Supplementary Online Content

Saxena AR, Frias JP, Brown LS, et al. Efficacy and safety of oral small molecule glucagon-like peptide 1 receptor agonist danuglipron for glycemic control among patients with type 2 diabetes: randomized clinical trial. *JAMA Netw Open*. 2023;6(5):e2314493. doi:10.1001/jamanetworkopen.2023.14493

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

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eMethods: Key exclusion criteria

Key exclusion criteria were type 1 diabetes, secondary forms of diabetes, or recent history of cardiovascular events. Also excluded were gastrointestinal conditions possibly affecting drug absorption, medullary thyroid carcinoma (suspected or personal/family history), multiple endocrine neoplasia syndrome type 2 (personal/family history), pancreatitis (acute or chronic), symptomatic gallbladder disease, history of active proliferative retinopathy and/or macular oedema, active liver disease, malignancy that was not considered cured, or a history of HIV.

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eTable 1. Protocol-Defined Hypoglycemic Events

Parameter	Placebo (n = 66) n (%)	Danuglipron 2.5 mg BID (n = 68) n (%)	Danuglipron 10 mg BID (n = 68) n (%)	Danuglipron 40 mg BID (n = 71) n (%)	Danuglipron 80 mg BID (n = 67) n (%)	Danuglipron 120 mg BID (n = 71) n (%)	Total (N = 411) n (%)
Asymptomatic hypoglycemia[a]	0	0	1 (1)	2 (3)	3 (4)	1 (1)	7 (2)
Documented symptomatic hypoglycemia[b]	0	1 (1)	0	1 (1)	2 (3)	2 (3)	6 (1)
Probable symptomatic hypoglycemia[c]	0	0	0	0	1 (1)	0	1 (0)
Severe hypoglycemia[d]	0	0	0	0	0	0	0

Safety analysis set. Data are number (%) of participants. Participants counted only once per treatment per category. Reports of treatment-emergent adverse events of hypoglycemia (**Table 3**) did not necessarily meet the criteria for protocol-defined hypoglycemic events reported here.
Abbreviation: BID, twice daily.
[a] Asymptomatic hypoglycemia: An event not accompanied by typical symptoms but a blood glucose value of <70 mg/dL using either a glucometer (fingerstick blood glucose) or sponsor-identified central laboratory (plasma glucose).
[b] Documented symptomatic hypoglycemia: An event during which typical symptoms are accompanied with a glucose value of <70 mg/dL using a glucometer (or sponsor-identified central laboratory), and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or intravenous glucose.
[c] Probable symptomatic hypoglycemia: An event during which symptoms are not accompanied by a glucose determination but was presumably caused by a blood glucose concentration of <70 mg/dL, and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or intravenous glucose.
[d] Severe hypoglycemia was event meeting three criteria: 1) The participant was unable to treat him/herself due to neurologic impairment and required the assistance of another person. 2) At least one neurological symptom from memory loss, confusion, uncontrolled behavior, irrational behavior; unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness. 3) Blood glucose was measured and was ≤54 mg/dL using a glucometer (or central laboratory); or if blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

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eTable 2. Least Squares Mean Change From Baseline in Pharmacodynamic Outcomes at Week 16

Parameter	Placebo Mean (SD)	Danuglipron 2.5 mg BID Mean (SD)	Danuglipron 10 mg BID Mean (SD)	Danuglipron 40 mg BID Mean (SD)	Danuglipron 80 mg BID Mean (SD)	Danuglipron 120 mg BID Mean (SD)
Fasting insulin (uIU/mL)						
Baseline	10.28 (5.815)	13.09 (13.789)	11.49 (7.740)	11.24 (7.695)	14.28 (12.784)	15.05 (11.735)
n (Week 16)	51	52	61	52	44	36
Change from baseline at Week 16, LS mean (90% CI)	1.27 (–1.39, 3.92)	2.35 (–0.25, 4.95)	1.07 (–1.36, 3.51)	4.51 (1.91, 7.11)	3.66 (0.82, 6.50)	0.92 (–2.10, 3.93)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	1.08 (–2.33, 4.50)	–0.19 (–3.47, 3.08)	3.24 (–0.14, 6.63)	2.40 (–1.18, 5.97)	–0.35 (–4.12, 3.41)
P value vs placebo	..	.60	.92	.12	.27	.88
HOMA-IR						
Baseline	4.50 (2.884)	5.28 (4.891)	4.82 (4.475)	4.57 (3.109)	6.16 (6.388)	6.80 (7.585)
n (Week 16)	51	51	61	51	44	36
Change from baseline at Week 16, LS mean (90% CI)	0.01 (–1.22, 1.24)	0.32 (–0.89, 1.54)	–0.59 (–1.72, 0.54)	0.44 (–0.78, 1.66)	0.92 (–0.40, 2.23)	–0.48 (–1.87, 0.91)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	0.31 (–1.28, 1.90)	–0.60 (–2.12, 0.92)	0.43 (–1.15, 2.01)	0.91 (–0.75, 2.57)	–0.49 (–2.23, 1.25)
P value vs placebo	..	.74	.52	.66	.37	.64
Fasting glucagon (pmol/L)						
Baseline	13.80 (8.791)	13.25 (10.557)	12.79 (6.429)	13.10 (6.938)	14.62 (6.785)	14.71 (7.840)
n (Week 16)	49	51	53	49	43	36
Change from baseline at Week 16, LS mean (90% CI)	–0.24 (–1.77, 1.28)	–1.67 (–3.14, –0.21)	–1.54 (–2.98, –0.09)	–0.37 (–1.89, 1.16)	–0.46 (–2.04, 1.13)	–1.27 (–2.93, 0.40)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	–1.43 (–3.18, 0.33)	–1.29 (–3.03, 0.44)	–0.12 (–1.89, 1.65)	–0.21 (–2.04, 1.61)	–1.02 (–2.94, 0.90)
P value vs placebo	..	.18	.22	.91	.85	.38

Data are for all evaluable participants. For participants who discontinued study medication and/or received glycemic rescue medication, all subsequent values were censored in the analysis. HOMA-IR = (fasting plasma insulin [uIU/mL] × fasting plasma glucose [mg/dL])/405. Baseline is closest result prior to dosing on Day 1. Mixed-model repeated-measures, including treatment, time, strata (metformin vs. diet and exercise alone) and the treatment-by-time interaction as fixed effects, baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and participant as a random effect. An unstructured covariance matrix was used to estimate the variances and covariance within participant across time points. All *P* values are two-sided.

Abbreviations: BID, twice daily; CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; LS, least squares; SD, standard deviation.

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eTable 3. Least Squares Mean Change From Baseline in Vital Signs at Week 16

Parameter	Placebo Mean (SD)	Danuglipron 2.5 mg BID Mean (SD)	Danuglipron 10 mg BID Mean (SD)	Danuglipron 40 mg BID Mean (SD)	Danuglipron 80 mg BID Mean (SD)	Danuglipron 120 mg BID Mean (SD)
Systolic BP (mmHg)						
Baseline	131.1 (9.95)	130.2 (11.41)	129.6 (11.16)	132.5 (11.73)	131.4 (11.32)	130.9 (10.44)
n (Week 16)	57	53	63	56	46	38
Change from baseline at Week 16, LS mean (90% CI)	–1.71 (–4.02, 0.61)	–2.79 (–5.15, –0.43)	–2.85 (–5.05, –0.64)	–3.43 (–5.69, –1.16)	–6.65 (–9.07, –4.23)	–3.25 (–5.75, –0.75)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	–1.08 (–4.14, 1.98)	–1.14 (–4.08, 1.80)	–1.72 (–4.71, 1.27)	–4.95 (–8.04, –1.85)	–1.54 (–4.73, 1.65)
P value vs placebo	..	.56	.52	.34	.009	.43
Diastolic BP (mmHg)						
Baseline	77.3 (7.67)	78.5 (8.03)	79.3 (7.11)	80.0 (8.49)	80.1 (9.17)	77.6 (7.80)
n (Week 16)	57	53	63	56	46	38
Change from baseline at Week 16, LS mean (90% CI)	–1.34 (–2.82, 0.14)	–1.18 (–2.68, 0.33)	–1.16 (–2.57, 0.25)	–1.01 (–2.46, 0.44)	–0.39 (–1.95, 1.16)	0.16 (–1.44, 1.76)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	0.16 (–1.80, 2.13)	0.18 (–1.71, 2.07)	0.33 (–1.60, 2.25)	0.95 (–1.05, 2.95)	1.50 (–0.55, 3.55)
P value vs placebo	..	.89	.88	.78	.44	.23
Pulse rate (bpm)						
Baseline	70.7 (9.68)	71.5 (9.36)	72.9 (11.69)	70.6 (9.75)	72.8 (9.22)	73.0 (10.39)
n (Week 16)	57	53	63	56	46	38
Change from baseline at Week 16, LS mean (90% CI)	5.33 (3.29, 7.37)	3.25 (1.17, 5.32)	2.90 (0.95, 4.84)	4.95 (2.97, 6.94)	6.45 (4.33, 8.57)	4.81 (2.65, 6.98)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	–2.08 (–4.81, 0.64)	–2.43 (–5.06, 0.19)	–0.38 (–3.03, 2.28)	1.12 (–1.63, 3.87)	–0.52 (–3.32, 2.29)
P value vs placebo	..	.21	.13	.82	.50	.76

Safety analysis set which includes all participants randomly assigned to study medication and who took at least 1 dose of study medication. Participants were analyzed according to the study medication they actually received and data post-discontinuation of study medication and/or post initiation of rescue medication were included in the analysis. Baseline is the mean of triplicate measurements collected closest prior to dosing on Day 1. Week 16, 2-hour timepoint results are presented. Means of replicates were used in the calculations. Mixed-model repeated-measures analysis including treatment, time, strata (defined as metformin vs. diet and exercise alone) and the treatment-by-time interaction as fixed effects, baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and participant as a random effect. An unstructured covariance matrix was used to estimate the variances and covariance within participant across time points. All *P* values are two-sided.

Abbreviations: BID, twice daily; BP, blood pressure; CI, confidence interval; LS, least squares; SD, standard deviation.

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eTable 4. Least Squares Mean Change From Baseline in Laboratory Measures at Week 16

Parameter	Placebo Mean (SD)	Danuglipron 2.5 mg BID Mean (SD)	Danuglipron 10 mg BID Mean (SD)	Danuglipron 40 mg BID Mean (SD)	Danuglipron 80 mg BID Mean (SD)	Danuglipron 120 mg BID Mean (SD)
Amylase (U/L)						
Baseline	62.864 (23.2702)	58.059 (27.7515)	58.206 (23.8087)	62.113 (24.1487)	56.134 (25.9632)	65.676 (32.2861)
n (Week 16)	59	53	65	61	58	54
Change from baseline at Week 16, LS mean (90% CI)	–1.27 (–5.70, 3.16)	–0.29 (–4.79, 4.21)	2.22 (–1.98, 6.42)	6.72 (2.46, 10.99)	5.51 (1.06, 9.96)	3.83 (–0.52, 8.18)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	0.98 (–4.58, 6.54)	3.49 (–1.82, 8.80)	7.99 (2.62, 13.36)	6.78 (1.32, 12.25)	5.10 (–0.43, 10.63)
P value vs placebo	..	.77	.28	.01	.04	.13
Triacylglycerol lipase (U/L)						
Baseline	43.152 (38.6313)	40.397 (32.8198)	33.044 (15.8014)	38.620 (15.0536)	43.343 (31.8317)	42.915 (28.2574)
n (Week 16)	59	53	65	61	58	54
Change from baseline at Week 16, LS mean (90% CI)	–4.01 (–11.32, 3.31)	–4.29 (–11.78, 3.21)	1.02 (–5.97, 8.02)	10.24 (3.17, 17.30)	17.36 (10.02, 24.70)	7.52 (0.30, 14.73)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	–0.28 (–9.47, 8.91)	5.03 (–3.79, 13.84)	14.24 (5.35, 23.13)	21.36 (12.37, 30.36)	11.53 (2.38, 20.67)
P value vs placebo	..	.96	.35	.009	<.001	.04
Calcitonin (pg/mL)						
Baseline	2.7318 (1.74883)	2.3819 (1.36279)	2.7885 (1.63734)	2.7628 (1.81132)	3.1020 (3.72510)	2.5573 (1.22797)
n (Week 16)	59	54	63	59	57	54
Change from baseline at Week 16, LS mean (90% CI)	–0.01 (–0.45, 0.42)	0.23 (–0.21, 0.66)	0.26 (–0.16, 0.67)	0.16 (–0.25, 0.58)	0.40 (–0.03, 0.84)	0.28 (–0.14, 0.70)
Difference from placebo at Week 16, LS mean difference (90% CI)	..	0.24 (–0.30, 0.77)	0.27 (–0.25, 0.78)	0.18 (–0.34, 0.70)	0.42 (–0.11, 0.94)	0.29 (–0.24, 0.82)
P value vs placebo	..	.46	.39	.58	.19	.36

Safety analysis set which includes all participants randomly assigned to study medication and who took at least 1 dose of study medication. Participants were analyzed according to the study medication they actually received and data post-discontinuation of study medication and/or post initiation of rescue medication were included in the analysis. Baseline is the result closest prior to, or on, Visit 3 (Day 1). Mixed-model repeated-measures analysis including treatment, time, strata (defined as metformin vs. diet and exercise alone) and the treatment-by-time interaction as fixed effects, baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and participant as a random effect. An unstructured covariance matrix was used to estimate the variances and covariance within participant across time points. All *P* values are two-sided.
Abbreviations: BID, twice daily; CI, confidence interval; LS, least squares; SD, standard deviation.

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eTable 5. Clinical Chemistry Laboratory Test Abnormalities

Parameter	Placebo n/N (%)	Danuglipron 2.5 mg BID n/N (%)	Danuglipron 10 mg BID n/N (%)	Danuglipron 40 mg BID n/N (%)	Danuglipron 80 mg BID n/N (%)	Danuglipron 120 mg BID n/N (%)
Gamma Glutamyl Transferase (U/L)						
>3.0 x ULN	3/65 (5)	3/68 (4)	6/68 (9)	3/71 (4)	0/67	0/71
Bile acid (umol/L)						
>1.0 x ULN	2/65 (3)	0/65	4/68 (6)	4/71 (6)	1/66 (2)	10/69 (14)
Calcitonin (pg/mL)						
>1.0 x ULN	8/65 (12)	4/65 (6)	12/68 (18)	8/71 (11)	10/66 (15)	8/70 (11)
Triacylglycerol lipase (U/L)						
>1.5 x ULN	3/65 (5)	2/65 (3)	3/68 (4)	2/70 (3)	7/66 (11)	3/69 (4)
Thyrotropin (uIU/mL)						
<0.8 x LLN	4/65 (6)	4/65 (6)	1/68 (1)	4/71 (6)	4/66 (6)	5/70 (7)
>1.2 x ULN	6/65 (9)	1/65 (2)	1/68 (1)	1/71 (1)	1/66 (2)	2/70 (3)
Free T4 (thyroxine) (ng/dL)						
>1.2 x ULN	3/65 (5)	1/65 (2)	1/68 (1)	3/71 (4)	7/66 (11)	8/70 (11)
LDL-C (mg/dL)						
>1.2 x ULN	8/65 (12)	11/65 (17)	12/68 (18)	13/70 (19)	12/66 (18)	11/70 (16)
HDL-C (mg/dL)						
<0.8 x LLN	12/65 (18)	7/65 (11)	9/68 (13)	9/70 (13)	11/66 (17)	12/70 (17)
Triglycerides (mg/dL)						
>1.3 x ULN	10/64 (16)	6/65 (9)	11/68 (16)	10/70 (14)	8/66 (12)	13/70 (19)

Safety analysis set. Incidence of clinical chemistry laboratory test abnormalities without regard to baseline abnormality with ≥5 occurrences in any treatment group. n = number of participants with a laboratory abnormality meeting specified criteria while on study treatment or during lag time; N = total number of participants with at least one observation of the given laboratory test while on study treatment or during lag time. Baseline was defined as the result closest prior to dosing at Visit 3 (Day 1). For data where the date/time was equal to the Visit 3 (Day 1) dosing date/time, this data was also considered as baseline. Unplanned measurements were included in analyses.
Abbreviations: BID, twice daily; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LLN, lower limit of normal; ULN, upper limit of normal.

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eTable 6. Categorization of Post-Baseline Electrocardiogram Data

Parameter	Placebo n/N (%)	Danuglipron 2.5 mg BID n/N (%)	Danuglipron 10 mg BID n/N (%)	Danuglipron 40 mg BID n/N (%)	Danuglipron 80 mg BID n/N (%)	Danuglipron 120 mg BID n/N (%)
PR interval not otherwise specified (msec)						
Value ≥300	0/65	0/67	0/68	0/71	0/67	1/71 (1)
%change ≥25/50%	3/65 (5)	0/67	0/68	0/71	1/67 (1)	0/71
QRS interval not otherwise specified (msec)						
Value ≥140	1/65 (2)	1/68 (1)	0/68	0/71	0/67	0/71
%change ≥50%	1/65 (2)	1/68 (1)	0/68	0/71	0/67	0/71
QTcF not otherwise specified (msec)						
450<value≤480	2/65 (3)	3/68 (4)	2/68 (3)	1/71 (1)	3/67 (4)	4/71 (6)
480<value≤500	0/65	0/68	0/68	0/71	0/67	1/71 (1)
Value >500	0/65	0/68	0/68	0/71	0/67	0/71
30<change≤60	2/65 (3)	3/68 (4)	2/68 (3)	6/71 (8)	3/67 (4)	6/71 (8)
Change >60	0/65	0/68	1/68 (1)	1/71 (1)	0/67	3/71 (4)

Safety analysis set. n = number of participants that met criteria, and N = number of participants evaluated against criteria. Means of replicates were used in the determination.
%change ≥25/50% denotes baseline >200 and ≥25% increase or baseline ≤200 and ≥50% increase.
Abbreviation: BID, twice daily.

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eTable 7: Sensitivity Analysis for Least Squares Mean Change From Baseline in HbA1c at Week 16

			Danuglipron				
Analysis	**Parameter**	**Placebo Mean (SD)**	**2.5 mg BID Mean (SD)**	**10 mg BID Mean (SD)**	**40 mg BID Mean (SD)**	**80 mg BID Mean (SD)**	**120 mg BID Mean (SD)**
Sensitivity analysis	**HbA1c (%)**						
	Baseline	8.24 (0.90)	8.10 (1.03)	8.01 (0.91)	8.00 (0.89)	8.07 (0.95)	8.05 (0.86)
	n (Week 16)	59	54	65	61	58	54
	Change from baseline at Week 16, LS mean (90% CI)	–0.13 (–0.34, 0.09)	–0.48 (–0.70, –0.26)	–0.91 (–1.11, –0.70)	–0.97 (–1.18, –0.77)	–0.68 (–0.89, –0.47)	–0.96 (–1.17, –0.74)
	Difference from placebo at Week 16, LS mean difference (90% CI)	..	–0.35 (–0.65, –0.06)	–0.78 (–1.07, –0.49)	–0.85 (–1.14, –0.56)	–0.55 (–0.85, –0.26)	–0.83 (–1.13, –0.54)
	P value vs placebo	..	**0.05**	**<0.001**	**<0.001**	**0.002**	**<0.001**

This prespecified sensitivity analysis was similar to the primary analysis (**Table 2**), except that it included all data collected after discontinuation from study treatment and/or initiation of rescue medication.

Abbreviations: BID, twice daily; CI, confidence interval; HbA1c, glycated hemoglobin; LS, least squares; SD, standard deviation.

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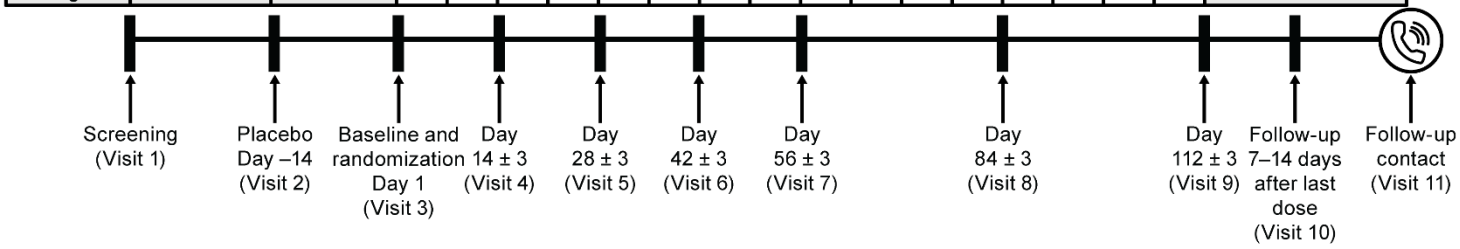
eFigure 1: Study Design

Study week	≤ 4 weeks	–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Danuglipron target dose (BID)	Screening	Placebo run-in		Double-blind treatment (danuglipron dose, mg BID)																Follow-up			
Placebo				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
2.5 mg				2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5				
10 mg				10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10				
40 mg				10	20	40	40	40	40	40	40	40	40	40	40	40	40	40	40				
80 mg				10	20	40	60	80	80	80	80	80	80	80	80	80	80	80	80				
120 mg				10	20	40	60	80	100	120	120	120	120	120	120	120	120	120	120				



For participants randomized to danuglipron target doses of 40 mg BID, 80 mg BID, and 120 mg BID, the target dose was reached following dose escalation for up to the first 6 weeks of the 16-week double-blind treatment period, as shown. No dose escalation was used for the 2.5 mg BID and 10 mg BID groups.
Abbreviation: BID, twice daily.

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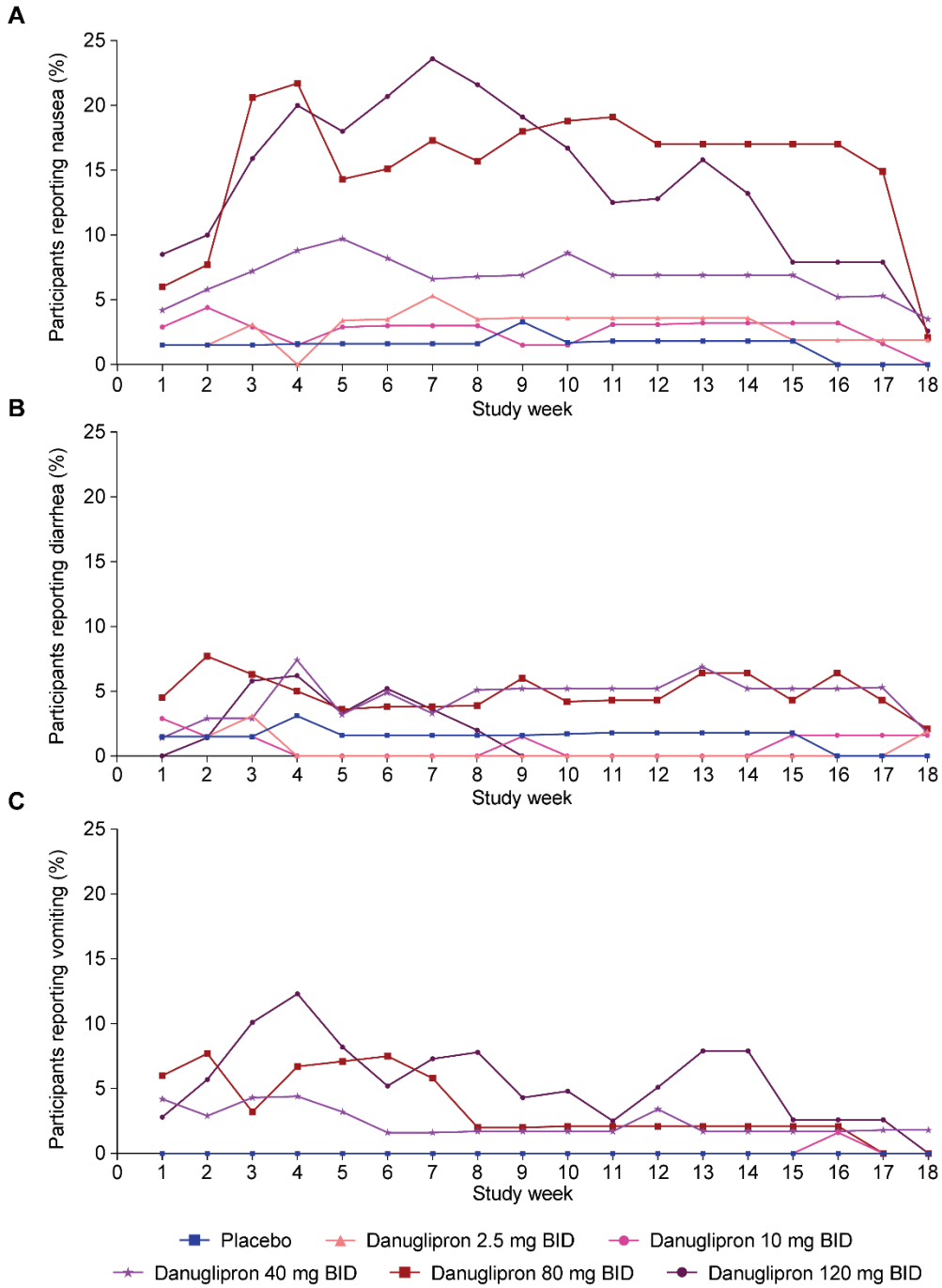
eFigure 2: Percentage of Participants With Treatment-Emergent Adverse Events (All Causality) of A) Nausea, B) Diarrhea, and C) Vomiting, by Study Week



Safety analysis set. Participants who experienced the specified TEAE at any time during the respective week. Denominator is the total number of participants who had not discontinued from study medication and/or the study prior to that respective week (if a participant did discontinue during the respective week they were included in the denominator).
Abbreviations: BID, twice daily; TEAE, treatment-emergent adverse event.

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