Supplemental material

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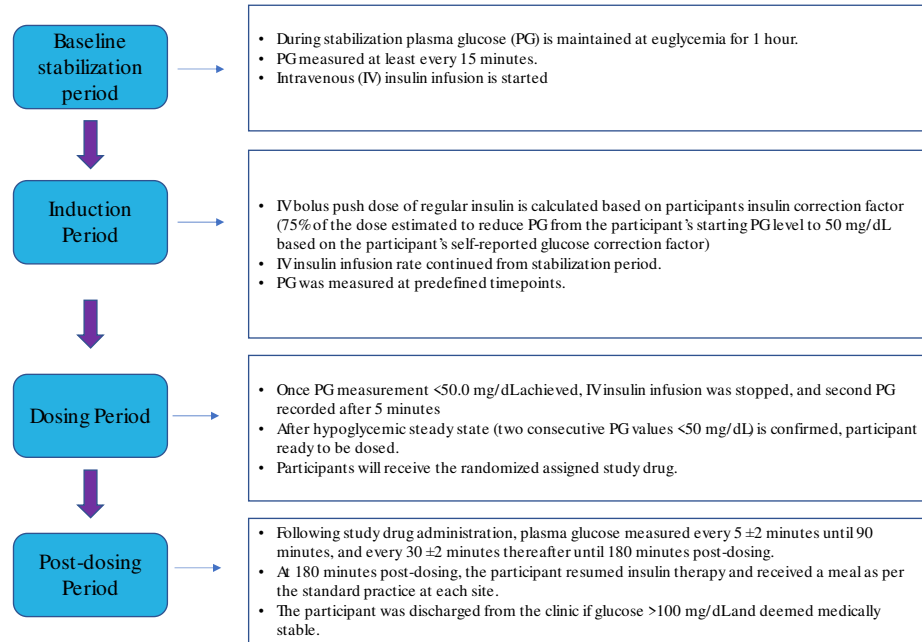
BMJ Open Diab Res Care

Supplemental Figure 1. Hypoglycemia Induction Study Procedure

See PDF document

Supplemental Figure 1. Hypoglycemia Induction Study Procedure

Baseline stabilization period
- During stabilization plasma glucose (PG) is maintained at euglycemia for 1 hour.
- PG measured at least every 15 minutes.
- Intravenous (IV) insulin infusion is started

Induction Period
- IV bolus push dose of regular insulin is calculated based on participants insulin correction factor (75% of the dose estimated to reduce PG from the participant's starting PG level to 50 mg/dL based on the participant's self-reported glucose correction factor)
- IV insulin infusion rate continued from stabilization period.
- PG was measured at predefined timepoints.

Dosing Period
- Once PG measurement <50.0 mg/dL achieved, IV insulin infusion was stopped, and second PG recorded after 5 minutes
- After hypoglycemic steady state (two consecutive PG values <50 mg/dL) is confirmed, participant ready to be dosed.
- Participants will receive the randomized assigned study drug.

Post-dosing Period
- Following study drug administration, plasma glucose measured every 5 ±2 minutes until 90 minutes, and every 30 ±2 minutes thereafter until 180 minutes post-dosing.
- At 180 minutes post-dosing, the participant resumed insulin therapy and received a meal as per the standard practice at each site.
- The participant was discharged from the clinic if glucose >100 mg/dL and deemed medically stable.

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Supplemental Table 1. Analysis of Plasma Glucose Parameters After Receiving Glucagon by Study and Treatment

Parameter	Statistic	XSGP-301[a]		XSGP-303[a]	
		GAI 1 mg (N=78)	GEK 1mg (N=79)	GAI 1 mg (N=76)	GEK 1 mg (N=78)
C_{max}, (mg/dL)	n	78	79	76	78
	Mean ± SD	202.73 ± 41.796	193.49 ± 42.247	238.32 ± 45.626	228.11 ± 46.567
	Range	111.0 – 304.5	102.0 – 303.5	130.0 – 321.5	138.5 – 327.0
	LS Mean Difference ± SE (95% CI)[b]		9.93 ± 4.923 (0.125, 19.741)		10.99 ± 4.119 (4.135, 17.849)
	p-value		0.047		0.009
T_{max} (min)	n	78	79	76	78
	Mean ± SD	111.27 ± 33.507	100.44 ± 42.722	125.67 ± 33.513	113.89 ± 31.908
	Range	60.0 – 240.0	45.0 – 240.0	59.9 – 181.5	54.2 – 181.2
	LS Mean Difference ± SE (95% CI)[b]		9.62 ± 4.803 (0.049, 19.184)		NA[c]
	p-value		0.049		Period 1: 0.3722[c] Period 2: 0.0570[c]
AUC_{0-90} (mg*min/dL)	n	78	79	76	78
	Mean ± SD	11651.37 ± 2406.856	12260.36 ± 2134.170	13312.63 ± 1986.227	13950.81 ± 2093.808
	Range	5263.9 – 18378.0	7089.5 – 16761.3	8478.4 – 18705.4	9987.4 – 18762.5
	LS Mean Difference ± SE (95% CI)[b]		-545.17 ± 226.863 (-997.107, -93.237)		-615.59 ± 192.370 (-935.864, -295.317)
	p-value		0.019		0.002

GAI = Glucagon Auto-Injector; GEK = Glucagon Emergency Kit
[a] Analysis is conducted for all randomized subjects based on actual treatment received. XSGP-301 statistics are based on Modified Intent-to-Treat Population. XSGP-303 statistics are based on Intent-to-Treat Population.
[b] Mixed Model was applied to compare difference in treatment groups accounting for period and sequence as covariates
[c] Non Normality was observed, and log transformation did not resolve. A non-parametric Kruskal-Wallis Test was applied excluding other covariates and conducted for each of the treatment periods separately.

Supplemental Table 2: Non-inferiority Analysis of Failure Scores by Study and Analysis Population

Outcome:	Statistic	XSGP-301			XSGP-303	
		ITT Population	PrPP Population	RePP Population	ITT Population	PP Population
Composite Endpoint: Failure to achieve a Plasma Glucose > 70 mg/dL or an increase in Plasma Glucose by ≥ 20 mg/dL within 30 minutes After Receiving Glucagon	N	80	80	80	81	73
	Dht	0.029	0.039	0.030	0.009	0.000
	SE	0.018	0.019	0.018	0.005	0.000
	Dht + Confidence Bound[a]	0.075	0.087	0.077	0.022	0.000

N = Number of patients for analysis type

Dht = For each Subject, derived score is the difference in failure scores between treatment and control.

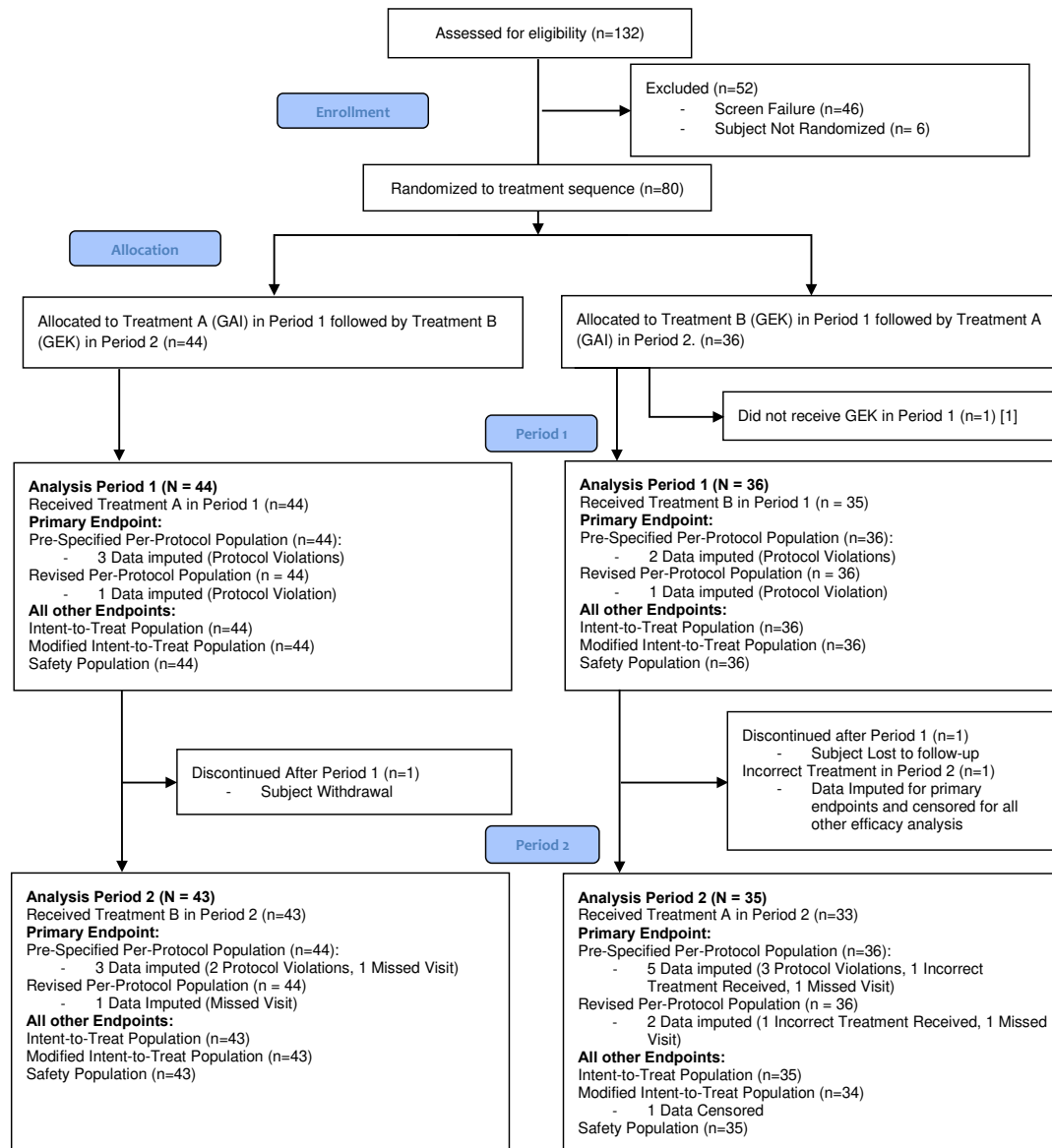ITT = Intent-to-Treat Population all subjects randomized.

PrPP = Pre-Specified Per Protocol Population, for XSGP-301includes observations in the ITT Population where observations were set to missing for visits where a major protocol violation occurred based on pre-specified criteria for major violation and analyzed by actual treatment received.

RePP = Revised Per Protocol Population, for XSGP-301 includes observations in the mITT Population where observations were set to missing for visits where a major protocol violation occurred based on revised criteria for major violation and analyzed by actual treatment received.

PP = Per Protocol Population, for XSGP-303 were all randomized subjects who, during both study periods, successfully completed the insulin induction procedure, fulfill the criteria for having achieved a hypoglycemic steady state, and successfully receive a dose of both study drugs.

[a] One-sided 95% confidence was 2.6 * SE for XSGP-301 and 2.8 * SE for XSGP-303.
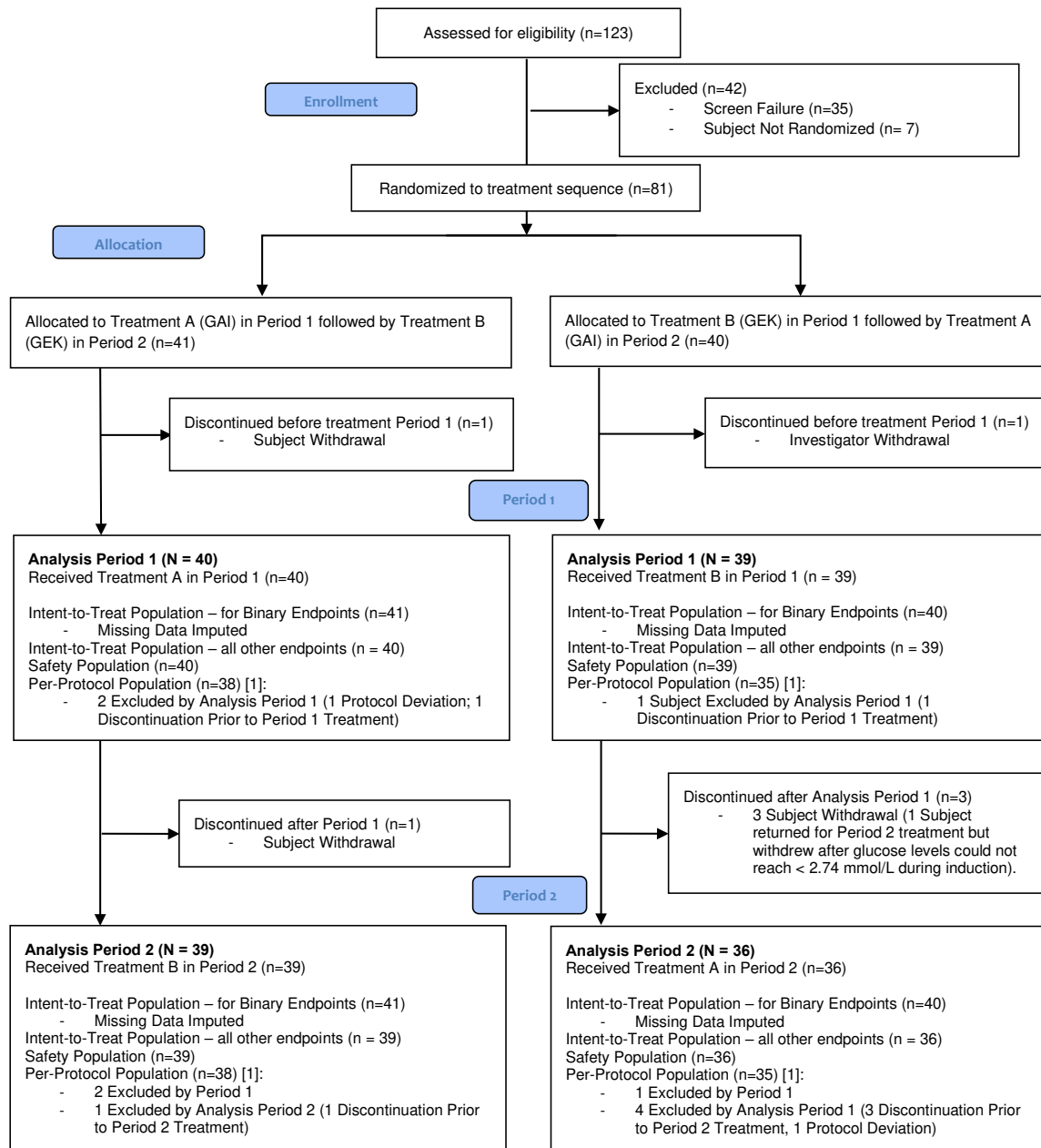
Supplemental Figure 2: Subject Disposition XSGP-301

Assessed for eligibility (n=132)

Enrollment

Excluded (n=52)
- Screen Failure (n=46)
- Subject Not Randomized (n= 6)

Randomized to treatment sequence (n=80)

Allocation

Allocated to Treatment A (GAI) in Period 1 followed by Treatment B (GEK) in Period 2 (n=44)

Allocated to Treatment B (GEK) in Period 1 followed by Treatment A (GAI) in Period 2. (n=36)

Did not receive GEK in Period 1 (n=1) [1]

Period 1

Analysis Period 1 (N = 44)
Received Treatment A in Period 1 (n=44)
Primary Endpoint:
Pre-Specified Per-Protocol Population (n=44):
- 3 Data imputed (Protocol Violations)
Revised Per-Protocol Population (n = 44)
- 1 Data imputed (Protocol Violation)
All other Endpoints:
Intent-to-Treat Population (n=44)
Modified Intent-to-Treat Population (n=44)
Safety Population (n=44)

Analysis Period 1 (N = 36)
Received Treatment B in Period 1 (n = 35)
Primary Endpoint:
Pre-Specified Per-Protocol Population (n=36):
- 2 Data imputed (Protocol Violations)
Revised Per-Protocol Population (n = 36)
- 1 Data imputed (Protocol Violation)
All other Endpoints:
Intent-to-Treat Population (n=36)
Modified Intent-to-Treat Population (n=36)
Safety Population (n=36)

Discontinued After Period 1 (n=1)
- Subject Withdrawal

Discontinued after Period 1 (n=1)
- Subject Lost to follow-up
Incorrect Treatment in Period 2 (n=1)
- Data Imputed for primary endpoints and censored for all other efficacy analysis

Period 2

Analysis Period 2 (N = 43)
Received Treatment B in Period 2 (n=43)
Primary Endpoint:
Pre-Specified Per-Protocol Population (n=44):
- 3 Data imputed (2 Protocol Violations, 1 Missed Visit)
Revised Per-Protocol Population (n = 44)
- 1 Data Imputed (Missed Visit)
All other Endpoints:
Intent-to-Treat Population (n=43)
Modified Intent-to-Treat Population (n=43)
Safety Population (n=43)

Analysis Period 2 (N = 35)
Received Treatment A in Period 2 (n=33)
Primary Endpoint:
Pre-Specified Per-Protocol Population (n=36):
- 5 Data imputed (3 Protocol Violations, 1 Incorrect Treatment Received, 1 Missed Visit)
Revised Per-Protocol Population (n = 36)
- 2 Data imputed (1 Incorrect Treatment Received, 1 Missed Visit)
All other Endpoints:
Intent-to-Treat Population (n=35)
Modified Intent-to-Treat Population (n=34)
- 1 Data Censored
Safety Population (n=35)

GAI = Glucagon Auto-Injector
GEK = Glucagon Emergency Kit
[1] One Subject received treatments in reverse order than their planned treatment sequence (Planned: BA; Actual: AB). This subject was included in all Analysis populations and analyzed according to actual treatment received in the Safety, Modified-Intent-to-Treat, and Per Protocol Populations.

Supplemental Figure 3: Subject Disposition XSGP-303

Assessed for eligibility (n=123)

Enrollment

Excluded (n=42)
- Screen Failure (n=35)
- Subject Not Randomized (n= 7)

Randomized to treatment sequence (n=81)

Allocation

Allocated to Treatment A (GAI) in Period 1 followed by Treatment B (GEK) in Period 2 (n=41)

Allocated to Treatment B (GEK) in Period 1 followed by Treatment A (GAI) in Period 2 (n=40)

Discontinued before treatment Period 1 (n=1)
- Subject Withdrawal

Discontinued before treatment Period 1 (n=1)
- Investigator Withdrawal

Period 1

Analysis Period 1 (N = 40)
Received Treatment A in Period 1 (n=40)

Intent-to-Treat Population – for Binary Endpoints (n=41)
- Missing Data Imputed
Intent-to-Treat Population – all other endpoints (n = 40)
Safety Population (n=40)
Per-Protocol Population (n=38) [1]:
- 2 Excluded by Analysis Period 1 (1 Protocol Deviation; 1 Discontinuation Prior to Period 1 Treatment)

Analysis Period 1 (N = 39)
Received Treatment B in Period 1 (n = 39)

Intent-to-Treat Population – for Binary Endpoints (n=40)
- Missing Data Imputed
Intent-to-Treat Population – all other endpoints (n = 39)
Safety Population (n=39)
Per-Protocol Population (n=35) [1]:
- 1 Subject Excluded by Analysis Period 1 (1 Discontinuation Prior to Period 1 Treatment)

Discontinued after Period 1 (n=1)
- Subject Withdrawal

Discontinued after Analysis Period 1 (n=3)
- 3 Subject Withdrawal (1 Subject returned for Period 2 treatment but withdrew after glucose levels could not reach < 2.74 mmol/L during induction).

Period 2

Analysis Period 2 (N = 39)
Received Treatment B in Period 2 (n=39)

Intent-to-Treat Population – for Binary Endpoints (n=41)
- Missing Data Imputed
Intent-to-Treat Population – all other endpoints (n = 39)
Safety Population (n=39)
Per-Protocol Population (n=38) [1]:
- 2 Excluded by Period 1
- 1 Excluded by Analysis Period 2 (1 Discontinuation Prior to Period 2 Treatment)

Analysis Period 2 (N = 36)
Received Treatment A in Period 2 (n=36)

Intent-to-Treat Population – for Binary Endpoints (n=40)
- Missing Data Imputed
Intent-to-Treat Population – all other endpoints (n = 36)
Safety Population (n=36)
Per-Protocol Population (n=35) [1]:
- 1 Excluded by Period 1
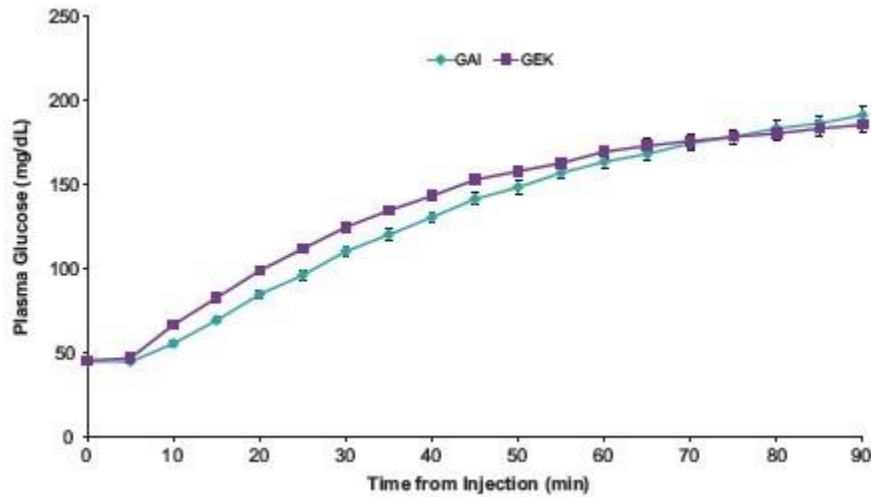- 4 Excluded by Analysis Period 1 (3 Discontinuation Prior to Period 2 Treatment, 1 Protocol Deviation)

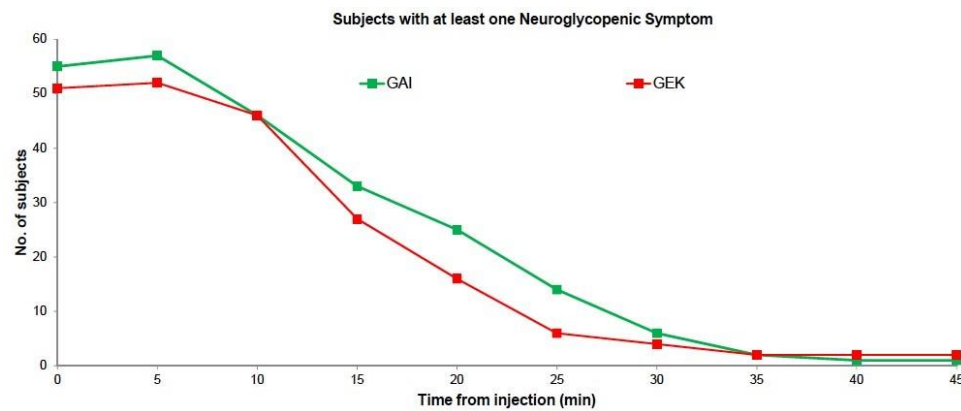GAI = Glucagon Auto-Injector
GEK = Glucagon Emergency Kit
[1] Per Protocol Analysis Population includes subjects who received both study drugs per treatment sequence and no major protocol deviations.

Supplement Figure 4. Mean plasma glucose levels over time (A); time to resolution of neuroglycopenic symptoms (B); and mean (SD) total symptom score, neuroglycopenic score, and autonomic symptom score (C) after Glucagon Auto-Injector (GAI) and Glucagon Emergency Kit (GEK) in XSGP-301.
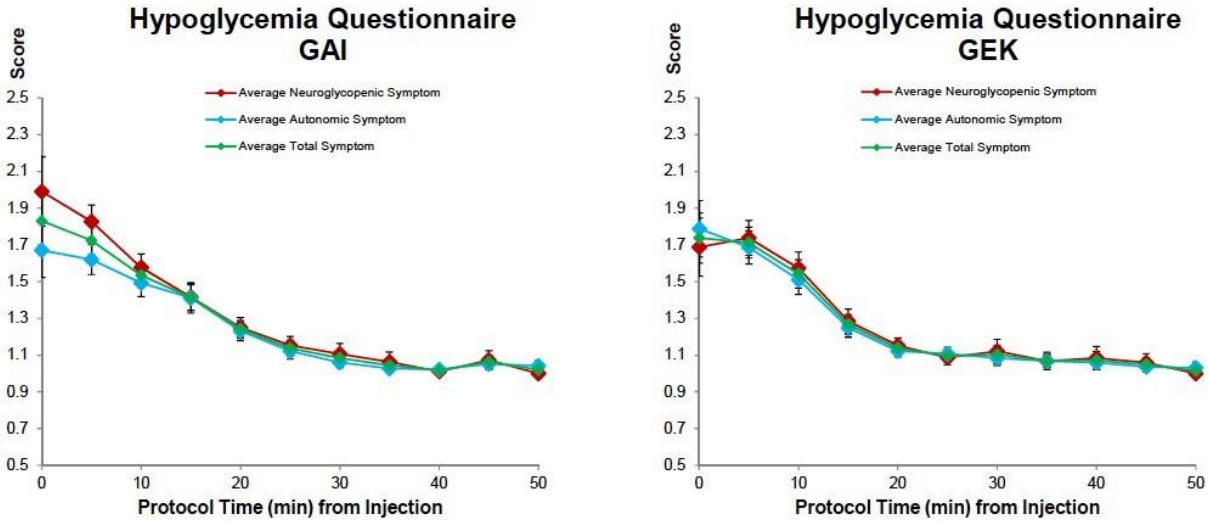
A

B

C

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Supplemental Figure 5. Mean (standard deviation) plasma glucose concentrations with GAI by ethnicity and race for the first 12 subjects in each population, which included: non-Hispanic Whites (n=12), Hispanic Whites (n=4), African-Americans (n=4), and other (n=3) had plasma glucose concentrations obtained to evaluated glucose PK.