Supplementary Appendix

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

Supplement to: **A Randomized Outpatient Trial Comparing Day and Night Glycemic Control between a Bionic Pancreas and Conventional Insulin Pump Therapy in Pre-adolescent Children with Type 1 Diabetes.**

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Clinical Protocol

METHODS

Institutional and regulatory oversight

In addition to institutional review board (IRB) oversight from both the Partners Human Research Committee (Massachusetts General Hospital) and Boston University, the studies were conducted under United States Food and Drug Administration Investigational Device Exemption #G130065, which was 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 using 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 study.

Eligibility criteria

Key exclusion criteria included current participation in another diabetes-related clinical trial that, in the opinion of the principal investigator, would compromise the results of the study or subject safety, end stage renal disease and on dialysis, pregnancy, history of liver disease expected to interfere with the anti-hypoglycemia action of glucagon or any other liver disease that could significantly compromise liver function, personal history of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, history of prolonged QT, arrhythmia, congenital heart disease, or current known cardiac disease, seizure disorder, history of seizure within the last two years, or ongoing treatment with anticonvulsants, untreated or inadequately treated mental illness, or treatment with second generation anti-psychotic medications known to affect glucose regulation, use of oral medications that assist in glycemic control, electrically powered implants that may be susceptible to radiofrequency interference, history of adverse reaction to glucagon including allergy besides nausea and vomiting, unwilling or unable to avoid acetaminophen for the entirety of the study, history of eating disorder such as anorexia, bulimia, or diabulemia, omission of insulin to manipulate weight, or history of intentional administration of insulin leading to severe hypoglycemia requiring treatment.

Hemoglobin A1c, glycemic stability or major or minor hypoglycemia were not included in the exclusion criteria.

Bionic pancreas algorithm

The insulin and glucagon control algorithms used were similar to those used in our previous studies[1–4], with the additional refinement of incorporating into the insulin dosing algorithm a feedback effect of the total glucagon dosing.

Experimental Protocol

Adverse events were documented by the nurses during both arms of the study. There were no episodes of severe hypoglycemia (requiring assistance from another person). All episodes of hypoglycemia were associated with mild symptoms and treated with oral carbohydrates. There were 7 instances of hyperketonemia in 5 different subjects during the control period that all resolved by replacing the insulin infusion set. There was no hyperketonemia during the bionic pancreas arm. Two subjects reported vomiting in their mouths. Nausea surveys were administered every day, recording a nausea rating on a scale of 0–10 (six ratings are reported per experiment, since experiments started in the afternoon and ended in the afternoon five days later). There was no significant difference in daily nausea scores between the bionic pancreas and the control period.

Table S1: Hypoglycemia interventions per 5 days by subject and arm

	Bionic Pancreas	Comparator
C201	0	0
C202	1	8
C203	1	14
C204	5	7
C205	4	0
C206	4	6
C207	8	4
C208	2	1
C209	0	0
C210	6	11
C211	0	3
C212	5	5
C213	0	4
C214	3	6
C215	4	4
C216	5	6
C217	0	2
C218	3	6
C219	3	5
Median	3	5
Min	0	0
Max	8	14
Total	54	92
p value		0.037*

***non-normally distributed data, p-value from Wilcoxon signed rank test**

Table S2. Primary and secondary outcomes (supplement to Table 2)

Variable	Bionic Pancreas		Control		Unadjusted p-value
	mean or median	*range*	*mean or median*	*range*	
Day and night					
CGM on days 2 to 5					
Mean - mmol/l	7.6±0.6	6.6—9.1	9.3±1.7	7.4—13.2	0.00037
<2.8 mmol/l – mean % of time	0.4±0.5	0—1.6	1.1±0.8	0—2.5	0.0034
<3.3 mmol/l – mean % of time	1.2±1.1	0—2.9	2.8±1.2	0—4.6	<0.0001
<3.9 mmol/l – mean % of time	2.9±2.1	0—6.3	6.1±2.8	0—10.9	<0.0001
3.9-10 mmol/l – mean % of time	80.6±7.4	65.7—91.8	57.6±14.0	24.3—80.5	<0.0001
>10 mmol/l – mean % of time	16.5±6.4	5.6—29.9	36.3±15.7	13.2—72.2	<0.0001
SD - mmol/l	2.8±0.9	1.7—5.1	4.2±1.0	2.6—5.7	<0.0001
Coefficient of variation - %	37±9	23—56	45±8	30—60	0.0017
Mean of daily differences - mmol/l/day	0.8±0.5	0.1—1.8	2.1±1.3	0.5—5.4	0.00083
Plasma glucose on days 1 to 5					
Mean - mmol/l	7.6±0.4	6.7—8.4	9.8±1.4	7.7—12.7	<0.0001
<3.3 mmol/l - % of time	0	0—6.7	3.3	0—6.7	0.065*
Carbohydrate Interventions – median no.	3	0—8	5.0	0—14	0.037*
Nighttime only					
CGM on nights 2 to 5					
Median - mmol/l	6.8	5.7—7.6	9.4	6.6—14.6	<0.0001*
<2.8 mmol/l – median % of time	0.0	0—1.3	1.2	0—3.6	0.012*
<3.3 mmol/l – mean % of time	0.6±0.8	0—2.3	2.8±2.7	0—8.3	0.0027
<3.9 mmol/l – mean % of time	1.8±1.6	0—5.7	4.7±4.0	0—12.2	0.0059
3.9-10 mmol/l - mean % of time	91.9±7.3	76.3—100.0	58.8±17.4	15.6—94.3	<0.0001
>10 mmol/l – mean % of time	6.4±6.4	0—20.8	36.5±18.3	0—76.0	<0.0001
SD - mmol/l	1.7±0.5	0.8—2.7	3.5±1.3	1.8—6.4	<0.0001
Coefficient of variation - %	25±6	12—38	35±9	18—48	0.00024
Plasma glucose on days 1 to 5					
Mean - mmol/l	7.6±0.7	6.3—9.1	9.8±1.8	7.7—15.4	<0.0001
<3.3 mmol/l - % of time	0	0—0	0	0—10.0	0.031*
Carbohydrate Interventions – median no.	0	0—1	1	0—4	0.0020*

*Non-normally distributed data; p-value from Wilcoxon signed rank test

Table S3. Carbohydrate intake by study subjects (g/kg/day) and change in subject weight (kg) over days 1-5

	Bionic Pancreas		Comparator		
Carbohydrate intake (g/kg/day)	Mean	SD	Mean	SD	p-value
Total meals and snacks	6.09	1.53	6.66	1.72	0.016
Breakfast	1.53	0.64	1.78	0.71	0.0049
Lunch	1.48	0.64	1.48	0.59	0.93
Afternoon snack*	0.31	0.22	0.33	0.25	0.44
Dinner	1.67	0.40	1.83	0.49	0.10
Bedtime snack	0.62	0.20	0.66	0.24	0.21
12:00 AM**	0.03	0.04	0.05	0.05	0.20
3:45 AM**	0.02	0.04	0.01	0.02	0.25
Unscheduled**	0.45	0.35	0.52	0.32	0.46
Change in subject weight (kg)	Median	Range	Meidan	Range	
Day 1 to day 5***	0.0	-1.9 –+1.1	0.2	-1.3 –+2.7	0.12[+]

*Afternoon snack was not provided on all days

**Includes carbohydrate interventions provided according to camp policy when the blood glucose was <80 mg/dl (or for symptoms at any glucose level) that were not counted as interventions for study purposes because blood glucose was ≥70 mg/dl

***Mean of body weight did not increased significantly during either periods (p=0.63 and p=0.15 for bionic pancreas and comparator arms, respectively)

[+]Non-normal data, p-value from Wilcoxon signed rank test

Table S4. Mean nausea scores by day and sex

Day	Mean Nausea Score		
	Both	**Girls**	**Boys**
		Bionic Pancreas	
0	0.8	1.2	0.0
1	1.1	1.1	1.0
2	1.9	2.5	0.7
3	1.4	1.3	1.7
4	1.2	1.2	1.0
5	1.2	0.8	2.2
mean	1.3	1.3	1.1
		Usual Care	
0	1.4	1.7	0.7
1	0.9	1.3	0.0
2	1.9	2.7	0.2
3	1.5	2.1	0.2
4	2.1	2.0	2.2
5	0.5	0.7	0.0
mean	1.4	1.7	0.5

There were no significant differences in nausea between girls and boys in either arm (bionic pancreas arm p=0.8, usual care arm p=0.2). There were no significant differences in nausea between the bionic pancreas or usual care arms for girls (p=0.5) or boys (p=0.5).

Table S5: Unschedule infusion set changes

Bionic pancreas				Comparator			
Subject	Site type	Day	Reason	Subject	Site type	Day	Reason
C201	insulin	5	fell out	C201	insulin	4	failure
C203	insulin	4	pain	C206	insulin	1	failure
C209	insulin	4	fell out	C210	insulin	5	failure
C210	insulin	2	fell out	C214	insulin	4	fell out
C212	insulin	3	pain, itching, redness	C219	insulin	1	failure
C214	insulin	5	failure	C219	insulin	2	failure
C215	insulin	3	failure				
C219	insulin	2	fell out				
C205	glucagon	5	fell out				
C208	glucagon	2	fell out				
C215	glucagon	1	pain, itching, redness				
C219	glucagon	1	fell out				

Summary

	Bionic pancreas		Comparator
Reason	Insulin	Glucagon	Insulin
fell out	4	3	1
failure	2	0	5
pain	2	1	0

Camp policy is to suspect failure of the infusion set whenever ketonemia occurs, so failures may not have actually been set failures, but rather failure to deliver enough insulin.

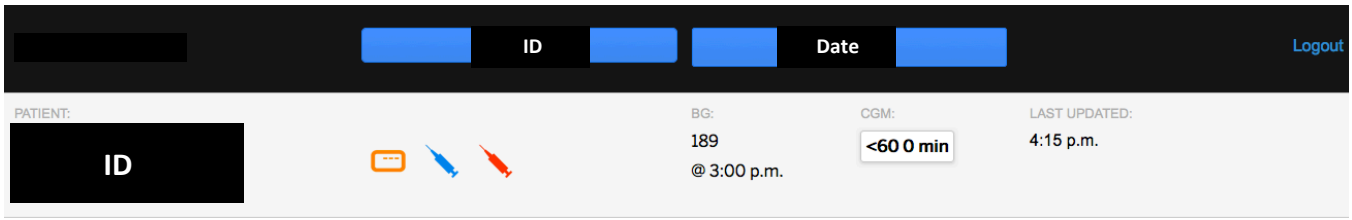

Figure S1. Schematic of the wearable bihormonal bionic pancreas system used in the outpatient studies. Top: The control algorithm, which is written in C++ in an app that runs on an Apple iPhone 4S (station 2 – Control system), responds to CGM glucose levels streamed online every five minutes using the 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 certain data fields from one of our experiments. The dashboard included live streaming of connection states between iPhone and CGM and iPhone and the pumps, as well as the current time CGM glucose has been below 60 mg/dl and the last fingerstick PG value entered in the app on the iPhone.

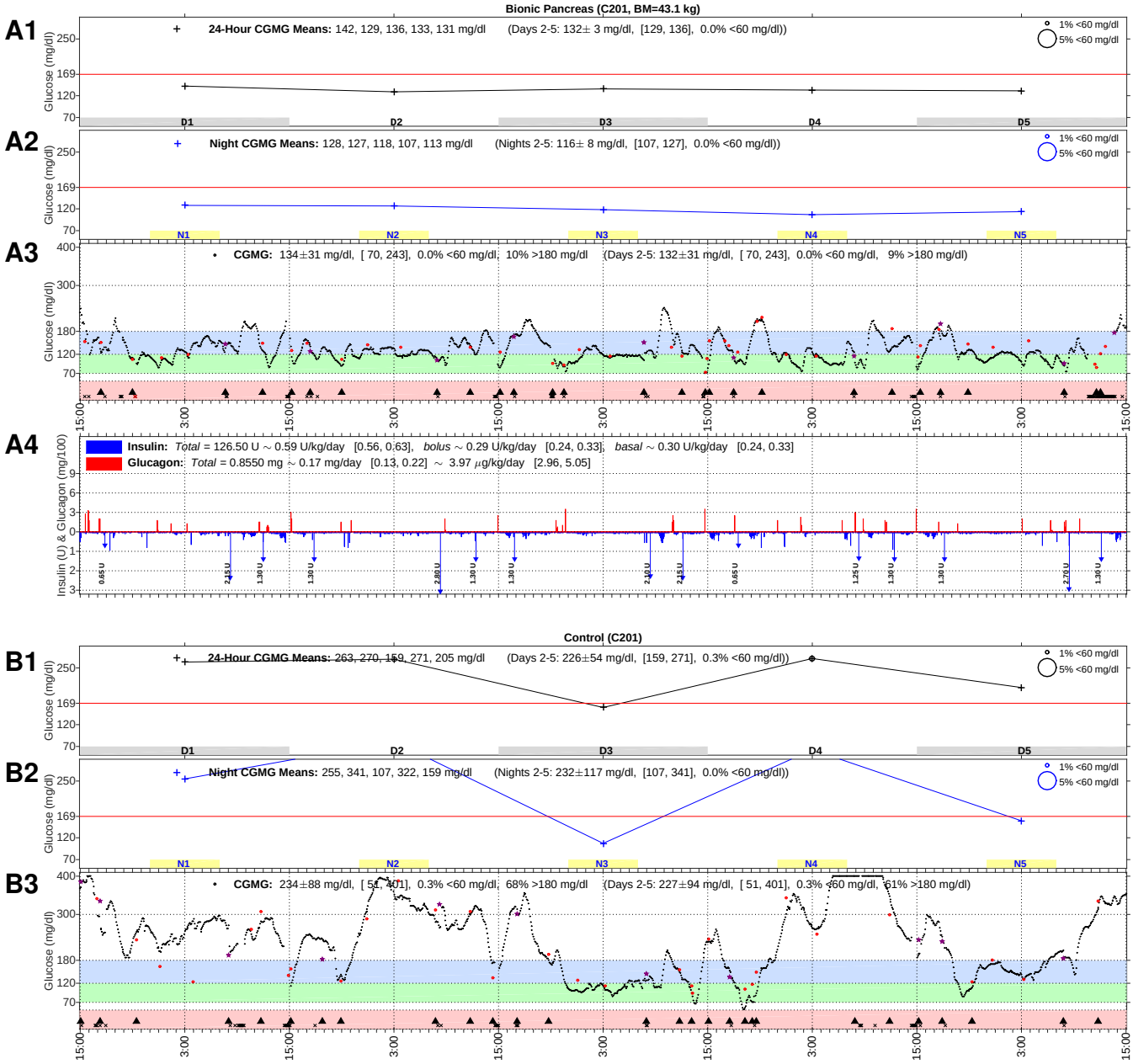

Figure S2. Outpatient experiments in pre-adolescent subject #C201. Panels **A1–4** refer to results achieved by the BP and respectively show a plot of successive 24-hour average CGMG values and percentages of times CGMG $<$ 60 mg/dl, a plot of successive night-time CGMG average values and percentage of times CGMG $<$ 60 mg/dl, a plot of overall CGMG trace, and a plot of the corresponding insulin and glucagon doses (respectively as downward blue and upward red bars) automatically administered by the BP. Panels **B1–3** show results achieved in the control period, analogous to **A1–3**. Fingerstick PG is superimposed as red filled circles, with calibration PG indicated by magenta stars. Along the timeline, carbohydrate treatments for hypoglycemia are indicated by black rectangles, and meals and snacks by black triangles. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 132 mg/dl, mean of night time CGMG was 116 mg/dl, insulin–glucagon dosing was respectively 0.59 U/kg/day and 3.70 μg/kg/day, CGMG was $<$ 60 mg/dl 0% of the time (0% at night) and $>$ 180 mg/dl 9% of the time, and there were 0 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 227 mg/dl, mean of night time CGMG was 232 mg/dl, CGMG was $<$ 60 mg/dl 0.3% of the time (0% at night), and $>$ 180 mg/dl 61% of the time, and there were 0 carbohydrate interventions over the 5-day period. During the BP period, a calibration was missed on day 1, the CGM sensor was replaced at 11:30 on day 5 after failing to report glucose values, an extra calibration was performed on day 5, and the insulin site fell out and was replaced at 18:09 on day 5. The subject had a blood ketone level of 0.6 mmol/dl on day 1 of the control period and was treated by the camp medical staff. The insulin site was replaced at 9:29 on day 4 of the control period due to suspected failure and a blood ketone value of 3.6 mmol/dl. Daily nausea scores on a scale of 0–10 were 0/0/0/0/1/0 during the BP period, and 0/0/3/0/5/0 during the control period.

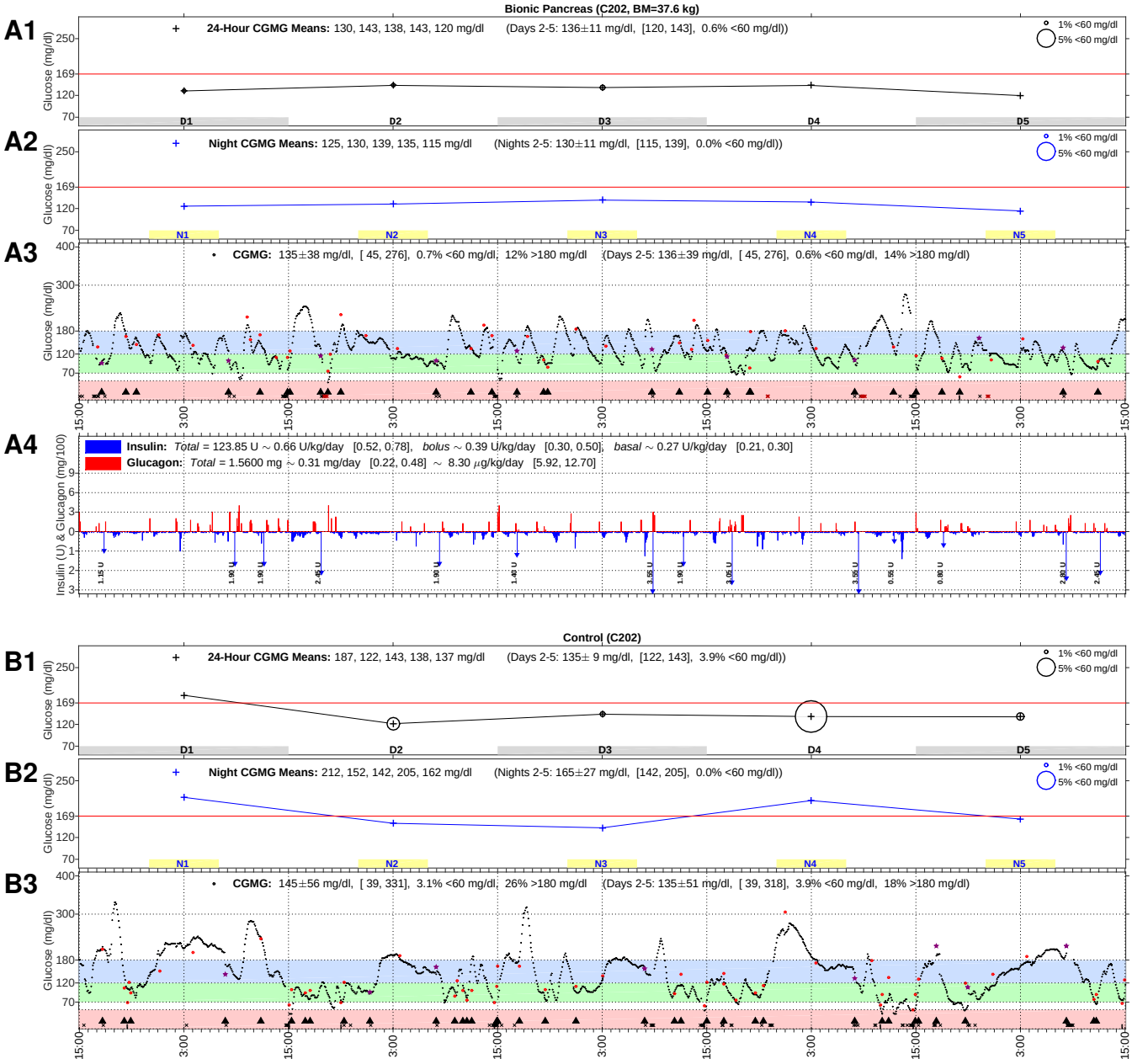

Figure S3. Outpatient experiments in pre-adolescent subject #C202. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 136 mg/dl, mean of night time CGMG was 130 mg/dl, insulin–glucagon dosing was respectively 0.69 U/kg/day and 7.20 μg/kg/day, CGMG was $<$ 60 mg/dl 0.6% of the time (0% at night) and $>$ 180 mg/dl 14% of the time, and there was 1 carbohydrate intervention over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 135 mg/dl, mean of night time CGMG was 165 mg/dl, CGMG was $<$ 60 mg/dl 3.9% of the time (0% at night), and $>$ 180 mg/dl 19% of the time, and there were 8 carbohydrate interventions over the 5-day period. Calibrations were missed during the control period on days 1, 3, and 4. An extra calibration was performed on day 5 of the control period. Daily nausea scores on a scale of 0–10 were 0/0/9/9/0/0 during the BP period, and 5/4/2/–/1/0 during the control period.

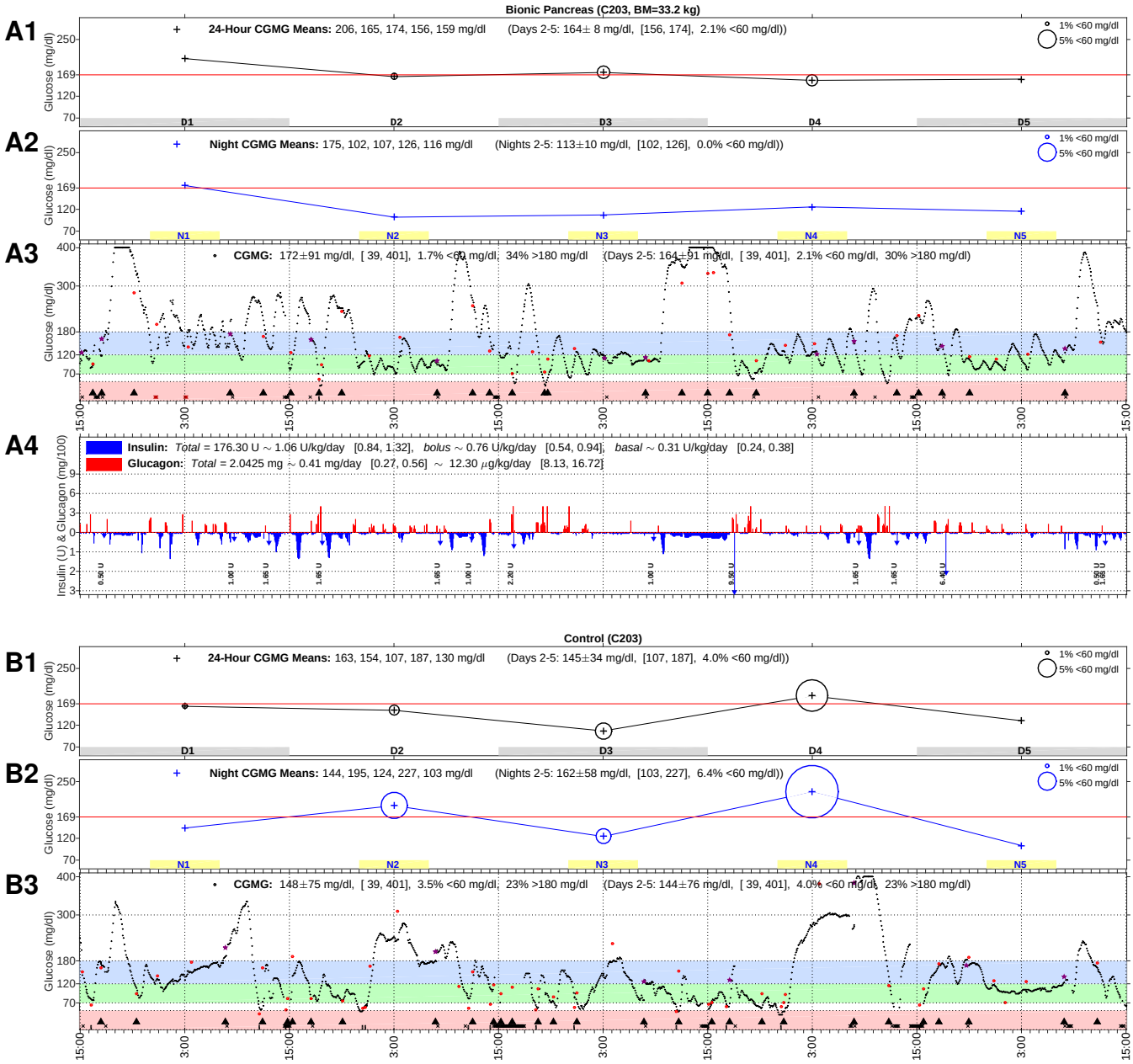

Figure S4. Outpatient experiments in pre-adolescent subject #C203. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 164 mg/dl, mean of night time CGMG was 113 mg/dl, insulin–glucagon dosing was respectively 1.08 U/kg/day and 12.84 μg/kg/day, CGMG was $<$ 60 mg/dl 2.1% of the time (0% at night) and $>$ 180 mg/dl 30% of the time, and there was 1 carbohydrate intervention over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 144 mg/dl, mean of night time CGMG was 162 mg/dl, CGMG was $<$ 60 mg/dl 4.0% of the time (6.5% at night), and $>$ 180 mg/dl 23% of the time, and there were 14 carbohydrate interventions over the 5-day period. The CGM sensor fell off and was replaced at 15:10 on day 3 of the control period. Calibrations were missed during the control period on days 1, 2 and 3. One calibration on day 2 of the BP period was documented as being within 30 minutes of carbohydrate intake. The insulin site was replaced at 15:00 on day 4 of the BP period when the subject reported pain after being hit with a dodgeball. The subject reported a headache on day 3 of the BP period. Daily nausea scores on a scale of 0–10 were 7/0/8/0/9/0 during the control period and 0/0/3/0/0/0 during the BP period.

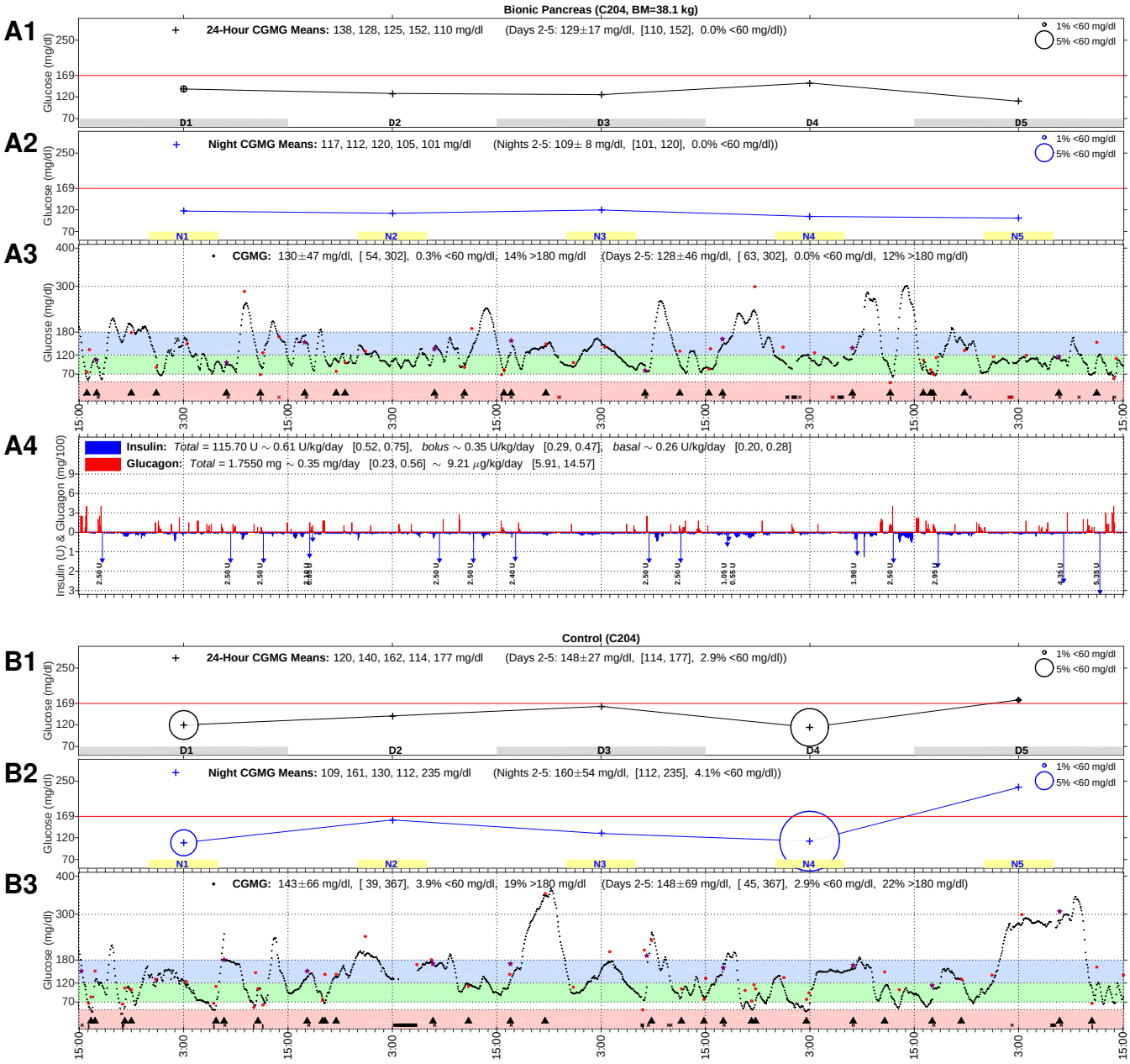

Figure S5. Outpatient experiments in pre-adolescent subject #C204. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 128 mg/dl, mean of night time CGMG was 109 mg/dl, insulin–glucagon dosing was respectively 0.63 U/kg/day and 8.14 μg/kg/day, CGMG was $<$ 60 mg/dl 0% of the time (0% at night) and $>$ 180 mg/dl 12% of the time, and there were 5 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 148 mg/dl, mean of night time CGMG was 159 mg/dl, CGMG was $<$ 60 mg/dl 2.9% of the time (4.2% at night), and $>$ 180 mg/dl 22% of the time, and there were 7 carbohydrate interventions over the 5-day period. Calibrations were missed on day 1 of the comparator period and on day 5 of the BP period. One calibration on day 1 of the control period is documented as being within 30 minutes of carbohydrate intake. The subject had a blood ketone level of 0.7 mmol/dl at bedtime on day 3 of the control period and was treated by camp medical staff. Daily nausea scores on a scale of 0–10 were 0/0/1/1/10/0 during the control period and 0/0/1/0/2/0 during the BP period. Subject reported that he vomited once in his mouth on day 4 of the control period.

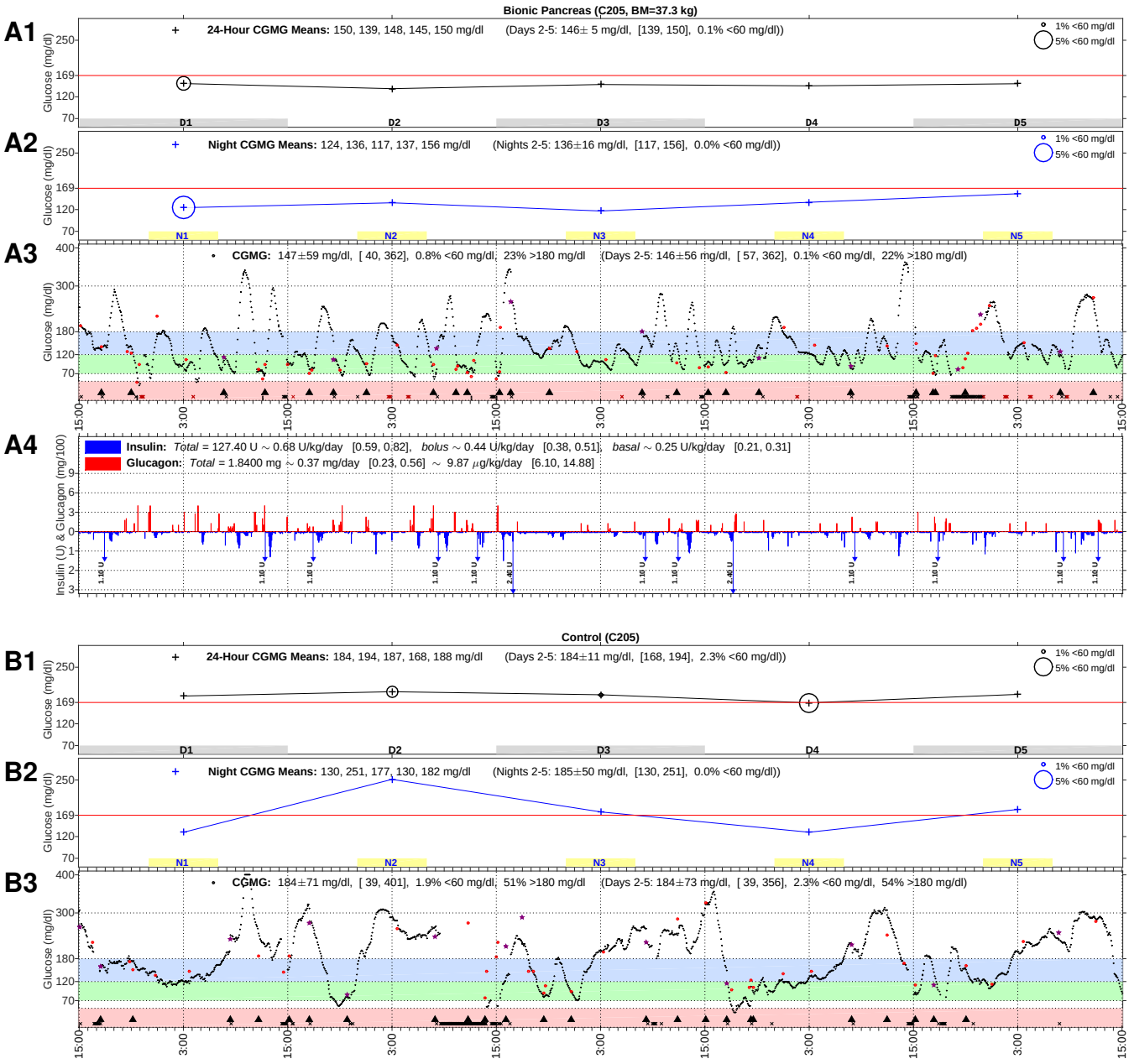

Figure S6. Outpatient experiments in pre-adolescent subject #C205. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 146 mg/dl, mean of night time CGMG was 136 mg/dl, insulin–glucagon dosing was respectively 0.70 U/kg/day and 8.61 μg/kg/day, CGMG was $<$ 60 mg/dl 0.1% of the time (0% at night) and $>$ 180 mg/dl 22% of the time, and there were 4 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 184 mg/dl, mean of night time CGMG was 185 mg/dl, CGMG was $<$ 60 mg/dl 2.3% of the time (0% at night), and $>$ 180 mg/dl 54% of the time, and there were 0 carbohydrate interventions over the 5-day period. One CGM sensor was replaced at 16:00 on day 5 of the BP period because it stopped reporting glucose values. A calibration was missed on day 1 of the BP period. Extra calibrations were performed on day 5 of the BP period, and days 2 and 3 of the control period. The glucagon site fell out and was replaced on day 5 of the BP period. Daily nausea scores on a scale of 0–10 were 4/0/5/0/0/0 during the BP period and 0/0/4/6/4/0 during the control period.

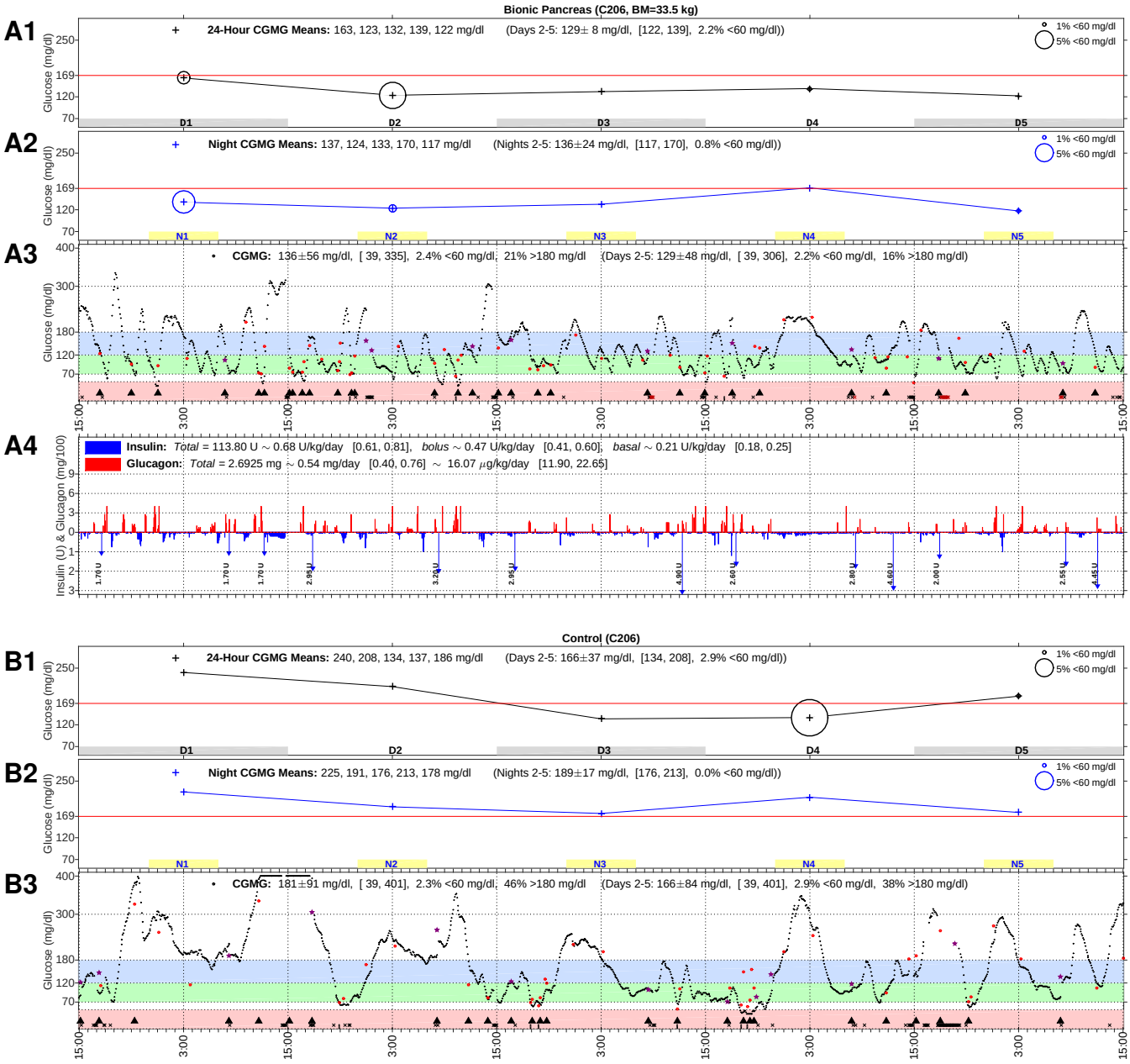

Figure S7. Outpatient experiments in pre-adolescent subject #C206. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 129 mg/dl, mean of night time CGMG was 136 mg/dl, insulin–glucagon dosing was respectively 0.65 U/kg/day and 14.43 μg/kg/day, CGMG was $<$ 60 mg/dl 2.2% of the time (0.8% at night) and $>$ 180 mg/dl 16% of the time, and there were 4 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 166 mg/dl, mean of night time CGMG was 190 mg/dl, CGMG was $<$ 60 mg/dl 2.9% of the time (0% at night), and $>$ 180 mg/dl 38% of the time, and there were 5 carbohydrate interventions over the 5-day period. A large bubble was found in the insulin pump tubing, occluding delivery at 3:20 on day 4 of the BP period. The insulin site was replaced at lunch time on day 1 of the control period due to a clinical suspicion of failure. Extra calibrations were performed on day 2 of the BP period and on day 4 of the control period. The subject reported a stomachache at 8:30 on day 2 of the BP period and did not eat breakfast. Daily nausea scores on a scale of 0–10 were 0/2/3/0/0/0 during the BP period and 0/0/0/0/0/0 during the comparator period.

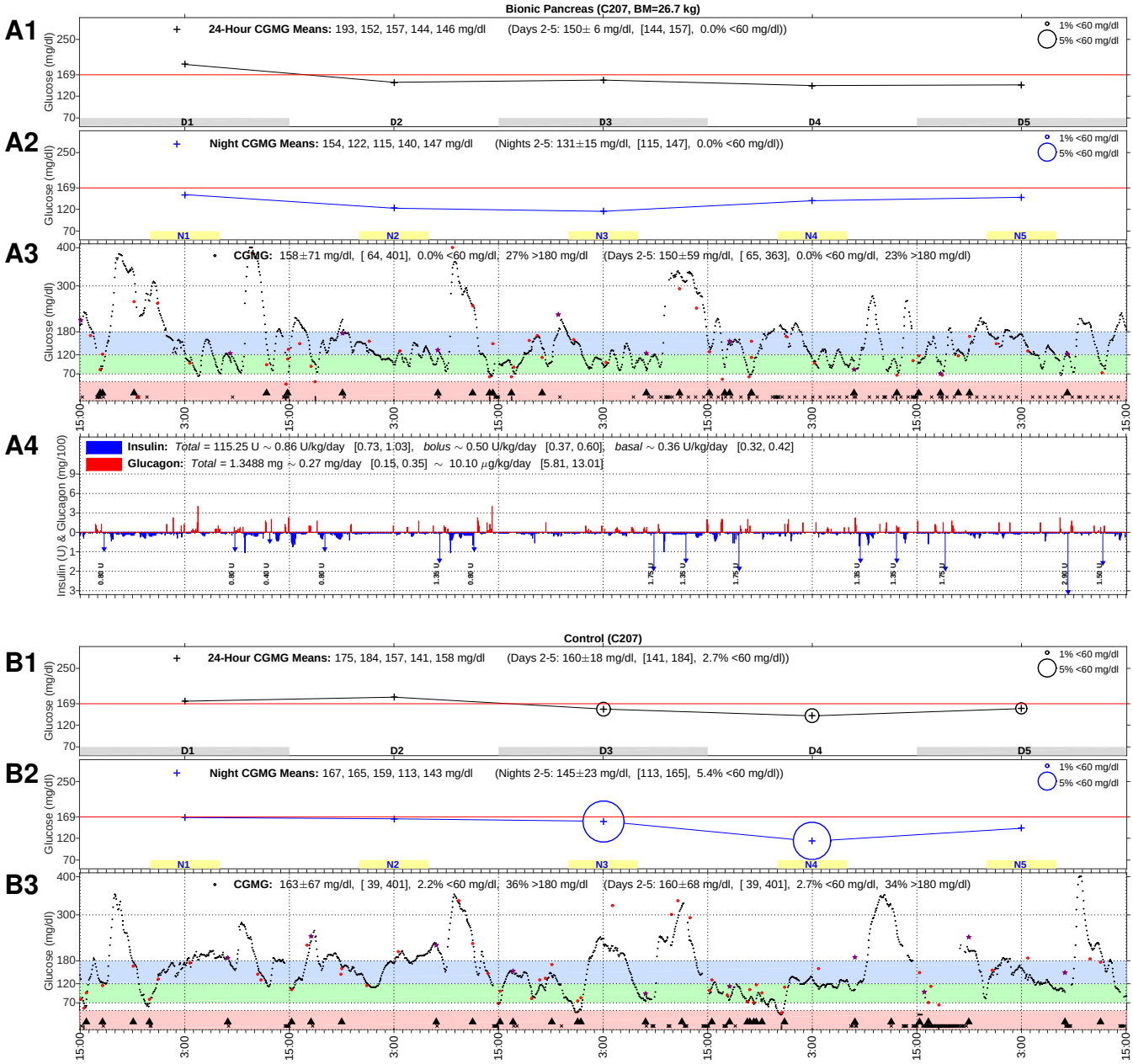

Figure S8. Outpatient experiments in pre-adolescent subject #C207. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 150 mg/dl, mean of night time CGMG was 131 mg/dl, insulin–glucagon dosing was respectively 0.86 U/kg/day and 9.38 μg/kg/day, CGMG was $<$ 60 mg/dl 0% of the time (0% at night) and $>$ 180 mg/dl 23% of the time, and there were 8 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 160 mg/dl, mean of night time CGMG was 145 mg/dl, CGMG was $<$ 60 mg/dl 2.7% of the time (5.5% at night), and $>$ 180 mg/dl 34% of the time, and there were 4 carbohydrate interventions over the 5-day period. The insulin pump was found to be empty at 3:00 on day 4 of the BP period and was refilled. The CGM sensor stopped reporting glucose values and was replaced at 18:00 on day 5 of the control period. An extra calibration was performed on day 5 of the control period, which is documented as being within 30 minutes of carbohydrate intake. Calibrations were missed on day 1 of the control period and day 1 of the BP period. Daily nausea scores on a scale of 0–10 were 4/6/7/8/0/9 during the comparator period and 9/4/9/8/10 during the BP period. Subject reported that she vomited once in her mouth and swallowed it on day 4 of the BP period.

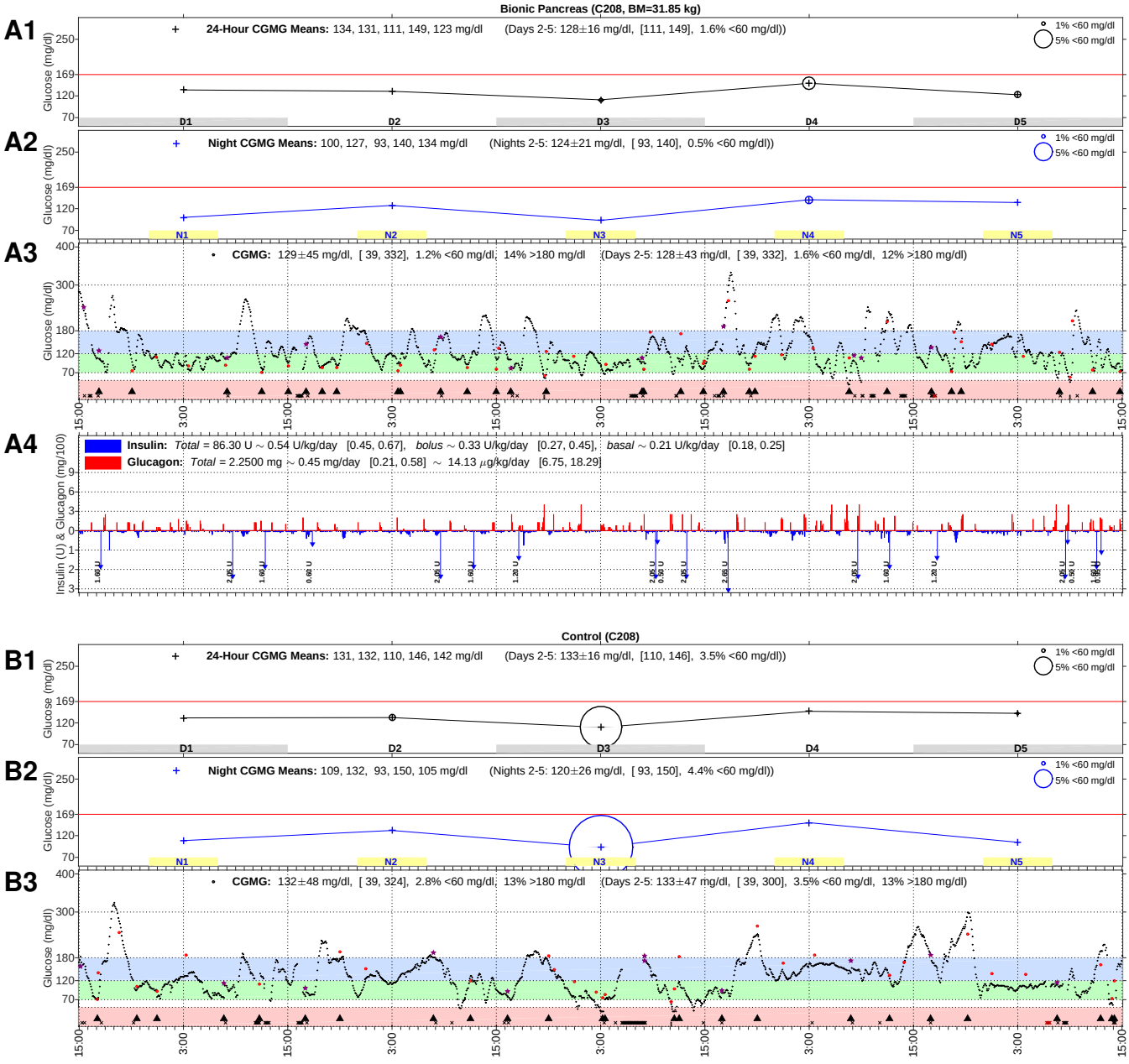

Figure S9. Outpatient experiments in pre-adolescent subject #C208. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 128 mg/dl, mean of night time CGMG was 124 mg/dl, insulin–glucagon dosing was respectively 0.55 U/kg/day and 14.82 μg/kg/day, CGMG was $<$ 60 mg/dl 1.6% of the time (0.5% at night) and $>$ 180 mg/dl 13% of the time, and there were 2 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 133 mg/dl, mean of night time CGMG was 119 mg/dl, CGMG was $<$ 60 mg/dl 3.5% of the time (4.4% at night), and $>$ 180 mg/dl 13% of the time, and there was 1 carbohydrate intervention over the 5-day period. The glucagon site fell out and was replaced at 22:10 on day 2 and 18:30 on day 4 of the BP period. An extra calibration was performed on day 4 of the BP period and is documented as being within 30 minutes of carbohydrate intake. Calibrations were missed on day 5 of the BP period and day 1 of the control period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/4/0 during the BP period and 0/0/0/0/0/0 during the control period.

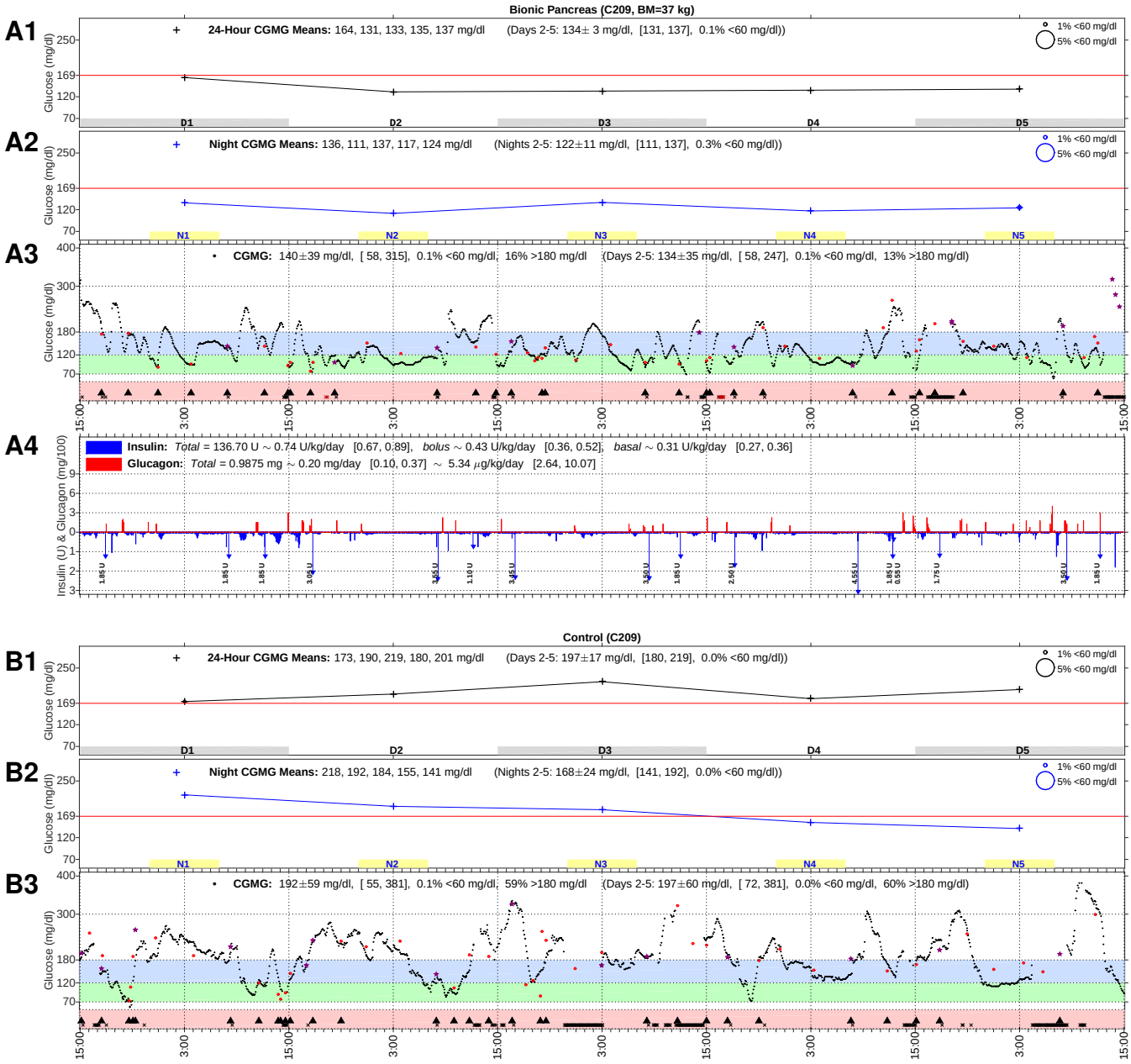

Figure S10. Outpatient experiments in pre-adolescent subject #C209. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 134 mg/dl, mean of night time CGMG was 123 mg/dl, insulin–glucagon dosing was respectively 0.70 U/kg/day and 5.54 μg/kg/day, CGMG was $<$ 60 mg/dl 0.1% of the time (0.3% at night) and $>$ 180 mg/dl 13% of the time, and there were 0 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 197 mg/dl, mean of night time CGMG was 168 mg/dl, CGMG was $<$ 60 mg/dl 0% of the time (0% at night), and $>$ 180 mg/dl 60% of the time, and there were 0 carbohydrate interventions over the 5-day period. The glucagon pump had to be replaced at 20:00 on day 2 of the BP period due to persistent error messages. The insulin site fell out and was replaced at 22:30 on day 4 of the BP period. The CGM sensor was replaced at 16:15 on day 4 of the BP period, and at 12:40 on day 4 of the control period. The CGM sensor stopped reporting glucose values at 13:40 on day 5 of the BP period. The CGM sensor stopped reporting glucose values at 23:34 on day 2 of the control period but was successfully restarted with the same sensor. Extra calibrations were performed on days 2 and 3 of the control period. A calibration was missed on day 1 of the BP period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0 throughout the BP period and 0/0/0/0/0/0 throughout the control period.

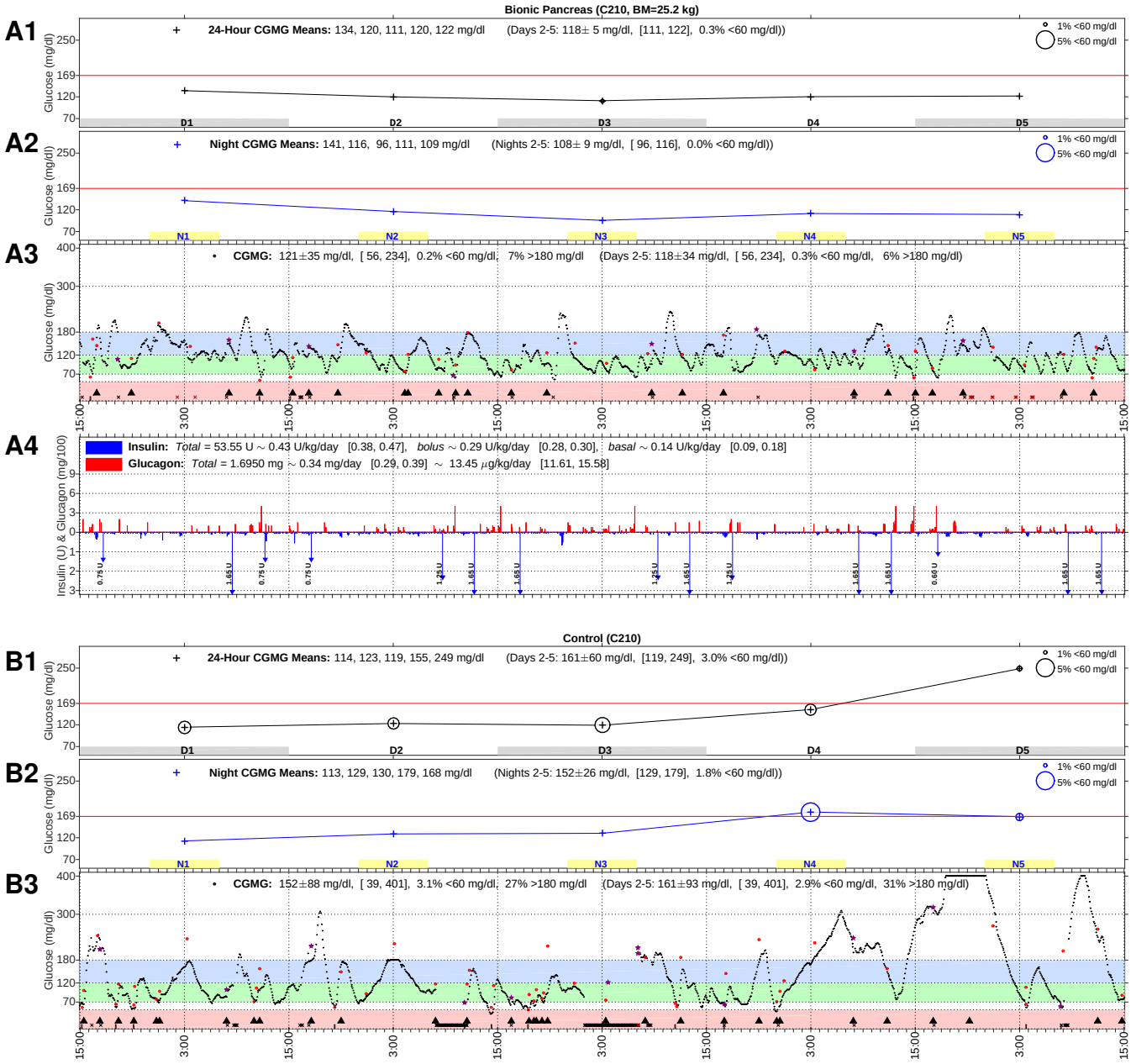

Figure S11. Outpatient experiments in pre-adolescent subject #C210. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 118 mg/dl, mean of night time CGMG was 108 mg/dl, insulin–glucagon dosing was respectively 0.43 U/kg/day and 13.47 μg/kg/day, CGMG was $<$ 60 mg/dl 0.3% of the time (0% at night) and $>$ 180 mg/dl 6% of the time, and there were 6 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 161 mg/dl, mean of night time CGMG was 151 mg/dl, CGMG was $<$ 60 mg/dl 2.9% of the time (1.8% at night), and $>$ 180 mg/dl 32% of the time, and there were 11 carbohydrate interventions over the 5-day period. The insulin site fell out and was replaced at 16:00 on day 2 of the BP period. The insulin site had to be replaced by the camp medical staff at 21:16 on day 5 of the control period due to a blood ketone value of 1.4 mmol/dl. The BP battery died at 8:15 on day 2 of the control period, so the CGM had to be restarted. Two extra calibrations were performed on day 3 of the control period. Calibrations were missed on days 3 and 5 of the BP period. Daily nausea scores on a scale of 0–10 were 0/6/0/10/0/9 during the BP period and 0/0/0/0/0/0 during the control period.

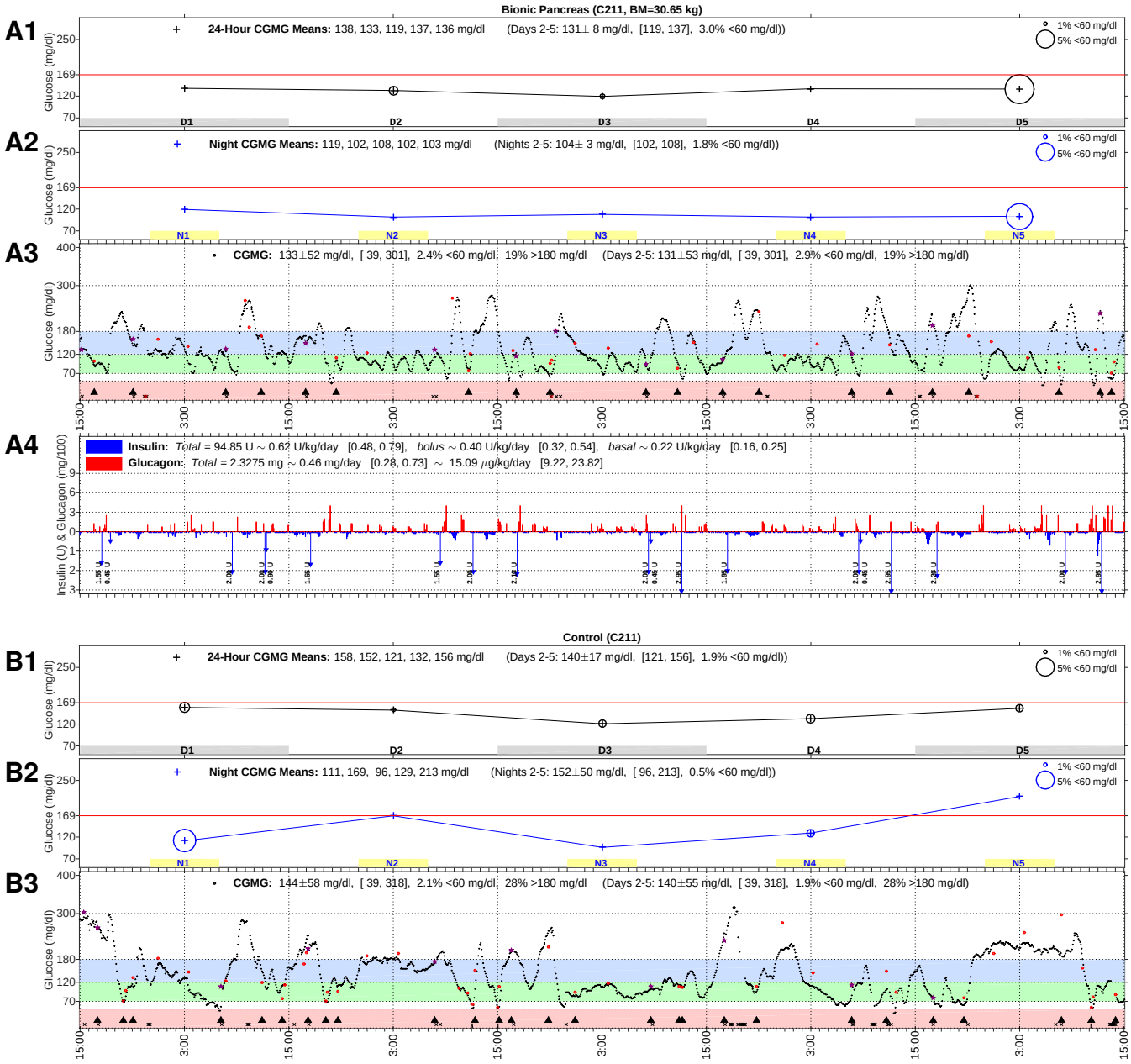

Figure S12. Outpatient experiments in pre-adolescent subject #C211. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 131 mg/dl, mean of night time CGMG was 103 mg/dl, insulin–glucagon dosing was respectively 0.63 U/kg/day and 16.68 μg/kg/day, CGMG was $<$ 60 mg/dl 2.9% of the time (1.8% at night) and $>$ 180 mg/dl 19% of the time, and there were 0 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 140 mg/dl, mean of night time CGMG was 152 mg/dl, CGMG was $<$ 60 mg/dl 1.9% of the time (0.5% at night), and $>$ 180 mg/dl 28% of the time, and there were 3 carbohydrate interventions over the 5-day period. An extra calibration was performed on day 3 of the BP period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/3/0 during the control period and 0/0/0/0/0/4 during the BP period.

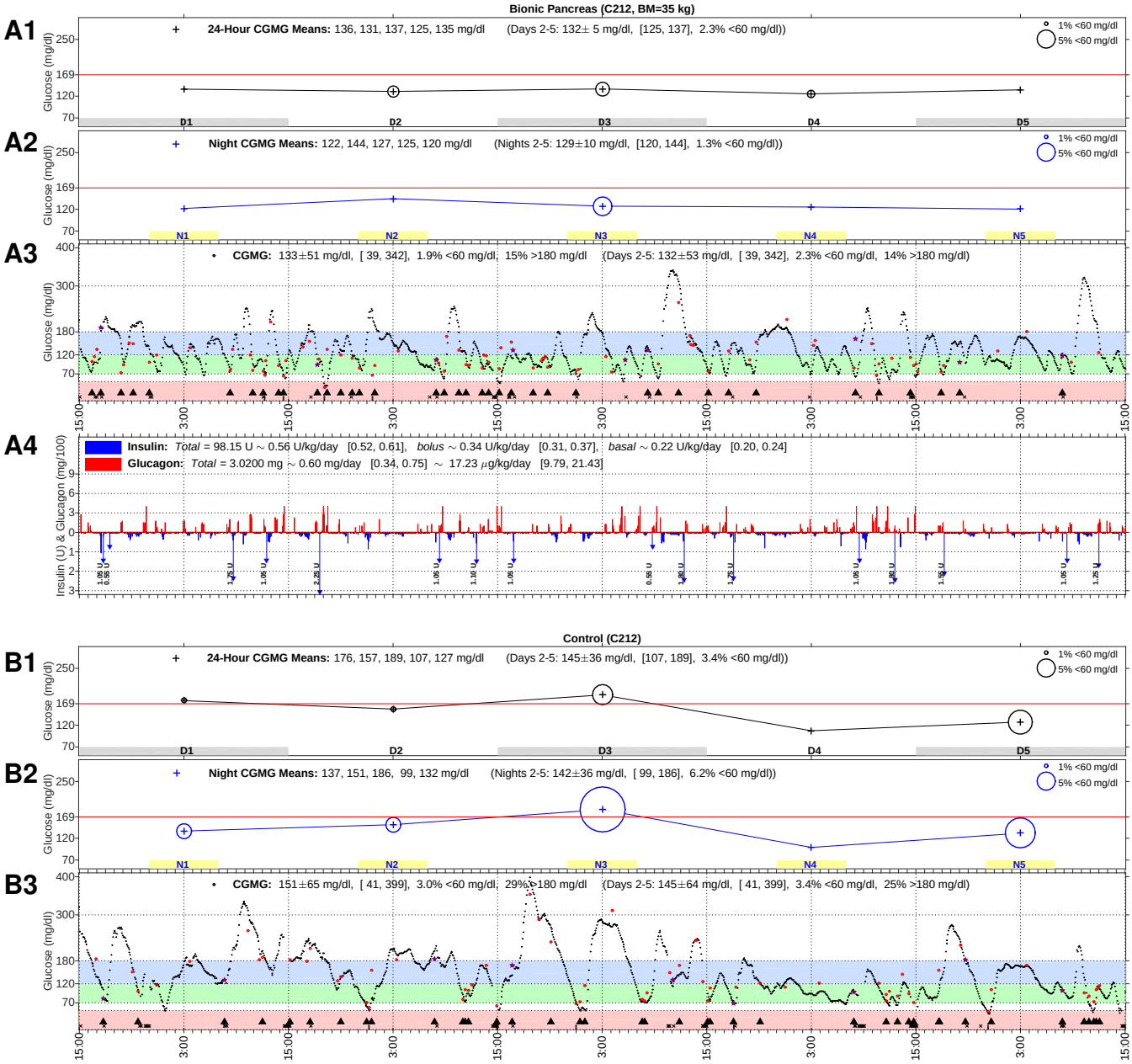

Figure S13. Outpatient experiments in pre-adolescent subject #C212. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 132 mg/dl, mean of night time CGMG was 130 mg/dl, insulin–glucagon dosing was respectively 0.56 U/kg/day and 16.62 μg/kg/day, CGMG was $<$ 60 mg/dl 2.3% of the time (1.3% at night) and $>$ 180 mg/dl 14% of the time, and there were 4 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 145 mg/dl, mean of night time CGMG was 142 mg/dl, CGMG was $<$ 60 mg/dl 3.4% of the time (6.2% at night), and $>$ 180 mg/dl 26% of the time, and there were 5 carbohydrate interventions over the 5-day period. The insulin site was replaced at 20:00 on day 3 of the BP period due to pain, itching and redness at the site. One calibration is documented as being performed within 30 minutes of carbohydrate intake on day 3 of the control period. Calibrations were missed on day 2 of the control period and day 1 of the BP period. Daily nausea scores on a scale of 0–10 were 6/7/6/5/4/0 during the control period and 0/0/0/0/0/0 during the BP period.

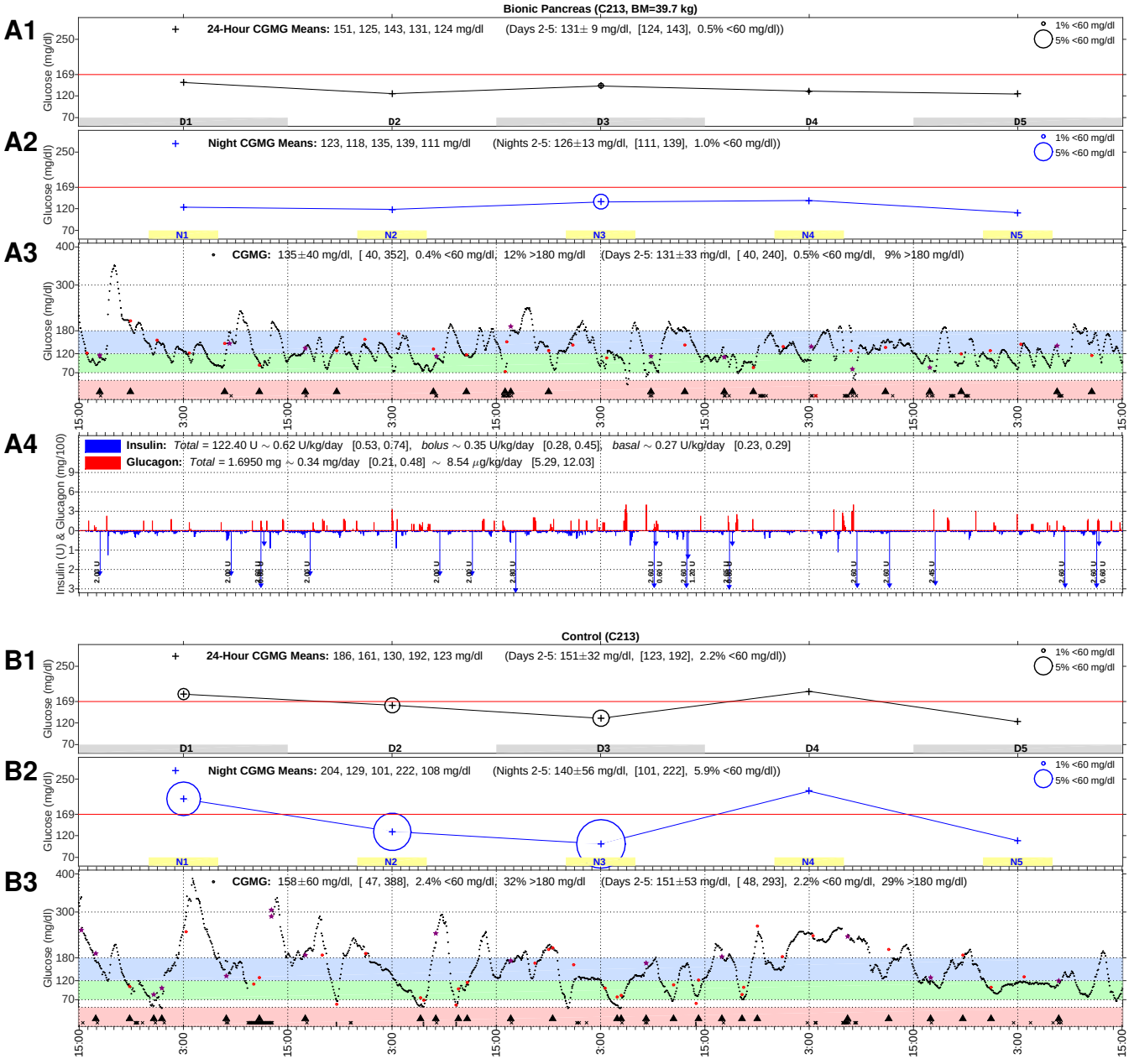

Figure S14. Outpatient experiments in pre-adolescent subject #C213. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 131 mg/dl, mean of night time CGMG was 126 mg/dl, insulin–glucagon dosing was respectively 0.61 U/kg/day and 9.35 μg/kg/day, CGMG was $<$ 60 mg/dl 0.5% of the time (1.0% at night) and $>$ 180 mg/dl 9% of the time, and there were 0 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 151 mg/dl, mean of night time CGMG was 140 mg/dl, CGMG was $<$ 60 mg/dl 2.2% of the time (6.0% at night), and $>$ 180 mg/dl 29% of the time, and there were 4 carbohydrate interventions over the 5-day period. The CGM sensor failed and was replaced at 11:02 on day 1 of the control period. Extra calibrations were performed on day 5 of the BP period, and days 1 and 2 of the control period. One calibration on day 4 of the BP period was documented as being within 15 minutes of glucagon and with a rapid rate of change on the CGM. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0 during the BP period and 0/0/0/0/0/0 during the control period.

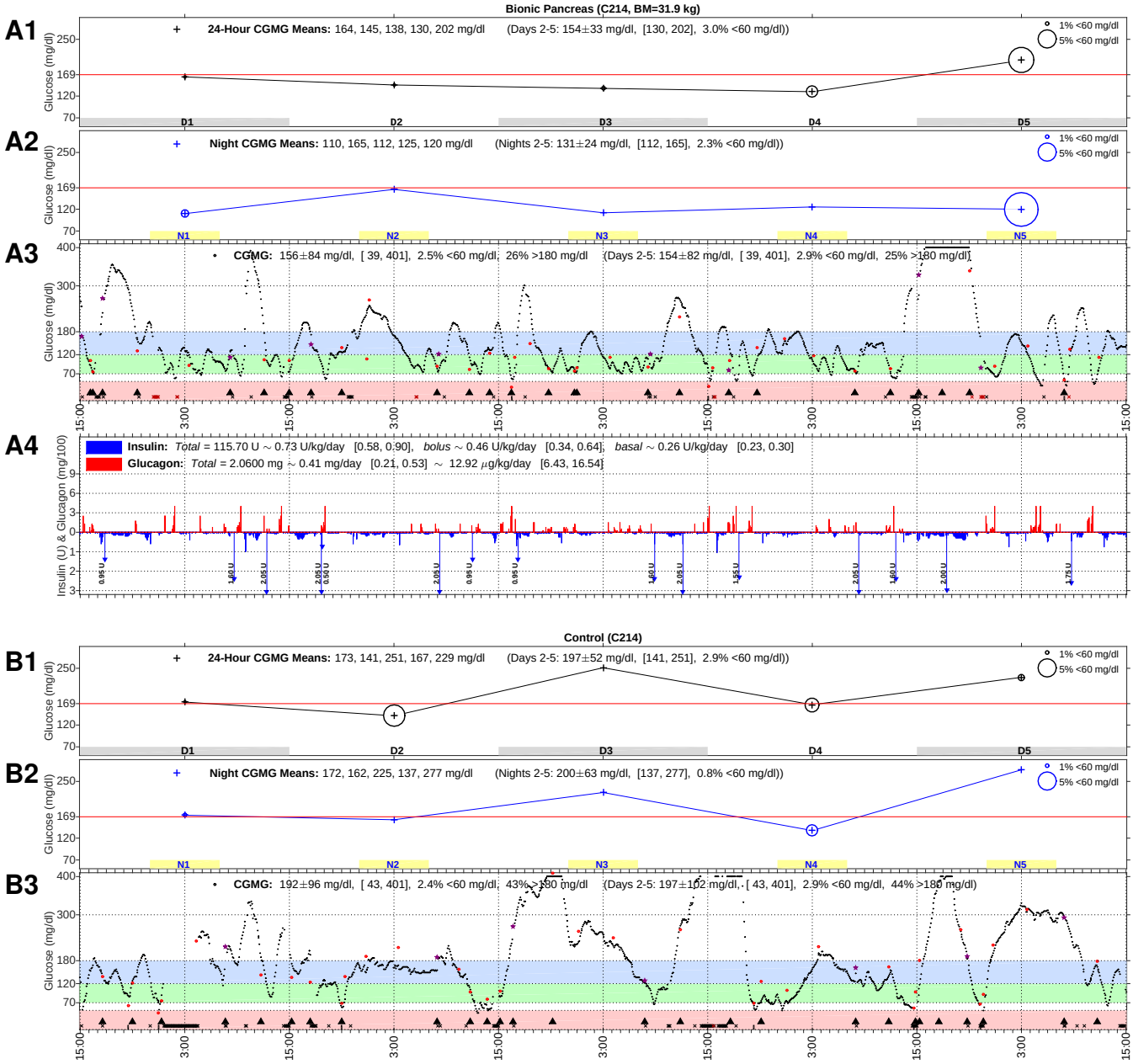

Figure S15. Outpatient experiments in pre-adolescent subject #C214. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 154 mg/dl, mean of night time CGMG was 131 mg/dl, insulin–glucagon dosing was respectively 0.73 U/kg/day and 12.01 μg/kg/day, CGMG was $<$ 60 mg/dl 2.9% of the time (2.3% at night) and $>$ 180 mg/dl 25% of the time, and there were 3 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 197 mg/dl, mean of night time CGMG was 200 mg/dl, CGMG was $<$ 60 mg/dl 2.9% of the time (0.8% at night), and $>$ 180 mg/dl 44% of the time, and there were 6 carbohydrate interventions over the 5-day period. The insulin site was replaced at 16:00 on day 4 of the control period. The insulin site was replaced at 18:30 on day 5 of the BP period due to a clinical suspicion of failure despite a blood ketone level of 0.4 mmol/dL. Calibrations were missed on days 1 and 2 of the control period, and days 4 and 5 of the BP period. One calibration on day 4 of the control period was with a blood glucose value of 579 mg/dl; this would have been rejected by the CGM and thus a calibration was missed. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0 during the control period and 0/7/0/0/0/0 during the BP period.

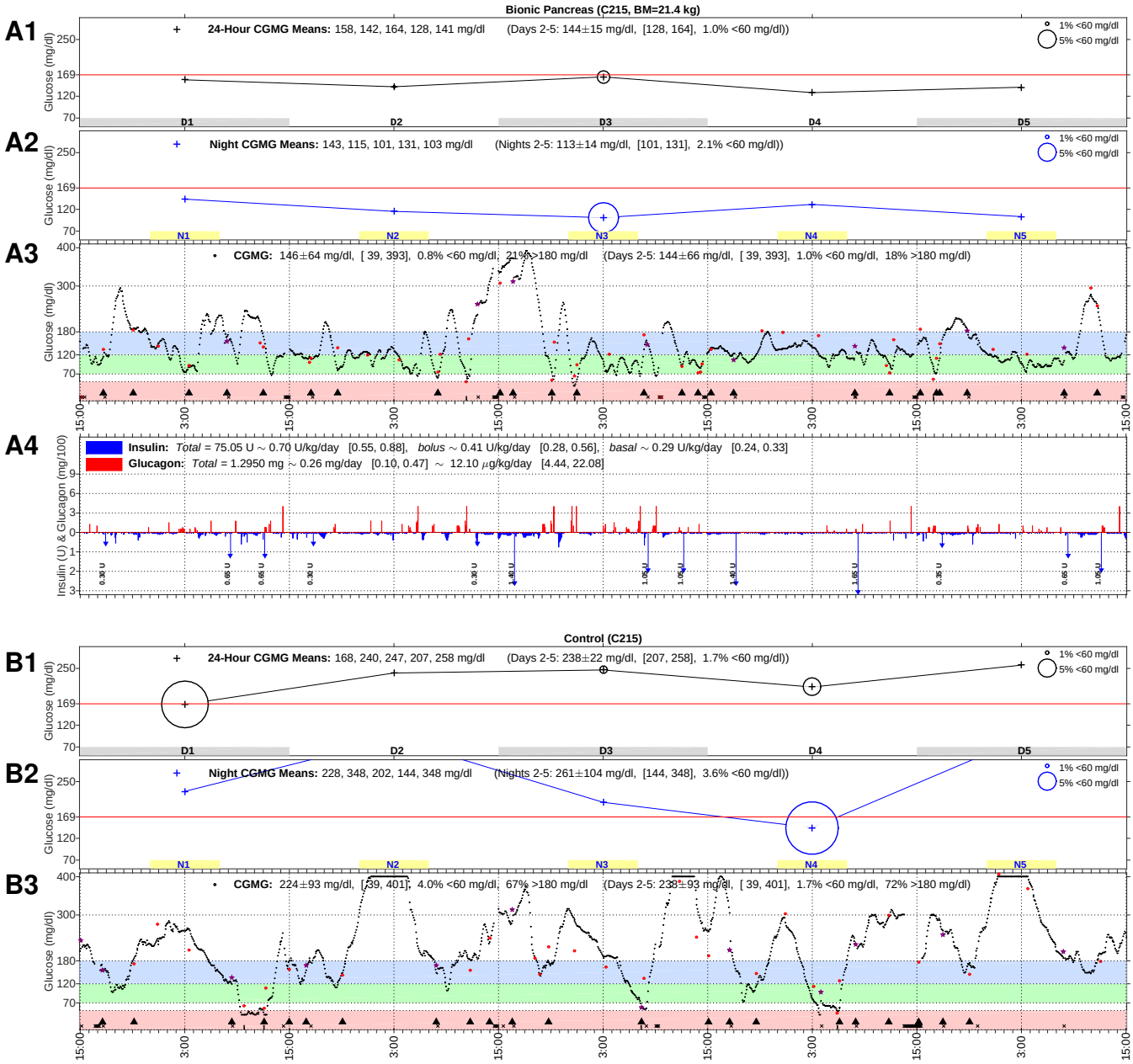

Figure S16. Outpatient experiments in pre-adolescent subject #C215. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 144 mg/dl, mean of night time CGMG was 113 mg/dl, insulin–glucagon dosing was respectively 0.71 U/kg/day and 12.56 μg/kg/day, CGMG was $<$ 60 mg/dl 1.0% of the time (2.1% at night) and $>$ 180 mg/dl 18% of the time, and there were 4 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 238 mg/dl, mean of night time CGMG was 262 mg/dl, CGMG was $<$ 60 mg/dl 1.7% of the time (3.6% at night), and $>$ 180 mg/dl 72% of the time, and there were 4 carbohydrate interventions over the 5-day period. The glucagon site was replaced at 19:22 on day 1 of the BP period due to pain, itching and redness at the site. The insulin cartridge had to be replaced at 19:28 on day 1 of the BP period due to repeated error messages in the pump. The insulin site was replaced at 17:43 on day 3 of the BP period due to a clinical suspicion of failure. One extra calibration was performed on day 4 of the control period. Calibrations were missed on days 1 and 2 of the BP period. Daily nausea scores on a scale of 0–10 were 3/1/0/0/0/1 during the BP period and 0/0/0/6/3/0 during the control period.

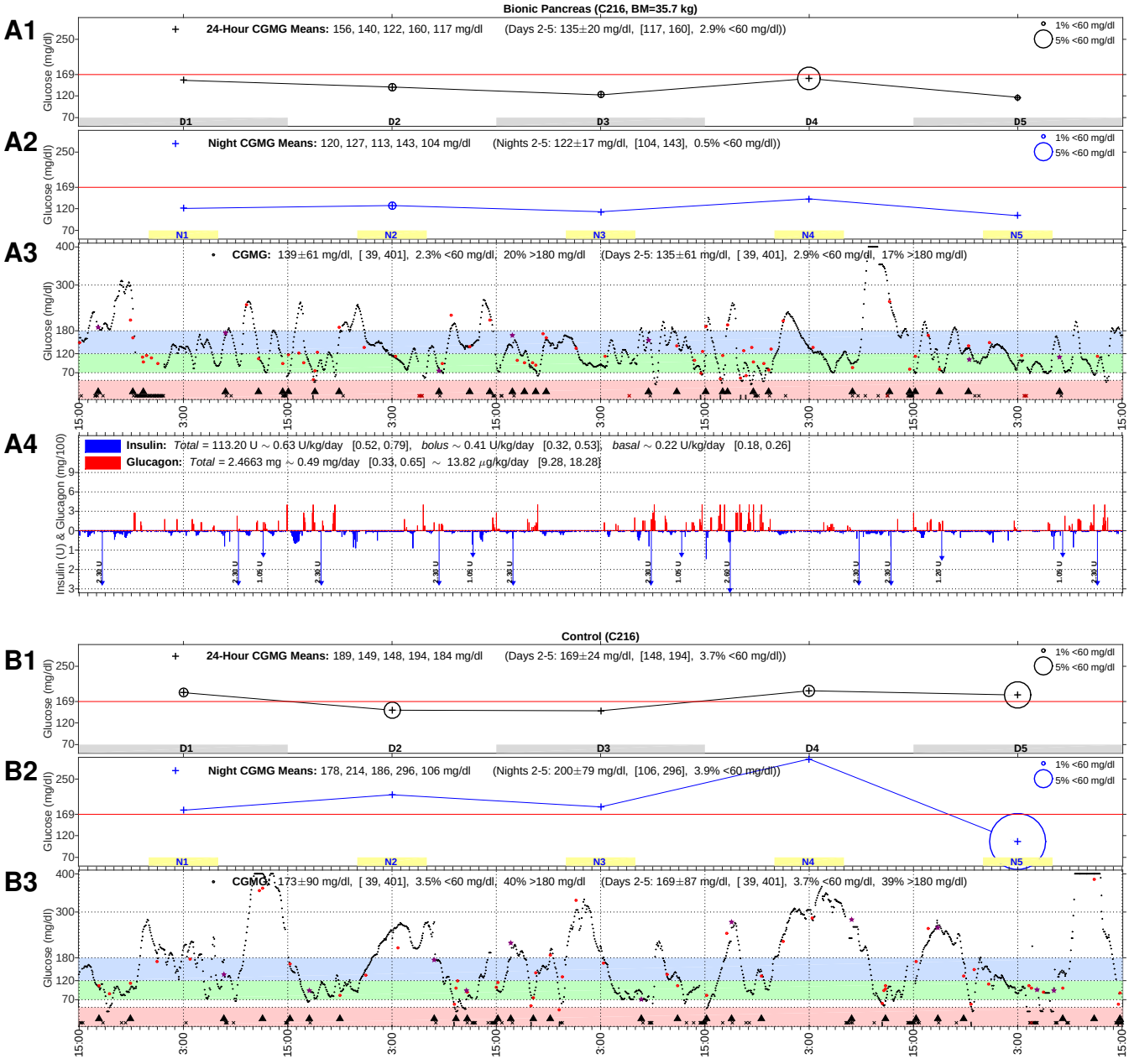

Figure S17. Outpatient experiments in pre-adolescent subject #C216. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 135 mg/dl, mean of night time CGMG was 122 mg/dl, insulin–glucagon dosing was respectively 0.63 U/kg/day and 14.95 μg/kg/day, CGMG was $<$ 60 mg/dl 2.9% of the time (0.5% at night) and $>$ 180 mg/dl 17% of the time, and there were 5 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 169 mg/dl, mean of night time CGMG was 201 mg/dl, CGMG was $<$ 60 mg/dl 3.7% of the time (3.6% at night), and $>$ 180 mg/dl 39% of the time, and there were 6 carbohydrate interventions over the 5-day period. Calibrations were missed on day 1 of the control period and days 2, 3 and 4 of the BP period. Extra calibrations were performed on day 2 of the control period because the CGM was out of ISO standards, and day 5 of the control period because the CGM was not reading. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0 during the control period and 0/0/0/0/0/0 during the BP period.

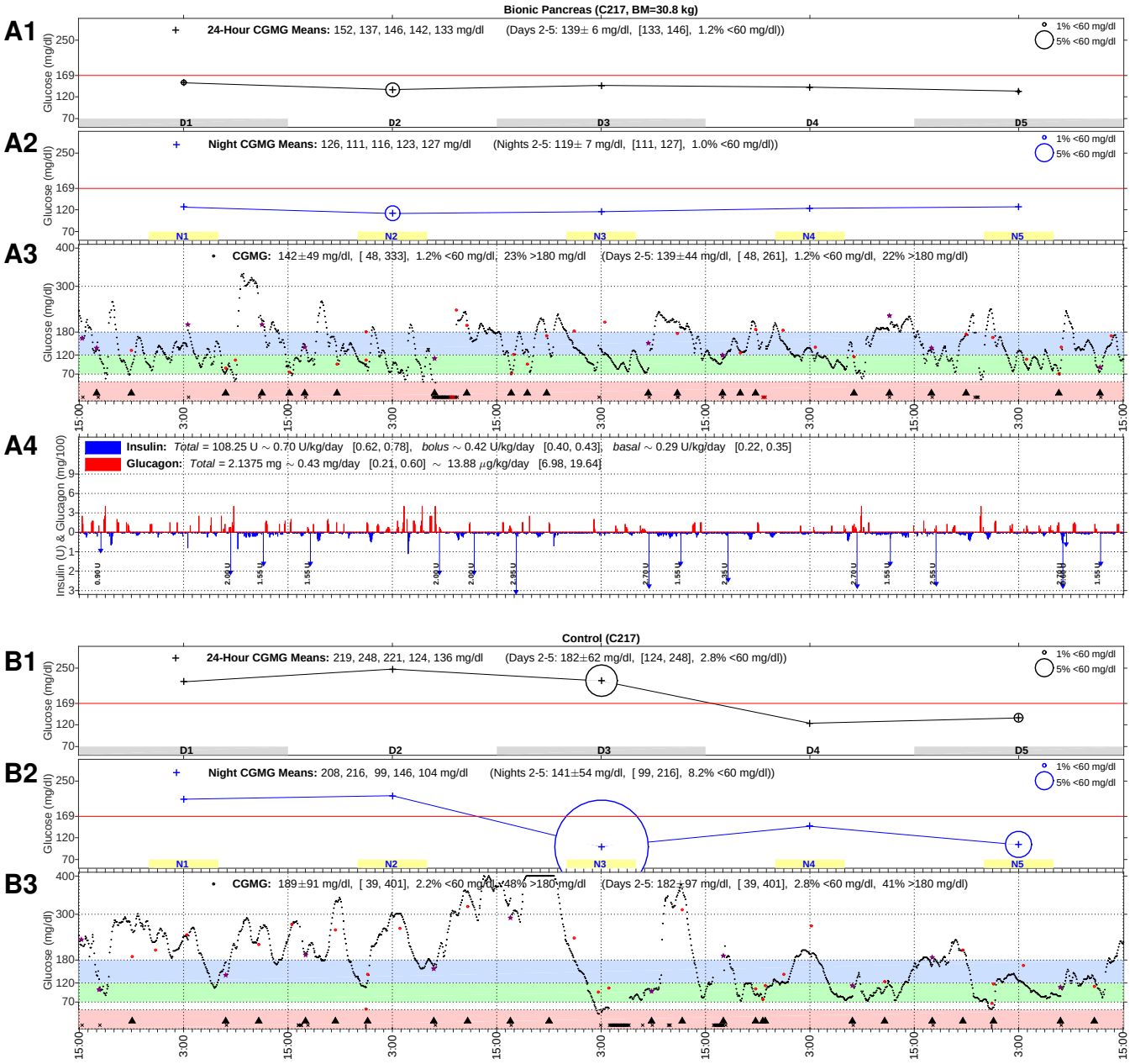

Figure S18. Outpatient experiments in pre-adolescent subject #C217. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 139 mg/dl, mean of night time CGMG was 119 mg/dl, insulin–glucagon dosing was respectively 0.72 U/kg/day and 12.44 μg/kg/day, CGMG was $<$ 60 mg/dl 1.2% of the time (1.0% at night) and $>$ 180 mg/dl 22% of the time, and there were 0 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 182 mg/dl, mean of night time CGMG was 142 mg/dl, CGMG was $<$ 60 mg/dl 2.8% of the time (8.3% at night), and $>$ 180 mg/dl 41% of the time, and there were 6 carbohydrate interventions over the 5-day period. An extra calibration was performed on day 1 of the BP period, and a calibration was missed on day 3 of the BP period. The subject had a blood ketone level of 1.1 mmol/dL at 20:17 on day 3 of the control period. The CGM was reading falsely low at 2:40 and 3:44 on day 3 of the control period, due to a possible compression artifact; repositioning the subject resolved the issue both times. Daily nausea scores on a scale of 0–10 were 4/0/0/0/0/0 during the control period and 0/0/3/0/0/0 during the BP period.

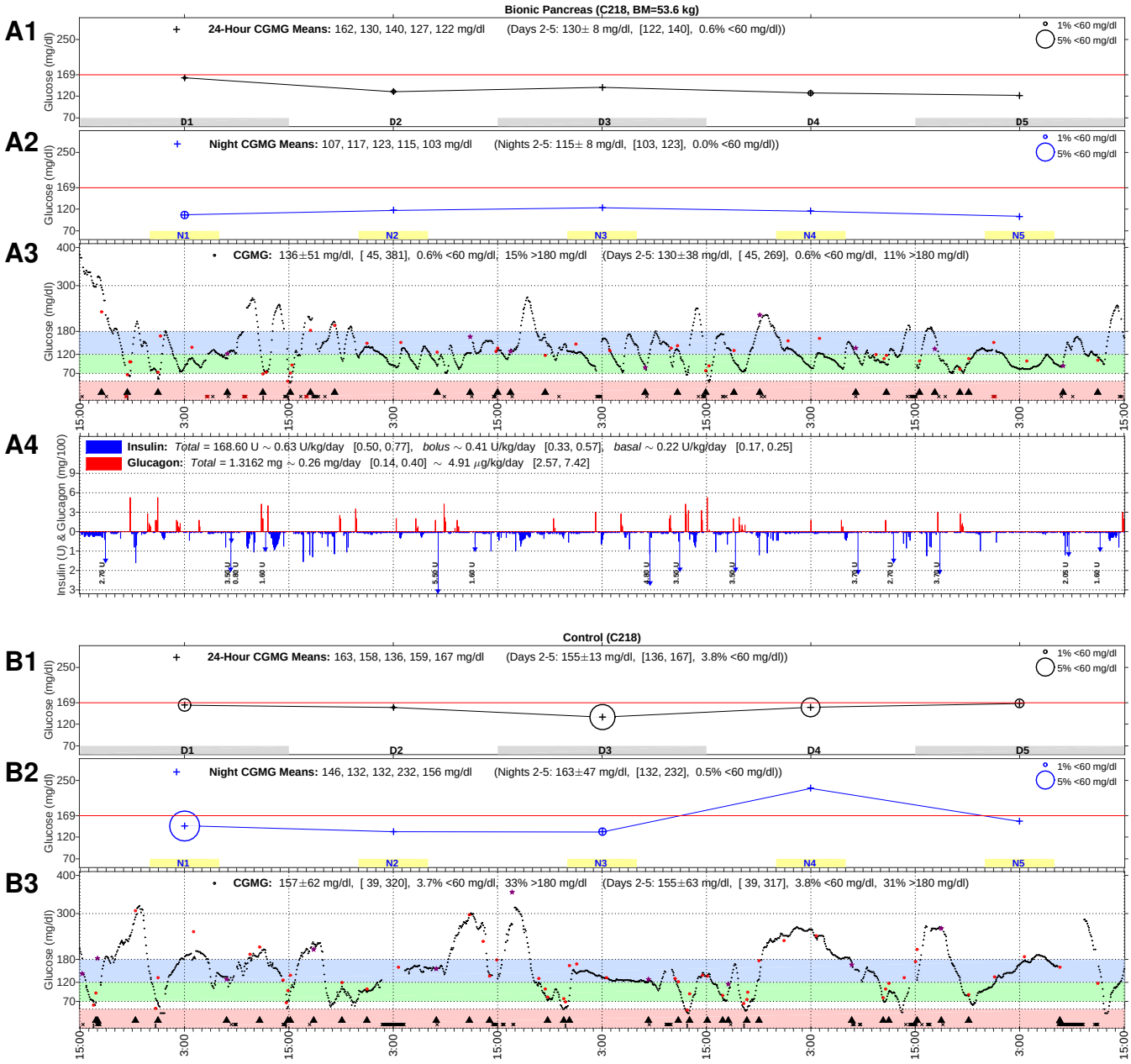

Figure S19. Outpatient experiments in pre-adolescent subject #C218. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 130 mg/dl, mean of night time CGMG was 115 mg/dl, insulin–glucagon dosing was respectively 0.59 U/kg/day and 4.29 μg/kg/day, CGMG was $<$ 60 mg/dl 0.6% of the time (0% at night) and $>$ 180 mg/dl 11% of the time, and there were 3 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 155 mg/dl, mean of night time CGMG was 163 mg/dl, CGMG was $<$ 60 mg/dl 3.8% of the time (0.5% at night), and $>$ 180 mg/dl 31% of the time, and there were 6 carbohydrate interventions over the 5-day period. Calibrations were missed on days 1 and 2 of the control period and day 5 of the BP period. Daily nausea scores on a 0–10 scale were 0/0/0/0/0/0 during the control period and 0/0/0/0/0/0 during the BP period.

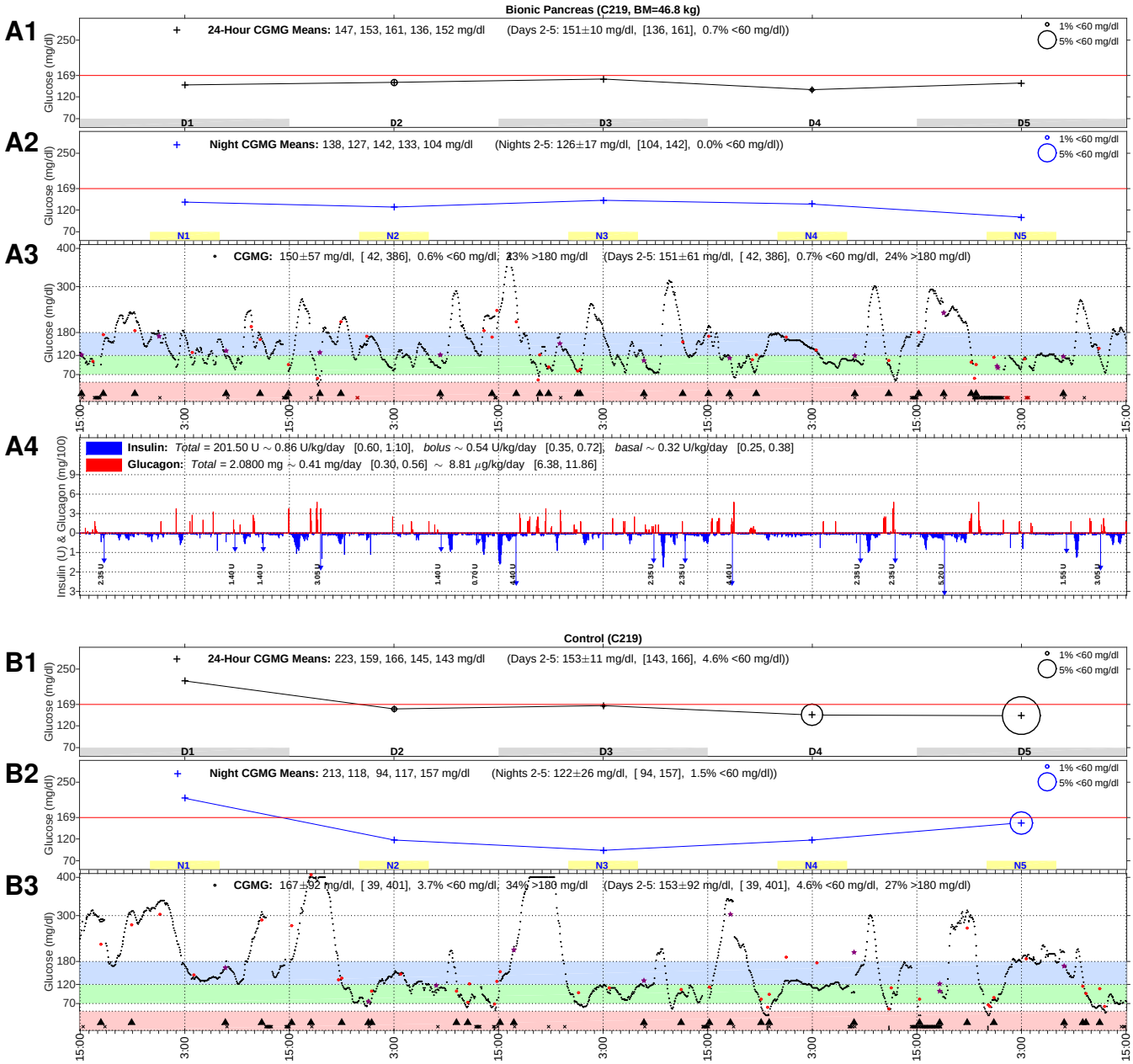

Figure S20. Outpatient experiments in pre-adolescent subject #C219. See Fig. S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 151 mg/dl, mean of night time CGMG was 127 mg/dl, insulin–glucagon dosing was respectively 0.93 U/kg/day and 9.27 μg/kg/day, CGMG was $<$ 60 mg/dl 0.7% of the time (0% at night) and $>$ 180 mg/dl 24% of the time, and there were 3 carbohydrate interventions over the 5-day period. On the other hand, beyond the first 24 hours in the control period, mean of overall daily CGMG was 153 mg/dl, mean of night time CGMG was 121 mg/dl, CGMG was $<$ 60 mg/dl 4.6% of the time (1.6% at night), and $>$ 180 mg/dl 28% of the time, and there were 4 carbohydrate interventions over the 5-day period. The glucagon site fell out at 14:50 on day 1 of the BP period. The insulin site fell out at 19:00 on day 2 of the BP period. The CGM battery died at 22:22 on day 5 of the BP period, requiring it to be restarted. The CGM sensor fell out and was replaced at 15:25 on day 5 of the control period. A calibration was missed on day 1 of the control period. One calibration was documented as being performed with a blood glucose of 238 mg/dl, when the actual blood glucose was 304 mg/dl. The subject had a blood ketone level of 0.6 mmol/dL at 00:00 and 17:30 on day 1, and 19:55 on day 2, which all resolved by replacing the insulin infusion set. Daily nausea scores on a scale of 0–10 were 0/0/5/0/0/0 during the control period and 0/0/3/0/5/0 during the BP period.

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ACKNOWLEDGMENTS

We thank Kari Galuski, Raquel Kochis, Maura Conners, Erin Heath, Nancy Shaffer, Jessica Kimmes, and Hannah Tupper, for their dedicated effort and careful execution of the experimental protocol; John Jiang for technical assistance; Mary Lee, Alyne Ricker, Angelina Bernier, Kevin Wilcoxen, Mark Bissell, Beth Rowe, and Sarah Gatti for their input and contributions to the study design and assistance in the implementation and execution of the experimental protocol; Paige Coles, Mariah Chang, Angela Voss, Rebecca Emmetts, Mark O'Brien, and Alexander O'Donovan for their tireless dedication and careful attention to telemetric monitoring and equipment maintenance at camp; Mary Larkin, Camille Collings, Nancy Kingori, and Irene Orzechowski for organizational and logistical support; Adam Greene, Justin Schumacher, Tom Peyser, Liam Pender, Sean Saint, for hardware and software support, technical advice, and support in kind; Niall Kavanagh, Hilary Orenberg, Trevor Macdowell for user interface software support; Fyodor Wolf, Inderpreet Singh, and Murugesh Vyravanadan for remote monitoring software support; Sheila Ramerman for software and hardware documentation support; Nicole Sherry, Geoffrey Walford, and Nancy Wei for serving on the data safety and monitoring board; the members of the Partners Human Research Committee and the Boston University Charles River Campus Institutional Review Board for their oversight of the study; and Stayce Beck, Yiduo Wu, Patricia Beaston, Courtney Lias, and Tessa Lebinger for their assistance during the process of obtaining the investigational device exemption approval for these studies.

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Clinical Protocol

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I. Background and Significance

I. a. Historical Background

Diabetes is a chronic, life-threatening disease that can result in serious acute and chronic deleterious consequences. Hypoglycemia may result in acute complications including convulsions, seizures, and coma, while chronic hyperglycemia can cause several long-term complications including cardiovascular disease (CVD), renal complications, vision disorders, nerve degeneration, and skin disorders. The risk of CVD alone is elevated by three- to five-fold with diabetes and the diabetes-specific complications (retinopathy, nephropathy and neuropathy) many fold more (1,2,3). Total diabetes health care costs in the US are above $170 billion annually and are steadily increasing. Diabetes causes over 200,000 deaths annually in the U.S.A. alone.

I. b. The Current Standard of Care

Prior to the discovery of insulin by Banting and Best in 1921 and its subsequent purification by Collip and Macleod (4,5), type 1 diabetes was an inescapably fatal disease. The availability of insulin transformed type 1 diabetes into a chronic disease, now managed by frequent blood glucose (BG) tests and administration of insulin to treat or prevent excursions of BG outside the normal range. The process was facilitated by hand-held BG meters capable of measuring glucose concentration very quickly from small blood samples, and more recently by continuous glucose monitors (CGM) that measure the glucose in the subcutaneous interstitial fluid and, once calibrated, provide an estimate of the blood glucose as often as once every minute. Flexibility in administration of insulin has been facilitated by small, precise insulin pumps that administer insulin into the subcutaneous space either continuously to supply basal requirements or as boluses to treat or prevent hyperglycemia from consumed carbohydrates. Analogs of human insulin have been developed that are absorbed more rapidly from the subcutaneous space into the blood, allowing patients to match their insulin dosing to food intake rather than planning meals to match the insulin taken hours earlier.

Even with modern tools, maintaining the blood glucose as close to the normoglycemic range as possible while avoiding hypoglycemia is a very challenging task. The importance of this task to the long term health of people with diabetes was demonstrated by the Diabetes Control and Complications Trial (DCCT), which compared the progression of complications in a group of subjects with type 1 diabetes under intensive BG control with another group under conventional therapy. The intensive control group achieved a mean hemoglobin A1c (HbA1c) of ~7% (mean BG of 154 mg/dl) while the control group achieved a mean HbA1c of ~9% (mean BG of 212 mg/dl). The reduction in mean BG with intensive therapy reduced the development of retinopathy, neuropathy, and nephropathy by as much as 76% relative to the control group (1). A followup study on the progression of cardiovascular disease in some DCCT subjects showed that intensive therapy also had long-term beneficial effects on the risk of cardiovascular disease (2).

The DCCT established that maintaining BG as close to normoglycemic range as safely possible

reduced long-term complications of type 1 diabetes and that the tighter this control was, the fewer and less severe were the complications. The drawbacks to tight control include the technical demands of carbohydrate counting, frequent BG monitoring, frequent dosing of insulin via a syringe or insulin pump, and the requirement of making frequent calculations and decisions regarding insulin dosing. The continuous demands of intensive therapy are challenging and painstaking for even the most diligent, motivated, and educated individual, and can be daunting for average individuals due to the training and self-management skills required. Intensive management is also more expensive in the short term, albeit less expensive when morbidity and mortality are considered. Most importantly, individuals who diligently keep their BG in near physiologic range are more prone to severe hypoglycemia, which can be life threatening.

Although intensive therapy is not a cure for type 1 diabetes and does have costs and drawbacks, it was the single most important technological breakthrough in the management of complications of the disease. Short of islet-cell or pancreas transplantation procedures, exogenous insulin administration, either through injection therapy or continuous subcutaneous (SC) insulin infusion therapy, is the only method available for maintaining near normoglycemia in type 1 diabetes patients.

With the recent emergence of practical continuous glucose monitoring (CGM) technologies approved for home use and the increasingly widespread use of insulin infusion pumps, the stage is set for the realization of automated bionic pancreas BG control. Achieving this goal requires the coordination of three main components into an integrated system; a CGM device, a continuous dual drug infusion system, and a controller or modulating unit. We have now completed five clinical studies of a bionic pancreas BG control device using algorithm-controlled infusions of insulin and glucagon (6-8, Appendix A).

I. c. Past Pre-clinical and Clinical Studies

Research efforts to develop bionic pancreas BG control systems have been ongoing for decades. The Biostator design of Clemens is one of the earliest (9). Like most glucose-control systems (10-13), the Biostator assumed the intravenous (IV) route for drug infusion, and, like most dual-infusion systems (14-16), it used dextrose as the counter-regulatory agent to insulin. While IV infusion results in faster drug bioavailability than SC infusion, its associated risks of infection, embolism, or thrombosis, and the challenge of maintaining permanent IV access, render the SC route more practical for ambulatory usage (17-18).

The SC route poses an additional challenge due to the delayed and attenuated absorption of the infused drug into the blood stream (6, 19-20). Delays in absorption create the possibility of excessive insulin accumulation in the SC tissue, which can result in delayed hypoglycemia (18), an event that must be safeguarded against in any practical glucose control system. One preventative measure is to use the naturally occurring hormone glucagon as the counter-regulatory agent (21-23). Unlike dextrose or other fast-acting sugars, exogenous glucagon mimics (24) a physiologic process deficient in people with type 1 diabetes (25), in which mobilization of the body's own glucose reserves raise BG. Another measure to prevent hypoglycemia is to have the control algorithm keep track of, and act in light of, the estimated accumulation of SC insulin based on its in vivo pharmacokinetics. Our bionic pancreas algorithm utilizes both of these strategies. Unlike any other BG control algorithm of which we are aware, our algorithm only requires the subject's weight (for the purpose of initialization only) and regularly-sampled BG for online operation (6-7,22, Appendix A), without any additional input, such as

carbohydrate counting, physical activity, or other user feed-forward information, that is required by other systems (26-28). It is the only existing BG control system that is truly self-running and self-tuning. We performed pre-clinical studies of this system in a swine model of type 1 diabetes (29) and showed that automated, bi-hormonal, bionic pancreas control of blood glucose was feasible (22).

To date, we tested the control algorithm in five successful clinical trials. The first of these trials used frequent measurements of venous BG and the SC infusion of insulin and glucagon to achieve and maintain normoglycemia in subjects with type 1 diabetes (6 – see Appendix A). These experiments were 27 hours in duration during which the subjects consumed three standardized meals. The only input to the control algorithm was the subject weight and venous BG measurements every 5 minutes. The key conclusion from these experiments was that the control system was able to achieve near-normal mean BG (aggregate mean BG 140 mg/dl, equivalent to a HbA1c of 6.5%) with negligible hypoglycemia in subjects with relatively rapid absorption of insulin lispro. In subjects with delayed lispro absorption, modifying the insulin pharmacokinetic assumptions of the control algorithm was required to prevent hypoglycemia, and this increased the aggregate mean BG achievable by the control system (mean BG 164 mg/dl, equivalent to a HbA1c of 7.4%). These results demonstrated the feasibility of a bi-hormonal artificial endocrine pancreas. However, the use of venous BG as the input to the algorithm limited the applicability of the system tested to the inpatient setting. In order to develop a system suitable for outpatient use, the BG input to the system need to be obtained using a less invasive method. In the same study we also compared the accuracy and reliability of three commercially available continuous glucose monitors (CGMs) in each subject. We found that one device (Abbott Diabetes Care FreeStyle Navigator) was sufficiently reliable and provided estimated BG measurements that were sufficiently accurate to be used as input for our bionic pancreas control algorithm (30). This finding suggested that bionic pancreas control could be achieved using CGM as the input, potentially making a bionic pancreas device for outpatient use feasible.

Based on our results from the first human study and preclinical studies in diabetic pigs, we hypothesized that glycemic control could be achieved in humans with type 1 diabetes using glucose values from the FreeStyle Navigator CGM as the sole input to the controller. The second phase of the our bionic pancreas controlled trials included testing this hypothesis in experiments more than two days in length that included six high-carbohydrate meals and a period of exercise as challenges to glycemic control (7). The only input signal was data from the Freestyle Navigator (Abbott Diabetes Care), an FDA-approved interstitial fluid continuous glucose monitor (CGM). A partial meal-priming bolus of insulin was also given at the beginning of each meal. Results showed the overall mean blood glucose (BG) was 158 mg/dl, with 68% of BG values in the 70–180 mg/dl range. Hypoglycemia (BG < 70 mg/dl) was rare, with 8 incidents during 576 hours of bionic pancreas control (0.7% of total time). During 192 hours of nighttime control, mean BG was 123 mg/dl with 93% of BG values in the 70–180 mg/dl range and only one episode of mild hypoglycemia (minimum BG, 62 mg/dl). The period of exercise markedly increased glucose clearance and was associated with increased glucagon dosing and levels during and immediately following the exercise period. The second trial of our bionic pancreas experiments showed that the bi-hormonal bionic endocrine pancreas achieved excellent glycemic control with minimal hypoglycemia over two days of continuous use despite high-carbohydrate meals and exercise.

After the second trial, we tested the same system in a small number of adolescent subjects. We learned that our control system that performed so well in an adult population could not achieve mean glucose levels in adolescents that were substantially different from the standard of care in that population (although with less hypoglycemia). Our attempts at increasing the aggressiveness of the control algorithm were successful in lowered the mean glucose levels in adolescent subjects, but at the cost of

significantly more hypoglycemia in adults. After substantially redesigning the algorithm to include methods which allowed the algorithm to adapt robustly online, we sought U.S. Food and Drug Administration (FDA) approval to begin testing our new control system in a cohort that included both pediatric and adult subjects.

Our third trial was designed to test this new ability of our control algorithm to adapt robustly online to the broad range of insulin needs of individual subjects. These new capabilities not only automatically adapted the aggressiveness of the insulin controller, it also allowed the control system to adapt the size of the meal priming bolus based on the amount of additional insulin that was required for previous meals. In this trial participants were randomized to bionic pancreas control with no meal priming bolus or bionic pancreas control with adaptive meal priming boluses (8). Otherwise, the trial was conducted with the same protocol as our second trial, where the bionic pancreas system used the Navigator CGM as the input in experiments that lasted more than two days, included six meals, and included a 30–40-minute period of exercise. BG was lower in the adaptive meal-priming bolus vs. fully reactive group in both adults (132 vs. 146 mg/dl, $p = 0.03$) and pediatric subjects (162 vs. 175 mg/dl, $p = 0.01$). The fraction of BG measurements < 70 mg/dl was not statistically different with or without adaptive meal-priming boluses in either adult (5.1% vs. 3.6%, $p = 0.7$) or pediatric subjects (0.3% vs. 0.4%, $p = 0.8$). These results demonstrate that effective BG control can be achieved over a wide range of insulin needs and subject ages with an adaptive bionic pancreas. These results showed that the changes that were made to the adaptation features of the algorithm clearly improved mean BG in children and reduced hypoglycemia in adults and thus would be used in subsequent trials.

In the third trial we also tested the accuracy and reliability of two new CGM devices, the G4 Platinum (DexCom) and the Enlite (Medtronic), in addition to the FreeStyle Navigator, over the full duration of each experiment. Venous BG measurements (GlucoScout, International Biomedical) obtained every 15 minutes ($n = 4294$ reference values) were paired in time with corresponding CGM glucose measurements (Appendix B). The accuracy and precision of the G4 Platinum was similar to the Navigator, with aggregate mean absolute relative differences (MARDs) of all paired points of 10.8% ± 9.9% and 12.5% ± 12.4%, respectively. Both were significantly better than the Enlite with a MARD of 18.2% ± 16.0%. We conclude that either the Navigator or the DexCom G4 Platinum have sufficient accuracy to drive bionic pancreas BG control. We have therefore built a mobile bionic pancreas using the DexCom G4 Platinum CGM as the input device.

The results of our third trial led us to design our first out-patient trial with a wearable bionic pancreas using the DexCom G4 Platinum CGM as the input and an iPhone 4s as the command center, housing the control algorithm. Two Tandem t:slim pumps served to delivery insulin and glucagon by subcutaneous infusion.

Our fourth trial, called the Beacon Hill Study, was a randomized control trial in which adult research subjects used the bionic pancreas device in an outpatient setting for 5 days and managed diabetes according to their usual care routine for 5 days (Appendix A). During the bionic pancreas arm, subjects were asked to remain within a 3 square mile area centered on the Beacon Hill neighborhood of Boston with direct nursing observation at all times, measure blood glucose a minimum of every two hours during the day and every 30 minutes during the night. There were no restrictions on food intake, exercise, activities and schedule in order to fully test the performance of the bionic pancreas. The comparator was a 5 day period at home and at work during which subjects used their own insulin pump as usual. The bionic pancreas achieved a lower mean CGM glucose level than usual care (133±13 versus 159±30 mg/dl, $p<0.001$), less time <70 mg/dl (4.1 versus 7.3%, $p=0.01$), and less time <60 mg/dl (1.5 versus 3.7%, $p=0.02$). The results of this trial demonstrate that excellent BG control can be

achieved with a bionic pancreas in an outpatient environment in which subjects have a great degree of freedom. We were thus ready to test the bionic pancreas in an outpatient trial in a pediatric population.

Our fifth trial enrolled adolescents, 12 – 20 years old, in a diabetes camp setting (Appendix A). Participants used the same wearable bionic pancreas as the previous adult study and a similar study design of a randomized control trial with 5 days each of bionic pancreas control versus 5 days of usual camp diabetes management. We chose the diabetes camp environment because it presented the bionic pancreas with challenges to blood glucose control that were as great or greater than would be faced in the daily life of children with diabetes, yet afforded the opportunity for close supervision and monitoring of multiple children participating in the study simultaneously. We were able to decrease the level of glucose monitoring and nursing care from the previous study; glucose levels were measured according to the usual camp schedule with the exception of an additional blood sugar check daily at ~3:45 AM and a hypoglycemia alert system which prompted extra glucose checks during nighttime if the glucose was perceived to be below 60 mg/dl. Meals and activities occurred according to usual camp schedule and thus were the same in both arms of the study. The mean BG level was 138±18 mg/dl (range 101–185 mg/dl) on the bionic pancreas and 157±27 mg/dl (range 103–221 mg/dl) in the comparator arm ($p=0.004$). The percentage of all scheduled BG measurements with values <70 mg/dl was 6.1% during the bionic pancreas arm and 7.6% during the comparator arm ($p=0.23$). The bionic pancreas reduced the mean frequency of treatments for hypoglycemia from once per 0.8 days to once per 1.6 days ($p<0.001$). There were no episodes of serious hypoglycemia on the bionic pancreas and one episode of PG = 19 mg/dl associated with confusion in the comparator group, which was successfully treated with oral carbohydrates.

The improvement in mean glycemia and the reduction in the need for carbohydrate treatment of hypoglycemia in the camp study in subjects 12-20 provides support for a study to test the bionic pancreas in a younger population. Therefore, we now propose repeating a study with a similar design to the completed camp study in 6 – 11 year olds.

Since our studies, Dexcom has developed a new calibration algorithm for the Dexcom G4 Platinum called the G4AP (Artificial Pancreas) algorithm. A study testing the algorithm against the stock G4 Platinum algorithm shows that accuracy was improved, with the MARD decreasing from 13.2% to 11.7% with improvements mainly in the hypoglycemic and normoglycemia range and in the first day of sensor use (31). Therefore, we have decided to use the Dexcom G4 Platinum with the AP algorithm to further enhance accuracy.

I. d. Rationale and Potential Benefits

Our experiments to date in human subjects with type 1 diabetes have demonstrated the practicality of a wearable automated, bionic pancreas control system for robust glucose regulation using continuous glucose monitoring devices as input to the controller. Despite technical limitations of the pump and CGM components, we have shown that a bi-hormonal bionic endocrine pancreas is capable of achieving good BG control with minimal hypoglycemia during five continuous days in the face of unrestrained meals and exercise. Control was particularly good at night, achieving mean BG values in the normal range with minimal hypoglycemia. The studies to date pave the way for longer-term out-patient studies in a broader population.

The bionic pancreas BG control system we have developed was able to provide automatic BG regulation, reduce hypoglycemic episodes, and spare the subjects in our completed trials the relentless

tasks of carbohydrate counting, frequent BG monitoring, and manual drug administration, which are painstaking, aggravating, and demand continuous diligence and vigilance. The degree of glycemic control achieved is predicted to dramatically reduce the deleterious and debilitating complications of type 1 diabetes.

The current study is designed to test the capabilities of the bionic pancreas system in a younger group of children during June through August of 2014 at the Joslin Diabetes Camp (boys) and the Clara Barton Diabetes Camp (girls). The success of the bionic pancreas in our previous camp study as well as our adult out-patient study leads us to test the device in a younger cohort with slightly less supervision and monitoring than in the previous camp study as described by this protocol.

II. Hypothesis and Specific Aims

We hypothesize that our wearable bionic pancreas can provide BG control in subjects age 6-11 years of age with type 1 diabetes using the estimated BG signal from a continuous glucose monitor (CGM) as the input signal to the controller in a diabetes camp environment that will minimally constrain the behavior of subjects while still allowing close observation for risk mitigation, high density data collection, and human factors analysis. The specific aims of this study are:

Aim 1. To test the safety and efficacy of the bi-hormonal bionic pancreas bionic pancreas that is mobile, wearable, and adaptive in regulating BG in youth 6-11 years of age in a diabetes camp environment.

The bionic pancreas will be compared to a comparator arm very similar to camp usual care in a crossover design in which each subject will serve as his or her own control. Each subject will be under bionic pancreas glucose control for five days and usual camp level of diabetes care for five days in random order with a one day washout period in between. The study will be carried out at the Clara Barton Diabetes Camp and the Joslin Diabetes Camp. Both camps are in North Oxford, MA and both are managed under the Barton Center for Diabetes Education with an integrated health care team and Medical Directors. Subjects will participate in the usual camp activities during the day, will eat the usual camp meals, and will stay in camp cabins at night. They will be fully integrated into the non-study population and will have blood glucose monitoring as usual during both bionic pancreas and comparator arms. Capillary BG checks for study subjects will be tested using an FDA approved and commercially available glucometer (Nova Biomedical StatStrip Xpress). Blinded continuous glucose monitoring will be done during the comparator arm. The primary outcome measures will be the difference between bionic pancreas and comparator arms in mean CGM glucose and the percentage of time with CGM glucose < 60 mg/dl on days 2-5. Secondary outcomes will include the number of hypoglycemic events requiring intervention with carbohydrate or rescue glucagon.

Aim 2. To document the interaction of the subjects with the bionic pancreas device for human factors analysis, with the goals of optimizing the user interface for the device.

Any problems with device functioning will be carefully documented with the efforts required for resolution. An electronic log will be created of all user interactions with the bionic pancreas device. Study staff will also document comments made by the subjects about the device over the course of the

study. The study staff's role will be observational, except for interventions required to maintain the safety of the subject (for instance, to treat hypoglycemia) and to maintain data integrity. There will be a brief survey for participants at the beginning of the study and at the end of the study to gather data on attitudes towards bionic pancreas BG control before and after an extended period of bionic pancreas control. This information will be used to assess user satisfaction with the device, and to document any specific complaints or suggestions for improvement.

III. Subject Selection

III. a. Inclusion Criteria

- Age 6-11 years with type 1 diabetes for at least one year
- Diabetes managed using an insulin infusion pump for ≥ three months
- Willing to wear two infusion sets and CGM sensor and change sets frequently (at least one new glucagon infusion set daily)
- Otherwise healthy (mild chronic disease such as asthma will be allowed if well controlled that do not require medications that result in exclusion)

No subjects will be excluded on the basis of gender or race. The requirement that subjects manage their diabetes using subcutaneous insulin infusion pump therapy is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

III. b. Exclusion Criteria

- Unable to provide informed consent, informed assent or parental consent
- Unable to comply with study procedures
- Current participation in another diabetes-related clinical trial that, in the judgment of the principal investigator, will compromise the results of this study or the safety of the subject
- End stage renal disease on dialysis (hemodialysis or peritoneal dialysis)
- Pregnancy (positive urine HCG)
- History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g. liver failure or cirrhosis). Other liver disease (i.e. active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the subject if it causes significant compromise to liver function or may do so in an unpredictable fashion
- Personal history of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma
- History of prolonged QT or arrhythmia, congenital heart disease or current known cardiac disease
- Acute illness (other than non-vomiting viral illness) or exacerbation of chronic illness other than T1D at the time of the study
- Seizure disorder, history of any seizure within the last two years, or ongoing treatment with anticonvulsants

- Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with second generation anti-psychotic medications, which are known to affect glucose regulation.
- Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference
- Use of oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) anti-diabetic medications
- History of adverse reaction to glucagon (including allergy) besides nausea and vomiting.
- Unwilling or unable to completely avoid acetaminophen during the comparator and bionic pancreas arms of the study
- History of eating disorder such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight
- History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment
- Any factors that, in the opinion of the principal investigator, would interfere with the safe completion of the study procedures

III. c. Source of Subjects

Subjects who fit the selection criteria will be considered as candidates for this study. Advertisements will be posted at the MGH Pediatric Diabetes Center and through the Barton email distribution list. Previous camp participants will be contacted through the Barton Camp Recruitment process. We will post basic information about the trial along with contact information on our website www.bioinicpancreas.org and www.clinicaltrials.gov. The study may be posted on the website of Children with Diabetes (a support and advocacy group), the Family Diabetes Network, and the Joslin Diabetes Center and University of Massachusetts Medical School websites. A letter will be sent to campers enrolled in the proposed weeks of camp study conduct, previous campers from past summers, and those interested in camp participation. Information on the trial may be posted on the camp website. We may also contact individuals who have previously inquired about participation in our studies and have asked us to keep their contact information on file.

IV. Subject Enrollment

IV. a. Number of Subjects

It is expected that we will have 24 subjects, 12 females and 12 males, complete the experimental protocol (5 days of bionic pancreas BG control). We will attempt to recruit participants in roughly equal numbers in the following age cohorts: 6-7 years, 8-9 years, and 10-11 years. We expect that the experiments can be accomplished over a period of 4 months. Up to 48 subjects with type 1 diabetes will sign the consent form in order to have 24 subjects complete the intervention portion of the study, 24 females and 24 males. In addition, up to 100 parents will give their verbal consent for the collection

of data from the camp records of their children. The upper bound is based on the expectation that some subjects will be excluded after the screening visit and the possibility that some experiments may have to be discontinued before completion (due to, for instance, intercurrent illness or subject withdrawal). Studies will be conducted sequentially at the two proposed sites.

We will also ask non-participants who are attending camp at the same time and who meet key criteria for study inclusion (age 6-11, use of insulin pump) for permission to review their camp records and to document pre-meal, pre-snack, bedtime, and midnight glucose values, as well as glucose interventions for hypoglycemia, and to get the result of their last A1c test prior to attending camp.

IV. b. Enrollment Procedures

Interested prospective participants' guardians will be briefed by a study staff member by phone regarding the study procedure and the inclusion and exclusion criteria. Potential subjects will be sent a packet containing a copy of the informed consent document by mail along with screening laboratory forms (to be used only after consent is obtained). They may also be sent an electronic copy of the packet via email. Subjects aged 7 - 11 will provide assent to participate in the study and their parent or guardian will provide consent. Subjects younger than 7 years of age will not be required to provide written assent, but their parent or guardian will provide consent. Study providers will evaluate the parent/child relationship by phone or by online video calls for signs of coercion and speak individually with subjects aged 6-11 to ensure they are personally interested in and able to comply with study procedures.

Non-participants will be asked for verbal consent at either camp intake or on the last day of camp. They will be given a one page information sheet and provide verbal consent.

IV. c. Consent Procedures

Once potential subjects have had time to review the consent document, they will either meet in person or have a telephone conference with a study physician or nurse practitioner who will explain the study, answer any questions, and administer informed consent. For all subjects the consent of a parent or legal guardian will be documented on the consent form, and the assent of the potential subject on the youth assent form.

In the event that a subject is a patient of one of the study physicians or nurse practitioners, another study physician or nurse practitioner will answer questions and administer consent.

Due to the great deal of interaction between the subject and camp study personnel, all subjects enrolled in the study must be able to speak and understand English sufficiently. In the event that a minor who is interested in our study and sufficiently speaks English but their parents do not speak English, parents may give permission to enroll their child through use of a "short form" following the guidelines set forth by the PHRC.

When consent is obtained by phone, subjects and/or subject guardians will sign and date both forms and return to our office at MGH. Telephone consent will be documented on a case report form. Once we receive the signed consent forms, we will sign both and send the subject one copy and keep one

copy for our files.

The study physician or nurse practitioner will also answer any questions that the subject may have during their participation. They will share any new information in a timely manner that may be relevant to the subject's willingness to continue participating in the trial. The subjects may choose to discontinue their participation at any time. Subjects and subject guardians will be informed that obtaining screening labs does not necessitate or guarantee participation in the study.

Non-participants will receive a one page information sheet. They will have the opportunity to ask a study staff member any questions they may have. Verbal consent will be obtained and documented in a confidential log. Non- participant data will be de-identified using a numeric code for each camper. The non-participant will be asked to complete a medical release form in order to obtain their most recent HbA1c result from their endocrinologist.

V. Study Procedures

Note that these study procedures apply only to study participants. The involvement of consenting non-participants will be limited to a retrospective review of their chart. They will have no direct contact with study staff, will not interact with study devices or drugs, and there will be no modification or real-time monitoring of their camp care.

V. a. Screening data

- Age
- Sex
- Race and ethnicity
- Date of diabetes diagnosis
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription) and date of last change in medication regimen
- Duration of insulin pump use
- Average total daily dose of insulin in the last 30 days (by report via phone screening)
- Weight by report via phone screening
- Hemoglobin A1c (if a value in the last 3 months is not available, one will be obtained at the start of the study)

V. b. Drugs

The bi-hormonal study involves subcutaneous administration of insulin lispro (Humalog, Lilly) and glucagon (Lilly). Both are commercially available by prescription and are indicated for patients with type 1 diabetes.

The control system can administer bolus doses of each drug up to every five minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose [30 µl] and a single meal-priming

dose, which is triggered by the user, will not exceed 12 units [120 µl]. A single bolus of glucagon will not exceed 80 µg [80 µl]. The insulin pumps can administer as little as 0.5 µl (0.05 units of U-100 insulin or 0.5 µg of 1 mg/ml glucagon) in single programmable bolus doses.

It is expected that the total daily dose of glucagon will be less than 1000 µg. The recommended dose of glucagon for a patient suffering from severe hypoglycemia is 1000 µg as a single injection. Mean glucagon levels in our previous bionic pancreas studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of subjects is expected to be modest.

V. c. Devices

Infusion sets:
Subjects will wear two FDA approved commercially available infusion sets in the subcutaneous area of the abdomen, buttocks, arms or legs; one for insulin infusion and one for glucagon infusion. If an infusion set falls off or is clinically suspected of failing, it will be replaced with a new one. The insulin set will be changed every 48 hours and the glucagon infusion set will be changed every 24 hours. The infusion sets can be placed on the subcutaneous area of the abdomen, buttocks, arms or legs.

Continuous glucose monitors:
One transcutaneous glucose sensor for the DexCom G4 Platinum AP will be inserted in subcutaneous tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly to the G4 receiver. If the G4 sensor fails for any reason during the experiment it will be replaced promptly (within 1 hour). The sensor can be placed on the subcutaneous area of the abdomen, buttocks, arms or legs..

Bionic Pancreas Control Unit:
The control unit consists of a stock iPhone 4S and a DexCom G4 Platinum AP receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.

The iPhone runs iOS 6 in "Guided Access" mode, where the only app accessible to the subject is the Beta Bionics app, which runs the control algorithm. Access to other functions on the iPhone (namely, the home screen and the Settings app) is password protected. This prevents accidental activation of other apps that could interfere with the function of the bionic pancreas. The control algorithm app has a graphical user interface (GUI) that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

The target BG for the bionic pancreas is 100 mg/dl by default (used for all previous studies), but a new feature allows the user to designate a higher target, up to 130 mg/dl. A higher target can be set indefinitely, or for a limited time with automatic expiration. When a temporary target it set, upon expiration the target will revert to the previous indefinite target, which may be greater than 100 mg/dl. Although our previous studies showed that the bionic pancreas decreased hypoglycemia and the need

for carbohydrate interventions relative to usual care, this will allow subjects to raise the BG target for additional safety during periods when hypoglycemia would be particularly problematic, such as when driving or otherwise unable to check or attend to their BG for a period of time, or periods when hypoglycemia is more likely, such as during exercise. It may also be used to raise the mean BG if the mean is unnecessarily low (some subject in earlier trials had 5-day averages as low as 105 mg/dl) and the user prefers to further reduce the risk of hypoglycemia. The use of this feature will be entirely optional – it will be presented to subjects as an option that they may use or not, as they wish. This feature is intended for use by the wearer, if an adult, or by the parent or guardian, if the patient is a child, so this feature will not be used in this study.

The user will also have the option to trigger the administration of a glucagon dose, intended to be used prior to device disconnection (e.g. for a shower or swimming). The size of the glucagon dose will be automatically determined by the bionic pancreas based on the subject's body mass and will be between 40 and 80 micrograms. This option will provide a means for subjects to raise their BG if they anticipate they will be at risk for hypoglycemia during a period of disconnection, based on their BG and BG trend at the time. This feature is intended for use by the wearer, if an adult, or by the parent or guardian, if the patient is a child. In this study, this feature will only used by a camp or study nurse. .

The GUI also displays visual alarms associated with an audio signal if communication is dropped between the CGM transmitter and the bionic pancreas control unit or between the control unit and the two insulin pumps. It also displays an alarm associated with an audio signal when the CGM glucose crosses a low threshold of 50 mg/dl (in both bionic pancreas mode and when used in passive monitoring). These alarms may be configured so that they require the entry of a code to dismiss.

The iPhone communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with two Tandem t:slim insulin pumps to deliver insulin and glucagon.

The bionic pancreas control unit can be used with two Tandem pumps to make up the bionic pancreas. It can also be used on its own to record blinded CGM data. In both configurations, if communication failures causing alarms are not resolved within15 minutes, they trigger alerts to study staff, who can then find the wearer and correct the problem. Also in both configurations, if the CGM glucose drops below 60 mg/dl and the user does not enter a BG into the bionic pancreas GUI within 15 minutes, this will trigger an alert to study staff, who can then make contact with the wearer according to the study protocol.

Tandem t:slim Pumps:
These pumps are FDA approved insulin pumps with reservoirs capable of holding 300 units (3 ml) of insulin or 3 ml of a glucagon solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~ 33 µl per minute (2 ml per hour). They are slave to the bionic pancreas control unit and are controlled wirelessly via the BTLE protocol by the iPhone 4S.

Nova Biomedical StatStrip Xpress Blood Glucose Meter:
The Nova Biomedical StatStrip Xpress is an FDA approved and commercially available blood glucose meter. Blood glucose measurements will be obtained via fingerstick with the StatStrip Xpress per camp schedule during the comparator arm and at least seven times per day during the bionic pancreas arm. Standard care at camp is for BG to be checked at least six to seven times per day so this will follow a similar regimen with (occasionally) only one to two extra readings per day. StatStrip Xpress measurements will also be used to calibrate CGM devices during the comparator and bionic pancreas

arms.

V. d. Experimental Procedures and Data Collection

V. d. i. Screening Visit:

- All subjects will have a screening visit either in person or by phone to confirm eligibility
- The subject will be interviewed and the case report form will be completed by a study nurse or study physician to establish whether the subject is eligible
- If a laboratory hemoglobin A1c drawn within 3 months of the time of screening is not available, one will be obtained.
- If the subject is post-menarche, a urine HCG will be obtained prior to study start. A positive pregnancy test will be reported to both the subject and parent.
- A study physician or nurse practitioner will review the case report form to determine subject eligibility

V. d. ii. Randomization of Visit Order

Once the eligibility of subjects has been established, they have confirmed that they will participate, and the subject has been consented, the order of the usual care monitoring and bionic pancreas visits will be randomized in blocks of two subjects.

V. d. iii. Summary of Normal Camp Policies and Procedures

During the comparator arm of the study, the usual camp procedures will be followed. The full medical policy manual is provided as Appendix C, but a summary is provided here for context. Note that this policy provides guidelines for camp staff, but it not always followed strictly. Only modifications to practice that could affect the safety of the subject or integrity of the data will be listed as deviations. In the event of a change in camp policy, the study will follow the new camp policy so that there is no distinction between the treatment of study subjects and non-participants except as specifically stipulated in the experimental protocol. During the bionic pancreas arm, the usual camp procedures will be followed except as explicitly noted in the protocol.

Opening Day:

- Campers check in
- Review of insulin regimen by resident camp physician who writes insulin orders
- Basal rates typically decreased by approximately 20%
- Carbohydrate ratios and correction factors usually unchanged, but target BG is changed to 120 mg/dl during the day and 150 mg/dl at night

Daily Routine:

- Breakfast ~7:30 AM on weekdays, 8:00 AM on weekends**

- Activity*
- Activity*
- Lunch 12:00PM**
- Activity*
- Activity*
- Dinner 5:45 PM**
- Activity*
- Snack 8:30 PM**
- 12:00 AM BG check (routine)
- 3:00 AM BG check if 12:00 AM check required intervention

*Activity periods are divided by intensity into More Active and Less Active categories. Campers typically have two More Active and two Less Active periods daily.

**BG checks are done 10–30 minutes before meals/snacks with insulin bolus 10–15 minutes before meals.

Nutrition:
The menu is developed prior to camp and assessed for balance and compliance with the USDA's nutritional requirement suggestions. Alternative menu options are provided for restricted diets and food allergies. During each session, the dietitian intern will continue to evaluate the meal choice for nutritional breakdown and impact on blood sugar readings and activity levels. In addition, the dietitian works closely with the kitchen staff to assure healthy food options and preparation as well as provide an accurate carbohydrate count for insulin dosing. The dietitian intern is responsible for connecting with families regarding dietary restrictions and food allergies. Meals are served family style.

Medical supervision:
The resident camp physician and health care team will review the camper chart and develop guidelines and a plan of care. The camp healthcare provider is responsible for health care needs and supervision of insulin administration. Tasks may be delegated as per Massachusetts Department of Public Health and the Nurse Practice Act. A resident camp physician is on site and is available by cell phone or satellite phone in cases of emergency or camper illness.

Blood sugar monitoring:
BG is checked prior to each meal, snacks and at 12:00 AM. There may be additional BG checks between midnight and 6 AM as determined by the resident camp physician.

Ketone monitoring:
Blood or urine ketones are checked when BG readings are ≥ 250 for two consecutive checks during the day, once at night or with complaints of illness. Blood ketone results are preferred when a camper is on Depokote, and cases of suspected diabetes ketoacidosis.

Pump failures:
Contact the resident camp physician or on-call physician for orders regarding change in diabetes management. Inform the camper's parents if the pump is defective and needs to be replaced.

Hyperglycemia management, BG is ≥250 mg/dl for two consecutive checks during the day, once at night or with complaints of illness :

- Check ketones (urine or blood)
- Negative ketones (trace urine ketones, < 0.6 mmol/l blood ketones)
  - Give a correction to the ordered target (typically 120–150) and increase fluids
  - May continue activity
  - Recheck in 1 hour if the blood sugar is coming down, recheck in another hour until BG < 250 mg/dl
  - If the blood sugar is going up, give the correction by injection and change the pump site
- Positive ketones (small urine ketones or ≥0.6 mmol/l blood)
  - Change the pump site and increase fluids
  - Give insulin correction by injection to ordered target (typically 120–150 mg/dl).
  - Obtain hourly blood glucose readings
  - Discontinue activity until ketones have cleared
  - Notify the physician of blood sugar reading >300 mg/dl and anytime there are positive ketones

Hypoglycemia preparedness:
Hypoglycemic reaction kits are located in each gathering location and are also carried by each member of the health care team. Reaction kits include: alcohol pads, single-use lancet device, glucometer, strips, cotton ball, reaction slips, pen, glucose tabs, juice or glucose gel, complex carb appropriate for nut allergies and celiac disease. Glucagon kits are available at the infirmary.

Mild hypoglycemia (mild signs and symptoms or BG 60–80 mg/dl, able to self treat):
- Give15 gm of rapid-acting carbohydrates (glucose tabs, juice, milk, gel, etc.)
- Wait 15–20 minutes and recheck BG
- If BG is >70 mg/dl, give15 grams of complex carbohydrate (typically snack crackers with peanut butter or cheese). Omit the 15 grams of complex carbohydrate if a meal or snack is scheduled within one hour
- If BG is <70 mg/dl, restart treatment algorithm

Moderate hypoglycemia (having difficulty treating self or BG<60 mg/dl):
- Treat with 15 gm glucose (gel, juice, glucose tabs) or low dose glucagon
- Low dose glucagon dosing:
  - 10 units for ages 10 and under
  - 15 units for ages 11–15
  - 20 units for ages > 15
- Consider setting a temporary basal rate of 0% for 60 minutes
- Wait 15–20 minutes and recheck BG
- If BG is > 70 mg/dl, give 15 gm of complex carbohydrate
- If BG is < 70 mg/dl, restart treatment algorithm (may repeat low dose glucagon once)

Severely impaired or unresponsive (does not follow commands or seizure activity):
- Attempt instant glucose in the cheek while waiting for health care team to arrive
- Suspend the pump or disconnect from the pump (do not remove the site)
- Administer glucagon 0.5 mg (for age 10 and under) and 1 mg (over the age of 10)
- Wait 15–20 and recheck the BG
- If the BG is>70 mg/dl after glucagon treatment and patient is alert enough to swallow, give water or sugar containing liquid before complex carbohydrates to assess vomiting
- Recheck BG in 15 minutes

- Continue to monitor blood glucose readings at least once per hour until individual is no longer vomiting and BG levels are stable
- If the BG is not rising, there is a need to repeat glucagon, or the camper continues having a seizure, the physician on site may consider calling 911 for assistance
- Notify the parent/guardian (if in the middle of the night, wait until the morning)

Hypoglycemia Prevention:

- Snacking for physical activity:
  - 30–40 grams for hiking
  - 15–20 grams for adventure activities like kayaking
- For impending hypoglycemia:
  - Treat with 15-20 gm of fast-acting carbs or low-dose glucagon, suspend activity for 15 minutes
  - Recheck BG. If blood glucose is trending up, eat a small snack with protein or a meal. If not, repeat fast-acting carbs or may repeat low dose glucagon once
- For especially intense physical activity:
  - Aim for a blood glucose target of 150–180 prior to activity
  - Pump: Set a reduced temporary basal of 50–75%for one hour before and up to 4 hours after the activity
  - If BG > 200 mg/dl, do not adjust insulin dose but monitor blood glucose throughout the activity. Consult with the physician prior to correcting the blood sugar.
  - If blood glucose is ≥ 300, correct the blood sugar to 200.
  - If ketones are present, do not exercise until they clear.

Meal and daytime snack insulin doses:

- Insulin dosing per resident camp physician orders

BG (mg/dl)	Treatment
> 80 mg/dl	Bolus/injection 15–20 minutes prior to the meal or snack
< 80 mg/dl	Treat low BG as usual and bolus for the meal at the table

Bedtime snack insulin management:

- Insulin dosing per resident camp physician orders

BG (mg/dl)	Treatment (based on 30 g carbohydrate snack)
< 70	Double snack (no coverage)
70–99	Free snack (no coverage)
100–149	One-half usual coverage for snack
150–199	Cover the snack, do not correct BG
≥ 200	Cover the snack, correct BG to 150 mg/dl

V. d. iii. Study-specific Procedures

General Policies:

- Subjects will be integrated with the other campers' accommodations. During bedtime hours study staff will have the ability to access all cabins so that they can respond to any issues or emergencies that may arise.
- Subjects will bring any routinely used medications. The camp will be responsible for dispensing

medications other than insulin and glucagon during the bionic pancreas arm of the experiment. During the comparator arm, all medications will be dispensed by the camp.

- Any medical advice needed by the subjects during their participation that is not directly related to BG control during the experiment should be obtained by them in the usual manner at camp.
- Subjects may take any over-the-counter medications that are recommended by the camp physician during the trial except acetaminophen, which will not be allowed due to potential interference with CGM sensing.
- If a subject develops an illness during the experiment camp guidelines will be used for sick day management. If vomiting occurs, a study physician or nurse practitioner will be notified and will evaluate the subject in person.
- Camp nurses will be responsible for diabetes care of the all campers including participants with the exception of calibrating CGMs, filling t:slim pumps, changing infusion sets during the bionic pancreas arm, initiating and troubleshooting the bionic pancreas device and responding to monitor alerts, all of which will be performed by research study staff.

Remote Monitoring During Both Study Arms

- The system will generate a local alarm for low (<50 mg/dl) threshold CGM glucose values. The monitoring station will receive an alert when the CGM glucose has been below 60 mg/dl for 15 minutes without a BG measurement being entered into the system, prompting study nurses to find the camper and check a blood glucose. The system also generates alarms if the wireless connection between the CGM transmitter and the bionic pancreas has been lost and has not spontaneously reconnected (after 15 minutes, both study arms) or if the wireless connection between the bionic pancreas control unit and a Tandem pump has been lost and has not spontaneously reconnected within 15 minutes (bionic pancreas arm). A central monitoring station that will be staffed 24 hours a day and will dispatch a study staff member to evaluate the subject in response to any of these alarms.

Surveys To Evaluate Attitudes, Expectations, and Satisfaction With the Bionic Pancreas

- Subjects will complete a survey after arrival at the camp and before starting either of the two study arms that will evaluate their attitudes and expectations regarding the bionic pancreas and participation in the trial, their self-perceived health, and the degree to which diabetes interferes with their daily life.
- Subjects will complete another survey after completing each of the two study arms (Bionic Pancreas and Comparator) that will evaluate their satisfaction with the care provided during the preceding period, their self-perceived health, and the degree to which the care interfered with their enjoyment of camp. After the bionic pancreas arm they will answer questions about their impressions of the bionic pancreas.

Bionic pancreas and Comparator Visit Day 1 – DexCom G4 Platinum AP **Sensor Placement:**

- Subjects will check in to the camp on the usual start day (Sunday), but will be asked to arrive no later than 10:00 AM so that a G4 sensor can be placed before noon.
- Female subjects post-menarche will provide a urine sample for urine pregnancy testing. If the test is positive, the subject and legal guardian will be informed of the result and they will be excluded from participating.
- Study staff will endeavor to place the DexCom G4 sensor as soon as possible, and in all cases before 11:30 AM. The sensor can be placed on the subcutaneous area of the abdomen, buttocks, arms or legs. The sensor will be linked to the CGM receiver in the bionic pancreas

control unit.

- Height, weight, blood pressure and temperature will be measured. A brief history and physical will be performed by a study physician or nurse practitioner.
- Initial calibration (at 2 hours after placement, in almost all cases before 1:30 PM) will be performed by the study staff using the StatStrip Xpress meter.
- The staff will start the bionic pancreas as close as possible to a minute divisible by 5 minutes (i.e. on a 5-minute mark) and before 2:00 PM.

CGM Monitoring during the Comparator Arm Days 1–6 (5 days):

- An additional calibration will be performed by the study staff just before study start using the StatStrip Xpress meter.
- The G4 CGM system will be blinded to the subjects during the comparator arm. This will ensure that subjects will not use this data to modify their BG control strategy. However, subjects will be encouraged to use their own CGM in the usual manner if they have one.
- The experimental period will begin at 3:00 PM on the first day of the camp session (Sunday).
- Over the next five days (3:00 PM Sunday to 3:00 PM Friday) subjects will have their BG managed according to the camp's policies. All BG measurements will be performed by study staff or camp healthcare providers with the StatStrip Xpress device. Study staff will calibrate the G4 before breakfast and before supper with the StatStrip Xpress BG meter.
- During the experiment the bionic pancreas control unit (blinded) will be worn by the subject or kept nearby (such as when sleeping) at all times to ensure good radio-frequency signal reception. The device may be removed for short periods of time (no more than 30 minutes) for showering and swimming.
- If during the course of an experiment, a DexCom G4 sensor fails (reports sensor failure, ceases to transmit data, reports multiple calibration failures, or reports questionable data) a new sensor will be inserted and calibrated.
- Camp nurses will be asked to document all BG measurements and any carbohydrate interventions for hypoglycemia. Low BG will be treated as usual according to the camp protocol.
- If the CGM glucose is < 60 mg/dl and no BG has been entered into the bionic pancreas within 15 minutes, a nurse will be sent to find the subject, check their BG, and administer carbohydrate if appropriate according to the camp protocol.
- As a difference from the camp usual care protocol, BG levels will be measured at midnight and ~3:45 AM (regardless of the value at 12:00 AM) using the StatStrip Xpress point of care BG meter. No insulin will be given for hyperglycemia at the ~3:45 check unless the 3:45 check was specifically ordered by a camp physician so that the act of monitoring the subjects does not change their care. Extra BG checks may be performed depending on how many episodes of hypoglycemia occur (which trigger more frequent measurements), or on order of the resident camp physician.
- If subjects use non-insulin injectable drugs to manage their diabetes (e.g. GLP-1 agonist drugs such as exenatide and liraglutide, or the amylin analog pramlintide) will be encouraged to do so during the usual care period. However, they will not be allowed to use them during the bionic pancreas arm of the study.
- At 3:00 PM on Day 6 (Friday) the comparator arm of the experiment will end. The DexCom CGM will be removed.
- The subject's insulin pump will be downloaded for information on insulin dosing and carbohydrate intake during the comparator arm.

Bionic pancreas Blood Glucose Control Days 1–6 (5 days):

- A member of the study staff will be monitoring the functioning of all bionic pancreas devices via telemetry (CGM streaming, algorithm operation, Bluetooth connection to the pumps) around the clock, although they will not have access to the CGM glucose information. The staff monitoring telemetry will be able to communicate with camp healthcare providers by radio or cell phone and there will be a study "runner" on call to deal with any issues that may arise with functioning of study device.
- Subjects will continue their normal basal insulin infusion through their own pump until the bionic pancreas is initiated on the first day of camp (Sunday).
- The reservoir of one of the Tandem infusion pumps will be filled with insulin lispro (Humalog, U-100) according to the manufacturer's instructions and the reservoir of the second Tandem infusion pump will be filled with glucagon prepared from a Lilly kit (Lilly glucagon, 1 mg/ml) according to the manufacturer's instructions. These infusion pumps and associated tubing and infusion sets will be labeled with the drug they contain. The insulin reservoir in the pump will be replaced every 48 hours. The glucagon reservoir will be replaced every 24 hours with one that contains freshly reconstituted glucagon prepared from a new Lilly kit according to the manufacturer's instructions. We have received an Investigational New Drug (IND) exemption from the FDA for use of glucagon in this application for up to 27 hours.
- Two infusion sets that are FDA approved for subcutaneous insulin infusion will be inserted in the abdomen, buttocks, arms or legs and infusion sites will be labeled. The infusion sets will be connected to the Tandem t:slim infusion pumps, one site for insulin and one for glucagon. The standard priming sequence will be performed according to manufacturer's instructions. The glucagon infusion set will be changed every 24 hours. The insulin infusion set will be changed at least every 48 hours. If an infusion set falls off or fails, a new infusion set will be placed immediately. BG values will be checked hourly during the period without streaming CGM information and will be entered into the bionic pancreas.
- The control algorithm will be initialized only with the subject's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the bionic pancreas (DexCom G4 Platinum AP, iPhone running the control algorithm, Tandem t:slim infusion pumps) are in good communication with each other.
- Just before the bionic pancreas is initiated, the subject's own insulin infusion pump will be stopped and disconnected, its infusion set will be removed, and bionic pancreas control will begin.
- There will be two RNs and one NP or MD provider on site at all times during the daytime and at least one RN and one NP or MD provider on site at all times at night. These study staff will be in addition to the camp providers, which consist of two camp physicians, one charge nurse, and one nurse or nursing school graduate (RN/NG) per cabin of campers.
- The DexCom G4 Platinum AP will not be blinded during the bionic pancreas study arm; the subject will be able to see CGM streaming. Subjects may ask for a BG check at any time based on their CGM data (or for any other reason) and will be treated based on the BG value obtained per usual camp protocol.
- During the day there is always one camp RN/NG with each group of campers wherever they are as a part of usual camp care. Campers may be grouped with their cabin mates or may be grouped with similar aged campers based on their choices for activities. During activities the camp RN/NGs set up a testing/hypoglycemia treatment station for that activity and monitor all of the campers doing that particular activity. In some cases when an activity has more than one cabin worth of campers, two RN/NGs may be assigned to the group. Each group of campers also has at least one counselor with them at all times, which allows the camp RN/NGs to focus

entirely on medical care.

- Study RNs and MD/NP providers will be available to assist in the routine camp monitoring of study subjects.
- During activity periods the subjects may be in up to five locations based on camp activities. During those times the study RNs will circulate between the locations where study subjects are located, focusing more time on activities that are more vigorous.
- There is no area of the camp that is commonly visited by campers that is more than ~ 300 yards from any other area, so it will be easy for study staff to circulate and to get from one area to another if needed. Under the unusual circumstances when campers go further than this (i.e. for a hike) a study staff member will accompany that group carrying all needed study-specific supplies. A camp RN/NG will also accompany such groups. The remaining members of the study team will remain at the main camp area.
- Before disconnecting from the device for shower:

CGMG	Treatment
< 120 mg/dl	Initiate a glucagon microburst or 15g snack (done by camp or study staff)
≥ 120 mg/dl	No action

  Note that the confirmation that the glucagon microburst was delivered should be confirmed by checking the front screen before the glucagon pump is disconnected (will take a maximum of 5 minutes depending when in the control cycle the command is given).
- Over the next five days (3:00 PM Sunday to 3:00 PM Friday) the bionic pancreas will control insulin and glucagon dosing and the subjects will otherwise be treated according to camp guidelines except for specifically noted exceptions in the protocol.
- During the experiment the bionic pancreas device will be worn by the subject or kept nearby (such as when sleeping) at all times to ensure good radio-frequency signal reception. The device may be removed for short periods of time (no more than 30 minutes) for showering and swimming.
- Meals will be announced to the control algorithm 15-20 minutes prior to the meal at the same time as meal boluses are delivered for other campers.
- Camp nurses will be asked to document all BG measurements and any carbohydrate interventions for hypoglycemia. Low BG will be treated as usual according to the camp protocol.
- If the CGM glucose is < 60 mg/dl and no BG has been entered into the bionic pancreas within 15 minutes, a study nurse will be sent to find the subject, check their BG, and administer carbohydrate if appropriate according to the camp protocol.
- We will ask parents/guardians to provide information regarding what is a typical small bite, smaller than usual, usual, and larger than usual meal for their child. We will then produce a subject specific range for each of these and note it in their chart. Study staff of camp RN/NGs will assist the subjects in announcing their meals based on the known carbohydrate content and these pre-determined ranges during the bionic pancreas period of the study.
- BG levels will be measured at approximately midnight and at ~3:45 AM. These measurements will be done in both bionic pancreas and comparator arms of the study. No insulin will be given for hyperglycemia based on ~3:45 checks unless the 3:45 check was ordered by a camp physician to maintain parity with the treatment of non-participants.
- The subject will be free to participate in all camp activities with the exception of any activities that require leaving camp grounds such as horseback riding.
- Regardless of location, camp healthcare providers will be able to reach subjects on short notice. Camp healthcare providers will have basic training on the bionic pancreas system and the key

elements of the protocol. They will keep a charged cell phone or radio with them at all times. If they have a question they will be able to immediately contact study personnel monitoring remotely. If the question or issue cannot be resolved over the phone, a study staff "runner" will be sent to the location. If there is a medical problem that cannot be resolved according to study protocol or camp medical procedures, they will call 911 immediately and provide their location.

- The camp healthcare provider will carry carbohydrates for hypoglycemia treatment and glucagon rescue kits for hypoglycemic emergencies. The central monitoring site will have spare insulin lispro, pump supplies, DexCom G4 sensors and transmitters, and bionic pancreas control units. If there is a problem with the bionic pancreas device, study staff will be called and will troubleshoot the system or replace devices as needed.
- Camp healthcare providers or counselors for each cabin will assist campers as required to announce their three main meals (but not snacks) to the bionic pancreas by indicating approximate meal size on one of the input screens on the device interface. The indicated meal size will be based on the report of typical meal sizes from the subject and their parents, study-specific information obtained during the check-in process, and the number of carbohydrates chosen by the subject for that meal. The bionic pancreas will then provide some of the insulin for the meal. The algorithm chooses the meal-priming bolus size using an adaptive algorithm that attempts to provide 75% of the insulin for meals of a similar size eaten at the same time of day in the past. The initial parameters are conservative and weight based and adapt over time.
- Snacks and carbohydrate interventions for hypoglycemia will not be announced to the bionic pancreas.
- Camp healthcare providers and counselors will carry any snack items needed for hypoglycemia. Study staff following patients will also have emergency supplies available including oral carbohydrates and glucagon kits.
- If there is an interruption in the DexCom G4 Platinum AP CGM output the bionic pancreas will automatically switch to giving basal insulin based on historical basal insulin needs at that time of the day. If the failure occurs early in the experiment before 24 hours of historical data has been accumulated by the device, the basal rate will be primarily based on the subject's weight. In addition, any BG measurements entered into the bionic pancreas will be used to dose insulin and glucagon as if they were CGM values and the system will continue to accept meal announcements.
- BG measurements will be performed hourly during interruptions in CGM output and will be entered into the bionic pancreas. The camp physician may order a reduction in basal insulin rate during periods without CGM input by up to 50% if they believe that the historical basal rate will be inappropriate for the subject based on a large difference in circumstance between those obtaining on previous days at the same time and the current period.
- If there is an interruption in the DexCom G4 Platinum AP CGM output, study staff will assist the subject in recovering CGM data streaming. This may involve forced calibrations or replacement of the sensor and calibration. Once it is back online, bionic pancreas BG control will resume automatically. During periods of CGM downtime, the BG may be checked up to hourly on a routine basis and more frequently based on clinical concern for hypoglycemia.
- Anytime a CGM sensor is lost or stops functioning it will be replaced within 1 hour.
- If there is a complete failure of bionic pancreas operation, BG control will default to usual care camp protocol and subjects will use their own insulin pump (which will be stored by the study staff) until the bionic pancreas can be brought back online.
- The DexCom G4 Platinum AP CGM will be calibrated each morning before breakfast and each evening before dinner using the StatStrip Xpress meter IF it is a good time to calibrate. A good time to calibrate means no glucagon boluses in the last 15 minutes and no carbohydrate intake

in the last 30 minutes (i.e. at least 30 minutes after the conclusion of a meal or a carbohydrate treatment for hypoglycemia). These conditions are intended to reduce the likelihood of performing a calibration when there are rapid changes in BG and when there are changes in BG that are not yet reflected in CGM glucose due to physiologic lag.

- Additional calibrations may be performed if the following criteria are met:
  - If the CGM reported value does not meet the ISO standard (< 15 mg/dl difference for BG values < 75 mg/dl, < 20% absolute difference for BG values > 75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes) a calibration will be performed.
  - If it is NOT a good time to calibrate, then at the next good time to calibrate a BG check will be performed and a calibration will be performed IF and ONLY IF the CGM is still not compliant with the ISO standard at the time of that additional BG check. This will avoid forcing extra calibrations when a large disparity between the CGM value and BG was due to the physiologic lag between BG and interstitial fluid glucose.
- If subjects use non-insulin injectable drugs to manage their diabetes (e.g. GLP-1 agonist drugs such as exenatide and liraglutide, or the amylin analog pramlintide) will be encouraged to do so during the usual care period. However, they are not allowed to use them during the bionic pancreas arm of the study.
- At 3:00 PM on day 6 (Friday) the bionic pancreas arm of the experiment will end. Infusion sets and CGM sensor will be removed. Subjects will insert one of their own infusion sets and start their own basal insulin rate. Blood glucose control will then resume under usual care camp protocols.

Transition Between Study Arms:

- After the first arm of the study is completed on Friday at 3:00 PM, subjects will go back to usual care camp protocols until Sunday morning, when a new DexCom G4 CGM sensor will be placed by noon.
- Subjects who were randomized to the bionic pancreas arm will switch to the comparator arm in the second week, and vice versa.

V. e. Response to Hypoglycemia

- All subjective symptoms of hypoglycemia will be investigated with a capillary BG using a StatStrip Xpress meter.
- Subjects in both of the study arms (bionic pancreas and comparator) will take carbohydrates to treat hypoglycemia or symptoms consistent with hypoglycemia according to the usual camp protocol.
- Camp healthcare providers and camp counselors will have rapid acting and complex carbohydrate interventions readily available to them at all times. All carbohydrate treatments for hypoglycemia will be documented by study staff (amount and time).
- In any case in which two rapid-acting carbohydrate interventions must be administered by camp protocol or if glucagon is administered manually by injection, a study staff member will check the operation of the bionic pancreas system. Consideration will be given to replacing the glucagon infusion set and/or recalibrating the CGM.
- If the subject experiences a seizure or unconsciousness associated with a hypoglycemia their

participation in the study will be discontinued.

V. f. Response to Hyperglycemia

- Any time a ketone check is mandated by camp protocol the bionic pancreas system will be checked for any malfunction and any such problems will be corrected. The insulin infusion set will be replaced if mandated by camp protocol or if there is any doubt as to its proper functioning.
- If no correctable fault is found, but there is doubt regarding the correct function of the bionic pancreas system, an entirely new backup bionic pancreas system may be started.
- While the new system is being replaced and calibrated the subject may use their own pump according to usual care camp protocols.
- If the blood ketone result is $\geq$ 0.6 mmol/dL a study physician or nurse practitioner will be notified and will evaluate the subject in person. The only modification to the usual camp protocol is that subjects in the closed loop arm will not get an injection of insulin by syringe if blood ketone result is $\geq$ 0.6 mmol/dL as long as any fault with the bionic pancreas system has been corrected.
- If the subject experiences diabetic ketoacidosis requiring hospitalization their participation in the study will be discontinued.

V. g. Response to Nausea/Vomiting and Other Medical Needs

- Minimal nausea was noted in clinical trial of the bi-hormonal bionic pancreas system to date. In most cases, nausea that occurred did not correspond in time to dosing of glucagon, which is intermittent. However, nausea is a potential side effect of glucagon.
- If vomiting occurs in the setting of glucagon administration (e.g. within 15 minutes of the last dose of glucagon) a study physician or nurse practitioner will be notified and will evaluate the subject in person.
- If the subject experiences any non-emergent medical concerns outside the scope of diabetes care, he or she will see the camp physician. If the subject experiences urgent or emergent medical concerns outside the scope of diabetes care and camp physicians, the camp will escort the subject to a local emergency room or call 911 according to camp protocol. If a subject in the bionic pancreas arm of the study is transported away from the camp site for any reason, they will be transitioned to open-loop usual care and their participation in the study will be suspended until they return.
- If the subject experiences persistent nausea and vomiting thought to be related to glucagon dosing their participation in the study will be discontinued.

V. h. Monitoring of Closed Loop Device Performance

- Co-investigators (and bionic pancreas inventors and developers) Edward Damiano, Firas El-Khatib and/or an engineer trained by them will be readily available by phone for consultation at all times during the course of each experiment and will be able to reach the camp within 1 hour to troubleshoot if necessary.

- They will have the capability of viewing diagnostic information about the bionic pancreas functioning remotely during the experiment, in order to monitor and assist in any needed troubleshooting.
- The connection will be secure and password protected, and will be set up so that only viewing of the screen is possible - no input or changes to the controller can be made remotely.
- For privacy reasons, no audio or video connection will be made to the iPhone.
- Real-time monitoring of the bionic pancreas device will be limited to the functioning of the device, including streaming of CGM data, regular stepping of the bionic pancreas algorithm every 5 minutes, and connectivity of the iPhone with the pumps. These are possible sources of device failure that will not be present in future, fully integrated versions of the device. The CGM glucose information will not be monitored in real-time because we do not envision monitoring this information in future trials.

V. i. Supervision by Study Staff

A study physician or nurse practitioner will be available at the camp at all times during the course of each experiment. Trained study staff will also be continuously monitoring the function (but only the function, not the CGM glucose values) of each bionic pancreas via remote telemetry 24 hours a day throughout the experiment from a central location in the camp. The clinicians will also have the capability of remotely viewing the function information on their iPhone or iPad and evaluating diagnostic information during the experiment to facilitate clear communication with nurses.

VI. Biostatistical Analysis

VI. a. Data Collected

Prior to start of experiment:

- Age
- Sex
- Race and ethnicity
- Urine HCG for female subjects post-menarche
- Date of diabetes diagnosis
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription) and date of last change in medication regimen
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
- Average total daily dose of insulin in the last 30 days as available (from pump history)
- Duration of insulin pump use
- Weight, height, and blood pressure
- Hemoglobin A1c
- History of personal use of CGM
- Completion of a survey

During the monitoring of comparator arm:

- CGMG (CGM glucose) every five minutes from the DexCom G4 Platinum AP CGM
- StatStrip Xpress BG measurements before meals, bedtime, 12:00 AM and ~3:45 AM
- Any additional StatStrip Xpress BG values
- Estimated carbohydrate intake (from camp healthcare provider documentation)
- Number of hypoglycemic events (BG < 70 mg/dl, from camp healthcare provider documentation)
- Number of carbohydrate interventions for hypoglycemia (from camp healthcare provider documentation)
- Total daily dose of insulin (from insulin pump download)
- Self report of nausea and vomiting
- Body weight at the beginning and end of the comparator arm
- Time without CGM monitoring data during the usual care arm
- Use of personal CGM
- Self report of nausea and vomiting and headaches (any episodes scored on a VAS with 0 = no nausea and 10 = vomiting) reported on a daily survey

During the bionic pancreas arm:

- CGMG every five minutes from the DexCom G4 Platinum AP CGM
- StatStrip Xpress BG measurements before meals, bedtime, 12:00 AM and ~3:45 AM
- Any additional StatStrip Xpress BG values
- Estimated carbohydrate intake (from camp healthcare provider documentation)
- Number of hypoglycemic events (BG < 70 mg/dl, from camp healthcare provider documentation)
- Number of carbohydrate interventions for hypoglycemia (from camp healthcare provider documentation)
- Insulin and glucagon doses administered by the control system
- Timing of meal announcements and size of meals announced
- Number of meal announcements
- Bionic pancreas downtime – number, timing, and duration of periods offline, reasons for being offline (CGM sensor loss, system crash, communication problem between CGM and bionic pancreas, communication problem between bionic pancreas and pumps, pump malfunction, tubing occlusion, infusion set failure/pulled out)
- Insulin and glucagon dosing during CGM downtime
- Self report of nausea and vomiting and headaches (any episodes scored on a VAS with 0 = no nausea and 10 = vomiting) reported on a daily survey.
- Body weight at the beginning and end of the bionic pancreas arm
- Time subjects were not under bionic pancreas control during the bionic pancreas arm
- List of technical faults associated with the bionic pancreas including cause and resolution
- Interaction with or comments about the bionic pancreas device
- Number of unscheduled (fell out or failed) insulin and glucagon infusion sets and reason for replacement
- Number of unscheduled CGM sensor changes and reason for replacement
- Use of personal CGM

After completion of each study arm

- Completion of a survey

For consenting non-participants:

- BG measurements before meals, bedtime, 12:00 AM, and, when available, at 3:00-4:00 AM
- Any additional BG values
- Estimated carbohydrate intake (from camp healthcare provider documentation)

- Number of hypoglycemic events (BG < 70 mg/dl, from camp healthcare provider documentation)
- Number of carbohydrate interventions for hypoglycemia (from camp healthcare provider documentation)
- Last HbA1c prior to attending camp

VI. b. Study Endpoints

Co-primary endpoint analysis:
Both of these metrics will be generated from the DexCom G4 Platinum AP CGM data during the bionic pancreas and comparator arms:

- Mean CGMG during days 2-5
- Fraction of time spent < 60 mg/dl during days 2-5

Secondary endpoint analyses – CGM:
All of following metrics will be generated from the DexCom G4 Platinum AP CGM data during the bionic pancreas and comparator arms. Each of these measures will be calculated for the entire period and separately for the nighttime (11:00 PM to 7:00 AM), for days 1-5, day 1, and days 2-5.

- Mean CGMG
- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dl
  - < 60 mg/dl
  - < 70 mg/dl
  - 70-120 mg/dl
  - 70-180 mg/dl
  - >180 mg/dl
  - >250 mg/dl
- Percentage of subjects with mean CGMG < 154 mg/dl (predicted A1c < 7%)
- Percentage of subjects with mean CGMG < 169 mg/dl (predicted A1c < 7.5%)
- Percentage of subjects with mean CGMG < 183 mg/dl (predicted A1c < 8.0%)
- Reliability index calculated as percent of possible values actually recorded by CGM.
- Number of hypoglycemic event (< 70 mg/dl, < 60 mg/dl, <50 mg/dl); a series of hypoglycemic measurements is defined as a single event until there is a break of ≥ 30 minutes between measurements below the defined threshold)

Secondary endpoint analyses - BG:
All of following metrics will be generated from the StatStrip Xpress data during the bionic pancreas and comparator arms and for the non-participants during those same periods. Each of these measures

will be calculated for the entire period and separately for the nighttime (11:00 PM to 7:00 AM), for days 1-5, day 1, and days 2-5.

- Average BG determined from the scheduled StatStrip Xpress measurements.
- Percentage of the scheduled BG values < 70 mg/dl, < 60 mg/dl, and < 50 mg/dl
- Percentage of subjects with mean BG < 154 mg/dl, < 169 mg/dl, and < 183 mg/dl using the scheduled StatStrip Xpress measurements
- Number of hypoglycemic events (BG < 70 mg/dl, BG < 60 mg/dl, BG < 50 mg/dl) as determined from all StatStrip Xpress measurements (a series of hypoglycemic measurements is defined as a single event until there is a break of ≥ 30 minutes between hypoglycemic measurements)

Secondary endpoint analyses – Non-glycemic:
All of following metrics will be generated during the bionic pancreas and comparator arms and (where applicable) for the non-participants during those same periods. Each of these measures will be calculated for the entire period and separately for the nighttime (11:00 PM to 7:00 AM), for days 1-5, day 1, and days 2-5.

- Fraction of days CGM used by participants in the usual care arm
- Number of carbohydrate interventions for hypoglycemia when BG < 70 mg/dl
- Grams of carbohydrate taken for hypoglycemia when BG < 70 mg/dl
- Mean insulin total daily dose
- Mean glucagon total daily dose
- Mean daily basal insulin dose
- Mean daily bolus insulin dose
- Mean meal carbohydrate content
- Number of unscheduled infusion set changes (for any reason, including accidental loss, insulin site and glucagon sites tabulated separately)
- Number and severity of local infusion site reactions (up to one reaction per day per site, quantitated with Draize scale, insulin site and glucagon sites tabulated separately)
- Number of unscheduled CGM sensor changes
- Change in body weight from beginning to end of each study arm
- Episodes of nausea and nausea index (sum of number of episodes times severity from VAS)
- Number of severe hypoglycemic events (subject unable to self-treat, requiring the assistance of another person)
- The following metrics will be generated from the bionic pancreas arm:
- Time subjects were not under bionic pancreas control during the bionic pancreas arm, subdivided where possible by cause (CGM signal loss, pump communication loss, pump malfunction, iPhone or algorithm fault)
- Time without CGM monitoring data during the usual care arm
- List of technical faults associated with the bionic pancreas including cause and resolution
- Fraction of subjects using a GLP-1 agonist during usual care
- Fraction of subjects using pramlintide during usual carew

We will calculate percentages, means, standard deviations, and ranges in descriptive analyses. We will use paired t-test for comparison of means.

VI. c. Power Analysis

The power analysis for this study is based on the data from the previous Camp Study. In that study, the difference between the mean CGMG in the bionic pancreas and usual care arms was 16 mg/dl (142±12 mg/dl versus 158±27 mg/dl, respectively). In order to detect this same difference in mean glycemia with a power of 80% and a p-value of 5% using a one-sided t-test (superiority analysis) a sample size of 24 subjects is required.

VI. d. Criteria for Success of the Study

The main criteria for success will be whether there is neither of the co-primary outcomes are inferior in the bionic pancreas arm vs. the comparator arm and at least one of the co-primary outcomes is superior in the bionic pancreas arm.

VII. Risks and Discomforts

Subjects may experience mild discomfort associated with the insertion of the infusion sets and DexCom CGM sensor into the SC tissue. Any discomfort is expected to be similar to that associated with injection of insulin. Once the infusion sets and sensors are in place, there should be no significant discomfort. The risk for developing inflammation in the SC tissue at the insertion sites is expected to be extremely low. There were no instances of inflammation or infection in the first three phases of experiments including over 100 subjects. In addition all subjects eligible for the study wear insulin infusion sets routinely.

There is a potential risk of nausea or vomiting in subjects due to the administration of exogenous glucagon. The experiments, however, involve small and infrequent SC glucagon doses. The recommended dose of glucagon for treatment of a pediatric patient with diabetes with hypoglycemia is 500-1000 mcg, given as a single subcutaneous injection. In practice, a smaller dose is sometimes used initially to reduce the risk of nausea and vomiting. Per camp protocol, age groups under 10 years of age receive 500 mcg of glucagon and >10 years of age receive 1000 mcg glucagon for severe unresponsive hypoglycemia. The largest single dose to be administered in our study is 80 mcg. Nausea was rare in the first five phases of our bionic pancreas studies. In most of the cases where nausea was reported, the episodes of nausea did not correlate with periods of glucagon dosing, which is intermittent. The risks for nausea or vomiting in our study are therefore expected to be small.

There is a potential risk of hypoglycemia, since exogenous insulin will be administered. Given (i) the small insulin doses that will be administered, (ii) the availability of glucagon doses to counter potentially excessive insulin dosing and prevent impending hypoglycemia, (iii) frequent BG monitoring, and (iv) frequent monitoring by camp healthcare providers, the risk of a hypoglycemic episodes leading to significant harm to subjects during the bionic pancreas arm is expected to be substantially lower than their risk during their usual therapy.

The only risk associated with chart review for the non-participants is taking the time to consent and provide contact information for their doctors.

VIII. Potential Benefits

Based on evidence from previous trials of the bionic pancreas, subjects enrolled in the study my benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose during the bionic pancreas arm.

Subjects are expected to benefit from continuous glucose monitoring with 24 hour monitoring of subject response to low and high glucose threshold alarms during both arms of the study, which is likely to reduce the risk of a severe hypoglycemic event.

The data derived from this study will allow us to improve the robustness and effectiveness of our bionic pancreas control system, and treatment is expected to systematically improve for subsequent participants and eventually for children with type 1 diabetes in general

The subjects will be financially compensated for participating in the study.

Non-participants (chart review only) will not benefit from consenting to the study.

IX. Data and Safety Monitoring

IX. a. Monitoring of Source Data

The principal investigator (Steven Russell), a study clinical research fellow (physician), or a study nurse practitioner will review the eligibility of each subject based on the case report from the screening visit.

During the experiment, StatStrip Xpress and CGM data will be collected in various ways. CGM data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the bionic pancreas device (from which it will be downloaded at intervals) and wirelessly streamed to the monitoring station where it will also be stored electronically to provide redundancy in data storage and mitigate the risk of data loss. StatStrip Xpress BG data will be entered into the bionic pancreas immediately after determination and then wirelessly streamed with the rest of the data to the monitoring station. All of the data will be combined in a single database that will be compared against the primary data files for integrity. The computer database will be backed up at least monthly and the backup media stored in a secure location.

The Study will be conducted by the staff of the MGH Diabetes Research Center, the engineering research team at Boston University, and the staff of Camp Barton and Camp Joslin. The PI and engineering team will be involved in education of the staff prior to the start of the protocol and will communicate with study staff at least twice a week to review Study progress, discuss any issues in study conduct, and review procedures. Study staff will be encouraged to raise any concerns they may

have or problems they have identified at any time. The PI, in consultation with the co-investigators, the staff of the camps, and the Medical Directors of the camp will decide a course of corrective action, and resolution or progress will be assessed no later than the next meeting.

An audit of procedures, regulatory documentation, and a sample of subject files is performed by a member of the Center at least biannually. The audit will be conducted by a Center staff member who is not directly involved in the conduct of the Study. This audit will include a review of regulatory documentation, such as IRB and FDA correspondence, and a review of subject files, including a review of consents, case report forms, and other data from study visits.

A numeric code will be substituted for the subjects personal identifying information in the study database, which will be password protected. The key linking the medical record number of the subject with the numeric code, along with case report forms, and all information that is personally identifiable, will be kept in a locked filing cabinet in an investigator's locked office. All electronic records will be kept in a password protected computer database. All printed computer data will be disposed of confidentially when no longer needed. Only the study staff will have access to the study database. Subjects may not withdraw from the de-identified database, but they may elect to have the key linking their medical record to the de-identified database destroyed.

The study data may be shared with collaborators outside of Partners, but only in a form in which all personally identifiable information has been removed (e.g. combined database including BG values, record of insulin and glucagon delivered by the device, and blood insulin and glucagon levels). Shared data will be in the form of a database in which only a number identifies subjects.

A de-identified dataset as described above will be stored for possible future analysis in the laboratory of the Boston University co-investigator Ed Damiano. Subjects may not withdraw their data, as it will be stored in non-personally identifiable form.

IX. b. Safety Monitoring

Once participants are enrolled in the study, a study physician, nurse practitioner or nurse will perform the insertion of the infusion sets and CGM sensor, ensuring that proper procedures are followed. Each of the BG measurements made will be available to the participant and staff for implementation of orders regarding the management of high and low BG values.

This study is considered moderate risk. An external Data and Safety Monitoring Board will oversee the conduct of the study and review its results on a regular basis. Additionally, the DSMB will be convened in the event that any subject has to be removed from the study due to an adverse event. The DSMB will be informed if there are any changes to the study protocol that could significantly impact the safety or scientific validity of the study. A final DSMB meeting will convene after the completion of the study. Safety and efficacy data will also be reported to the FDA in compliance with applicable regulations.

As noted above, the participation of individual subjects in the bionic pancreas arm of the study will be discontinued if they experience:

- Diabetic ketoacidosis requiring hospitalization

- Seizure or unconsciousness associated with a hypoglycemia
- Persistent nausea and vomiting thought to be related to glucagon dosing

If more than six subjects must be withdrawn from the study for these reasons, the study will stop and a vote of the DSMB will be required to restart it. All serious and unexpected events will be reported to the DSMB within 72 hours.

Note that subjects may discontinue participation at any time and subjects may be removed from the trial for other reasons, for instance failure to comply with study procedures or intercurrent illness that is unrelated to the bionic pancreas but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

It should be noted that there were no serious adverse events in the first five phases of our closed loop studies including more than 150 subjects. There were instances of biochemical hypoglycemia which were treated according to protocol with oral carbohydrates. No subjects reported more than mild symptoms associated with the biochemical hypoglycemia, and only oral carbohydrates have been used for treatment in all other cases.

IX. c. Adverse Event Reporting Guidelines

The Principal Investigator and Co-investigators will review any adverse events after each experiment. Adverse events will be reported promptly to the Partner's IRB and to the BU IRB according to their respective adverse event reporting guidelines. Co-investigator Ed Damiano is the sponsor of a pending Investigational Device Exception (IDE) for the closed loop device to be used in this trial. Reports of adverse events will be made to the FDA in compliance with the terms of IDE.

X. Subject Compensation

Financial compensation will be provided to all subjects who complete the Screening Visit (which is typically completed either at MGH or remotely). Subjects will be paid $50 for completing the Screening Visit. Study participants will be compensated $1,000 for completing the camp portion of the study. The total compensation for a subject who completed the screening visit and the camp portion of the study would be $1,050. Subjects who are unable to complete the study or chose to stop participation will receive prorated compensation at a rate of $4.00 per completed hour (10 days X 24 hours per day X $4.00 per hour = $960). Subjects who must stop the study due to circumstances beyond their control will receive a minimum of $500.

Non-participants (chart review only) will not be compensated for their participation.

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