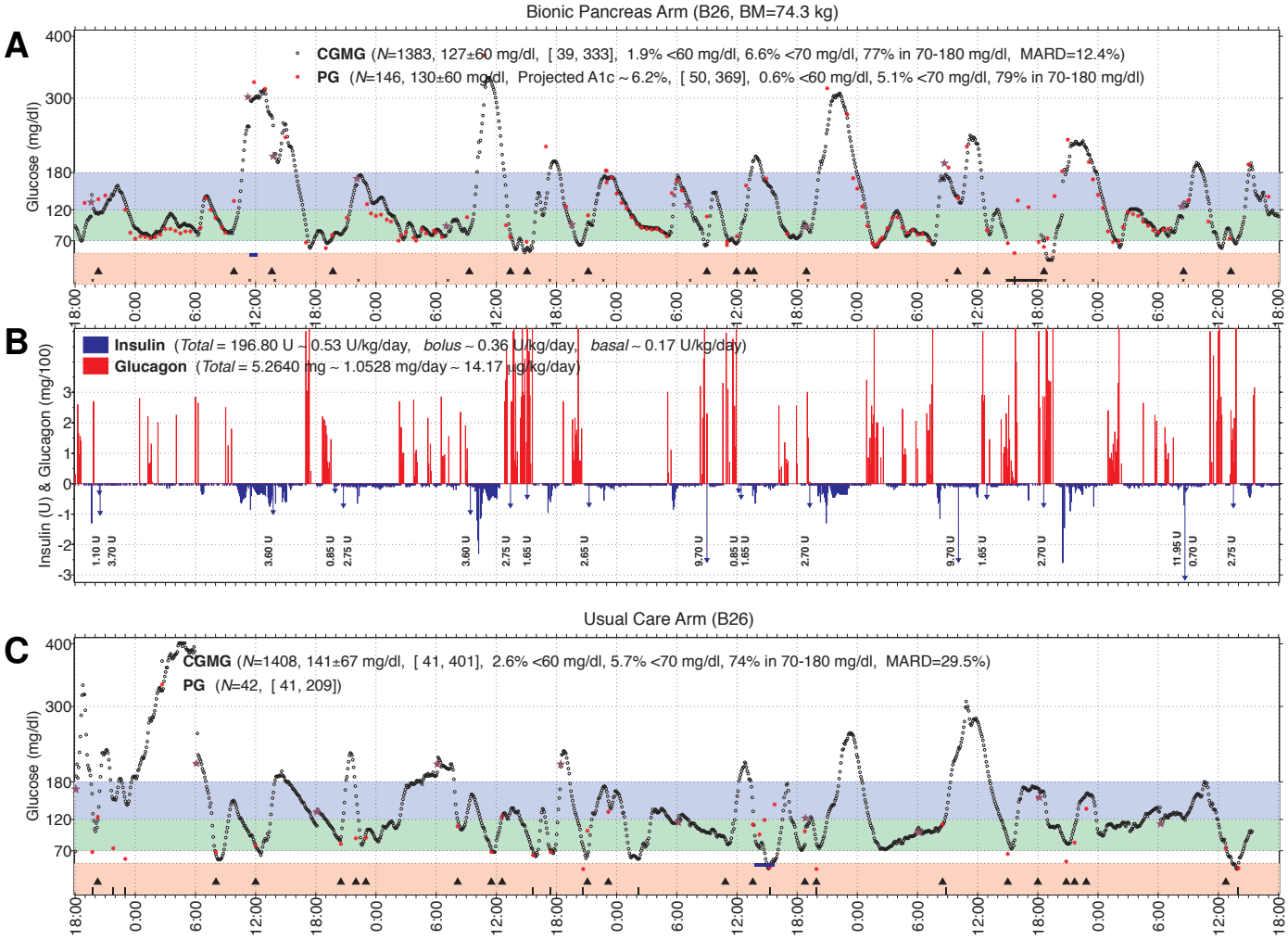


Figure S16. Outpatient experiments in adult subject #B26. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 127 mg/dl (130 mg/dl for PG), and average dosing was 0.53 U/kg/day and 14.17 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas system has undergone most of its online adaptation, mean CGMG was 124 mg/dl (127 mg/dl for PG), average dosing was 0.54 U/kg/day and 15.84 μg/kg/day, CGMG was $<$ 60 mg/dl 2.3% of the time (0.8% for PG), within 70–180 mg/dl 77.1% of the time (80.6% for PG), and there was 1 carbohydrate intervention (1 day, 0 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 141 mg/dl, CGMG was $<$ 60 mg/dl 2.6% of the time, and within 70–180 mg/dl 74.0% of the time. There were 10 carbohydrate interventions (8 day, 2 night) under usual care. On day 4 of the bionic pancreas arm, the CGM was offline from approximately 15:00 to 18:00. In addition to providing automatically determined basal insulin during this period, the five fingerstick PG values entered when the CGM was offline allowed the bionic pancreas to automatically administer three glucagon boluses and two insulin boluses. The subject exercised for approximately 60 minutes on day 1 during the bionic pancreas arm with no carbohydrate interventions required. On day 3 of the usual care arm the subject exercised for approximately 60 minutes and required one carbohydrate intervention.

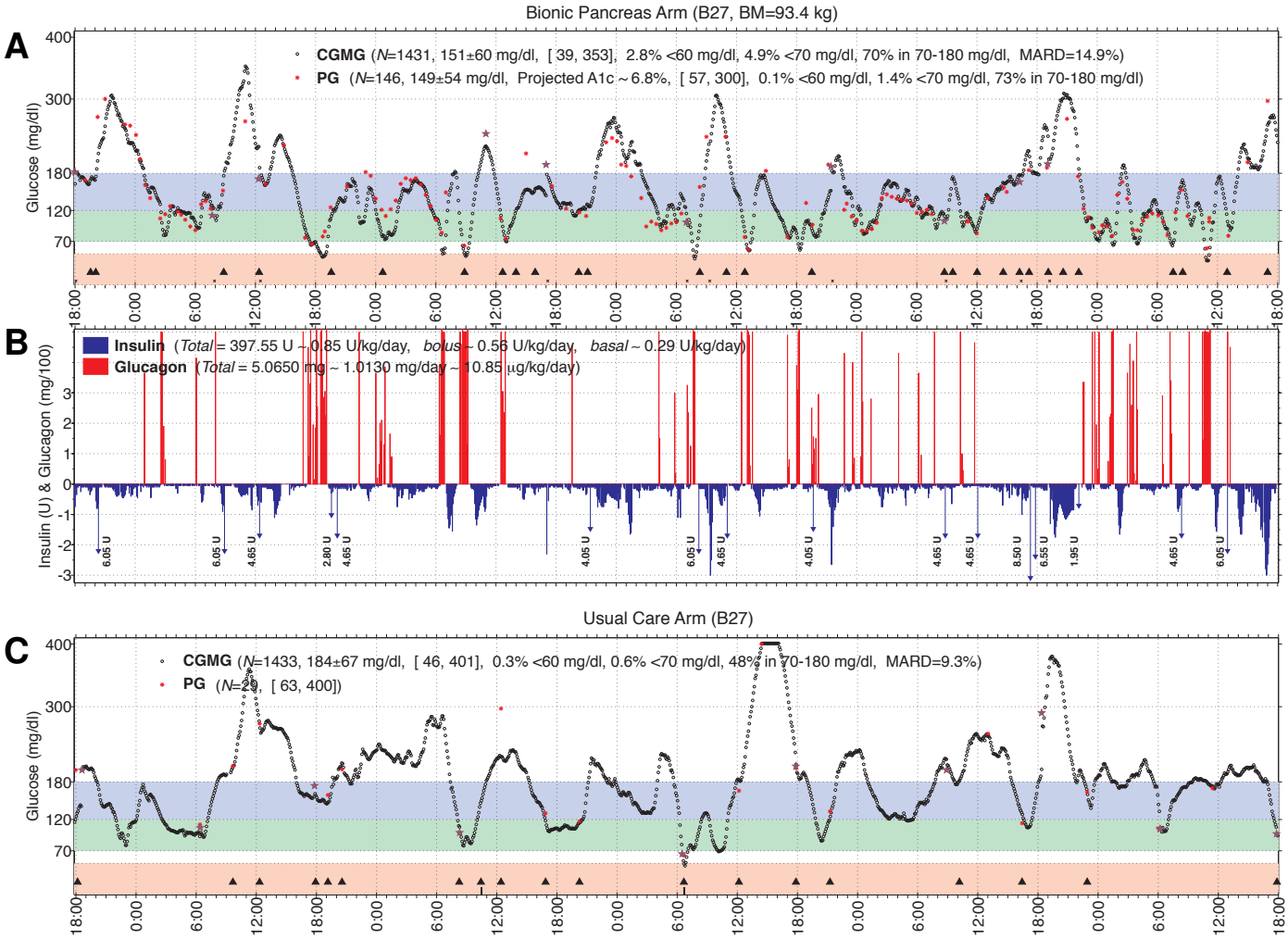


Figure S17. Outpatient experiments in adult subject #B27. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 151 mg/dl (149 mg/dl for PG), and average dosing was 0.85 U/kg/day and 10.85 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 143 mg/dl (142 mg/dl for PG), average dosing was 0.90 U/kg/day and 12.34 μg/kg/day, CGMG was $<$ 60 mg/dl 3.5% of the time (0.2% for PG), within 70–180 mg/dl 74.3% of the time (78.2% for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 184 mg/dl, CGMG was $<$ 60 mg/dl 0.3% of the time, and within 70–180 mg/dl 48.3% of the time. There were 2 carbohydrate interventions (1 day, 1 night) under usual care. During the bionic pancreas arm, the subject experienced a headache at 13:47 on day 1 and 20:45 on day 2. No glucagon had been dosed within 5 hours and 100 minutes of each of these symptoms, respectively. There were no other reports of nausea on the bionic pancreas. On day 3, the GlucoScout failed at 04:30 and fingerstick PG measurements were obtained every 30 minutes until 07:00.

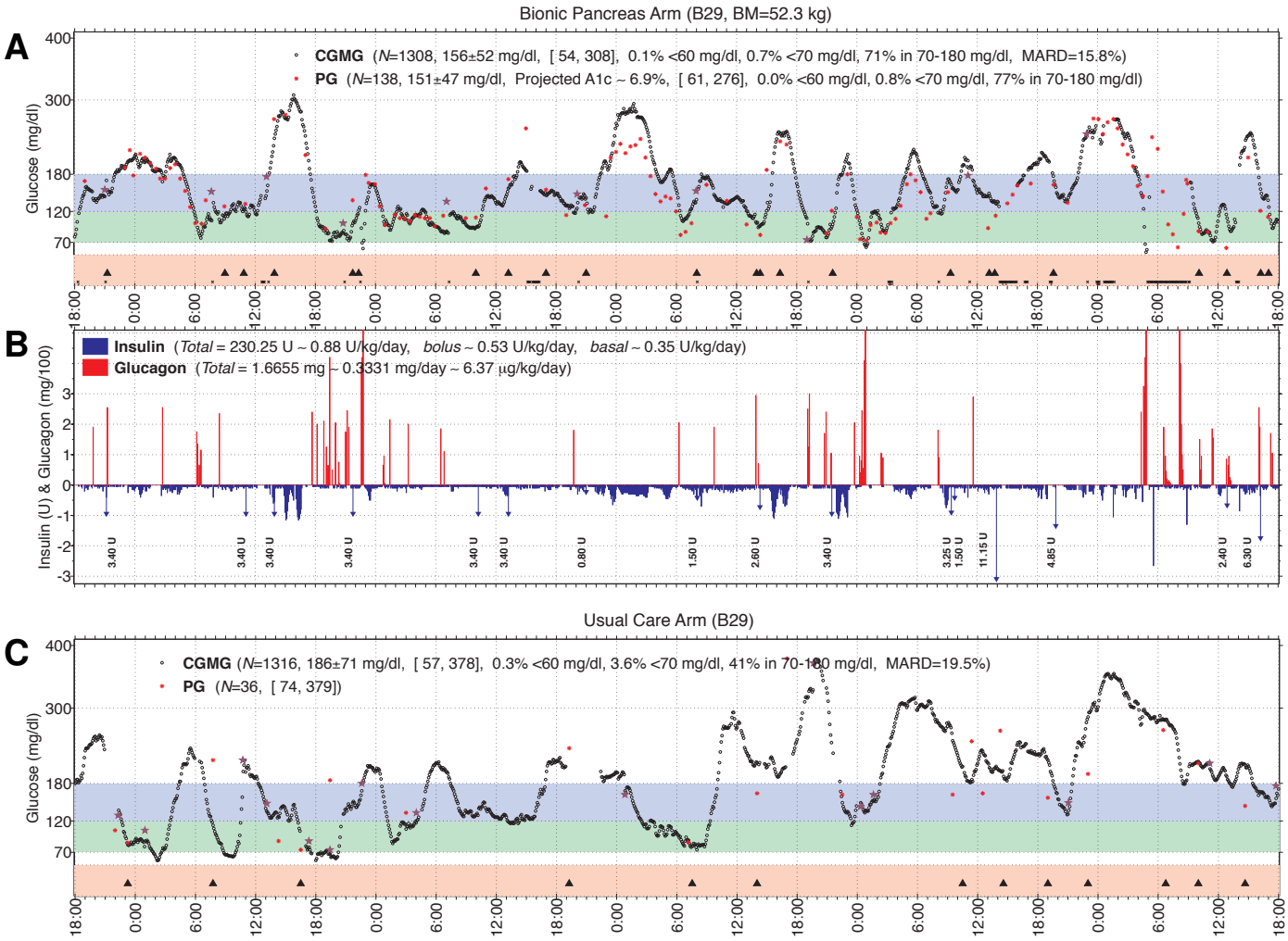


Figure S18. Outpatient experiments in adult subject #B29. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 156 mg/dl (151 mg/dl for PG), and average dosing was 0.88 U/kg/day and 6.37 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas system has undergone most of its online adaptation, mean CGMG was 152 mg/dl (145 mg/dl for PG), average dosing was 0.90 U/kg/day and 7.15 μg/kg/day, CGMG was $<$ 60 mg/dl 0.2% of the time (0.0% for PG), within 70–180 mg/dl 74.4% of the time (80.5% for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 186 mg/dl, CGMG value was $<$ 60 mg/dl 0.3% of the time, and within 70–180 mg/dl 41.1% of the time. There were no carbohydrate interventions under usual care. On day 1 of the bionic pancreas arm, the insulin pump was unpaired for 30 minutes at 02:31 so that no insulin boluses were delivered during that time. At 16:00, the insulin site was changed due to tubing concerns and inflammation noted at the site. On day 3 on the bionic pancreas, the CGM was offline for 80 minutes at 15:00 and for 20 minutes at 21:16. On day 4, the CGM was offline from 14:20 until 15:15. Fingerstick PG measurements were obtained every 30 minutes until the CGM came back online. In addition to providing automatically determined basal insulin during these periods, the fingerstick PG values entered when the CGM was offline allowed the bionic pancreas to automatically administer several insulin and glucagon boluses. On day 4, the subject accidentally announced a meal twice and then required a carbohydrate intervention at 09:32. On day 5 during the nighttime, fingerstick PG values were obtained every 30 minutes because of GlucoScout failure. At 04:58, the CGM was out of ISO range (CGMG value of 58 mg/dl with PG value of 177 mg/dl) and an additional calibration was performed.

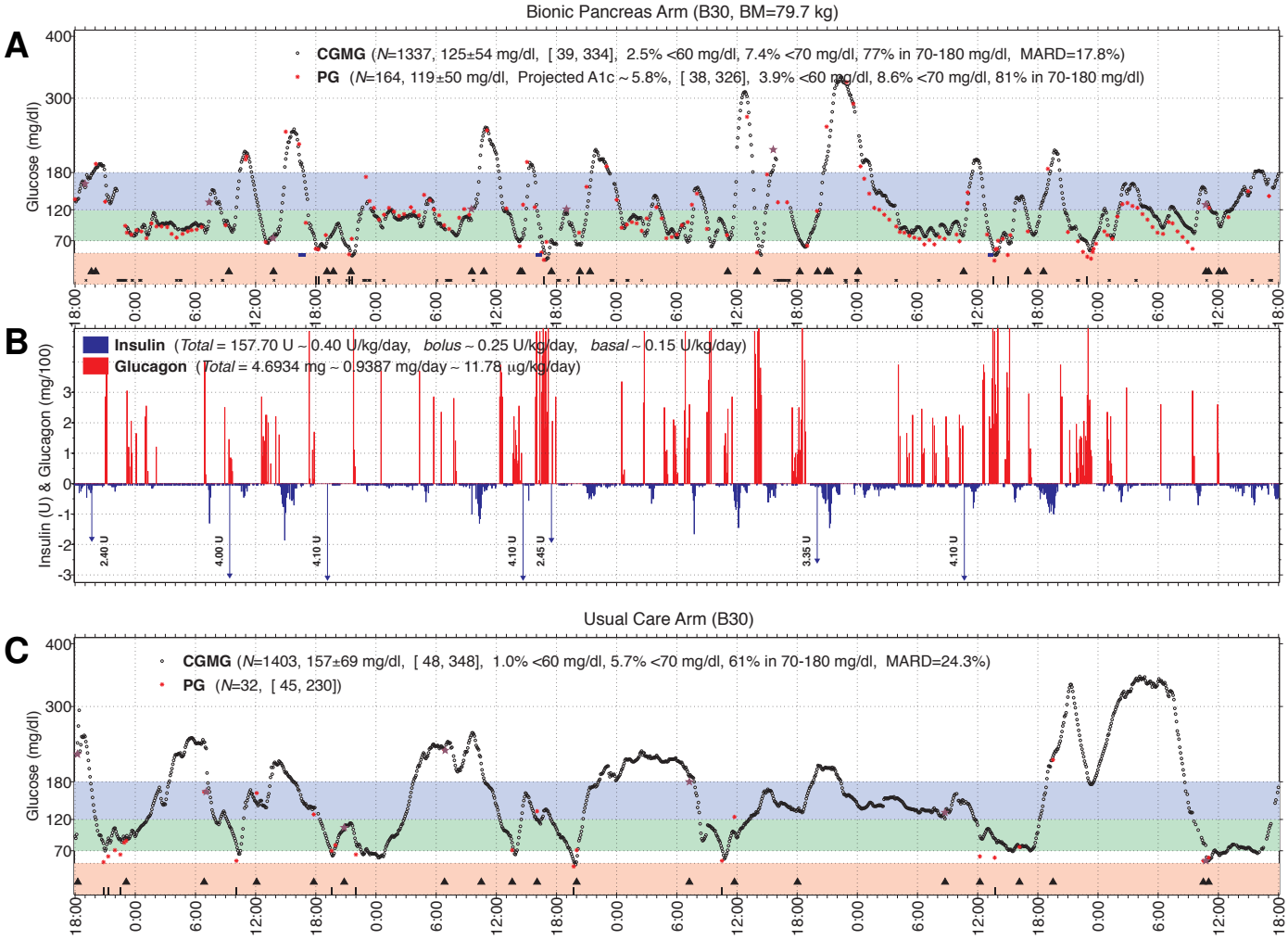


Figure S19. Outpatient experiments in adult subject #B30. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 125 mg/dl (119 mg/dl for PG), and average dosing was 0.40 U/kg/day and 11.78 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 125 mg/dl (117 mg/dl for PG), average dosing was 0.40 U/kg/day and 12.75 μg/kg/day, CGMG was $<$ 60 mg/dl 3.1% of the time (4.9% for PG), within 70–180 mg/dl 76.2% of the time (80.1% for PG), and there were 8 carbohydrate interventions (8 day, 0 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 157 mg/dl, CGMG was $<$ 60 mg/dl 1.0% of the time, and within 70–180 mg/dl 60.9% of the time. There were 8 carbohydrate interventions (8 day, 0 night) under usual care. On day 2 of the bionic pancreas system, the glucagon pump had an occlusion alarm and became unpaired at 17:35, when the PG was 57 mg/dl, followed by a carbohydrate intervention. The glucagon pump could not be repaired and the pump was replaced at approximately 21:00. On day 2, both insulin and glucagon pumps had tubing occlusion; at 13:00 for the insulin pump and 14:50 for the glucagon pump. Both tubing sets were subsequently changed. The subject exercised on days 1, 2 and 4 for approximately 30-50 minutes with 1 carbohydrate intervention required on day 2 and 1 carbohydrate intervention required on day 4.

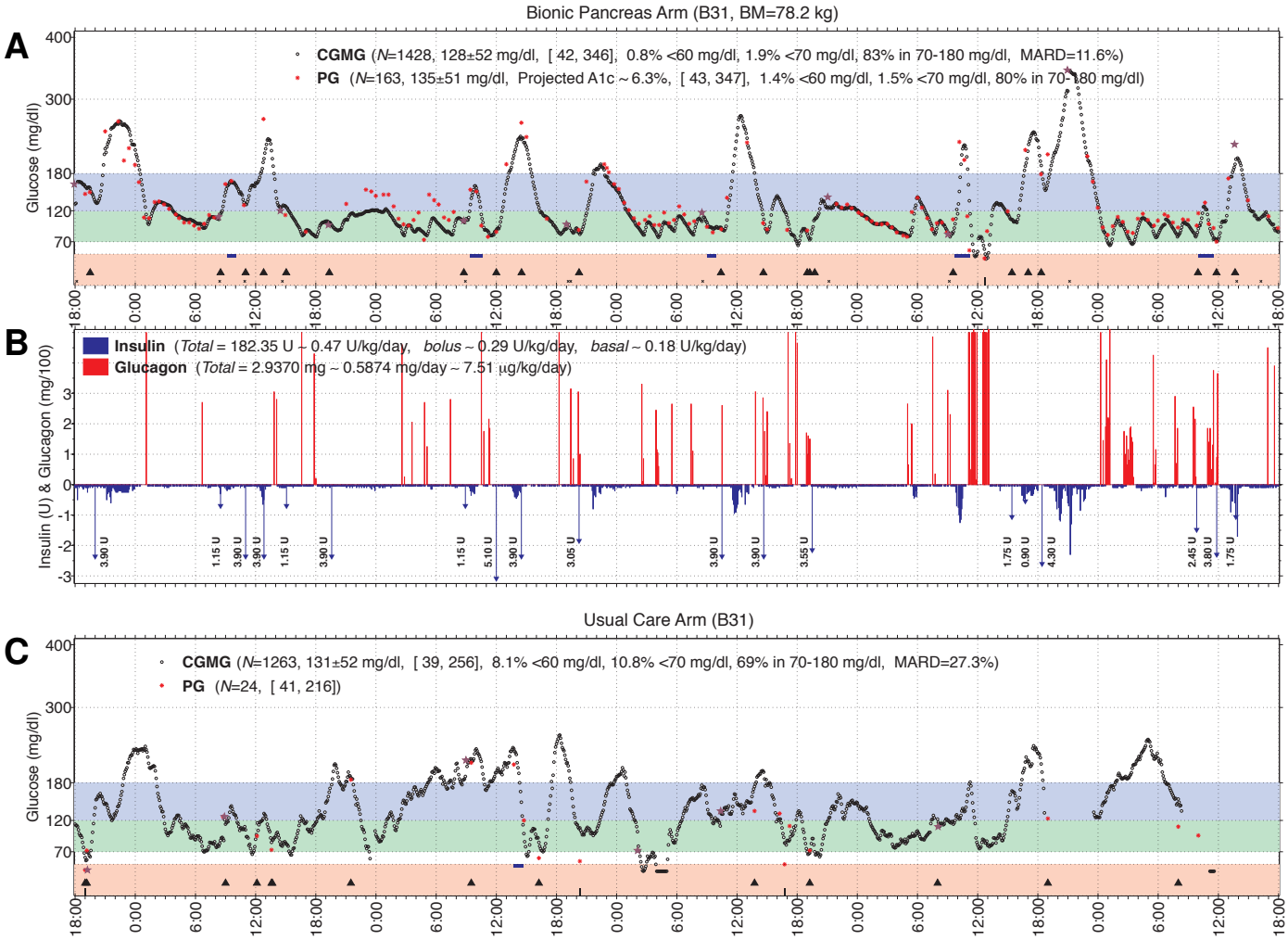


Figure S20. Outpatient experiments in adult subject #B31. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 128 mg/dl (135 mg/dl for PG), and average dosing was 0.47 U/kg/day and 7.51 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas system has undergone most of its online adaptation, mean CGMG was 123 mg/dl (131 mg/dl for PG), average dosing was 0.46 U/kg/day and 8.81 μg/kg/day, CGMG was $<$ 60 mg/dl 1.0% of the time (1.7% for PG), within 70–180 mg/dl 83.7% of the time (82.3% for PG), and there was 1 carbohydrate intervention (1 day, 0 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 131 mg/dl, CGMG was $<$ 60 mg/dl 8.1% of the time, and within 70–180 mg/dl 69.2% of the time. There were 4 carbohydrate interventions (4 day, 0 night) under usual care. On day 4, the subject experienced nausea at 15:40. No glucagon was dosed within 2.5 hours prior to the symptoms. There were no other reports of nausea during the bionic pancreas arm. On day 2, HemoCue PGs were done every 30 minutes overnight following GlucoScout failure. The subject exercised for approximately 45-90 minutes on days 1-5 during the bionic pancreas arm without carbohydrate interventions required. One day 2 of the usual care arm the subject exercised for approximately 60 minutes without carbohydrate interventions required.

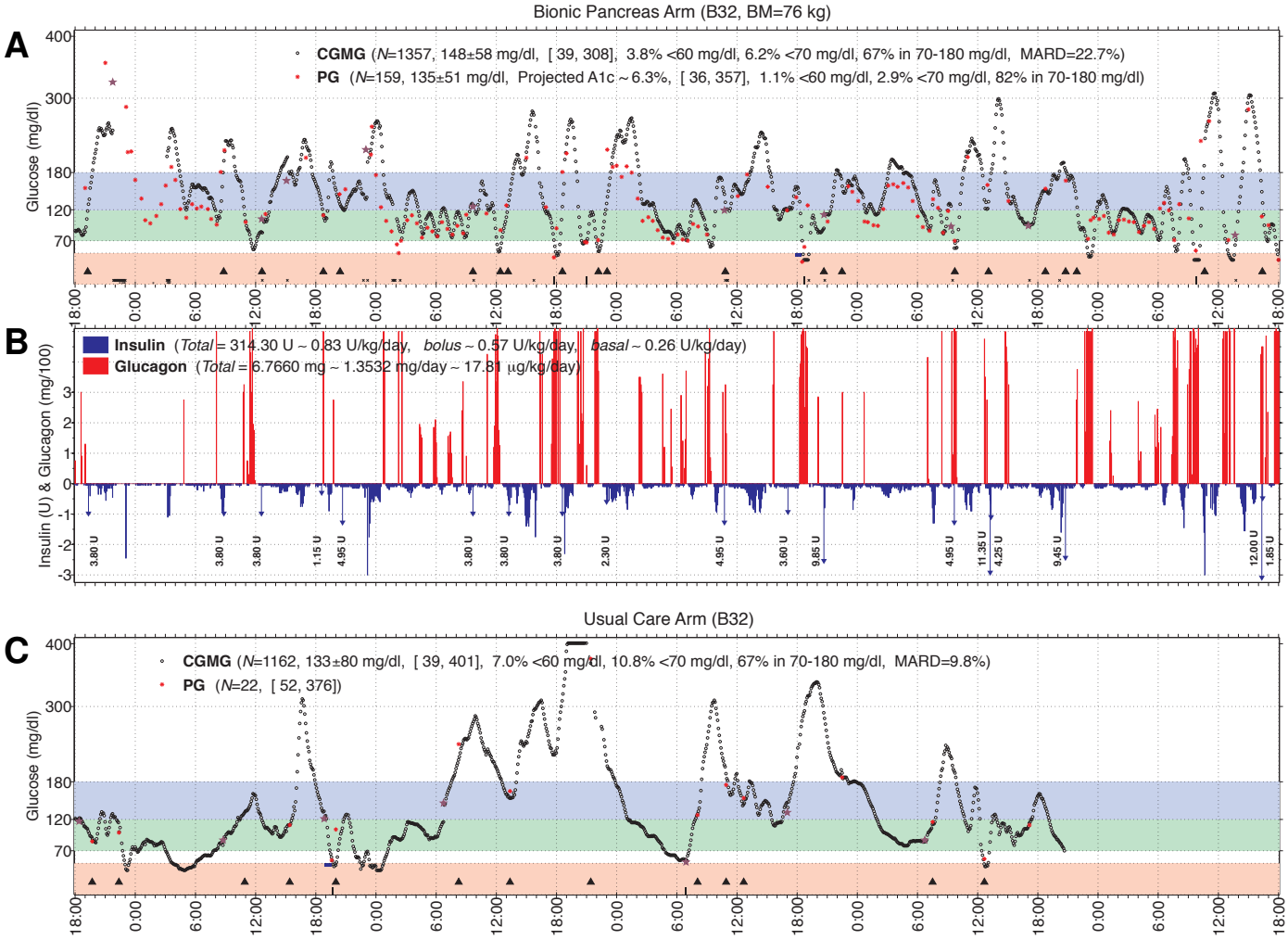


Figure S21. Outpatient experiments in adult subject #B32. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 148 mg/dl (135 mg/dl for PG), and average dosing was 0.83 U/kg/day and 17.81 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 140 mg/dl (127 mg/dl for PG), average dosing was 0.90 U/kg/day and 20.94 μg/kg/day, CGMG was $<$ 60 mg/dl 4.4% of the time (1.3% for PG), within 70–180 mg/dl 72.0% of the time (85.2% for PG), and there were 5 carbohydrate interventions (5 day, 0 night). On the other hand, over the entire 5-day period under usual care, mean CGMG was 133 mg/dl, CGMG was $<$ 60 mg/dl 7.0% of the time, and within 70–180 mg/dl 66.8% of the time. There were 2 carbohydrate interventions (1 day, 1 night) under usual care. On day one, the CGM was out of ISO range at 21:45 and there was a forced calibration. The CGM sensor was offline for 30 minutes starting at 23:00. The CGM displayed a failed sensor alert at 23:30. A new sensor was placed and calibrated by 03:00. In addition to providing automatically determined basal insulin during this period, the fingerstick PG values entered when the CGM was offline allowed the bionic pancreas to automatically administer an insulin bolus. On day four on the bionic pancreas, the subject exercised for approximately 30 minutes and required one carbohydrate intervention.

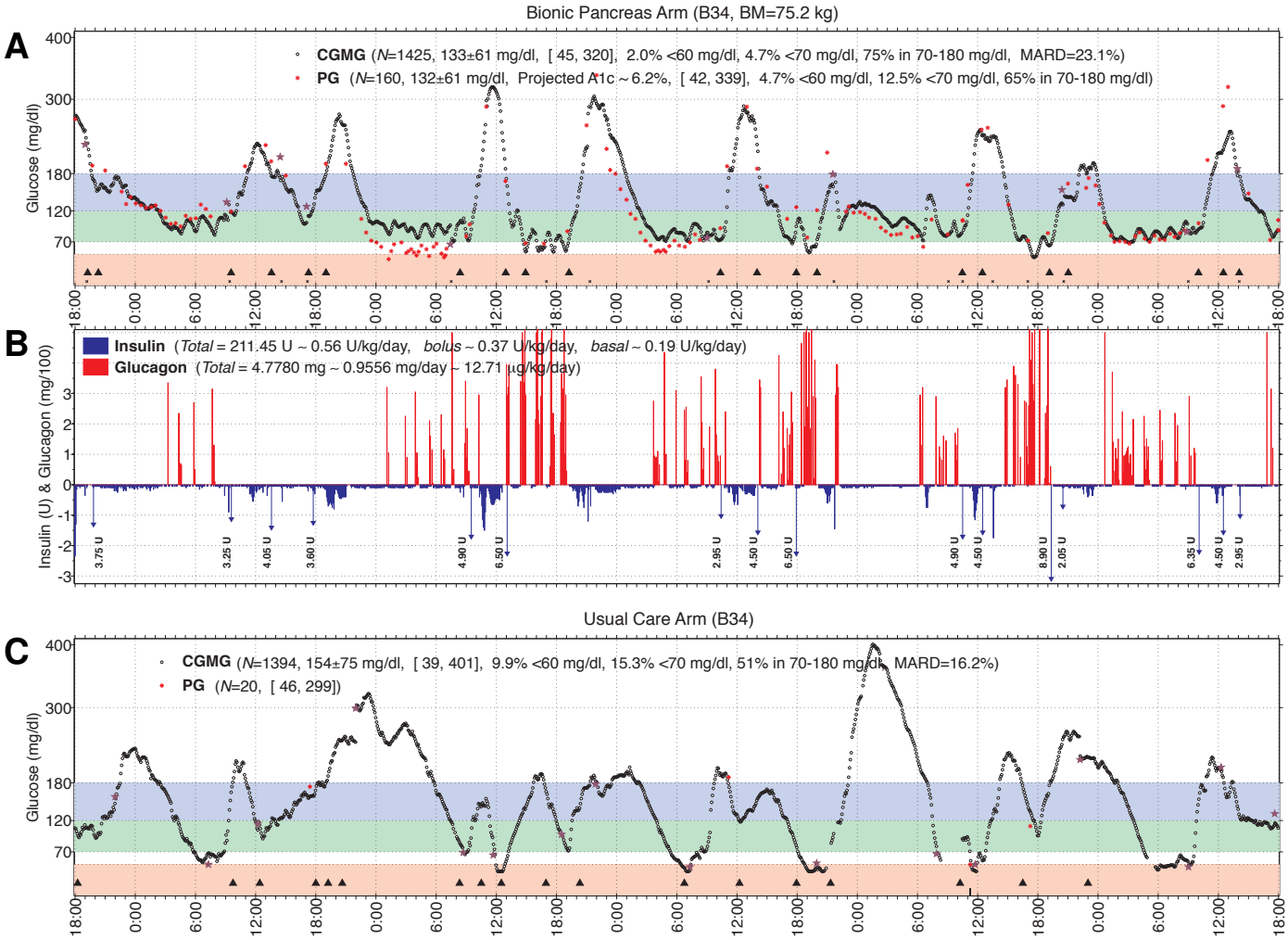


Figure S22. Outpatient experiments in adult subject #B34. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 133 mg/dl (132 mg/dl for PG), and average dosing was 0.56 U/kg/day and 12.71 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 130 mg/dl (126 mg/dl for PG), average dosing was 0.57 U/kg/day and 15.39 μg/kg/day, CGMG was $<$ 60 mg/dl 2.5% of the time (5.9% for PG), within 70–180 mg/dl 73.4% of the time (63.8% for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 154 mg/dl, CGMG was $<$ 60 mg/dl 9.9% of the time, and within 70–180 mg/dl 50.9% of the time. There was 1 carbohydrate intervention (1 day, 0 night) under usual care. On day 2 of the bionic pancreas arm the subject announced the breakfast meal at the end of the meal rather than at the beginning.

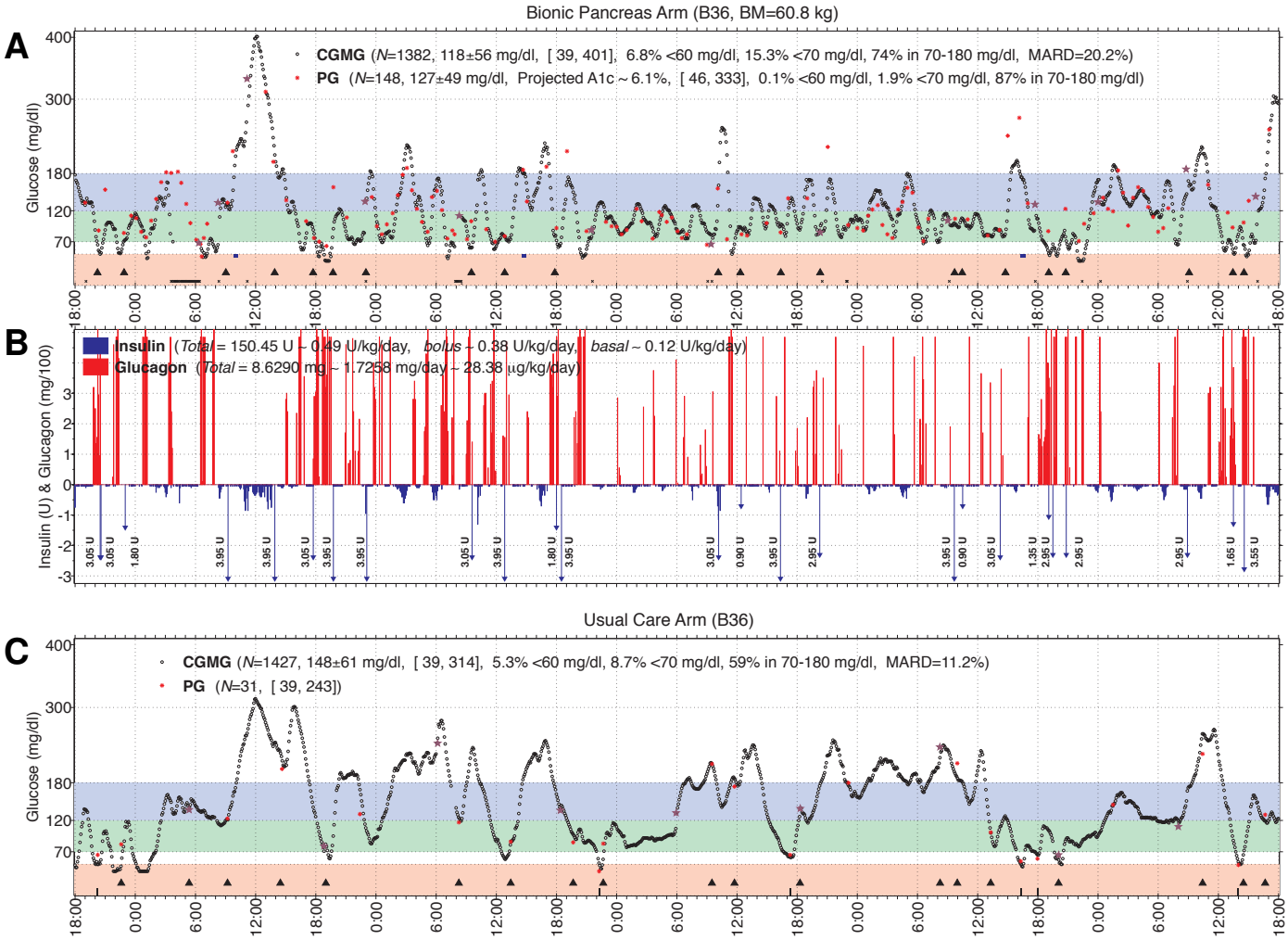


Figure S23. Outpatient experiments in adult subject #B36. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject under usual care. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 118 mg/dl (127 mg/dl for PG), and average dosing was 0.49 U/kg/day and 28.38 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 115 mg/dl (121 mg/dl for PG), average dosing was 0.46 U/kg/day and 28.79 μg/kg/day, CGMG was $<$ 60 mg/dl 6.0% of the time (0.0% for PG), within 70–180 mg/dl 79.6% of the time (90.4% for PG), and there were no carbohydrate interventions. On the other hand, over the entire 5-day period under usual care, mean CGMG was 148 mg/dl, CGMG was $<$ 60 mg/dl 5.3% of the time, and within 70–180 mg/dl 58.5% of the time. There were 6 carbohydrate interventions (6 day, 0 night) under usual care. The subject missed glucagon boluses at approximately 07:42 because the glucagon pump was unpaired. On day 1 of the bionic pancreas arm, the subject did not receive insulin from 07:00 to 07:43 because the insulin pump was unpaired. On day 3, fingerstick PG measurements were obtained every 30 minutes from 03:35 until 07:00 due to GlucoScout failure. On day 5 the glucagon pump site and cartridge were changed at 22:15 due to occlusion alarms. The subject exercised for approximately 30 minutes on day 1, 2, and 4 without any carbohydrate interventions.

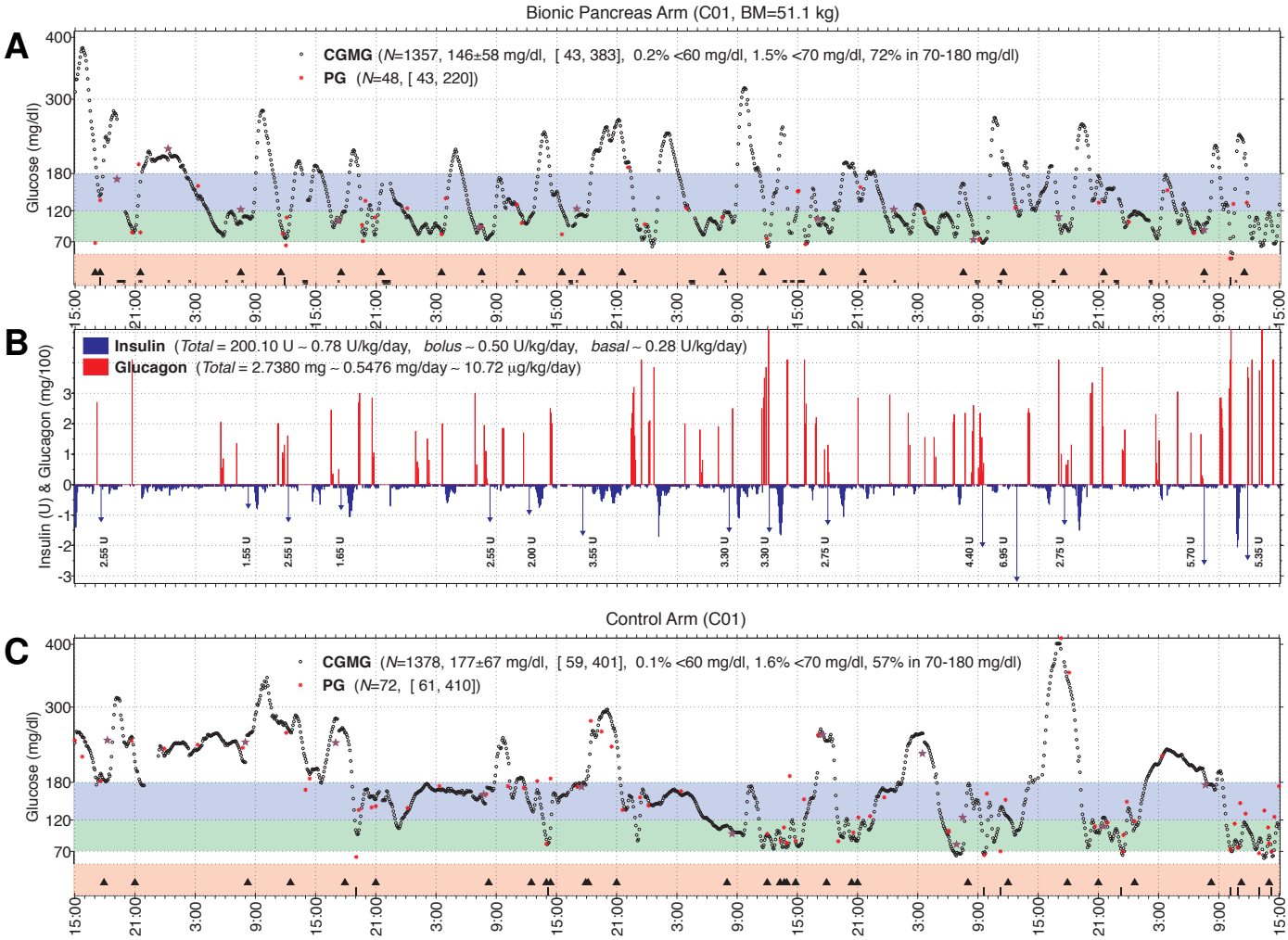


Figure S24. Outpatient experiments in adolescent subject #C01. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 146 mg/dl, average dosing was 0.78 U/kg/day and 10.72 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 139 mg/dl, average dosing was 0.83 U/kg/day and 12.40 μg/kg/day, CGMG was $<$ 60 mg/dl 0.3% of the time, within 70–180 mg/dl 76.6% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 177 mg/dl, CGMG was $<$ 60 mg/dl 0.1% of the time, within 70–180 mg/dl 57.1% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 110 versus 184 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 130 versus 185 mg/dl, and there were 3 carbohydrate interventions versus 8 carbohydrate interventions with PG $<$ 80 mg/dl and 2 carbohydrate interventions versus 3 carbohydrate interventions with PG $<$ 70 mg/dl.

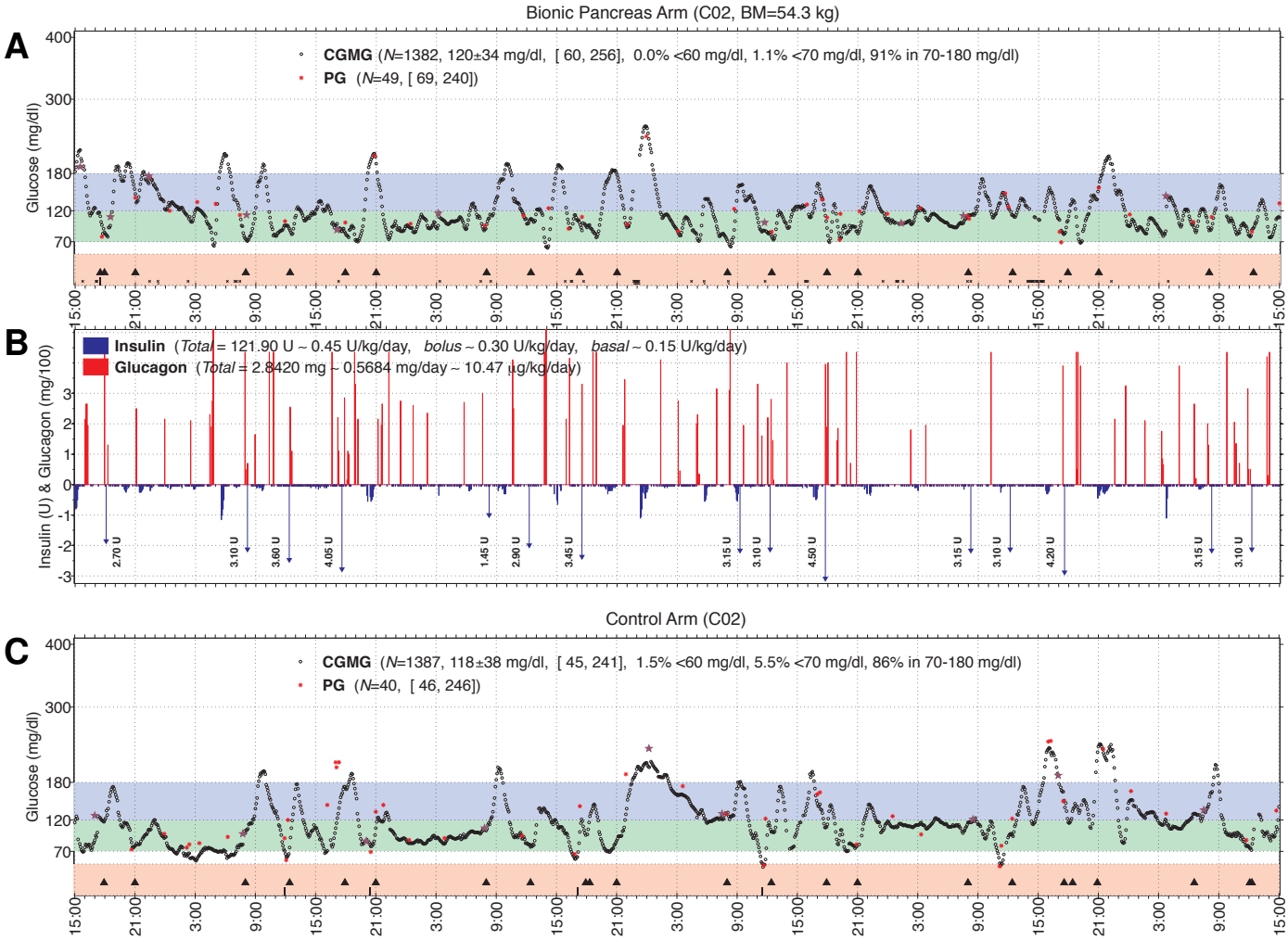


Figure S25. Outpatient experiments in adolescent subject #C02. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 120 mg/dl, average dosing was 0.45 U/kg/day and 10.47 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 117 mg/dl, average dosing was 0.44 U/kg/day and 10.49 μg/kg/day, CGMG was $<$ 60 mg/dl 0.0% of the time, within 70–180 mg/dl 92.8% of the time. On the other hand, over the entire 5-day in the comparator arm of the study, mean CGMG was 118 mg/dl, CGMG was $<$ 60 mg/dl 1.5% of the time, within 70–180 mg/dl 86.1% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 112 versus 129 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 129 versus 129 mg/dl, and there was 1 carbohydrate intervention versus 4 carbohydrate interventions with PG $<$ 80 mg/dl and 0 carbohydrate interventions versus 4 carbohydrate interventions with PG $<$ 70 mg/dl.

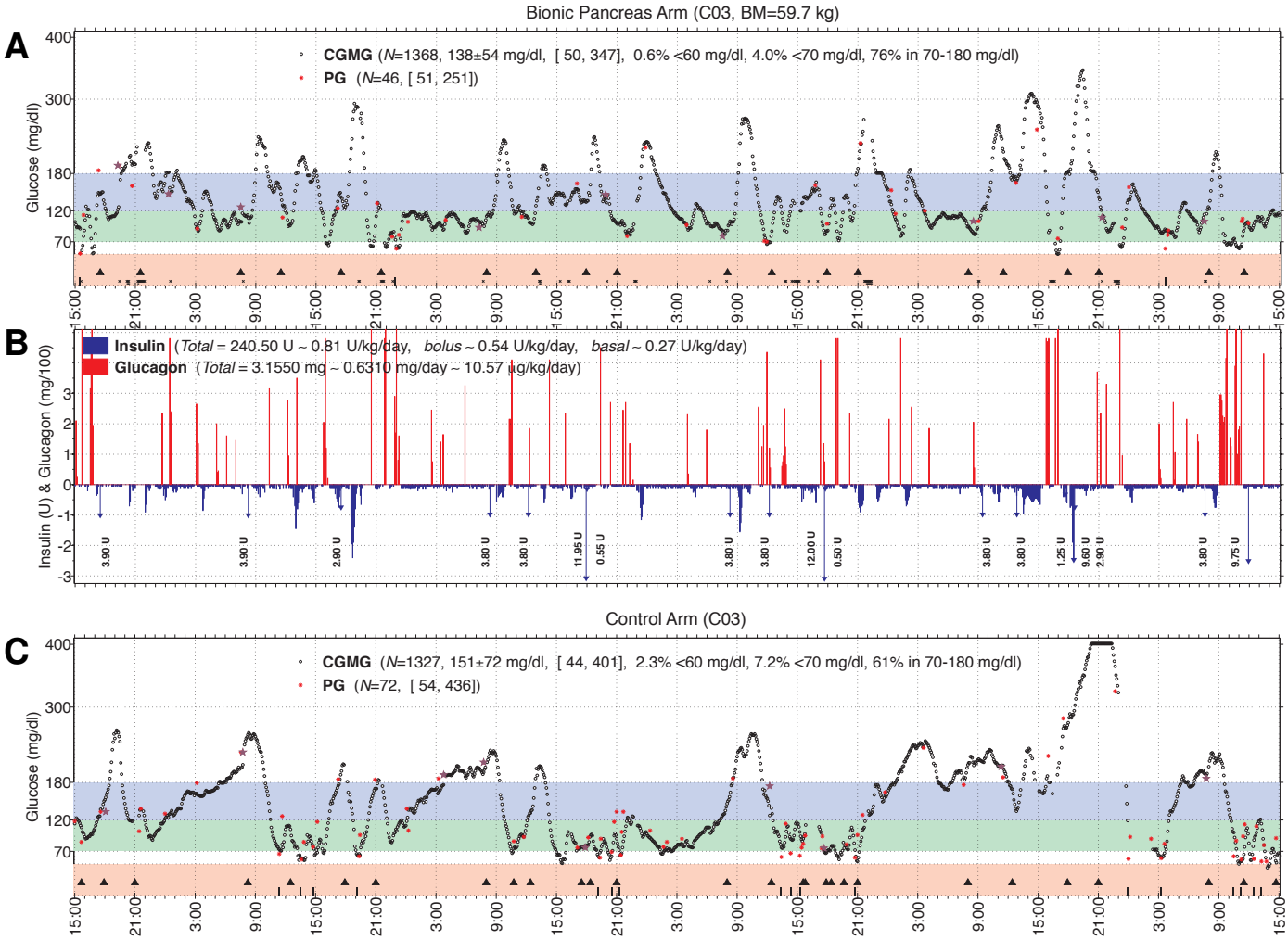


Figure S26. Outpatient experiments in adolescent subject #C03. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 138 mg/dl, average dosing was 0.81 U/kg/day and 10.57 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 136 mg/dl, average dosing was 0.87 U/kg/day and 10.78 μg/kg/day, CGMG was $<$ 60 mg/dl 0.5% of the time, within 70–180 mg/dl 76.6% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 151 mg/dl, CGMG was $<$ 60 mg/dl 2.3% of the time, within 70–180 mg/dl 61.3% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 121 versus 167 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 125 versus 136 mg/dl, and there were 3 carbohydrate interventions versus 17 carbohydrate interventions with PG $<$ 80 mg/dl and 3 carbohydrate interventions versus 16 carbohydrate interventions with PG $<$ 70 mg/dl.

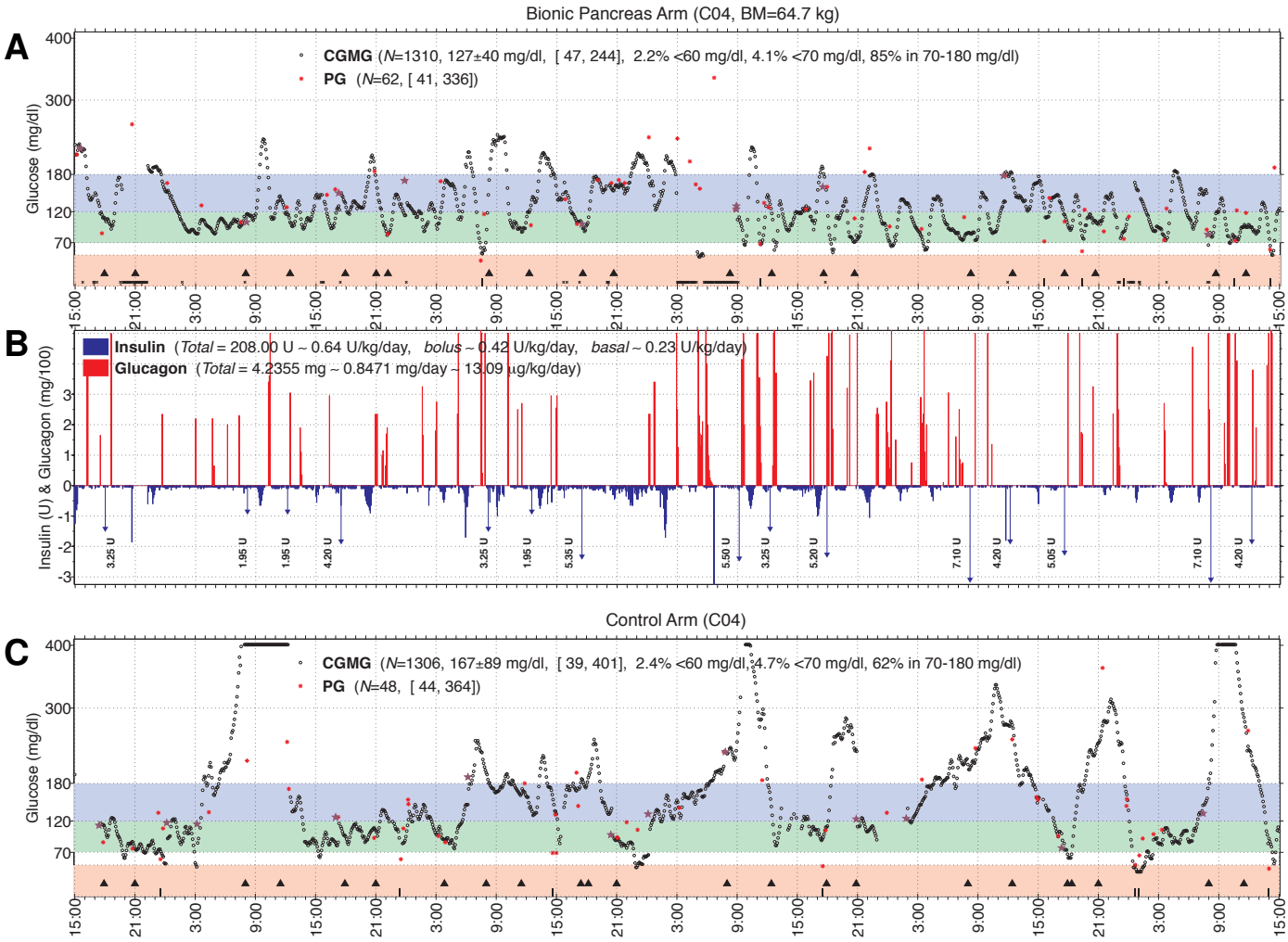


Figure S27. Outpatient experiments in adolescent subject #C04. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 127 mg/dl, average dosing was 0.64 U/kg/day and 13.09 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 125 mg/dl, average dosing was 0.69 U/kg/day and 14.76 μg/kg/day, CGMG was $<$ 60 mg/dl 2.7% of the time, within 70–180 mg/dl 85.2% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 167 mg/dl, CGMG was $<$ 60 mg/dl 2.4% of the time, within 70–180 mg/dl 62.2% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 126 versus 170 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 149 versus 133 mg/dl, and there were 7 carbohydrate interventions versus 7 carbohydrate interventions with PG $<$ 80 mg/dl and 4 carbohydrate interventions versus 7 carbohydrate interventions with PG $<$ 70 mg/dl. One CGM sensor was replaced during the bionic pancreas period (day 3) and 2 CGM sensors were replaced during the comparator period (days 3 and 4) due to CGM signal loss.

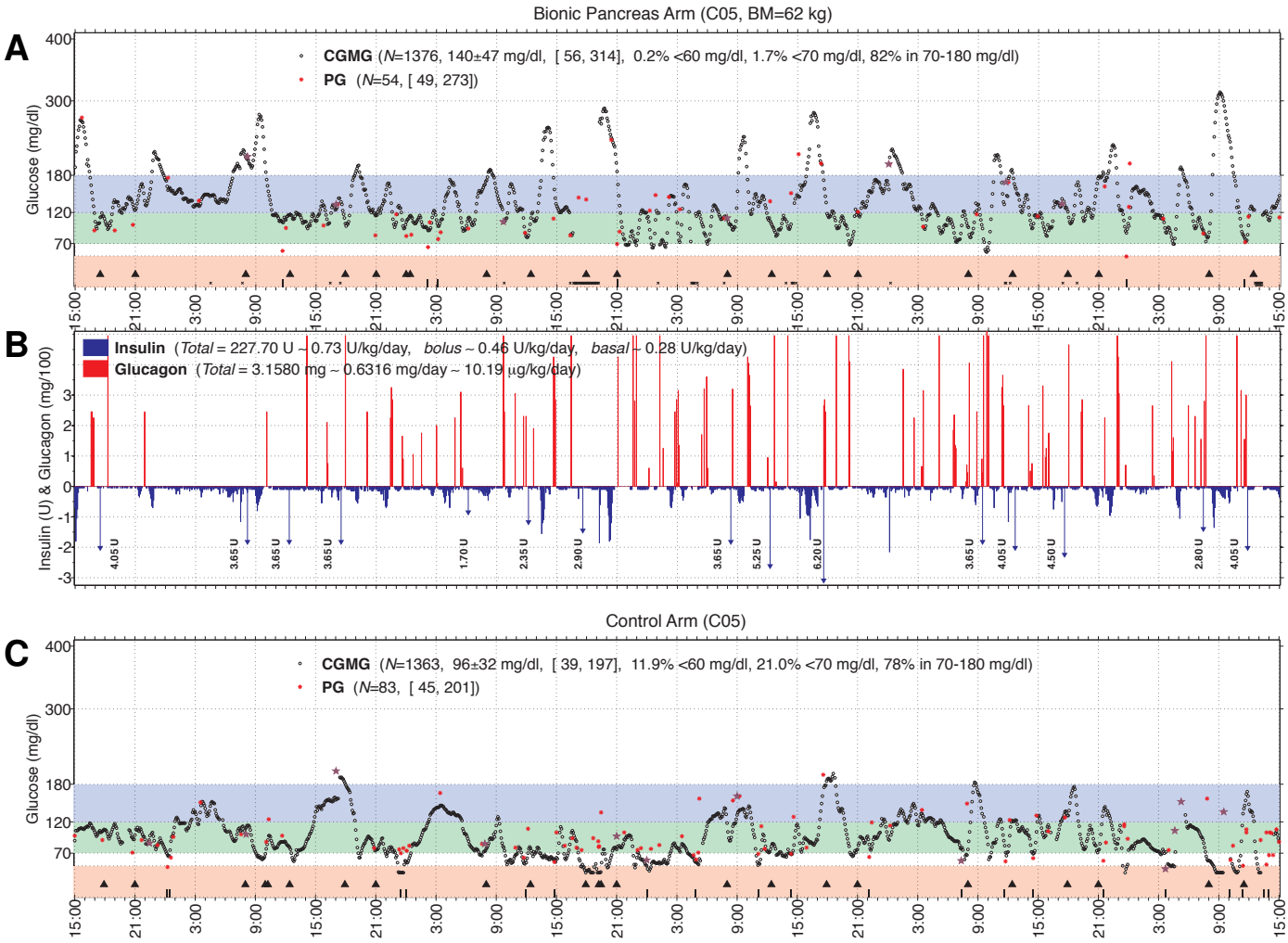


Figure S28. Outpatient experiments in adolescent subject #C05. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 140 mg/dl, average dosing was 0.73 U/kg/day and 10.19 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 136 mg/dl, average dosing was 0.74 U/kg/day and 11.76 μg/kg/day, CGMG was $<$ 60 mg/dl 0.3% of the time, within 70–180 mg/dl 83.4% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 96 mg/dl, CGMG was $<$ 60 mg/dl 11.9% of the time, within 70–180 mg/dl 77.7% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 128 versus 106 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 127 versus 103 mg/dl, and there were 6 carbohydrate interventions versus 20 carbohydrate interventions with PG $<$ 80 mg/dl and 4 carbohydrate interventions versus 18 carbohydrate interventions with PG $<$ 70 mg/dl. One CGM sensor was replaced during the bionic pancreas period (day 3) because the sensor fell off. On the third night of the bionic pancreas period the subject was found to be sleeping on the transmitter, which coincided with the CGMG level significantly underestimating the PG value.

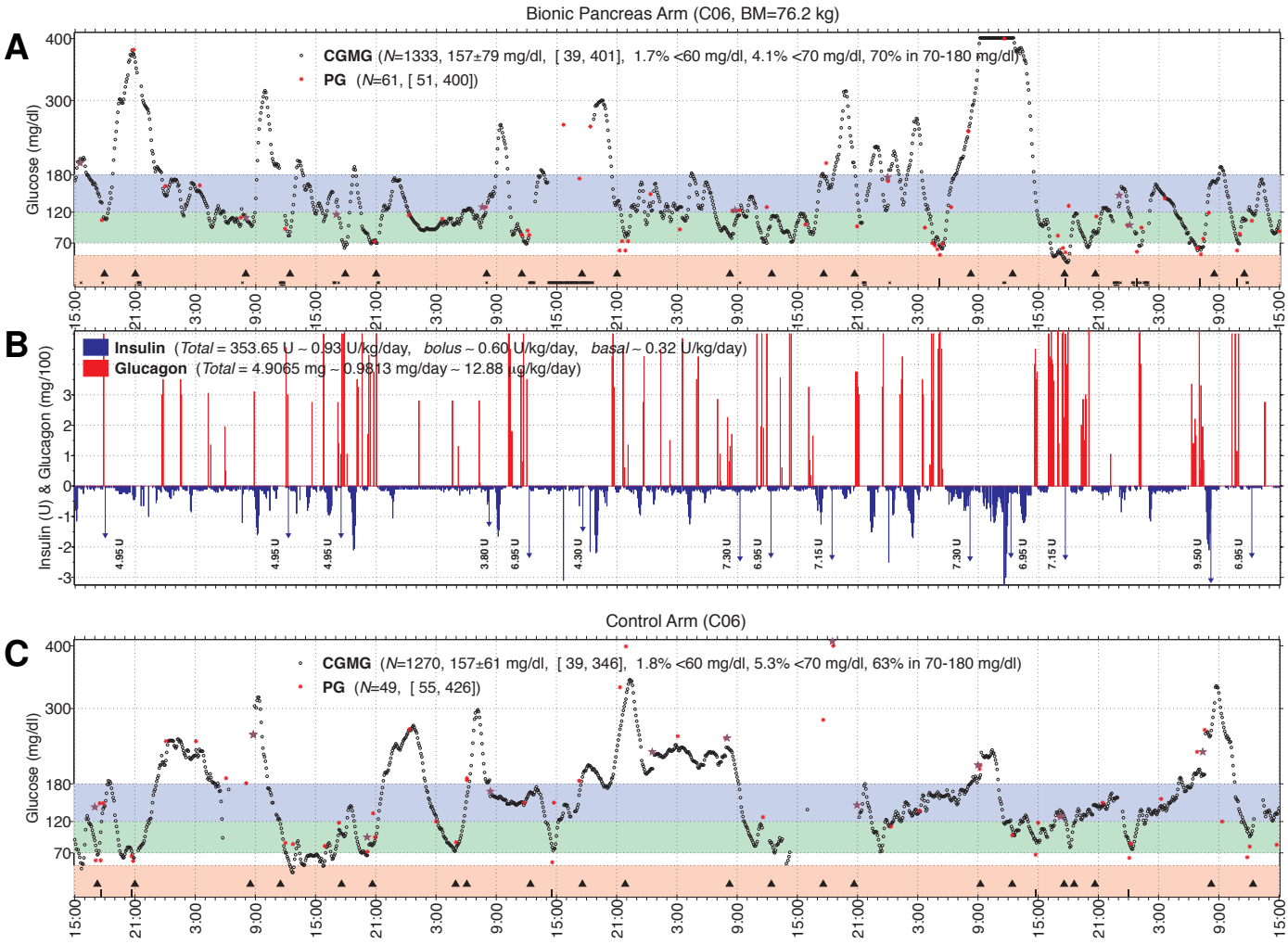


Figure S29. Outpatient experiments in adolescent subject #C06. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period under on the bionic pancreas, mean CGMG was 157 mg/dl, average dosing was 0.93 U/kg/day and 12.88 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 151 mg/dl, average dosing was 0.98 U/kg/day and 14.84 μg/kg/day, CGMG was $<$ 60 mg/dl 2.1% of the time, within 70–180 mg/dl 71.9% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 157 mg/dl, CGMG was $<$ 60 mg/dl 1.8% of the time, within 70–180 mg/dl 62.6% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 145 versus 161 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 130 versus 169 mg/dl, and there were 5 carbohydrate interventions versus 5 carbohydrate interventions with PG $<$ 80 mg/dl and 5 carbohydrate interventions versus 5 carbohydrate interventions with PG $<$ 70 mg/dl. One CGM sensor was replaced during the bionic pancreas period (day 2) because the sensor fell off. Two CGM sensors were replaced during the comparator period (days 3 and 4) due to CGM signal loss. During the bionic pancreas period (day 4) there was a suspected insulin infusion set failure associated with a blood ketone value of 1.1 mmol/dl. The infusion set was replaced, the bionic pancreas regulated the glycemic excursion autonomously, and the hyperketonemia resolved. During this episode the CGMG reached its upper limit of 400 mg/dl. The CGM input to the bionic pancreas was briefly interrupted to allow a single PG value to be manually entered per protocol and a bolus was autonomously delivered by the bionic pancreas in response. Normal CGM input was then restored.

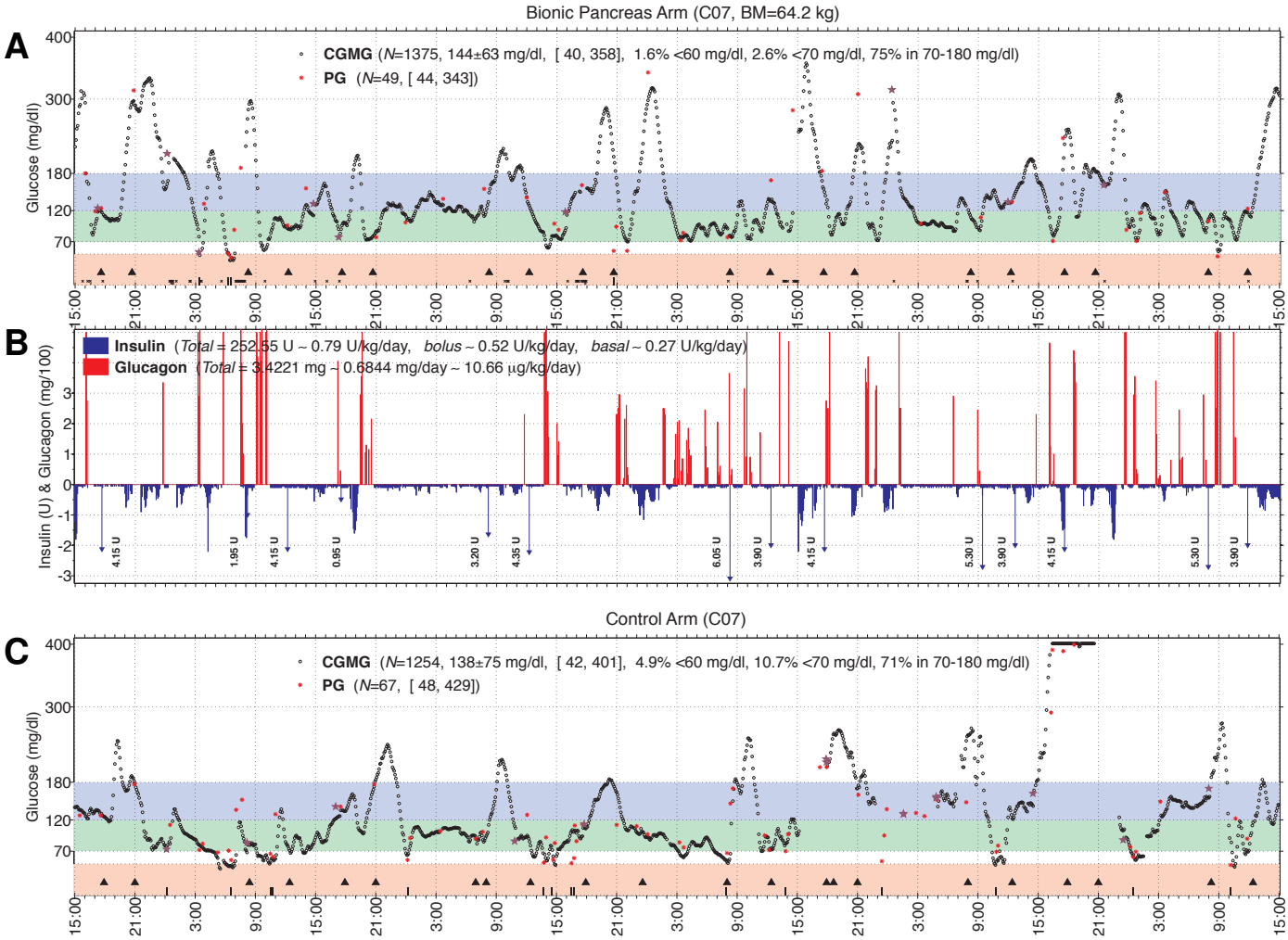


Figure S30. Outpatient experiments in adolescent subject #C07. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 144 mg/dl, average dosing was 0.79 U/kg/day and 10.66 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 139 mg/dl, average dosing was 0.80 U/kg/day and 10.05 μg/kg/day, CGMG was $<$ 60 mg/dl 0.3% of the time, within 70–180 mg/dl 79.6% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 138 mg/dl, CGMG was $<$ 60 mg/dl 4.9% of the time, within 70–180 mg/dl 70.6% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 150 versus 155 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 158 versus 96 mg/dl, and there were 4 carbohydrate interventions versus 15 carbohydrate interventions with PG $<$ 80 mg/dl and 4 carbohydrate interventions versus 13 carbohydrate interventions with PG $<$ 70 mg/dl. During the bionic pancreas period (day 1) occlusion alarms on the glucagon pump were noted during the administration of carbohydrate interventions for hypoglycemia. The infusion set was replaced. Also during bionic pancreas period (day 4) an insulin pump infusion set was replaced because it was leaking and the site was inflamed. One CGM sensor was replaced during the comparator period (day 4) because it fell off.

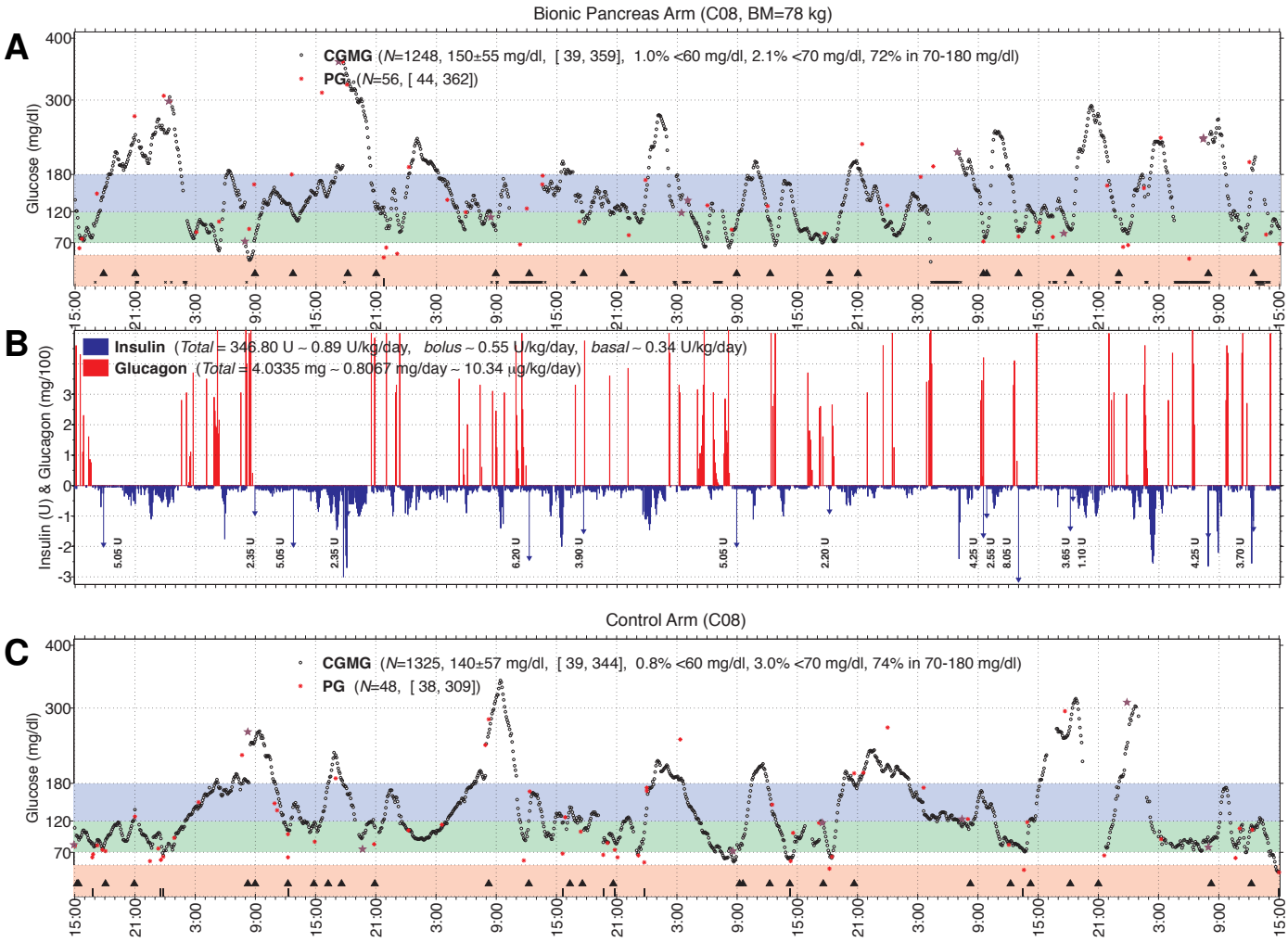


Figure S31. Outpatient experiments in adolescent subject #C08. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 150 mg/dl, average dosing was 0.89 U/kg/day and 10.34 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 150 mg/dl, average dosing was 0.93 U/kg/day and 10.19 μg/kg/day, CGMG was $<$ 60 mg/dl 0.4% of the time, within 70–180 mg/dl 73.9% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 140 mg/dl, CGMG was $<$ 60 mg/dl 0.8% of the time, within 70–180 mg/dl 73.7% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 147 versus 135 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 162 versus 169 mg/dl, and there were 1 carbohydrate interventions versus 11 carbohydrate interventions with PG $<$ 80 mg/dl and 1 carbohydrate interventions versus 10 carbohydrate interventions with PG $<$ 70 mg/dl. Three CGM sensors were replaced during the bionic pancreas period due to CGM signal loss (days 2, 4 and 5).

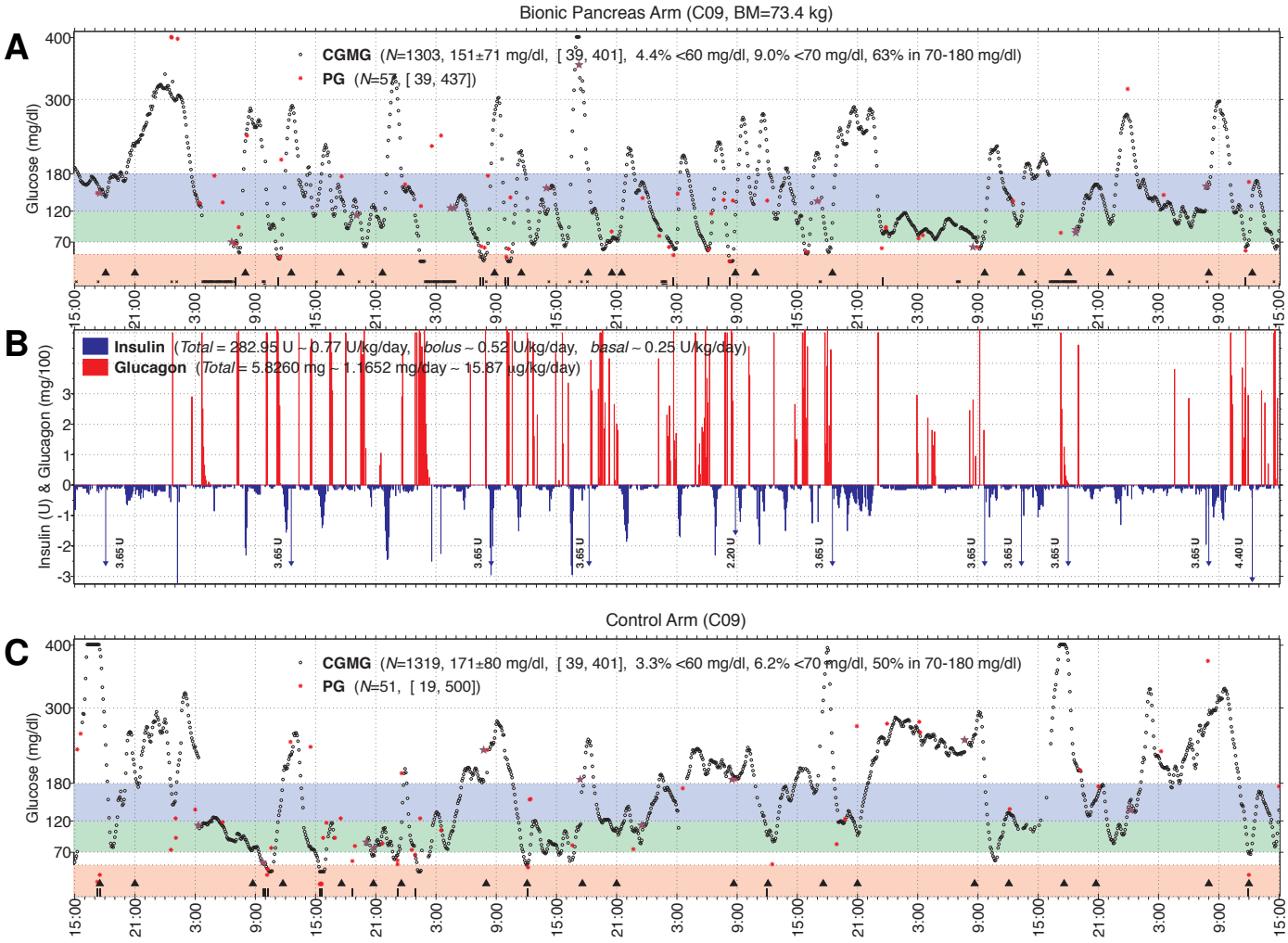


Figure S32. Outpatient experiments in adolescent subject #C09. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas closed-loop glucose and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 151 mg/dl, average dosing was 0.77 U/kg/day and 15.87 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 142 mg/dl, average dosing was 0.79 U/kg/day and 17.13 μg/kg/day, CGMG was $<$ 60 mg/dl 4.9% of the time, within 70–180 mg/dl 67.0% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 171 mg/dl, CGMG was $<$ 60 mg/dl 3.3% of the time, within 70–180 mg/dl 50.0% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 137 versus 184 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 190 versus 168 mg/dl, and there were 11 carbohydrate interventions versus 14 carbohydrate interventions with PG $<$ 80 mg/dl and 11 carbohydrate interventions versus 14 carbohydrate interventions with PG $<$ 70 mg/dl. During the bionic pancreas period (day 1) the subject's PG rose to 437 mg/dl. The CGM input was briefly interrupted to enter the fingerstick PG value and a bolus was autonomously delivered by the bionic pancreas in response. Normal CGMG input was then resumed. Three CGM sensors were replaced during the bionic pancreas period due to CGMG signal loss (days 1, 2, and 5). During the comparator period (day 4), there was a suspected insulin infusion set failure and the infusion set was replaced by the camp medical team.

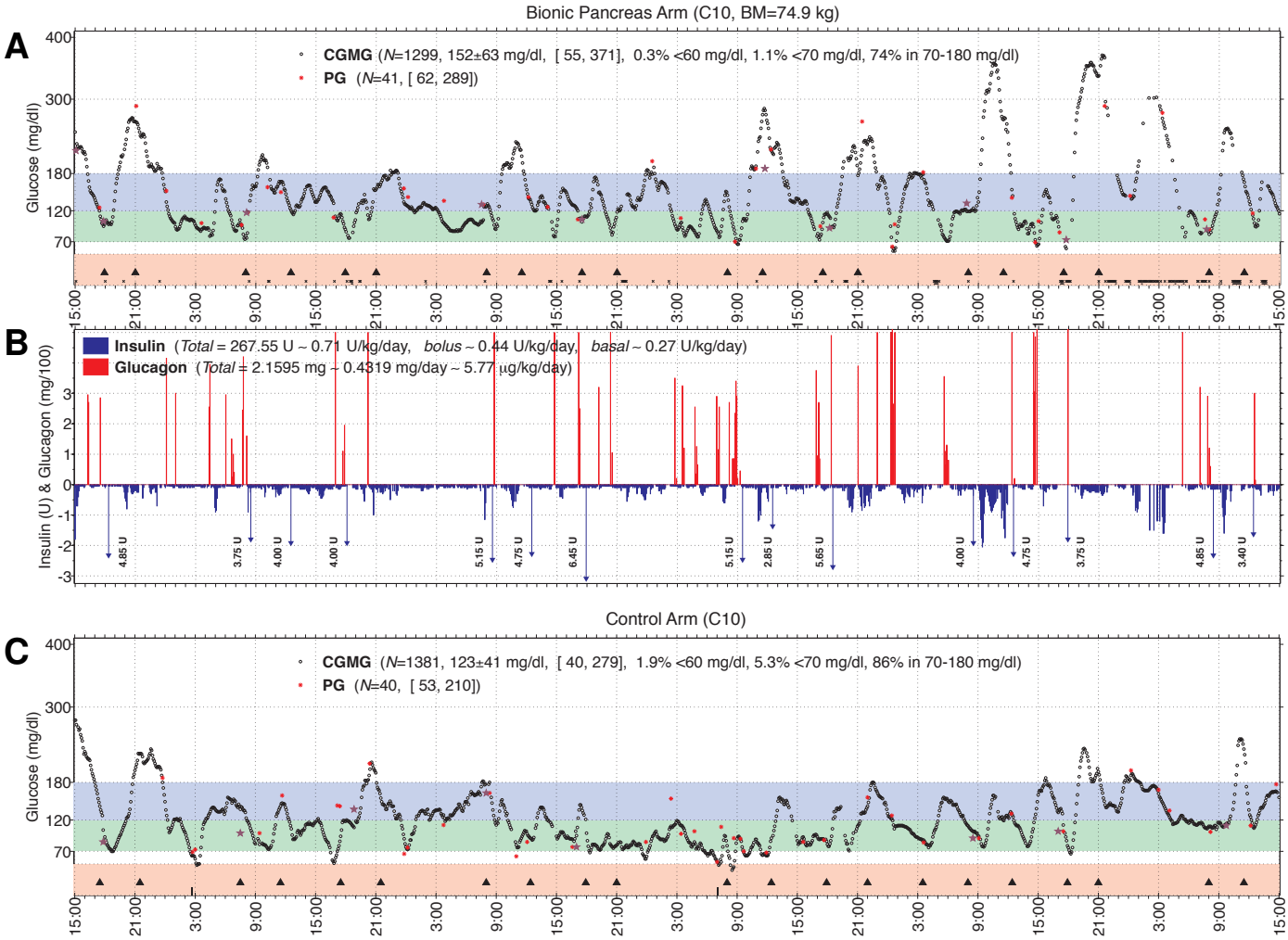


Figure S33. Outpatient experiments in adolescent subject #C10. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 152 mg/dl, average dosing was 0.71 U/kg/day and 5.77 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 152 mg/dl, average dosing was 0.74 U/kg/day and 5.99 μg/kg/day, CGMG was $<$ 60 mg/dl 0.3% of the time, within 70–180 mg/dl 74.3% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 123 mg/dl, CGMG was $<$ 60 mg/dl 1.9% of the time, within 70–180 mg/dl 85.6% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 145 versus 116 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 150 versus 120 mg/dl, and there were 0 carbohydrate interventions versus 2 carbohydrate intervention with PG $<$ 80 mg/dl and 0 carbohydrate interventions versus 2 carbohydrate interventions with PG $<$ 70 mg/dl. During the bionic pancreas period (day 4), an error occurred in which the algorithm session was restarted and system adaptation information from days 1 through 4 was lost. This error likely reduced the effectiveness of the bionic pancreas on days 4 and 5.

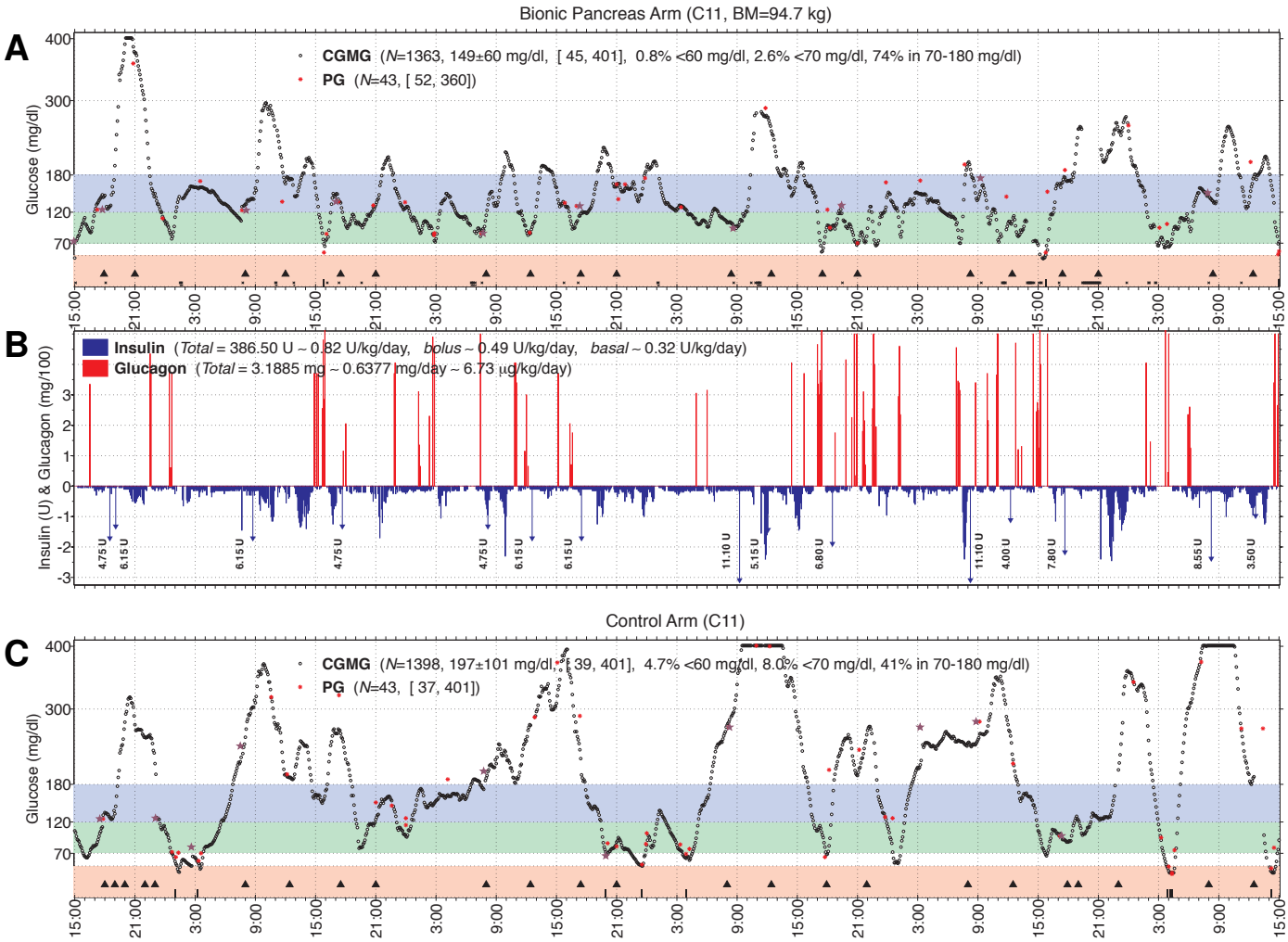


Figure S34. Outpatient experiments in adolescent subject #C11. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 149 mg/dl, average dosing was 0.82 U/kg/day and 6.73 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 142 mg/dl, average dosing was 0.82 U/kg/day and 7.76 μg/kg/day, CGMG was $<$ 60 mg/dl 1.0% of the time, within 70–180 mg/dl 75.5% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 197 mg/dl, CGMG was $<$ 60 mg/dl 4.7% of the time, within 70–180 mg/dl 41.5% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 155 versus 228 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 150 versus 147 mg/dl, and there were 3 carbohydrate interventions versus 9 carbohydrate interventions with PG $<$ 80 mg/dl and 3 carbohydrate interventions versus 9 carbohydrate interventions with PG $<$ 70 mg/dl.

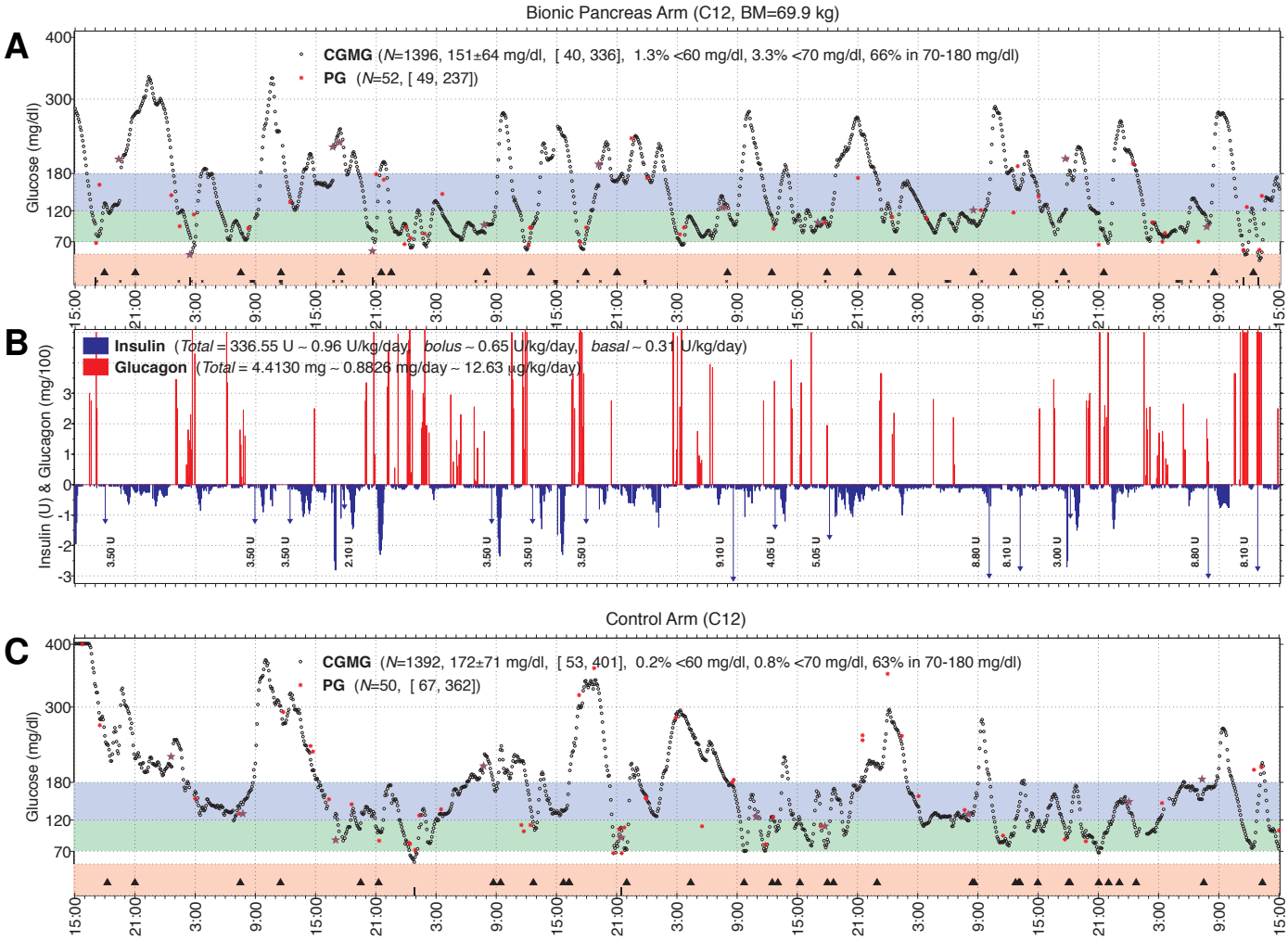


Figure S35. Outpatient experiments in adolescent subject #C12. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 151 mg/dl, average dosing was 0.96 U/kg/day and 12.63 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 144 mg/dl, average dosing was 1.00 U/kg/day and 13.59 μg/kg/day, CGMG was $<$ 60 mg/dl 1.6% of the time, within 70–180 mg/dl 68.5% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 172 mg/dl, CGMG was $<$ 60 mg/dl 0.2% of the time, within 70–180 mg/dl 62.7% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 127 versus 162 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 126 versus 184 mg/dl, and there were 5 carbohydrate interventions versus 2 carbohydrate interventions with PG $<$ 80 mg/dl and 5 carbohydrate interventions versus 2 carbohydrate interventions with PG $<$ 70 mg/dl.

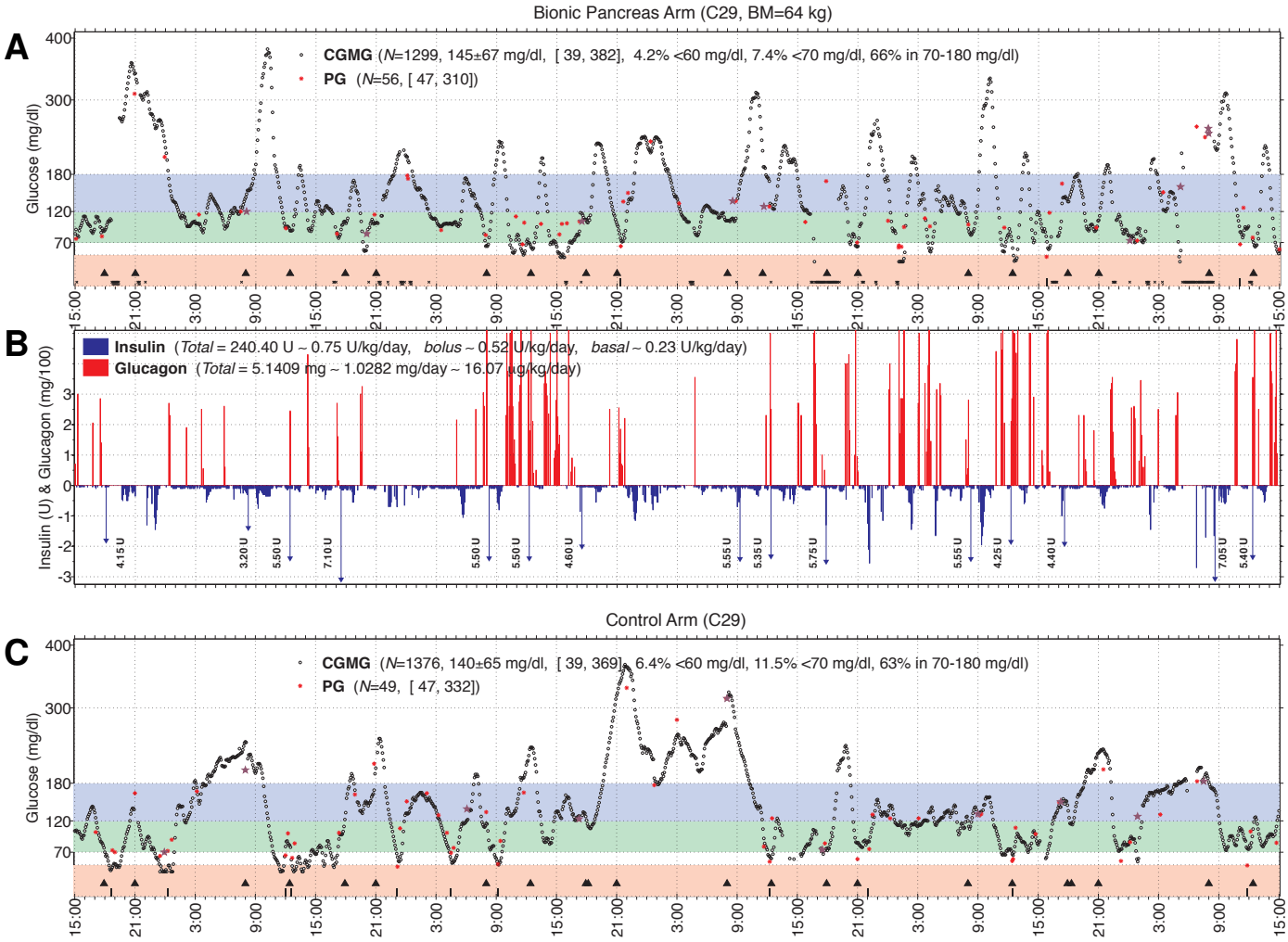


Figure S36. Outpatient experiments in adolescent subject #C29. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 145 mg/dl, average dosing was 0.75 U/kg/day and 16.07 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 139 mg/dl, average dosing was 0.76 U/kg/day and 19.28 μg/kg/day, CGMG was $<$ 60 mg/dl 5.2% of the time, within 70–180 mg/dl 65.8% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 140 mg/dl, CGMG was $<$ 60 mg/dl 6.4% of the time, within 70–180 mg/dl 63.4% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 120 versus 144 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 140 versus 144 mg/dl, and there were 3 carbohydrate interventions versus 11 carbohydrate interventions with PG $<$ 80 mg/dl and 3 carbohydrate interventions versus 8 carbohydrate interventions with PG $<$ 70 mg/dl. One CGM sensor was replaced during the bionic pancreas period (day 5) due to CGM signal loss. There was a suspected insulin pump infusion set failure during the bionic pancreas period (day 5 at 07:55) associated with a blood ketone value of 1.9 mmol/dl. The infusion set was replaced, the bionic pancreas regulated the glycemic excursion autonomously, and the hyperketonemia resolved.

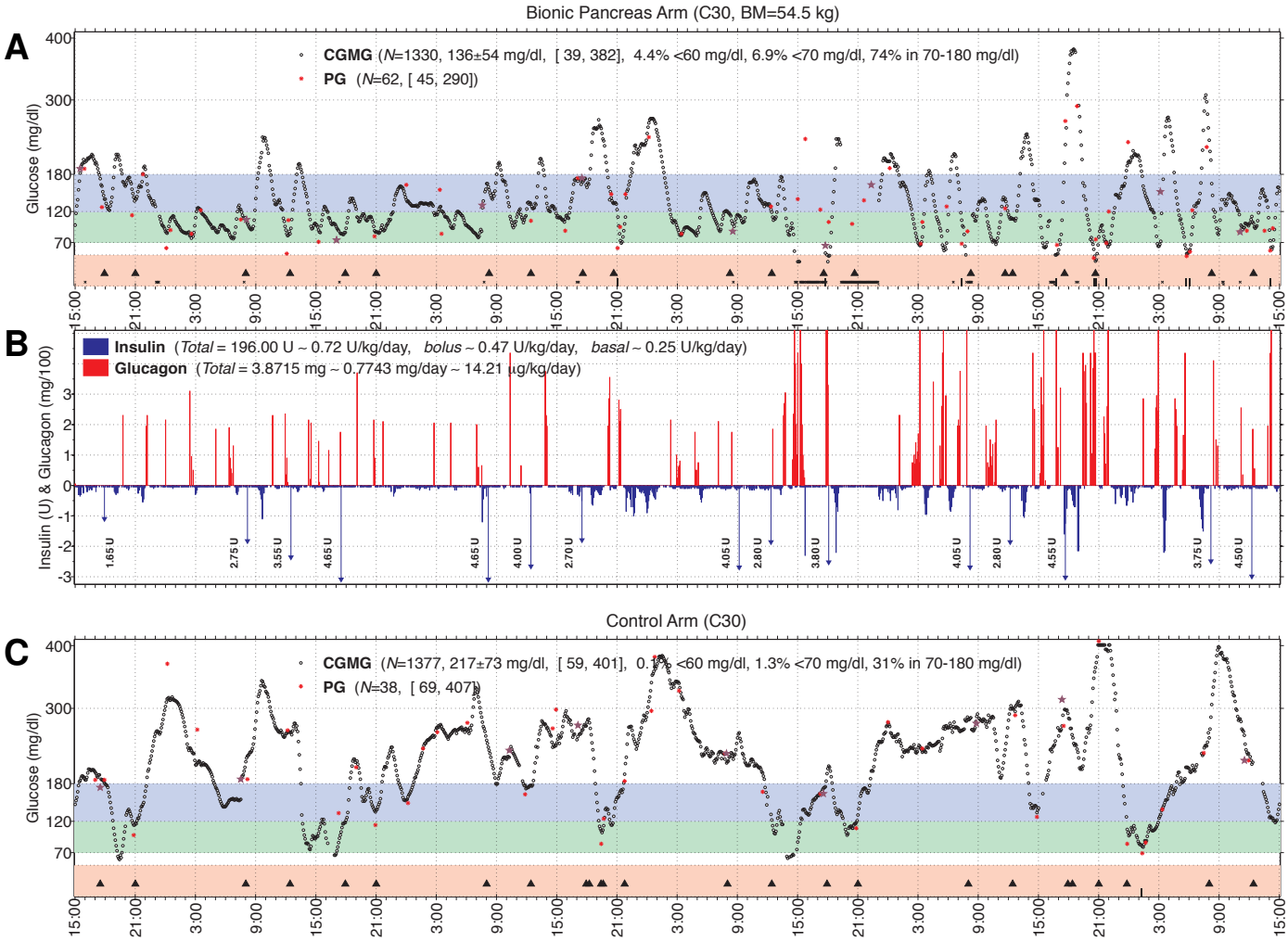


Figure S37. Outpatient experiments in adolescent subject #C30. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 136 mg/dl, average dosing was 0.72 U/kg/day and 14.21 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 136 mg/dl, average dosing was 0.77 U/kg/day and 16.56 μg/kg/day, CGMG was $<$ 60 mg/dl 5.6% of the time, within 70–180 mg/dl 72.7% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 217 mg/dl, CGMG was $<$ 60 mg/dl 0.1% of the time, within 70–180 mg/dl 30.7% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 117 versus 211 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 143 versus 241 mg/dl, and there were 10 carbohydrate interventions versus 1 carbohydrate intervention with PG $<$ 80 mg/dl and 9 carbohydrate interventions versus 1 carbohydrate interventions with PG $<$ 70 mg/dl. One CGM sensor was replaced during the bionic pancreas period (day 4) because it fell off. On the following morning, a “cartridge empty” alarm on the glucagon pump was noted during the administration of a carbohydrate intervention for hypoglycemia and the cartridge was replaced ahead of schedule.

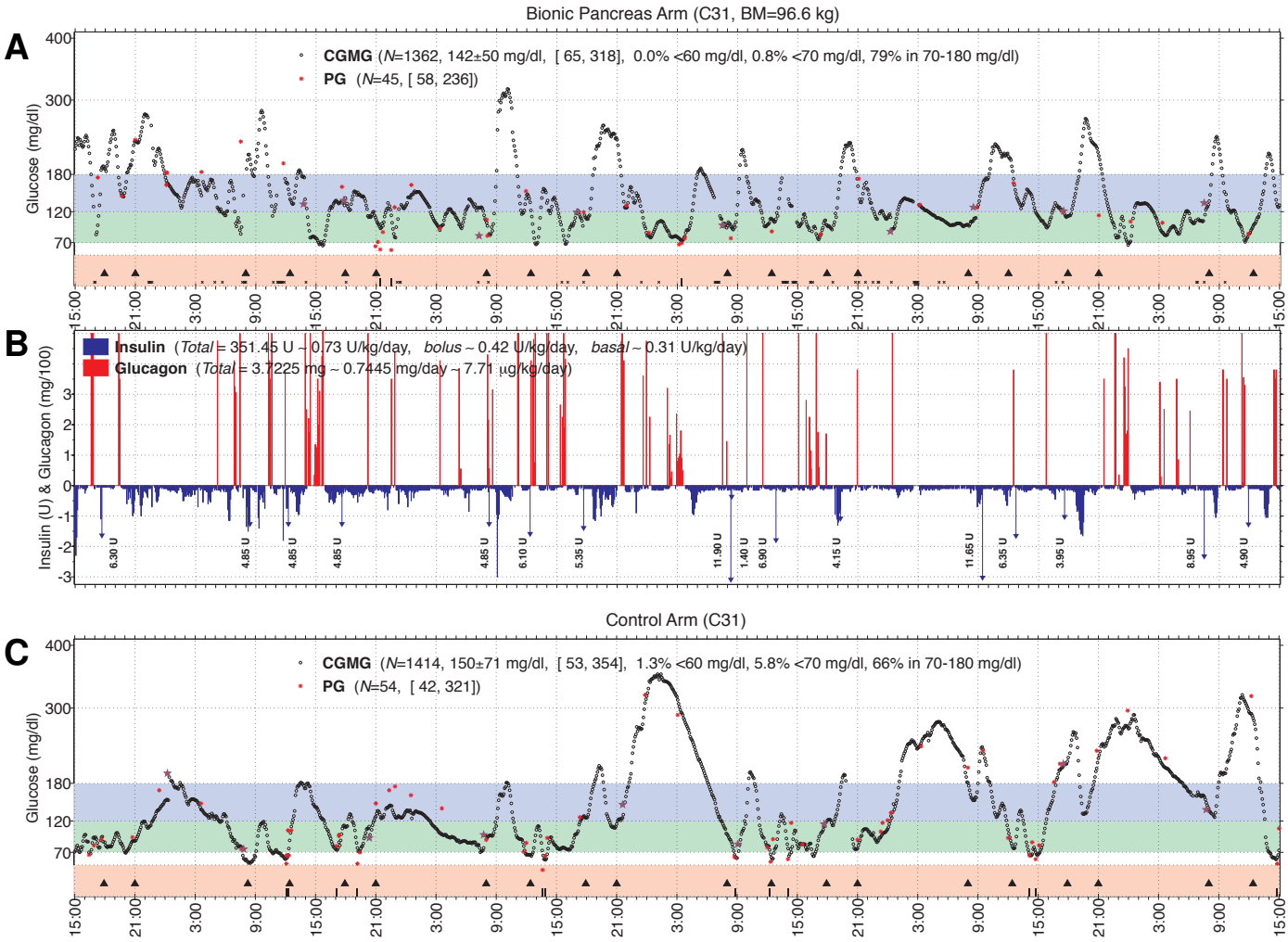


Figure S38. Outpatient experiments in adolescent subject #C31. Panels **A** and **B** respectively show the 5-day glycemic control achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 142 mg/dl, average dosing was 0.73 U/kg/day and 7.71 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 139 mg/dl, average dosing was 0.69 U/kg/day and 7.48 μg/kg/day, CGMG was $<$ 60 mg/dl 0.0% of the time, within 70–180 mg/dl 84.2% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 150 mg/dl, CGMG was $<$ 60 mg/dl 1.3% of the time, within 70–180 mg/dl 65.7% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 136 versus 126 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 120 versus 213 mg/dl, and there were 3 carbohydrate interventions versus 12 carbohydrate interventions with PG $<$ 80 mg/dl and 3 carbohydrate interventions versus 11 carbohydrate interventions with PG $<$ 70 mg/dl. During the comparator period (day 3 at 03:04), there was a suspected insulin infusion site failure associated with a blood ketone value of 0.8 mmol/dl. The set was replaced by the camp medical team, insulin was dosed according to camp policy, and the hyperketonemia resolved.

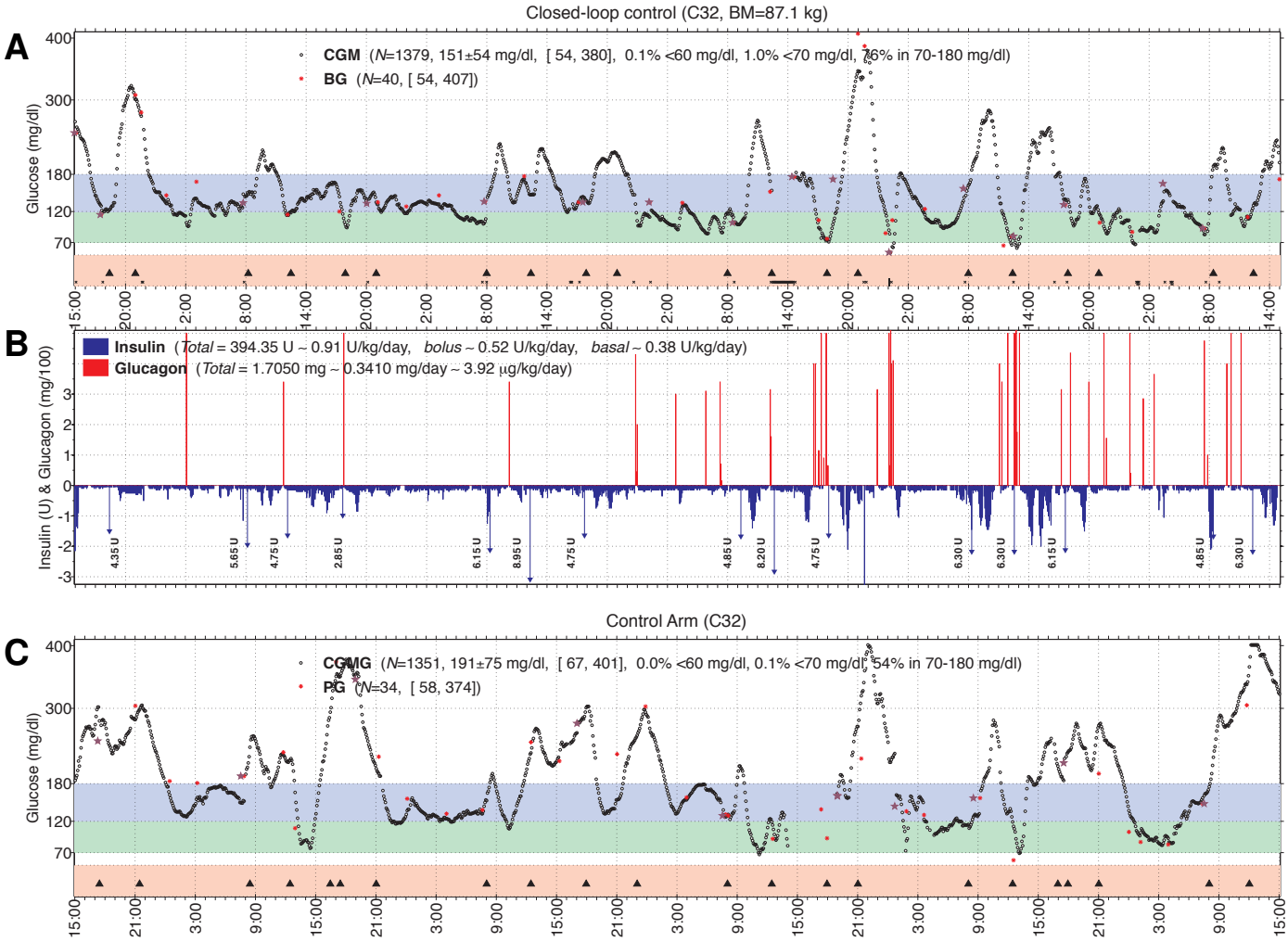


Figure S39. Outpatient experiments in adolescent subject #C32. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 151 mg/dl, average dosing was 0.91 U/kg/day and 3.92 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 147 mg/dl, average dosing was 0.95 U/kg/day and 4.65 μg/kg/day, CGMG was $<$ 60 mg/dl 0.2% of the time, within 70–180 mg/dl 77.3% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 191 mg/dl, CGMG was $<$ 60 mg/dl 0.0% of the time, within 70–180 mg/dl 53.6% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 146 versus 197 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 129 versus 157 mg/dl, and there was 1 carbohydrate interventions versus 0 carbohydrate interventions with PG $<$ 80 mg/dl and 1 carbohydrate interventions versus 0 carbohydrate interventions with PG $<$ 70 mg/dl. One CGM sensor was replaced during the bionic pancreas period (day 3) and one was replaced during the comparator period (day 4) due to CGMG signal loss. During the bionic pancreas period (day 4 at 21:00) an insulin pump infusion set was found to be partially removed. The infusion set was replaced and the bionic pancreas regulated the glycemic excursion autonomously.

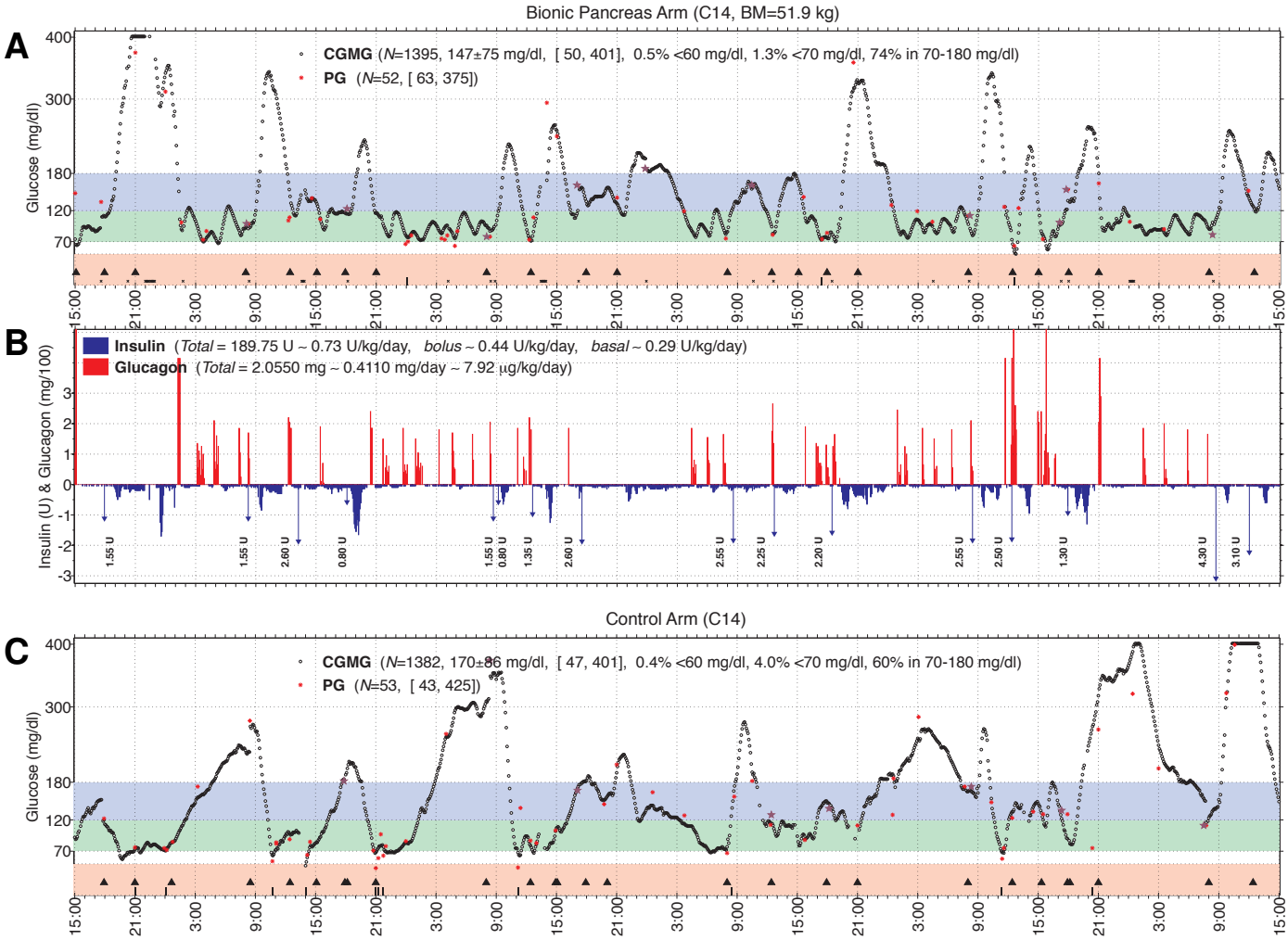


Figure S40. Outpatient experiments in adolescent subject #C14. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 147 mg/dl, average dosing was 0.73 U/kg/day and 7.92 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 137 mg/dl, average dosing was 0.73 U/kg/day and 7.67 μg/kg/day, CGMG was $<$ 60 mg/dl 0.6% of the time, within 70–180 mg/dl 77.3% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 170 mg/dl, CGMG was $<$ 60 mg/dl 0.4% of the time, within 70–180 mg/dl 59.7% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 134 versus 162 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 127 versus 182 mg/dl, and there were 3 carbohydrate interventions versus 11 carbohydrate interventions with PG $<$ 80 mg/dl and 1 carbohydrate interventions versus 8 carbohydrate interventions with PG $<$ 70 mg/dl. During the comparator period (day 2) there was a suspected insulin infusion set failure associated with a blood ketone value of 0.6 mmol/dl. The set was replaced by the camp medical team, insulin was dosed according to camp policy, and the hyperketonemia resolved.

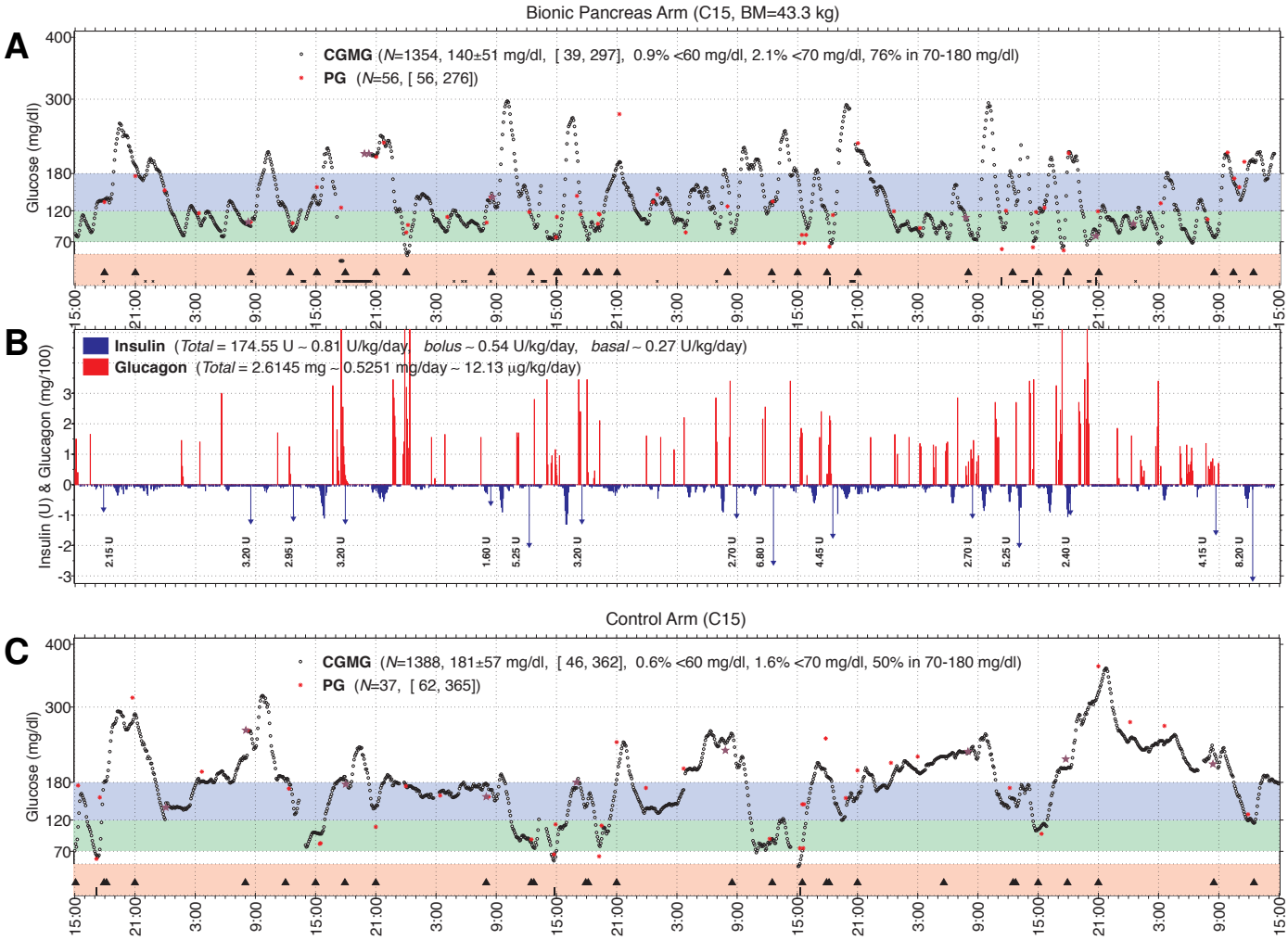


Figure S41. Outpatient experiments in adolescent subject #C15. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 140 mg/dl, average dosing was 0.81 U/kg/day and 12.13 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 140 mg/dl, average dosing was 0.87 U/kg/day and 14.30 μg/kg/day, CGMG was $<$ 60 mg/dl 1.1% of the time, within 70–180 mg/dl 74.6% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 181 mg/dl, CGMG was $<$ 60 mg/dl 0.6% of the time, within 70–180 mg/dl 50.0% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 133 versus 191 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 112 versus 202 mg/dl, and there were 6 carbohydrate interventions versus 3 carbohydrate interventions with PG $<$ 80 mg/dl and 4 carbohydrate interventions versus 2 carbohydrate interventions with PG $<$ 70 mg/dl.

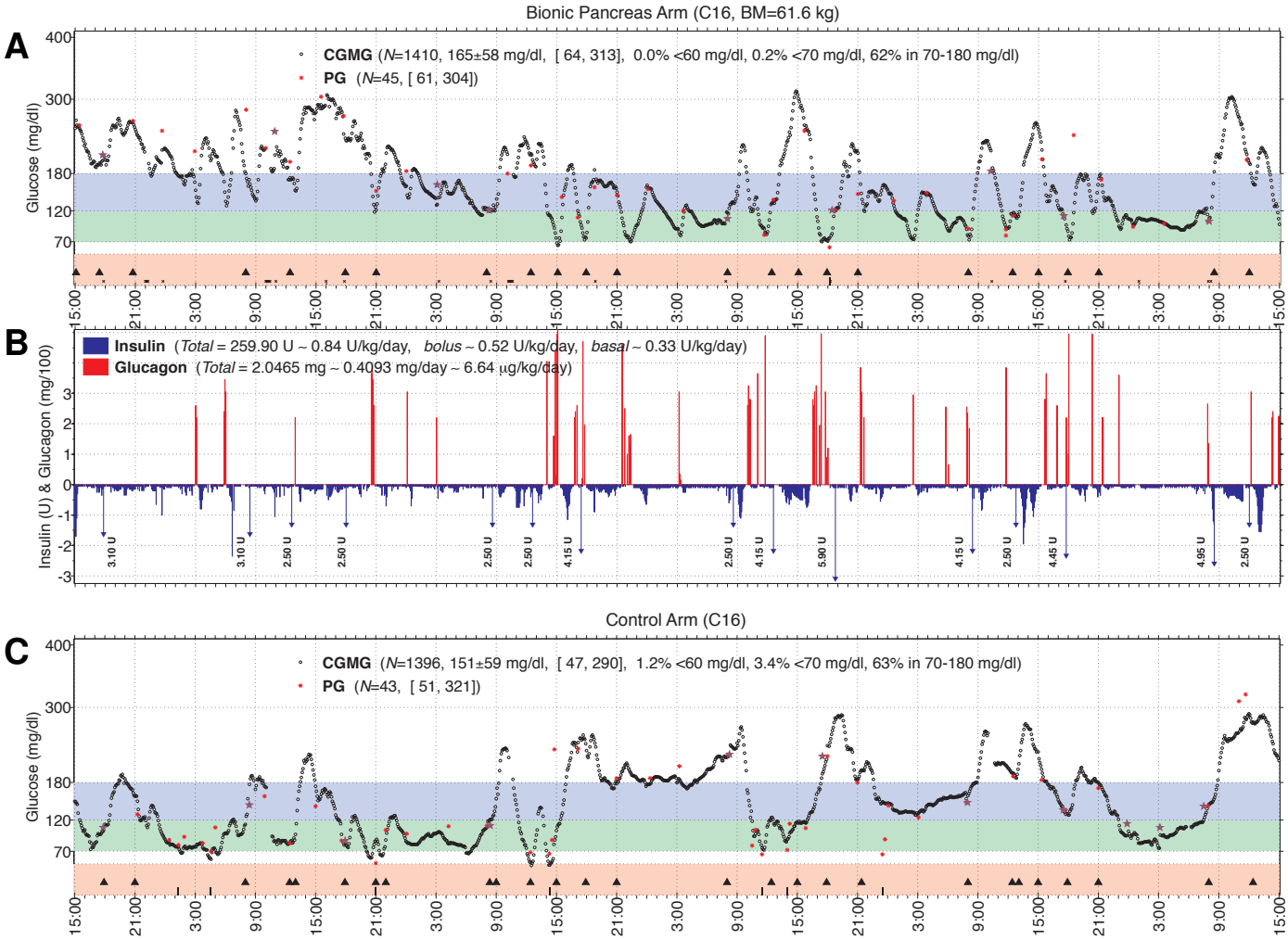


Figure S42. Outpatient experiments in adolescent subject #C16. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period the bionic pancreas, mean CGMG was 165 mg/dl, average dosing was 0.84 U/kg/day and 6.64 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 154 mg/dl, average dosing was 0.86 U/kg/day and 7.86 μg/kg/day, CGMG was $<$ 60 mg/dl 0.0% of the time, within 70–180 mg/dl 71.6% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 151 mg/dl, CGMG was $<$ 60 mg/dl 1.2% of the time, within 70–180 mg/dl 63.4% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 160 versus 150 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 156 versus 126 mg/dl, and there was 1 carbohydrate intervention versus 6 carbohydrate interventions with PG $<$ 80 mg/dl and 1 carbohydrate interventions versus 4 carbohydrate interventions with PG $<$ 70 mg/dl.

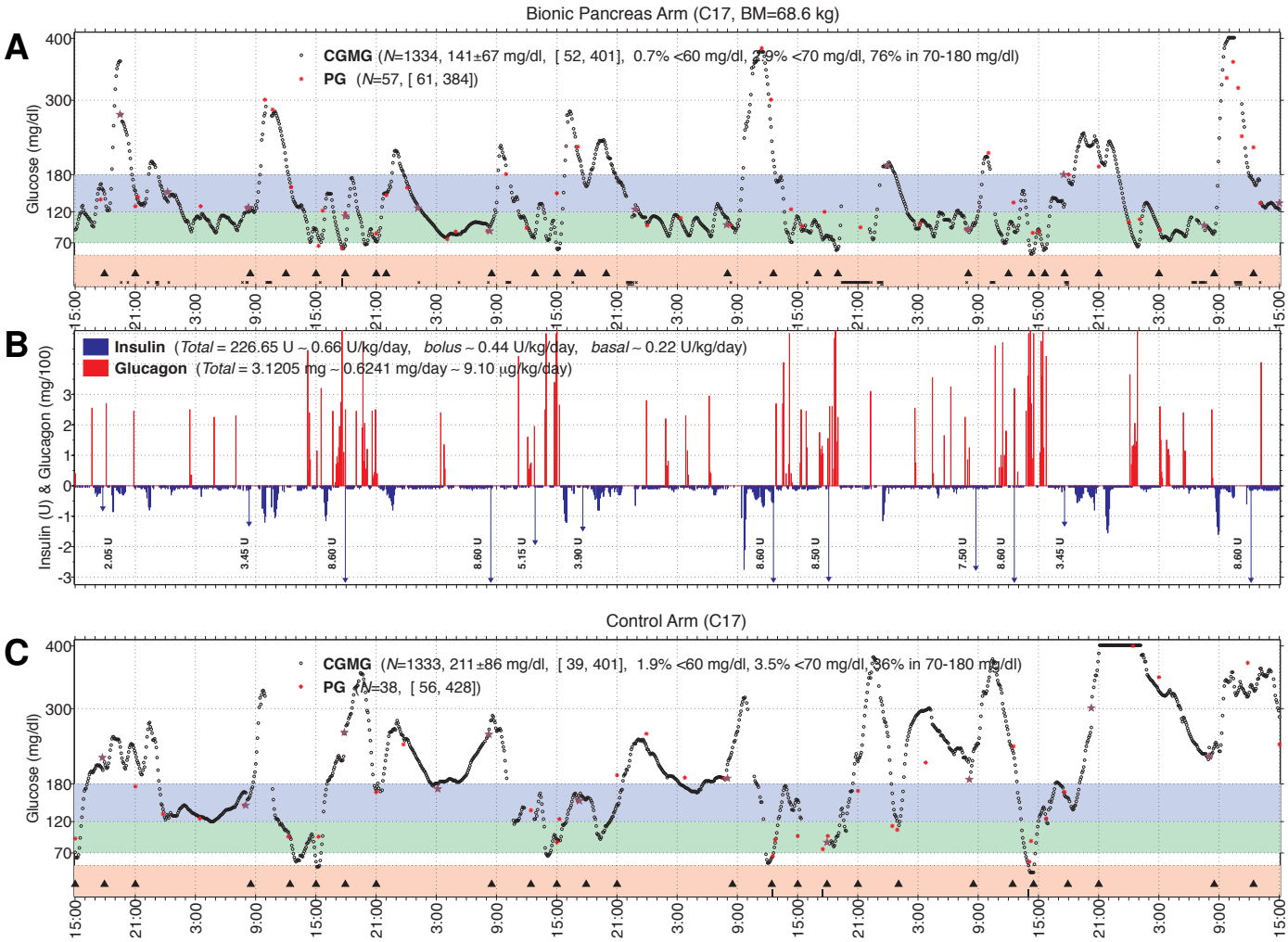


Figure S43. Outpatient experiments in adolescent subject #C17. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 141 mg/dl, average dosing was 0.66 U/kg/day and 9.10 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 138 mg/dl, average dosing was 0.69 U/kg/day and 10.79 μg/kg/day, CGMG was $<$ 60 mg/dl 0.9% of the time, within 70–180 mg/dl 76.0% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 211 mg/dl, CGMG was $<$ 60 mg/dl 1.9% of the time, within 70–180 mg/dl 36.2% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 139 versus 197 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 121 versus 220 mg/dl, and there was 1 carbohydrate intervention versus 3 carbohydrate interventions with PG $<$ 80 mg/dl and 1 carbohydrate interventions versus 2 carbohydrate interventions with PG $<$ 70 mg/dl. During the bionic pancreas period (day 4 at 16:00) an insulin infusion set was replaced because it fell off.

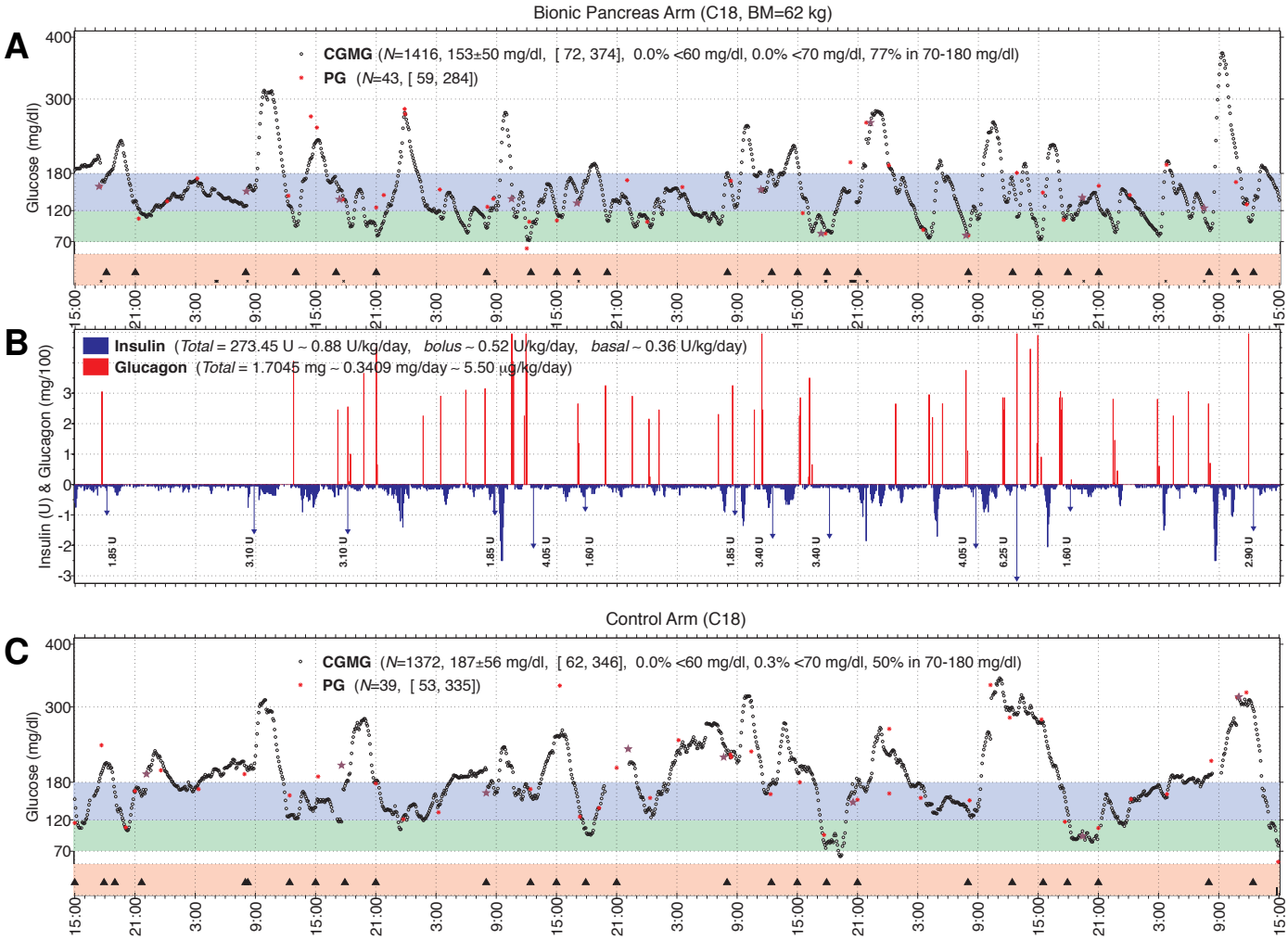


Figure S44. Outpatient experiments in adolescent subject #C18. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 153 mg/dl, average dosing was 0.88 U/kg/day and 5.50 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 149 mg/dl, average dosing was 0.94 U/kg/day and 6.59 μg/kg/day, CGMG was $<$ 60 mg/dl 0.0% of the time, within 70–180 mg/dl 79.6% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 187 mg/dl, CGMG was $<$ 60 mg/dl 0.0% of the time, within 70–180 mg/dl 49.8% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 137 versus 183 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 162 versus 165 mg/dl, and there were 0 carbohydrate interventions versus 1 carbohydrate intervention with PG $<$ 80 mg/dl and 0 carbohydrate interventions versus 1 carbohydrate interventions with PG $<$ 70 mg/dl. During the bionic pancreas period (day 1) both insulin and glucagon infusions sets had to be replaced because they fell out. The bionic pancreas regulated the glycemic excursion autonomously.

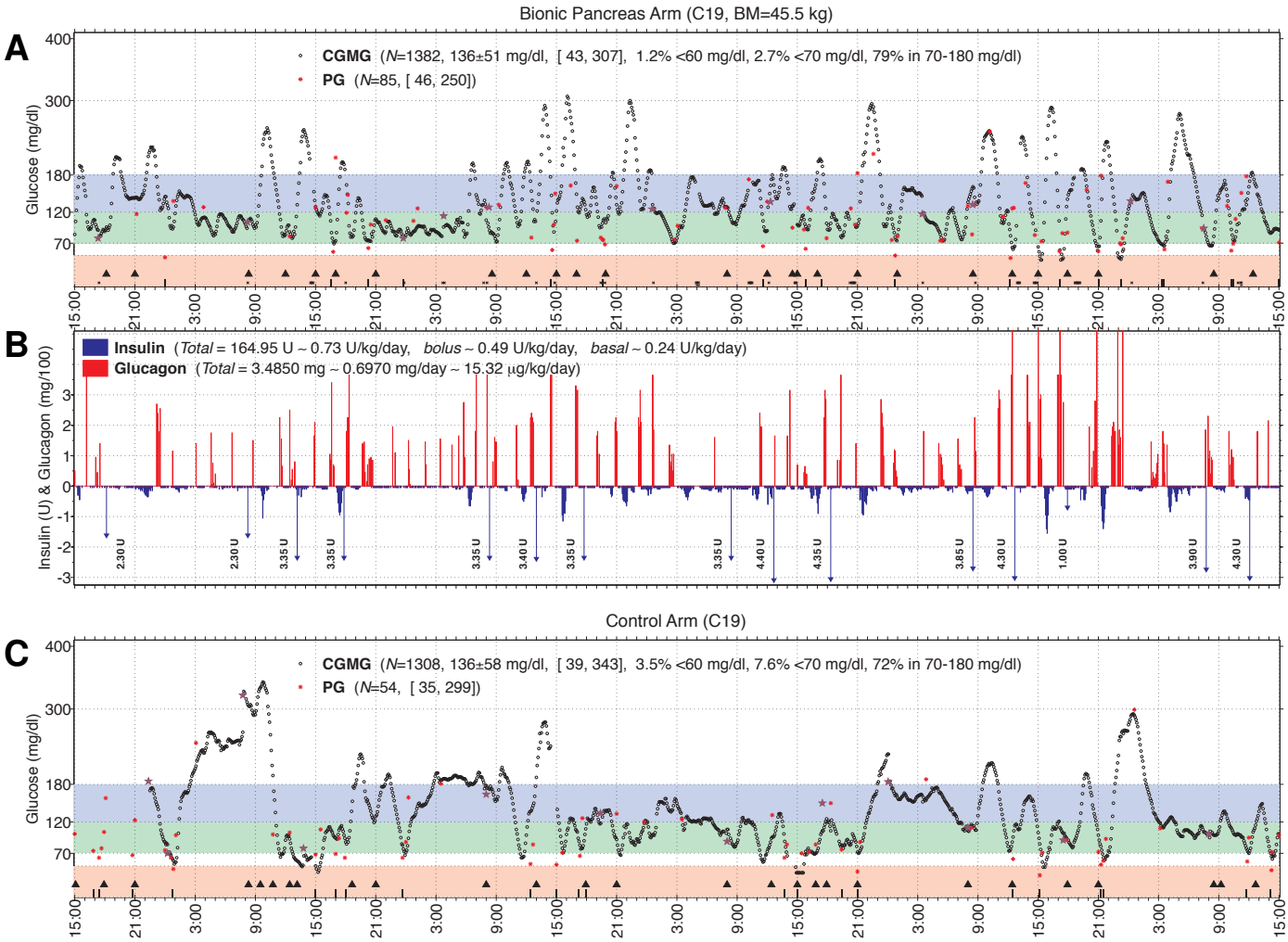


Figure S45. Outpatient experiments in adolescent subject #C19. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 136 mg/dl, average dosing was 0.73 U/kg/day and 15.32 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 136 mg/dl, average dosing was 0.78 U/kg/day and 17.57 μg/kg/day, CGMG was $<$ 60 mg/dl 1.6% of the time, within 70–180 mg/dl 78.9% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 136 mg/dl, CGMG was $<$ 60 mg/dl 3.5% of the time, within 70–180 mg/dl 72.4% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 102 versus 102 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 98 versus 162 mg/dl, and there were 19 carbohydrate interventions versus 22 carbohydrate interventions with PG $<$ 80 mg/dl and 15 carbohydrate interventions versus 19 carbohydrate interventions with PG $<$ 70 mg/dl.

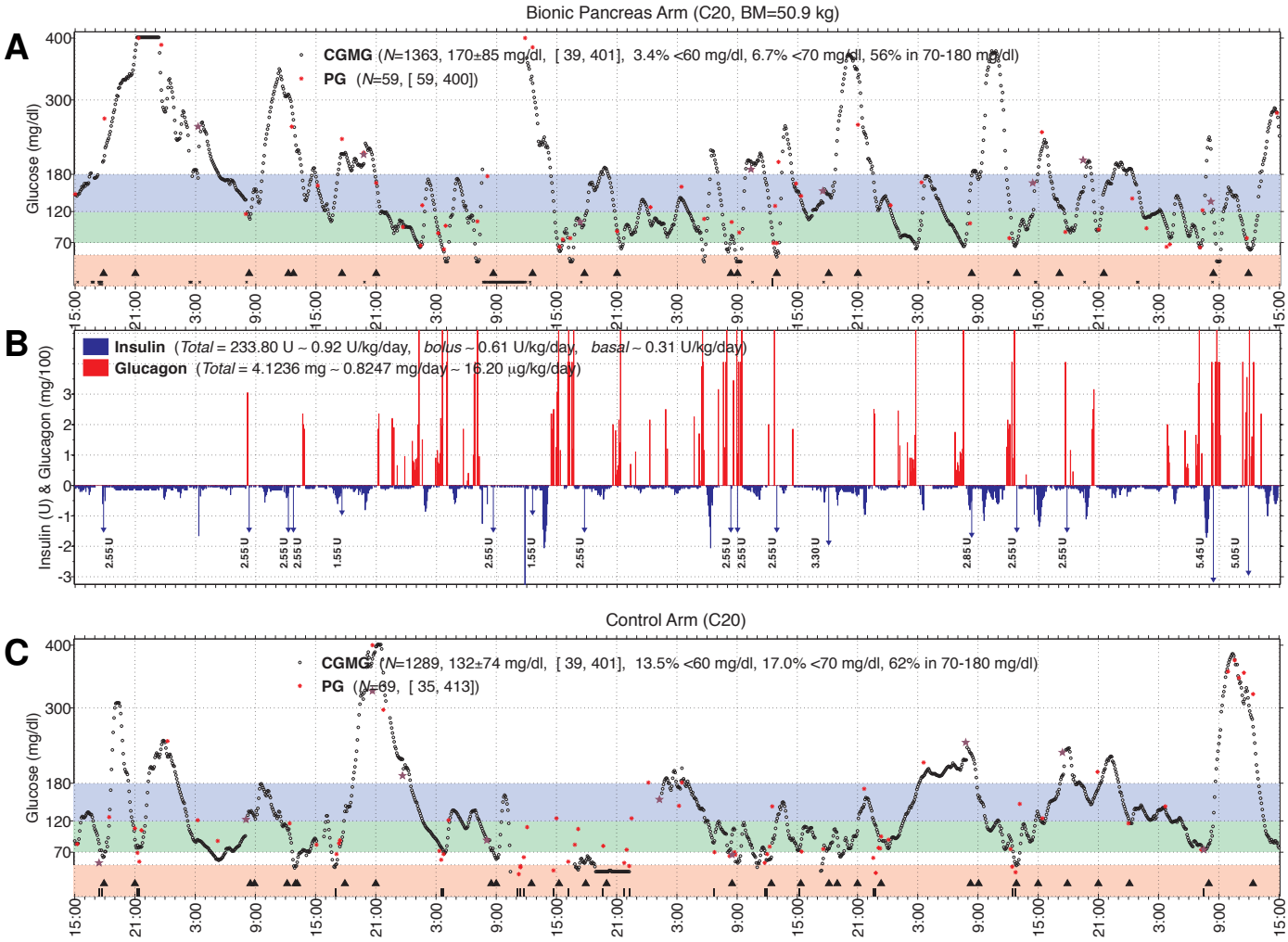


Figure S46. Outpatient experiments in adolescent subject #C20. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 170 mg/dl, average dosing was 0.92 U/kg/day and 16.20 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 151 mg/dl, average dosing was 0.95 U/kg/day and 19.95 μg/kg/day, CGMG was $<$ 60 mg/dl 4.3% of the time, within 70–180 mg/dl 62.7% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 132 mg/dl, CGMG was $<$ 60 mg/dl 13.5% of the time, within 70–180 mg/dl 61.8% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 168 versus 132 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 159 versus 154 mg/dl, and there was 1 carbohydrate intervention versus 23 carbohydrate interventions with PG $<$ 80 mg/dl and 1 carbohydrate interventions versus 20 carbohydrate interventions with PG $<$ 70 mg/dl. One CGM sensor was replaced during the bionic pancreas period (day 3). The fingerstick PG value at the time of initial calibration for the new sensor was “HIGH” so 400 mg/dl was entered. The bionic pancreas regulated the glycemic excursion autonomously. One CGM sensor was replaced during the comparator period (day 3) due to signal loss.

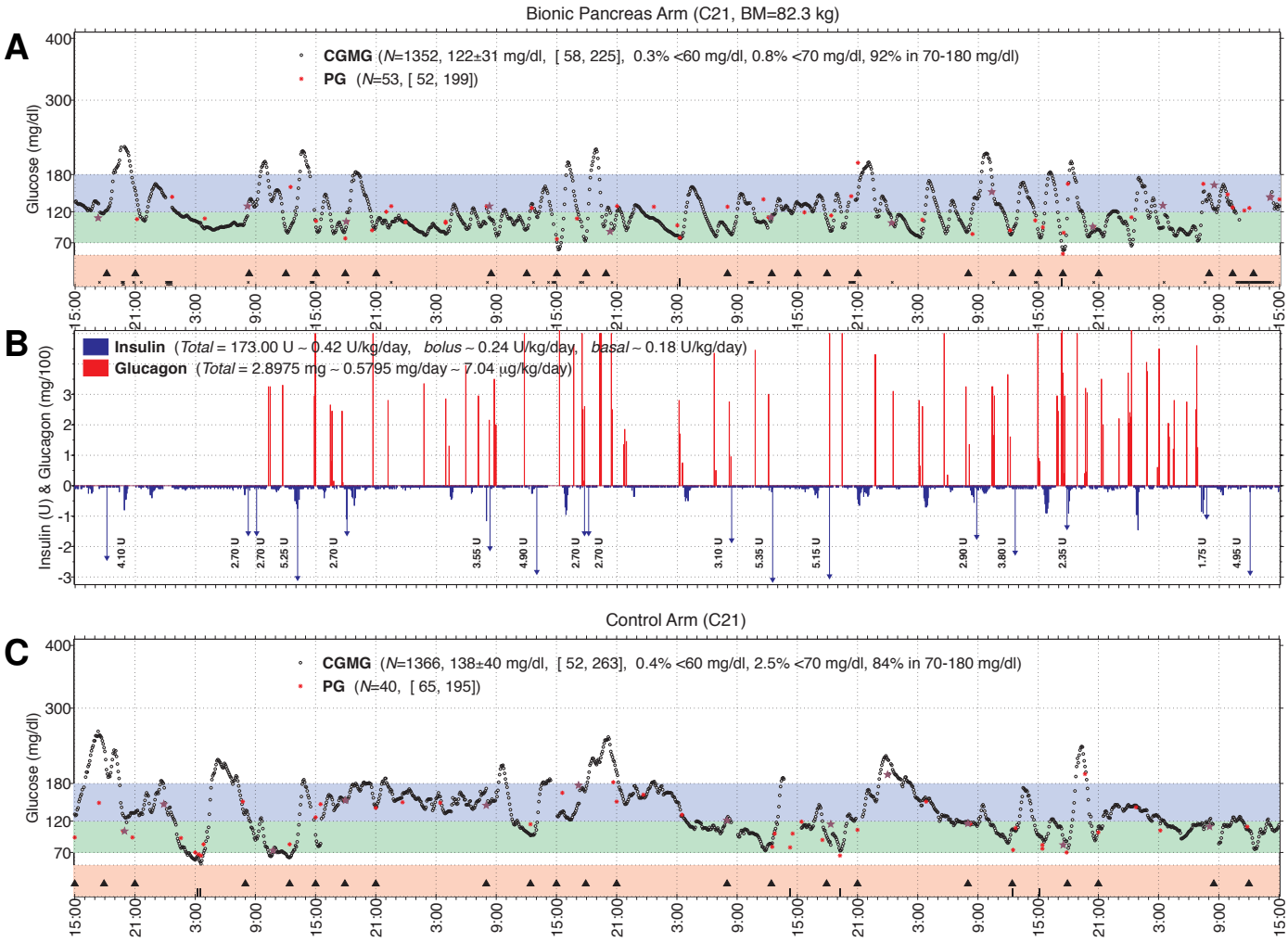


Figure S47. Outpatient experiments in adolescent subject #C21. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 122 mg/dl, average dosing was 0.42 U/kg/day and 7.04 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 119 mg/dl, average dosing was 0.41 U/kg/day and 8.29 μg/kg/day, CGMG was $<$ 60 mg/dl 0.3% of the time, within 70–180 mg/dl 94.1% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 138 mg/dl, CGMG was $<$ 60 mg/dl 0.4% of the time, within 70–180 mg/dl 83.6% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 114 versus 118 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 111 versus 139 mg/dl, and there were 2 carbohydrate interventions versus 6 carbohydrate interventions with PG $<$ 80 mg/dl and 1 carbohydrate interventions versus 3 carbohydrate interventions with PG $<$ 70 mg/dl. During the comparator period (day 2) the CGM did not meet ISO accuracy criteria and a calibration was forced.

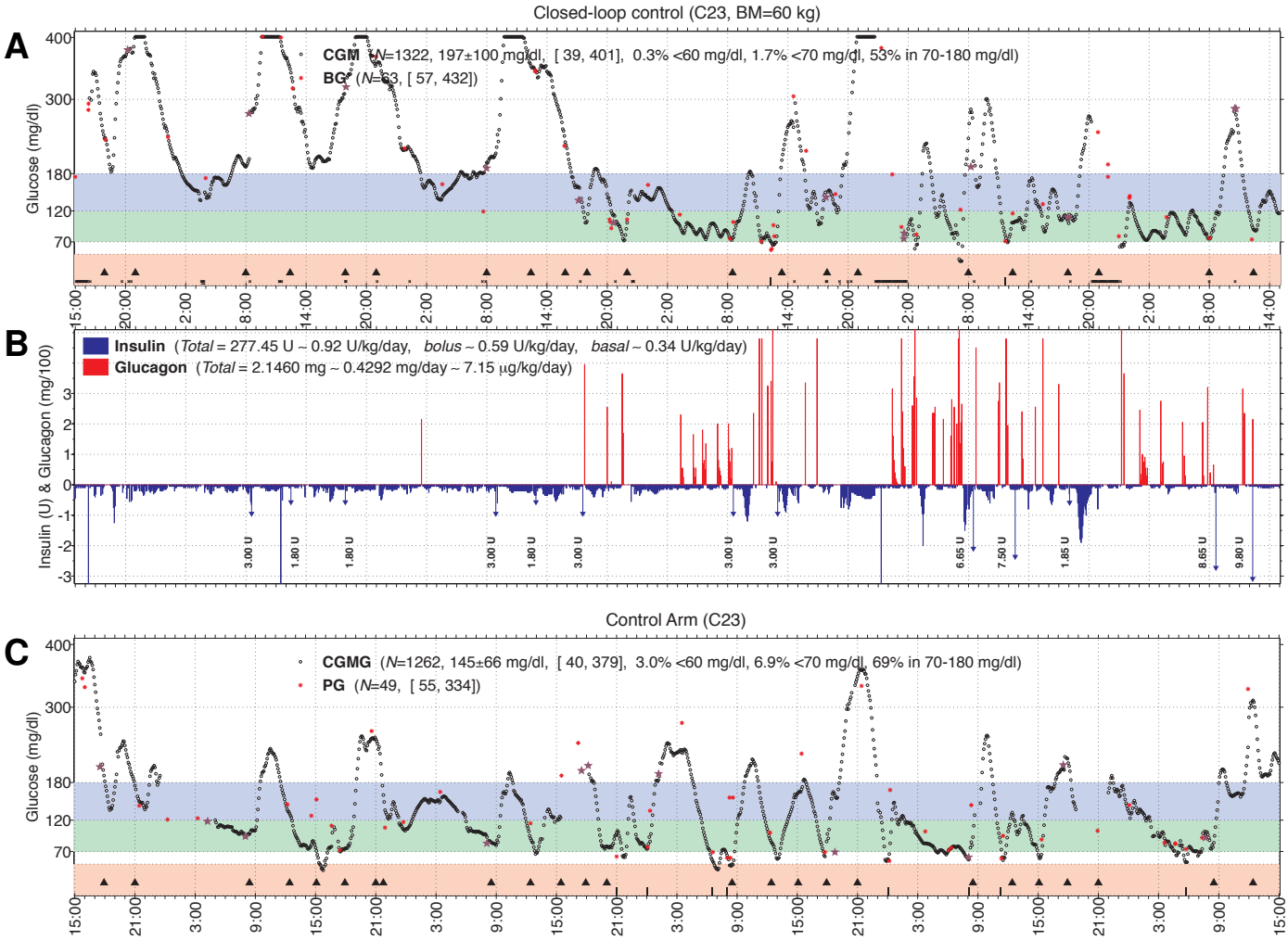


Figure S48. Outpatient experiments in adolescent subject #C23. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 197 mg/dl, average dosing was 0.92 U/kg/day and 7.15 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 179 mg/dl, average dosing was 0.96 U/kg/day and 8.94 μg/kg/day, CGMG was $<$ 60 mg/dl 0.4% of the time, within 70–180 mg/dl 61.4% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 145 mg/dl, CGMG was $<$ 60 mg/dl 3.0% of the time, within 70–180 mg/dl 68.8% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 200 versus 140 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 158 versus 126 mg/dl, and there were 2 carbohydrate interventions versus 8 carbohydrate interventions with PG $<$ 80 mg/dl and 1 carbohydrate interventions versus 6 carbohydrate interventions with PG $<$ 70 mg/dl. During day 1 of the bionic pancreas period the CGMG reached 400 mg/dl for one hour. The CGM input was briefly interrupted to manually enter a PG value and a bolus was autonomously delivered by the bionic pancreas in response. CGM input was then restored. Blood ketones during this episode were 0.7 mmol/dl and subsequently resolved. The bionic pancreas algorithm was constrained from adaptation until the glucose level reached 120 mg/dl for the first time, which was approached but not achieved in the first two days. Given the limited time duration of the 5-day experiment, the CGM input was briefly interrupted at 08:00 on day 2 and a PG value of 120 mg/dl was entered. CGM input was then restored. The glycemic control improved thereafter. A CGM sensor was replaced on day 4 of the bionic pancreas period because it fell out. On day 5 of the bionic pancreas period, the CGM session was restarted because the receiver lost battery charge. During the comparator period (day 0) there was a suspected insulin infusion set failure associated with a blood ketone value 0.7 mmol/dl. The set was replaced by the camp medical team, insulin was dosed according to camp policy, and the hyperketonemia resolved. One CGM sensor was replaced during the comparator period (day 1) because it fell off. One CGM session was restarted during the comparator period (day 2) because the receiver lost battery charge.

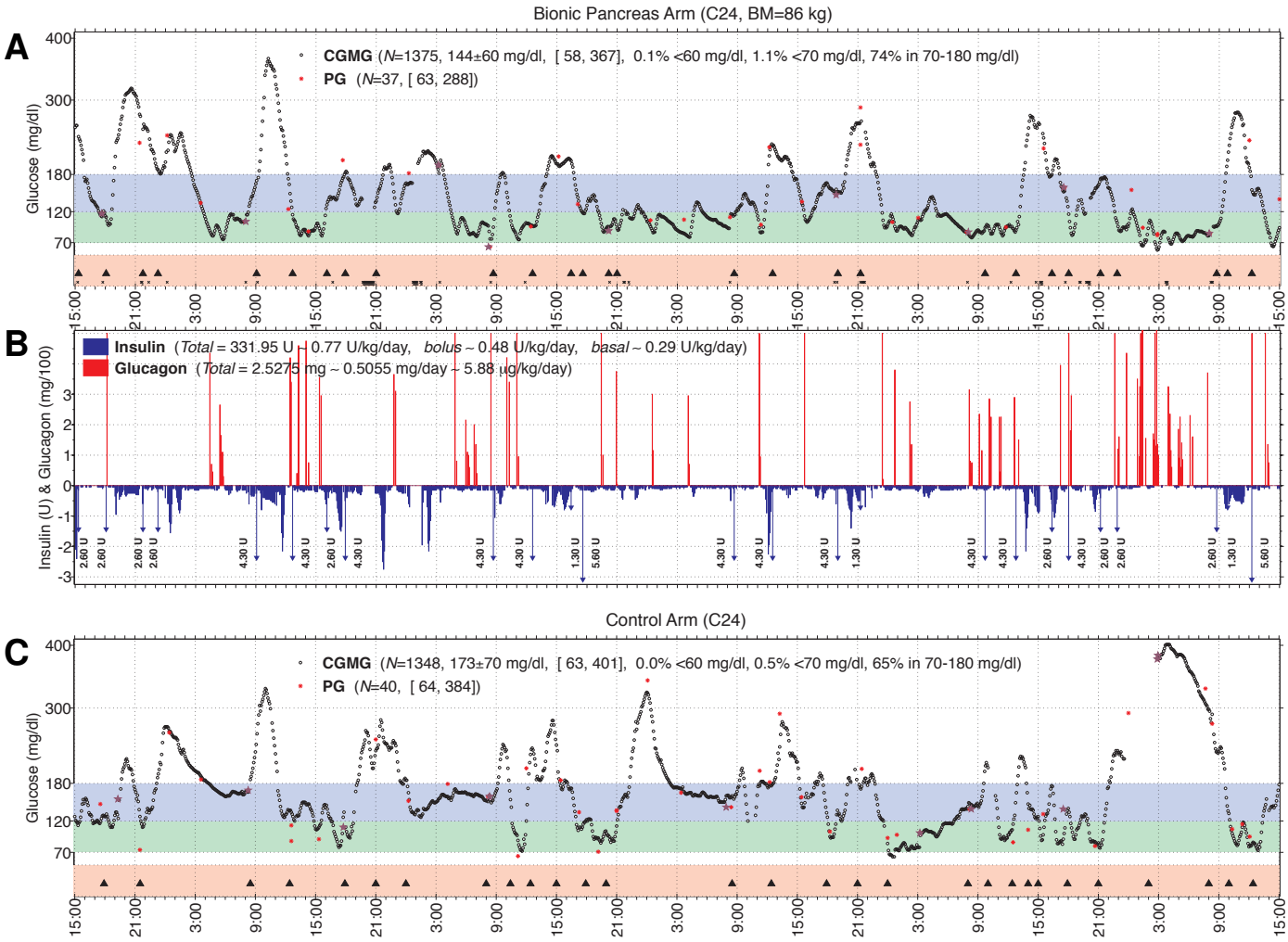


Figure S49. Outpatient experiments in adolescent subject #C24. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 144 mg/dl, average dosing was 0.74 U/kg/day and 5.88 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 134 mg/dl, average dosing was 0.74 U/kg/day and 6.32 μg/kg/day, CGMG was $<$ 60 mg/dl 0.2% of the time, within 70–180 mg/dl 79.7% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 173 mg/dl, CGMG was $<$ 60 mg/dl 0.0% of the time, within 70–180 mg/dl 64.5% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 141 versus 145 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 142 versus 216 mg/dl, and there were 0 carbohydrate interventions versus 0 carbohydrate interventions with PG $<$ 80 mg/dl and 0 carbohydrate interventions versus 0 carbohydrate interventions with PG $<$ 70 mg/dl. During the comparator period (day 5) the CGM session was restarted because the receiver battery lost charge.

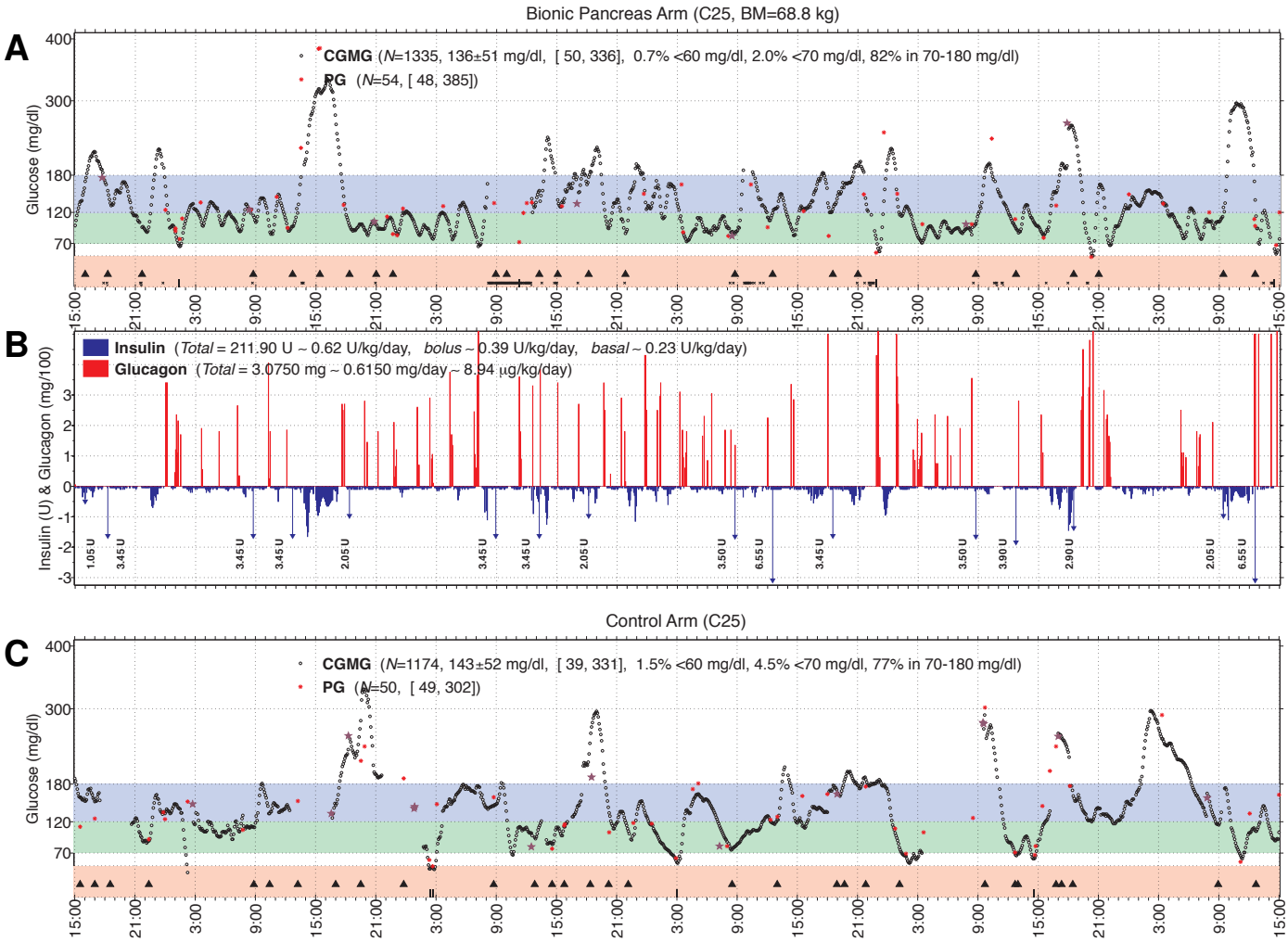


Figure S50. Outpatient experiments in adolescent subject #C25. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 136 mg/dl, average dosing was 0.62 U/kg/day and 8.94 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 135 mg/dl, average dosing was 0.63 U/kg/day and 9.92 μg/kg/day, CGMG was $<$ 60 mg/dl 0.9% of the time, within 70–180 mg/dl 81.9% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 143 mg/dl, CGMG was $<$ 60 mg/dl 1.5% of the time, within 70–180 mg/dl 77.4% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 123 versus 149 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 146 versus 143 mg/dl, and there were 4 carbohydrate interventions versus 4 carbohydrate interventions with PG $<$ 80 mg/dl and 2 carbohydrate interventions versus 4 carbohydrate interventions with PG $<$ 70 mg/dl. During the bionic pancreas period (day 1 at 15:20 and day 2 at 15:45) infusion sets for insulin and glucagon, respectively, were replaced because they fell off. CGM sensors were replaced during the bionic pancreas period (day 2) and the comparator period (day 1) because of signal loss. During the comparator period (day 4) the CGM session was restarted because the receiver battery lost charge.

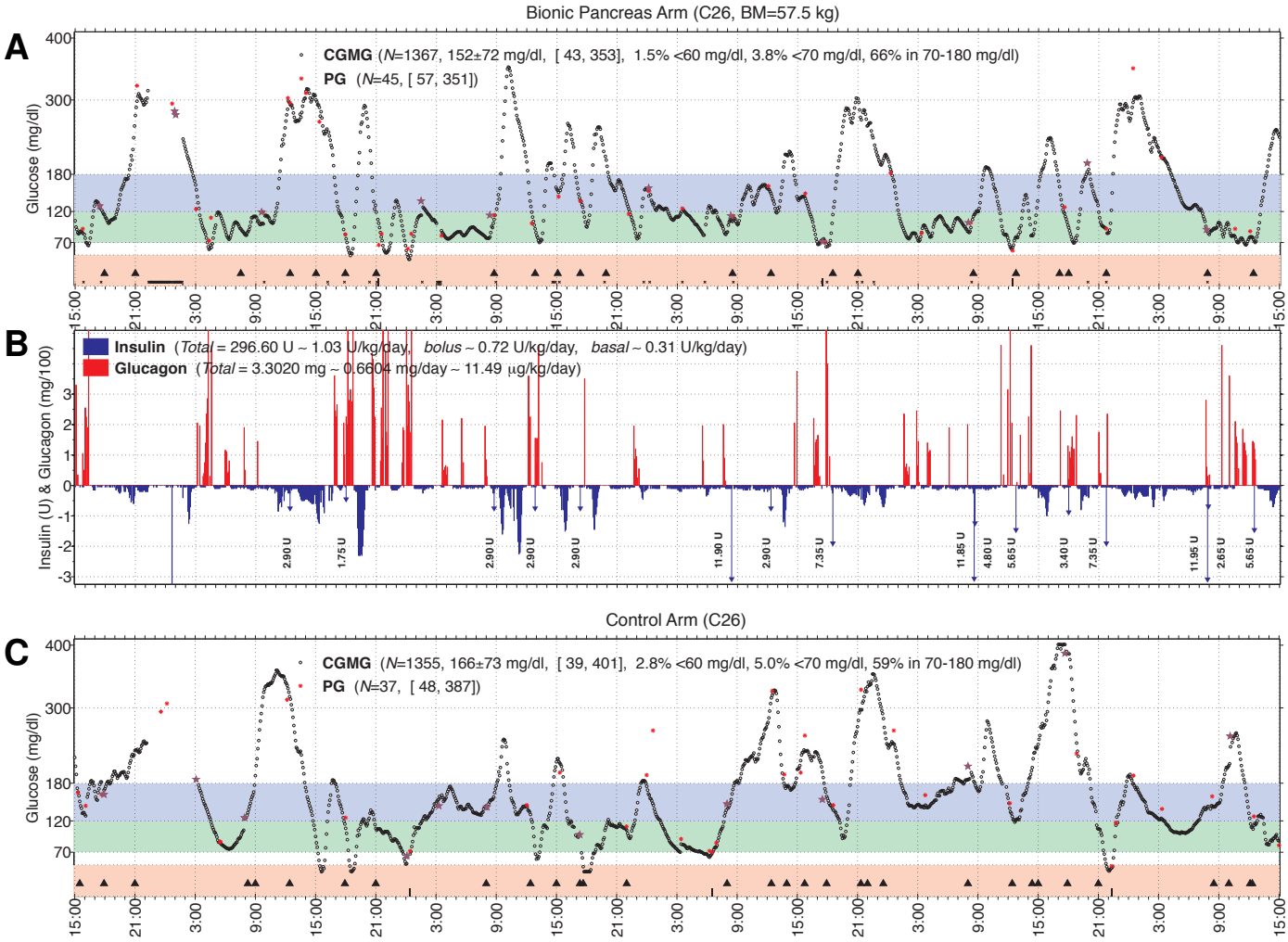


Figure S51. Outpatient experiments in adolescent subject #C26. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 152 mg/dl, average dosing was 1.03 U/kg/day and 11.49 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 146 mg/dl, average dosing was 1.10 U/kg/day and 12.02 μg/kg/day, CGMG was $<$ 60 mg/dl 1.7% of the time, within 70–180 mg/dl 69.3% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 166 mg/dl, CGMG was $<$ 60 mg/dl 2.8% of the time, within 70–180 mg/dl 59.3% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 126 versus 181 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 167 versus 174 mg/dl, and there were 3 carbohydrate interventions versus 2 carbohydrate interventions with PG $<$ 80 mg/dl and 3 carbohydrate interventions versus 1 carbohydrate interventions with PG $<$ 70 mg/dl. During the bionic pancreas (day 0) the subject experienced nausea at 19:30 and vomited at 20:45. Glucagon was last dosed at 16:50, 2 hours and 40 minutes prior to the start of symptoms. During the bionic pancreas period (day 1) the CGM session was restarted because the receiver battery lost charge.

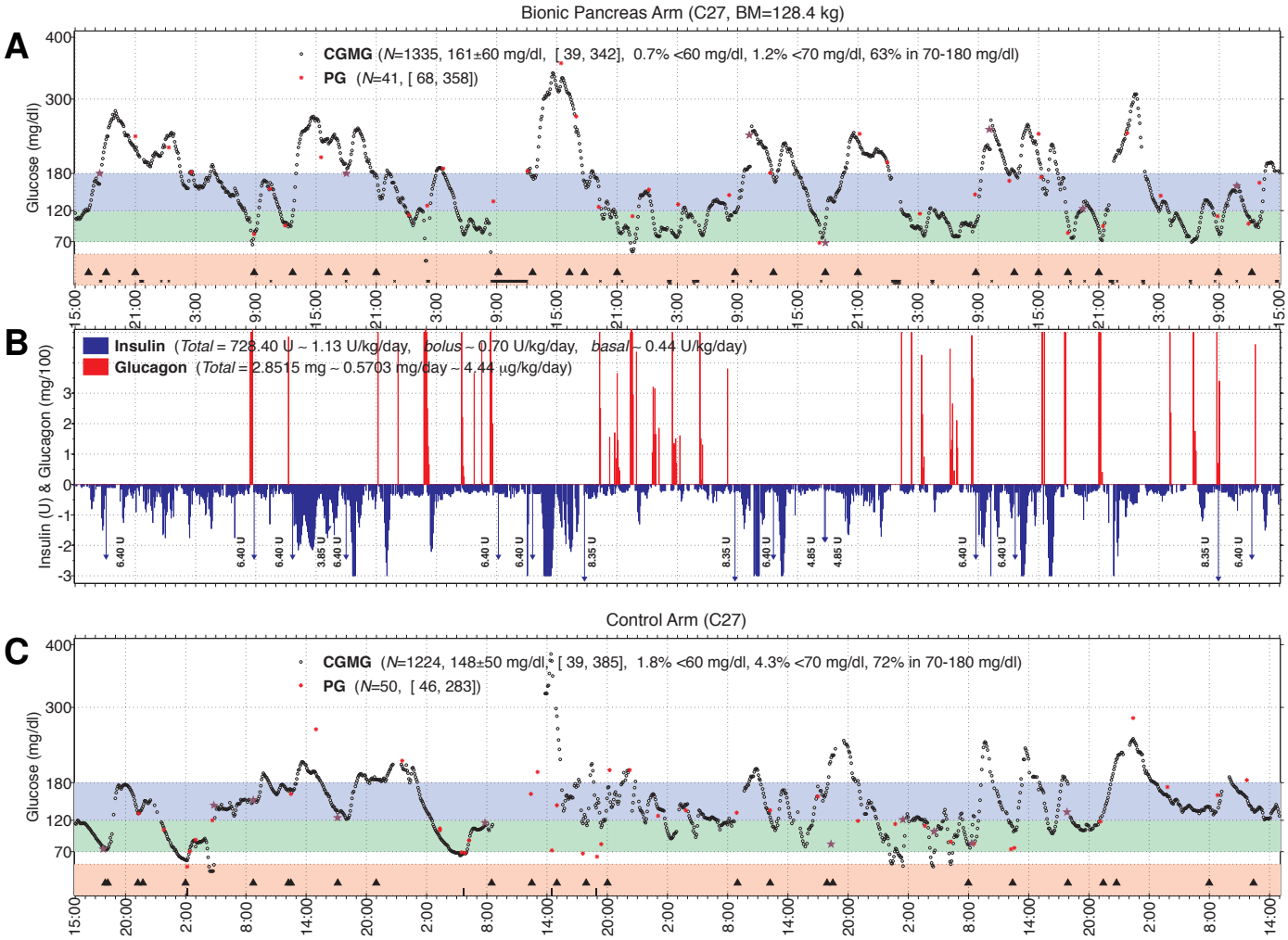


Figure S52. Outpatient experiments in adolescent subject #C27. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 161 mg/dl, average dosing was 1.13 U/kg/day and 4.44 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 156 mg/dl, average dosing was 1.13 U/kg/day and 5.02 μg/kg/day, CGMG was $<$ 60 mg/dl 0.9% of the time, within 70–180 mg/dl 64.8% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 148 mg/dl, CGMG was $<$ 60 mg/dl 1.8% of the time, within 70–180 mg/dl 72.4% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 148 versus 125 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 169 versus 146 mg/dl, and there were 0 carbohydrate interventions versus 4 carbohydrate interventions with PG $<$ 80 mg/dl and 0 carbohydrate interventions versus 3 carbohydrate interventions with PG $<$ 70 mg/dl. CGM sensors were replaced during the bionic pancreas period (day 2) and the comparator period (day 2) due to signal loss. During the bionic pancreas period (day 1) the subject vomited at 10:45, 2 hours after the last glucagon dose.

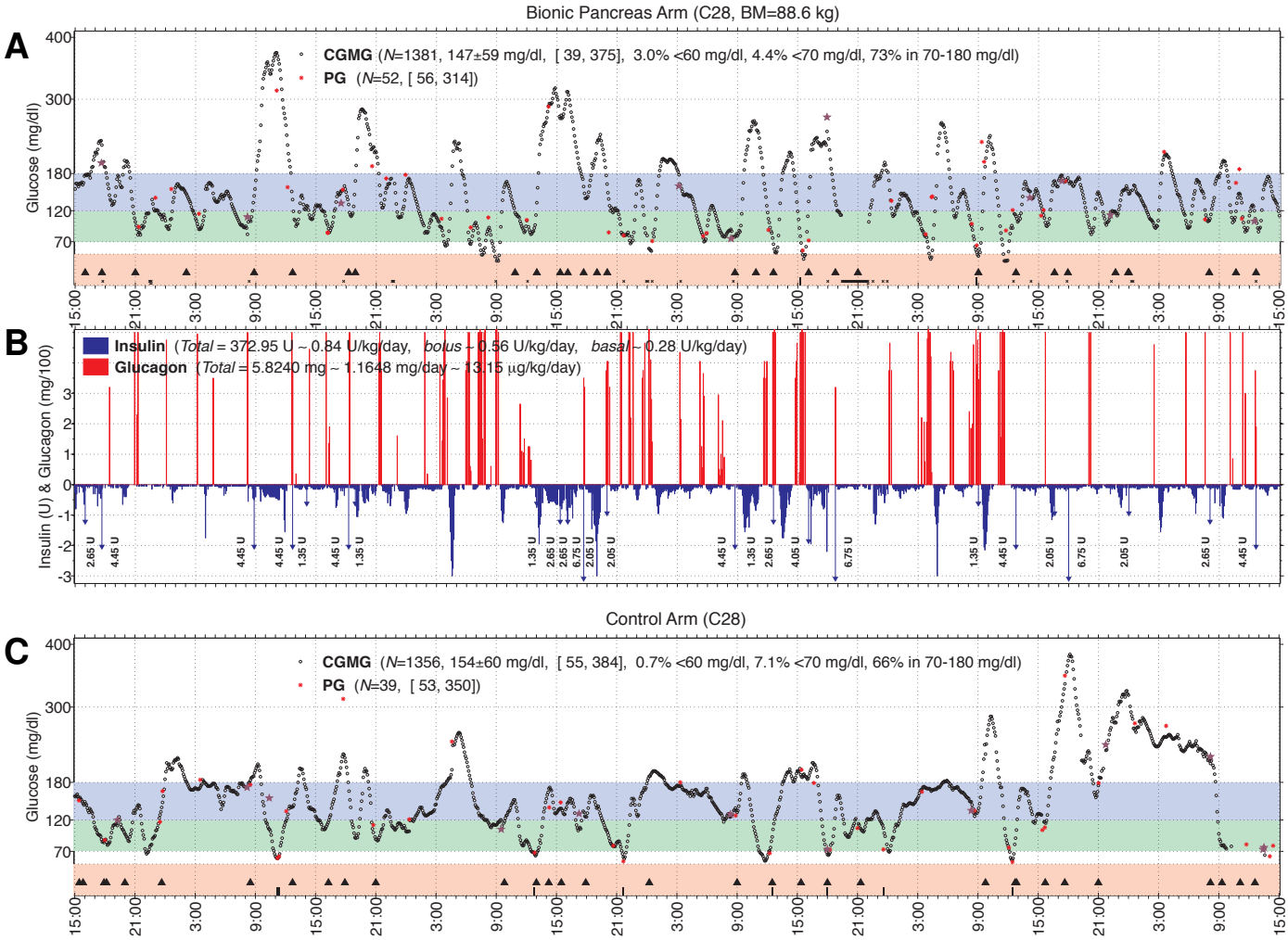


Figure S53. Outpatient experiments in adolescent subject #C28. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 147 mg/dl, average dosing was 0.84 U/kg/day and 13.15 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 144 mg/dl, average dosing was 0.90 U/kg/day and 15.10 μg/kg/day, CGMG was $<$ 60 mg/dl 3.7% of the time, within 70–180 mg/dl 72.7% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 154 mg/dl, CGMG was $<$ 60 mg/dl 0.7% of the time, within 70–180 mg/dl 66.3% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 128 versus 137 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 135 versus 186 mg/dl, and there were 2 carbohydrate interventions versus 8 carbohydrate interventions with PG $<$ 80 mg/dl and 2 carbohydrate interventions versus 5 carbohydrate interventions with PG $<$ 70 mg/dl.

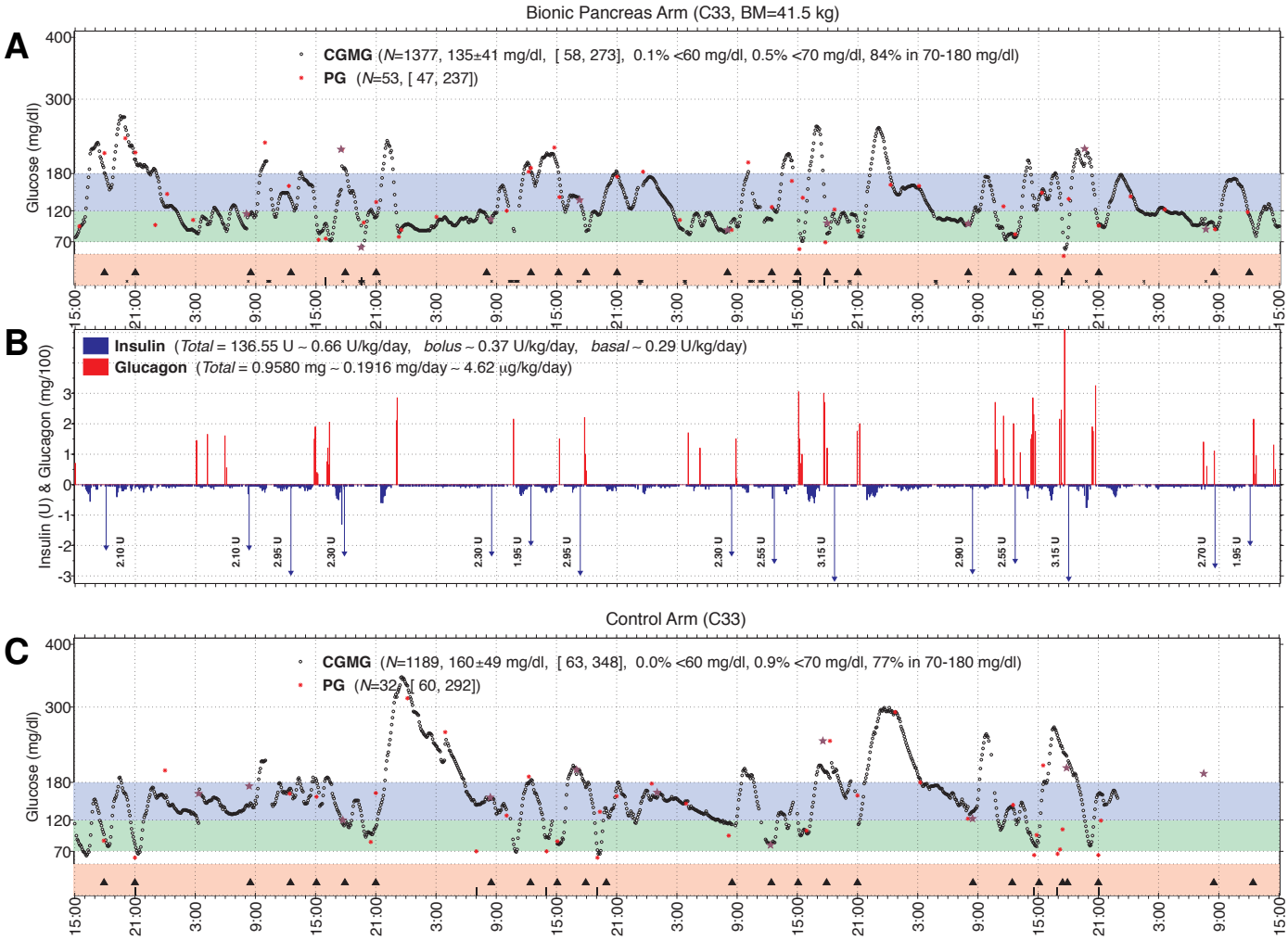


Figure S54. Outpatient experiments in adolescent subject #C33. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 135 mg/dl, average dosing was 0.66 U/kg/day and 4.62 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 132 mg/dl, average dosing was 0.66 U/kg/day and 5.21 μg/kg/day, CGMG was $<$ 60 mg/dl 0.1% of the time, within 70–180 mg/dl 87.2% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 160 mg/dl, CGMG was $<$ 60 mg/dl 0.0% of the time, within 70–180 mg/dl 77.2% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 128 versus 143 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 133 versus 216 mg/dl, and there were 5 carbohydrate interventions versus 7 carbohydrate interventions with PG $<$ 80 mg/dl and 4 carbohydrate interventions versus 5 carbohydrate interventions with PG $<$ 70 mg/dl.

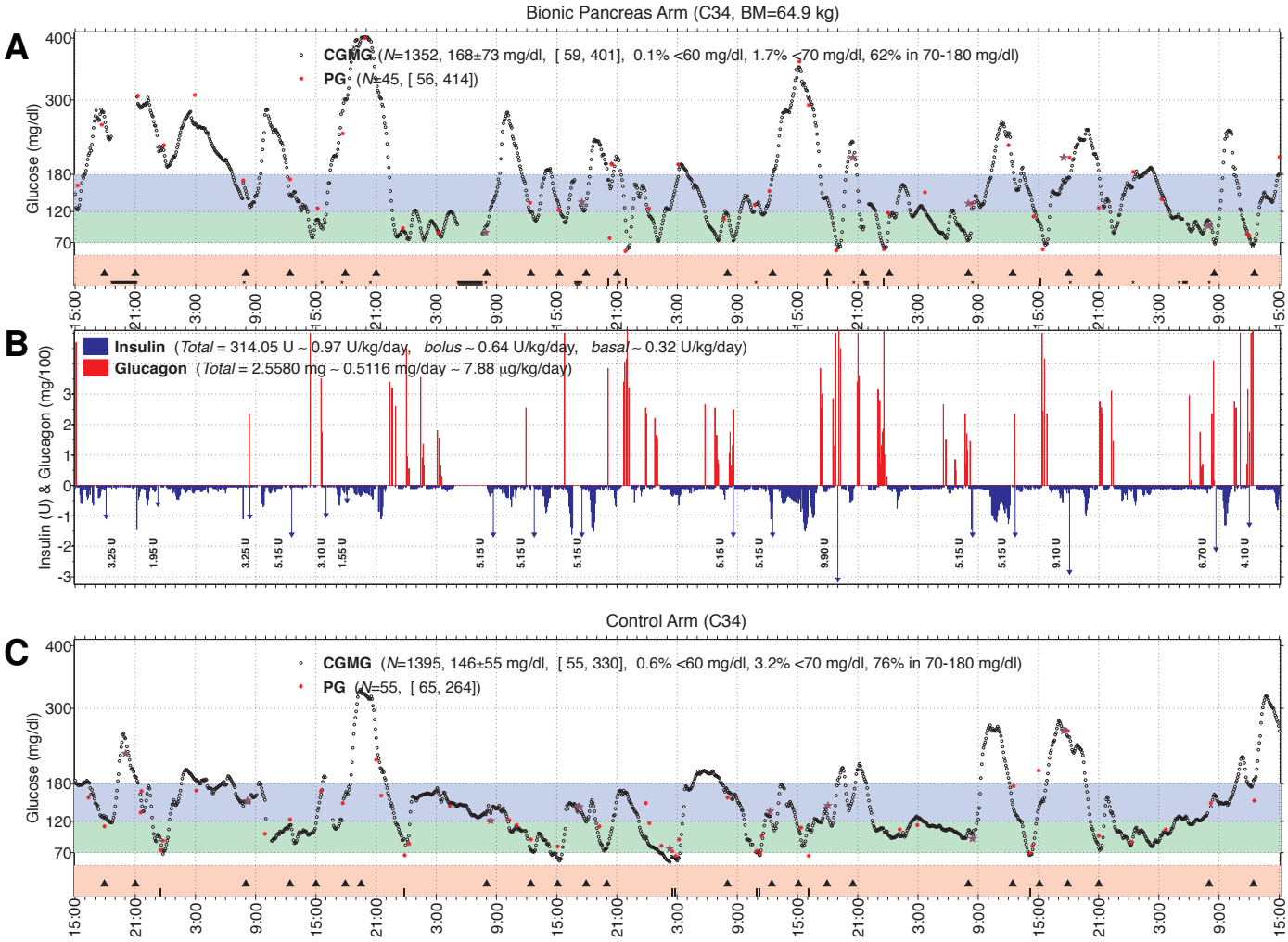


Figure S55. Outpatient experiments in adolescent subject #C34. Panels **A** and **B** respectively show the 5-day glucose trace achieved by the bionic pancreas and the corresponding insulin–glucagon doses automatically administered by the bionic pancreas, and panel **C** shows the 5-day glucose trace in the same subject in the comparator arm of the study. See Fig. S4 for explanation of figure symbols. Over the entire 5-day period on the bionic pancreas, mean CGMG was 168 mg/dl, average dosing was 0.97 U/kg/day and 7.88 μg/kg/day for insulin and glucagon, respectively. However, beyond the first 24-hours, after the bionic pancreas has undergone most of its online adaptation, mean CGMG was 156 mg/dl, average dosing was 1.02 U/kg/day and 9.39 μg/kg/day, CGMG was $<$ 60 mg/dl 0.1% of the time, within 70–180 mg/dl 70.9% of the time. On the other hand, over the entire 5-day period in the comparator arm of the study, mean CGMG was 146 mg/dl, CGMG was $<$ 60 mg/dl 0.6% of the time, within 70–180 mg/dl 75.6% of the time. As outcome measures over the entire 5-day period, in respective order on bionic pancreas versus comparator arm, mean PG before scheduled meals/snacks was 175 versus 143 mg/dl, mean PG at scheduled nights checks (around midnight and 03:45) was 163 versus 112 mg/dl, and there were 5 carbohydrate interventions versus 8 carbohydrate interventions with PG $<$ 80 mg/dl and 4 carbohydrate interventions versus 5 carbohydrate interventions with PG $<$ 70 mg/dl. During the bionic pancreas period (day 1) the subject experienced nausea without vomiting at 20:27, five hours after the last glucagon dose of 47 μg (the only glucagon dose that had been delivered at that point in the experiment). During the bionic pancreas period (day 3) the CGM session was restarted because the receiver battery lost charge.

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