Quantifying and Predicting Mean A1C Reductions for Exenatide QW and BID: Importance of Baseline A1C and Other Patient Characteristics

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Background and Objective

- The GLP-1 receptor agonist exenatide, available in twice-daily (exenatide BID) and once-weekly (exenatide QW) formulations, reduces A1C in type 2 diabetes[1]
  - Exenatide BID is short acting with a greater effect on PPG, while exenatide QW is long acting with a greater effect on A1C and fasting glucose[2]
- **The objective of this analysis was to examine the specific patient characteristics associated with A1C response to exenatide BID or exenatide QW at 6 months**

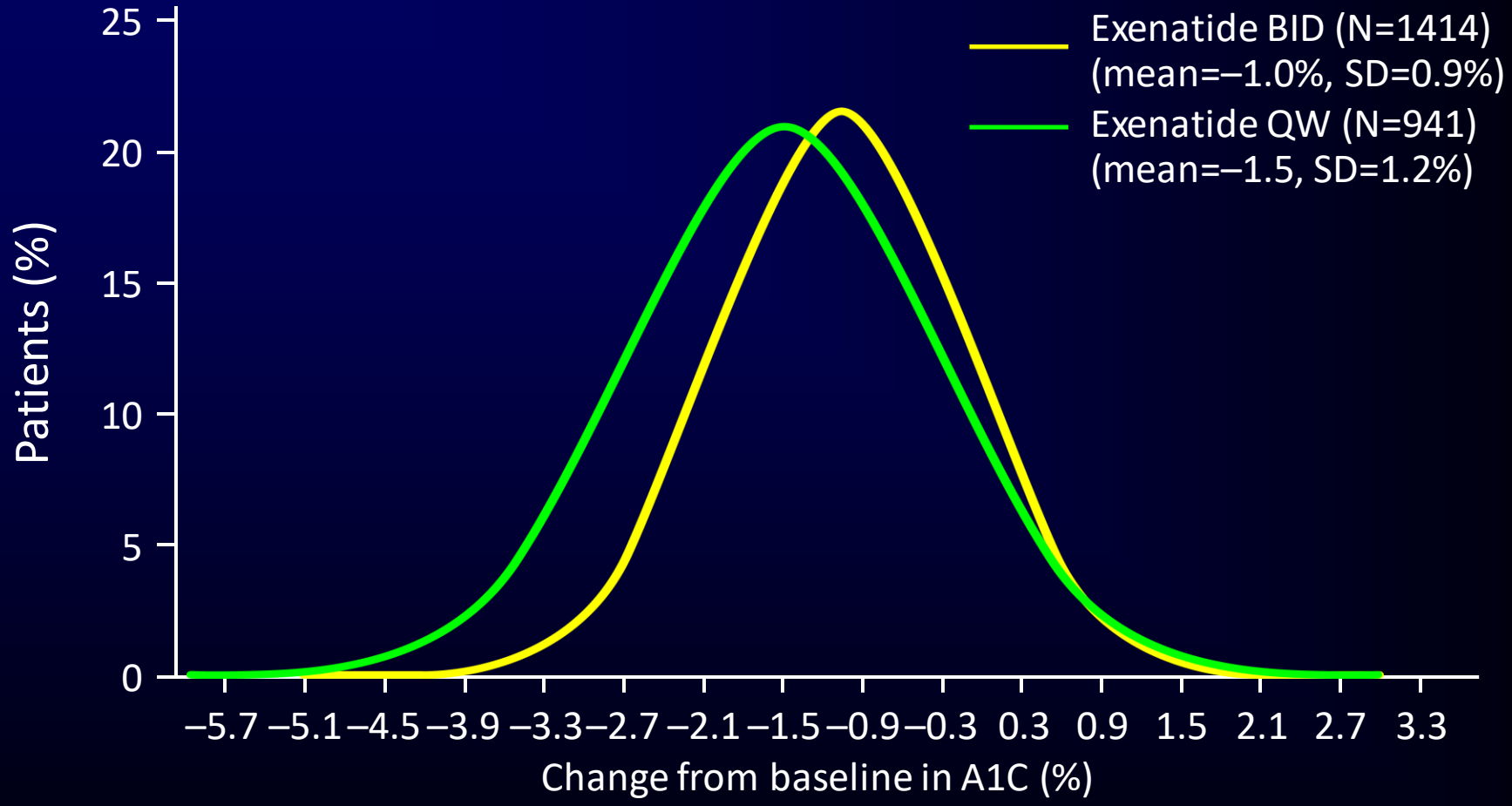
BID, twice daily; GLP-1, glucagon-like peptide-1; QW, once weekly; PPG, postprandial glucose

1. Blevins T, et al. *J Clin Endocrinol Metab.* 2011;96:1301–1310.
2. Drucker DJ, et al. *Lancet.* 2008;372:1240–1250.

Methods

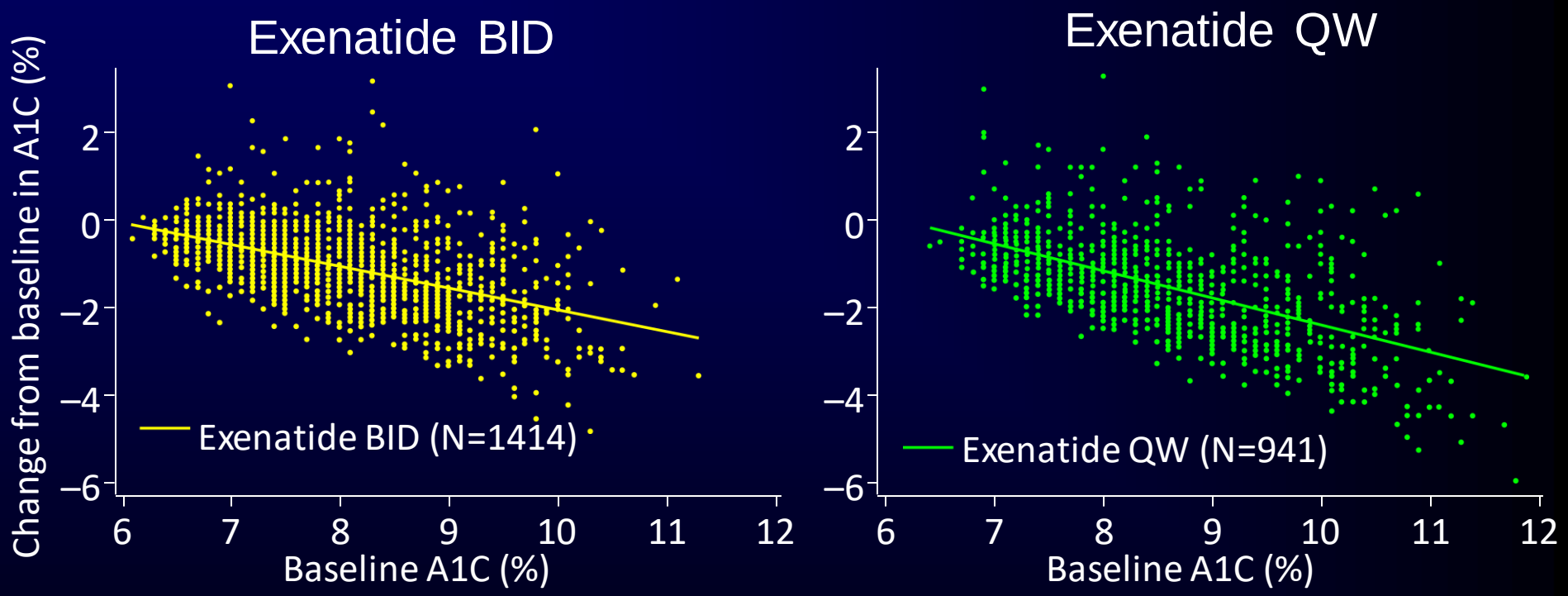
- Exenatide BID data were pooled from 8 trials (N=1414) and exenatide QW data were pooled from 5 trials (N=941)
  - All studies had durations ≥24 weeks
  - All had self-monitored blood glucose measurement so PPG could be determined
- The distribution of A1C change across the population was determined for both drugs
- The linear relationship between baseline A1C and change in A1C after 24 weeks was determined for each therapy

A1C Reductions After 24 Weeks Were Normally Distributed, but Mean Reductions Differed Between Exenatide BID and Exenatide QW

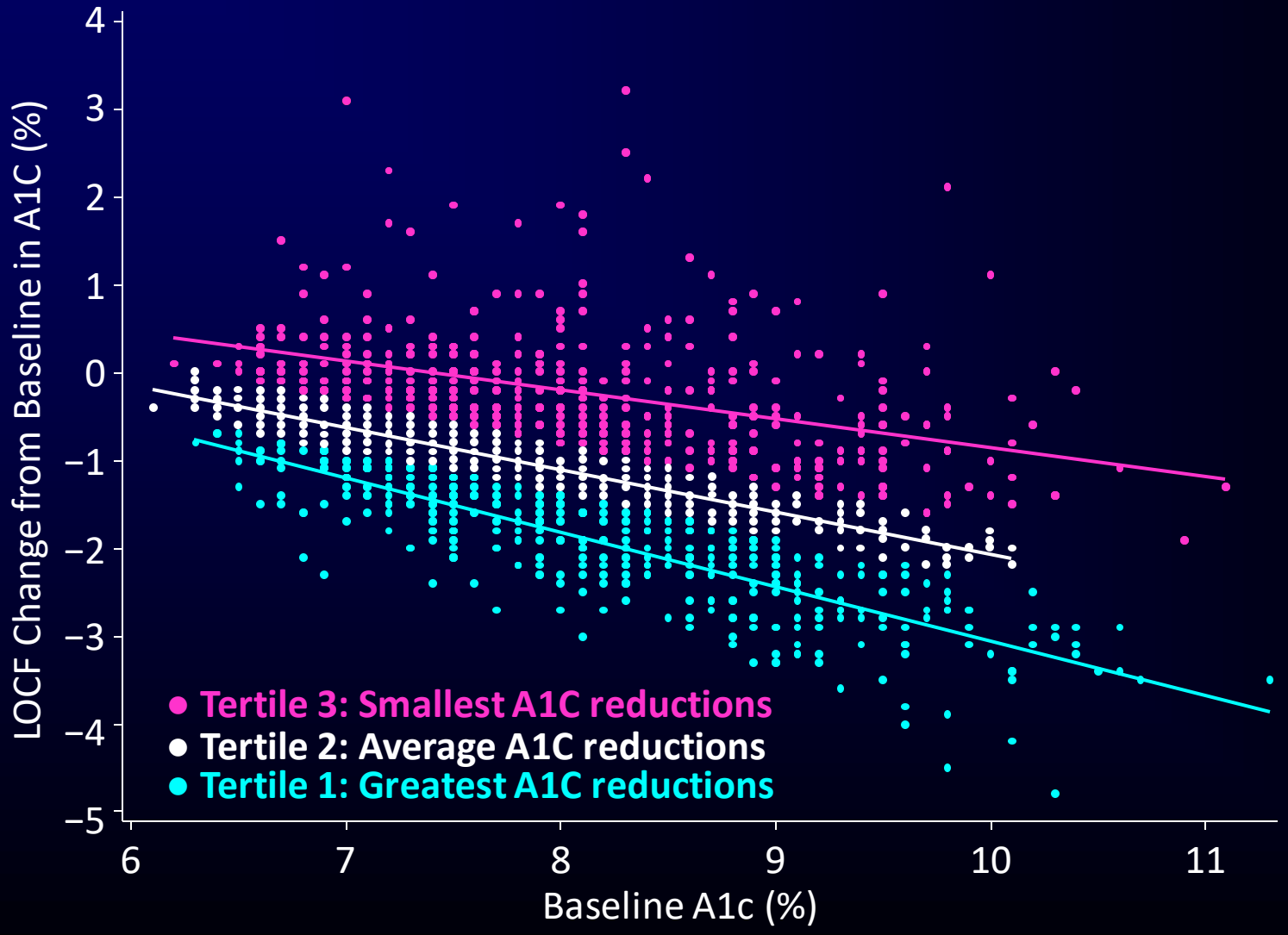


SD, standard deviation.

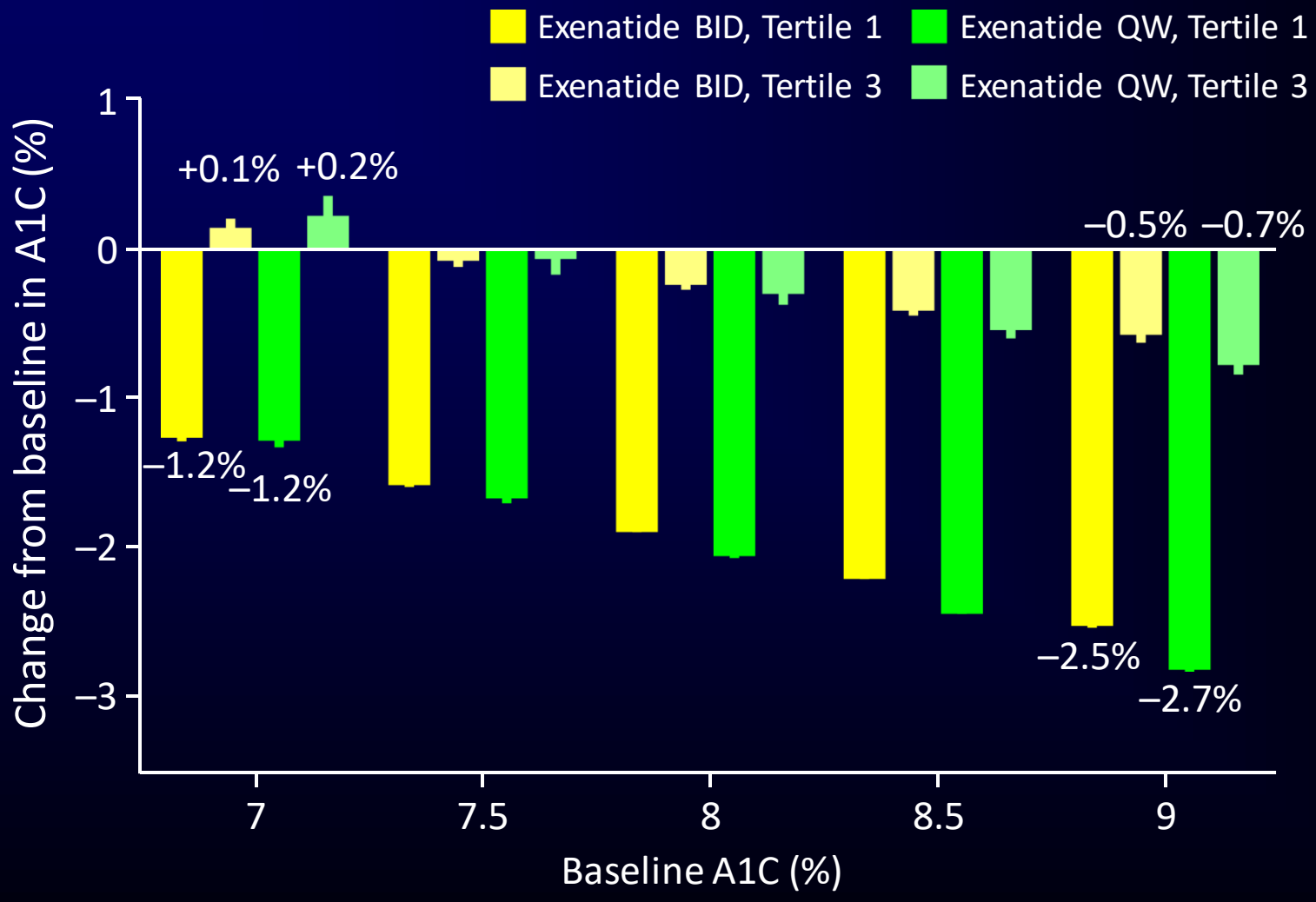
Baseline A1C and Change in A1C Were Significantly Correlated for Patients Treated With Exenatide BID and Exenatide QW



To identify Predictors Other Than A1C, Tertiles of Response Were Defined



Differences in A1C Response Were Seen Between Highest and Lowest Responders



BID, twice daily; QW, once weekly

Methods

- Exploratory univariate regression analyses identified baseline characteristics potentially associated with A1C response
- Potential independent predictors were entered into a stepwise multivariate linear regression and tested for their correlation with response
- Collinear (highly-related) variables were identified and only one was used in the overall model
- Baseline characteristics from the stepwise multivariate linear model (with a significance level of $P<0.15$) were included in a multivariate GEE model and tested for a significant correlation with response ($P<0.05$)

GEE, generalized estimating equation.

Baseline Characteristics Examined for Exenatide Response

Categorical Variables

- Sex
- Ethnicity
  - White, Asian, Black or African American, Hispanic, Other
- Glucose-lowering background therapy
  - Non, metformin, sulfonylurea, dual therapy, triple therapy
- eGFR category
  - ≥30–<60 mL/1.73 m^2, ≥60–<90 mL/min/1.73 m^2, ≥90 mL/min/1.73 m^2

Continuous Variables

- Age
- Weight
- Body mass index
- A1C
- Fasting glucose
- Diabetes duration
- SMBG
  - Pre- and post-meals
  - Summary measures, including post-meal glucose excursions
- eGFR

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eGFR, estimated glomerular filtration rate; SMBG, self-monitored blood glucose.

Baseline Characteristics for the Highest (Tertile 1) and Lowest (Tertile 3) Responders to Exenatide BID or Exenatide QW

	Exenatide BID		Exenatide QW	
Characteristic	**Tertile 1 (n=472)**	**Tertile 3 (n=471)**	**Tertile 1 (n=312)**	**Tertile 3 (n=314)**
Continuous variables at baseline, mean (95% confidence interval)				
Age, years	58.2 (57.30, 59.01)	55.2 (54.32, 56.03)	54.9 (53.77, 56.04)	54.1 (52.89, 55.32)
Baseline A1C, %	8.14 (8.06, 8.23)	8.08 (8.00, 8.17)	8.70 (8.57, 8.82)	8.62 (8.50, 8.74)
Fasting glucose, mg/dL	170.1 (166.3, 173.9)	184.4 (179.9, 188.8)	172.8 (167.4, 178.2)	178.4 (172.8, 184.0)
SMBG measures, mg/dL				
Pre-breakfast	165.4 (162.1, 168.6)	170.3 (166.7, 174.0)	177.3 (172.1, 182.3)	177.5 (172.3, 182.7)
PPG excursion for breakfast	50.9 (46.5, 55.1)	40.1 (36.0, 44.1)	55.8 (50.0, 61.4)	59.2 (53.6, 64.8)
Pre-lunch	164.1 (159.5, 168.6)	164.8 (160.0, 169.7)	173.9 (167.8 180.2)	181.8 (173.9, 186.7)
PPG excursion for lunch	38.5 (34.3, 42.7)	29.6 (25.5, 33.7)	42.8 (37.6, 48.1)	45.2 (39.2, 51.1)
Pre-dinner	162.1 (157.8, 166.4)	164.1 (159.5, 168.7)	178.0, (171.7, 184.5)	180.4 (174.4, 186.1)
PPG excursion for dinner	38.7 (34.1, 43.2)	35.8 (31.5, 40.1)	43.9 (38.3, 49.5)	50.0, (44.5, 55.6)
Mean daily blood glucose	183.2 (179.5, 186.9)	181.9 (178.1, 185.8)	199.3 (193.7, 204.7)	204.1 (198.9, 209.3)

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Baseline Characteristics for the Highest (Tertile 1) and Lowest (Tertile 3) Responders to Exenatide BID or Exenatide QW

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Characteristic	Exenatide BID		Exenatide QW	
	Tertile 1 (n=472)	Tertile 3 (n=471)	Tertile 1 (n=312)	Tertile 3 (n=314)
Categorical variables at baseline, n (%)				
Ethnicity				
White	363 (76.9)	411 (87.3)	186 (52.0)	168 (46.9)
Asian	78 (16.5)	32 (6.8)	123 (39.4)	153 (48.7)
Hispanic	26 (5.5)	23 (4.9)	40 (12.8)	19 (6.1)
Background therapy				
Diet and exercise only	25 (5.3)	32 (6.8)	86 (27.6)	52 (16.6)
Metformin only	176 (37.3)	199 (42.3)	132 (42.3)	103 (32.8)
Sulfonylurea	11 (2.3)	4 (0.8)	10 (3.2)	12 (3.8)
Dual therapy	225 (47.7)	208 (44.2)	79 (25.3)	141 (44.9)
Triple therapy	33 (7.0)	24 (5.1)	5 (1.6)	4 (1.3)
eGFR category				
≥30–<60 mL/min/1.73 m^2	35 (7.4)	23 (4.9)	22 (7.1)	21 (6.7)
≥60–<90 mL/min/1.73 m^2	217 (46.0)	209 (44.4)	174 (55.8)	146 (46.5)
≥90 mL/min/1.73 m^2	216 (45.8)	233 (49.5)	116 (37.2)	147 (46.8)

Results of Stepwise Multivariate Linear Regression Analyses for Exenatide BID and Exenatide QW

- Exenatide BID
  - Parameters negatively correlated with change in A1C:
    - Pre-breakfast blood glucose
    - PPG excursion for breakfast
    - Asian versus non-Asian ethnicity
    - Age
- Exenatide QW
  - Parameters negatively correlated with change in A1C:
    - Mean daily blood glucose
    - Fasting glucose

Factors Associated With High Responsiveness to Exenatide BID by Multivariate GEE Modeling

Baseline Characteristic	Estimated Odds	Confidence Limits for Estimated Odds		*P*-Value
Ethnicity (Asian vs non-Asian)	2.1128	1.5131	2.9502	<0.0001
Age (per 5 years older)	1.1242	1.0679	1.1835	<0.0001
Pre-breakfast blood glucose (per 10-mg/dL increase)	0.9760	0.9503	1.0024	0.0744
PPG excursion for breakfast (per 10-mg/dL increase)	1.0219	0.9990	1.0452	0.0608

- For Asian patients, the odds of being in the highest response tertile (1) were 2.1 times the odds for non-Asian patients
- The odds of being in Tertile 1 were 1.1 times greater with every 5-year increase in age

Factors Associated With High Responsiveness to Exenatide QW by Multivariate GEE Modeling

Baseline Characteristic	Estimated Odds	Confidence Limits for Estimated Odds		*P*-Value
Fasting glucose (per 10-mg/dL increase)	0.9989	0.9629	1.0364	0.9553
Mean daily blood glucose (per 10-mg/dL increase)	0.9833	0.9479	1.0199	0.3667

Conclusions

- At least two-thirds of patients respond markedly to exenatide and baseline A1C is the most important predictor of response
- After accounting for baseline A1C, the multivariate GEE model found:
  - Asian ethnicity was the most important predictor of treatment success for exenatide BID
  - No factors predicted greater responsiveness to exenatide QW
- These results are similar to a study of another GLP-1 receptor agonist, dulaglutide[1]
  - Baseline A1C was the key factor associated with treatment success
  - Age, fasting glucose, fasting insulin and eGFR were also minor factors associated with treatment success
- The difference in predictors for exenatide QW and exenatide BID appears real
  - Variability may be due to known pharmacokinetic and pharmacodynamic differences between the two formulations
- Additional studies are needed to examine biomarkers of response and to validate these findings in an independent dataset

1. Wysham C, et al. *Diabetes Obes Metab.* 2016;[Epub ahead of print].

Acknowledgments

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Additional slides

Collinearity

- Potentially important characteristics were examined for collinearity with other possibly related variables; variables with high collinearity were examined separately in multivariate regression models
- For exenatide BID, the variable "mean daily blood glucose" was highly correlated with other mealtime glucose variables
  - Based on the known mechanism of action of exenatide BID, the mealtime blood glucose concentrations were examined in the GEE model instead of the mean daily blood glucose to avoid collinearity
- For exenatide QW, the variable "mean daily blood glucose" was correlated with pre-meal glucose measures and post-meal glucose excursions
  - Based on the known mechanism of action of exenatide QW, the mean daily blood glucose concentrations were examined in the GEE model instead of the mealtime blood glucose to avoid collinearity