

Supplementary Data

Assessment of efficacy, glucose fluctuation, and risk for hypoglycemic events across 100 virtual patients derived from expected glucose profiles after isocaloric meal. Individual dose for each patient has been identified using virtual uptitration following the given titration rule. The number of virtual patients with a blood glucose <70 mg/dL during uptitration is given as “#VP-BG70, uptitration.” For the resulting individualized dose, the mean value across 100 virtual patients is given. The risk for hypoglycemia for each treatment/dosing regimen after virtual uptitration is derived us-

ing an established metric, the “low blood glucose index” (LBGI).^{14,15} Three hypoglycemia risk categories have been defined based on LBGI: low (LBGI <2.5), moderate (LBGI between 2.5 and 5), and high (LBGI >5). Each virtual patient was individually uptitrated and the LBGI for the glucose profile was calculated. For all treatments/dosing regimens, the mean LBGI across all 100 virtual patients was calculated (“hyporisk-LBGI, final dose”). T_t and T_H describe the average time in the given glucose target range (average for 100 virtual patients).

SUPPLEMENTARY TABLE S1. TITRATION RULE SCAN FOR AT-MEAL DOSING

<i>Time of glucose control (min)</i>	<i>Glucose target (mg/dL)</i>	<i>Dose (U TI)</i>	<i>PPG-2h (mg/dL)</i>	<i>BG-AUC4h (mg/dL·min)</i>	<i>MPG-6h (mg/dL)</i>	T_t (%)	T_H (%)	<i>#VP-BG70, uptitration</i>	<i>Hyporisk-LBGI, final dose</i>
60	130	30.1	140	31,800	128	97.8	72.3	9	0.19
60	140	25	151	34,000	137	93.1	59.8	4	0.11
60	150	19.1	166	37,000	150	85.1	38.3	1	0.05
60	160	15	176	38,800	158	77.6	28.1	0	0.02
90	130	33.6	131	30,100	121	99.4	82.7	11	0.33
90	140	29.5	139	31,800	128	98.9	73.3	6	0.18
90	150	26.3	147	33,200	134	97.5	61.9	3	0.12
90	160	21.7	158	35,400	144	91.2	45.3	1	0.09
120	130	37.6	121	28,300	114	99.8	88.6	17	0.53
120	140	33.6	130	30,100	122	99.7	83.8	7	0.28
120	150	30	138	31,600	128	99	73.6	4	0.18
120	160	26.7	145	32,900	133	97.7	62.5	3	0.13
150	130	39.4	118	27,700	112	100	91.3	18	0.53
150	140	35.9	125	29,100	117	100	89.6	11	0.34
150	150	32.7	132	30,400	123	99.8	83.2	7	0.17
150	160	29.4	140	31,800	129	99.4	72.5	3	0.11
180	130	39.2	118	27,800	112	100	91.3	23	0.51
180	140	35.8	126	29,200	118	100	90.2	11	0.29
180	150	32.6	132	30,400	123	100	83.7	6	0.18
180	160	28.9	141	32,100	130	99.8	70.9	1	0.10

BG, blood glucose; LBGI, low blood glucose index; PPG, postprandial glucose; VP, virtual patient.

SUPPLEMENTARY TABLE S2. TITRATION RULE SCAN FOR POSTMEAL DOSING (15 MIN SHIFT TIME)

<i>Time of glucose control (min)</i>	<i>Glucose target (mg/dL)</i>	<i>Dose (U TI)</i>	<i>PPG-2h (mg/dL)</i>	<i>BG-AUC4h (mg/dL·min)</i>	<i>MPG-6h (mg/dL)</i>	<i>T_r (%)</i>	<i>T_n (%)</i>	<i>#VP-BG70, up-titration</i>	<i>Hyporisk-LBGI, final dose</i>
60	130	35.3	127	30,200	119	99.5	81.5	28	0.48
60	140	29.7	139	32,400	129	98.3	70.1	13	0.27
60	150	23.8	152	34,900	139	93.8	51.3	6	0.15
60	160	18.1	167	37,600	151	84.7	33.8	2	0.08
90	130	34	129	30,500	121	99.6	82.3	22	0.36
90	140	29.8	137	32,200	128	99.5	73.7	12	0.21
90	150	26.6	144	33,400	133	98.3	62.6	5	0.17
90	160	21.9	155	35,500	142	93.9	45.4	4	0.12
120	130	36.5	123	29,500	117	99.9	86.5	22	0.44
120	140	32.3	132	31,200	124	99.6	81.2	12	0.22
120	150	29.1	139	32,400	129	99.5	71.1	4	0.18
120	160	25.9	146	33,700	134	98.4	59.6	2	0.14
150	130	38.2	119	28,900	114	100	89.2	19	0.46
150	140	34.7	127	30,300	120	100	87.3	10	0.27
150	150	31.1	134	31,600	126	99.8	78.4	4	0.19
150	160	28	141	32,800	131	99.6	68	2	0.13
180	130	37.7	121	29,100	115	100	89.9	13	0.43
180	140	34.9	126	30,100	119	100	87.9	6	0.28
180	150	31.1	134	31,500	125	100	78.8	3	0.20
180	160	27.6	142	33,100	132	99.3	67.6	1	0.09

SUPPLEMENTARY TABLE S3. TITRATION RULE SCAN FOR SPLIT DOSING (15-MIN SPLIT TIME)

<i>Time of glucose control (min)</i>	<i>Glucose target (mg/dL)</i>	<i>Dose (U TI)</i>	<i>PPG-2h (mg/dL)</i>	<i>BG-AUC4h (mg/dL·min)</i>	<i>MPG-6h (mg/dL)</i>	<i>T_r (%)</i>	<i>T_n (%)</i>	<i>#VP-BG70, up-titration</i>	<i>Hyporisk-LBGI, final dose</i>
60	130	32.7	134	31,200	124	98.4	76.3	18	0.37
60	140	27	146	33,500	134	94.7	63.1	10	0.20
60	150	21	162	36,300	147	87.3	40.9	4	0.12
60	160	16.3	173	38,400	156	79.5	29.9	1	0.05
90	130	33.8	130	30,400	121	99.5	83.4	18	0.33
90	140	29.9	138	31,900	128	99.3	73.6	8	0.24
90	150	26.1	146	33,400	134	97.7	60.8	4	0.16
90	160	21.8	157	35,500	143	92.1	44.7	2	0.14
120	130	36.8	122	29,000	116	99.9	88	19	0.47
120	140	32.8	131	30,700	123	99.5	82.6	9	0.25
120	150	29.6	138	32,000	128	99.3	72.8	3	0.20
120	160	26.1	145	33,300	134	98	61.8	3	0.12
150	130	38.6	119	28,400	113	100	90.4	16	0.50
150	140	35.1	126	29,800	119	100	87.9	9	0.32
150	150	31.7	133	31,000	124	99.9	81	5	0.19
150	160	28.6	140	32,400	130	99.5	70.3	3	0.11
180	130	38.5	118	28,400	113	100	91.5	13	0.49
180	140	34.9	127	29,900	119	100	89.7	7	0.26
180	150	31.6	133	31,000	124	100	81.2	3	0.19
180	160	28	142	32,600	131	99.5	70	1	0.08