SUPPLEMENTARY MATERIAL

Manuscript Title

Frequency and Severity of Hypoglycemia Under Conditions of Increased Hypoglycemic Risk with Treatment of Insulin Efsitora Alfa Versus Insulin Glargine in Participants with Type 2 Diabetes

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Supplemental Table 1. Glargine Dosing Guidance

Fasting plasma glucose (mg/dL)	Glargine Dose Adjustment
Hypoglycemia[a]	-2 to 4 U
101 to 120	+2 U
121 to 140	+4 U
141 to 180	+6 U
>180	+8 U

[a]Hypoglycemia was defined as multiple events with FPG <70 mg/dL, ≥1 severe event (required assistance), or ≥1 event with FPG ≤54 mg/dL in the preceding week.
Abbreviations: FPG, fasting plasma glucose

Supplemental Table 2. Efsitora First Dose Guidance

Median Baseline Fasting Glucose (mg/dL)	Efsitora First Dose (mg)
<80	[Basal Insulin Dose (U) ÷ 7 - 1 mg] x 3
80 to 100	[Basal Insulin Dose (U) ÷ 7] x 3
101 to 140	[Basal Insulin Dose (U) ÷ 7 + 0.5 mg] x 3
141 to 180	[Basal Insulin Dose (U) ÷ 7 + 1 mg] x 3
182-220	[Basal Insulin Dose (U) ÷ 7 + 2 mg] x 3
>220	[Basal Insulin Dose (U) ÷ 7 + 3 mg] x 3
Basal insulin equivalent dose is multiplied by 3 to obtain a one-time starting dose.	

Supplemental Table 3. Efsitora Dosing Guidance

Median FG (mg/dL)[a]	Efsitora second dose (mg)	Efsitora subsequent doses (mg)
<70 mg/dL or ≤80 mg/dL and have any nocturnal hypoglycemia or multiple (≥3) episodes of hypoglycemia	-1.75 mg	-1.25 mg
≤80 mg/dL and no nocturnal hypoglycemia or <3 episodes of hypoglycemia	-1.5 mg	-1 mg
80 to 100 mg/dL	-1 mg	-0.5 mg
101 to 130 mg/dL	No change	No change
131 to 180 mg/dL	+3 mg	+1.5 mg
>180 mg/dL	+4 mg	+2 mg

[a]Based on median fasting glucose from at least 4 SMPG readings from the previous week

Supplemental Table 4. Sensitivity Analyses of Hypoglycemia Results

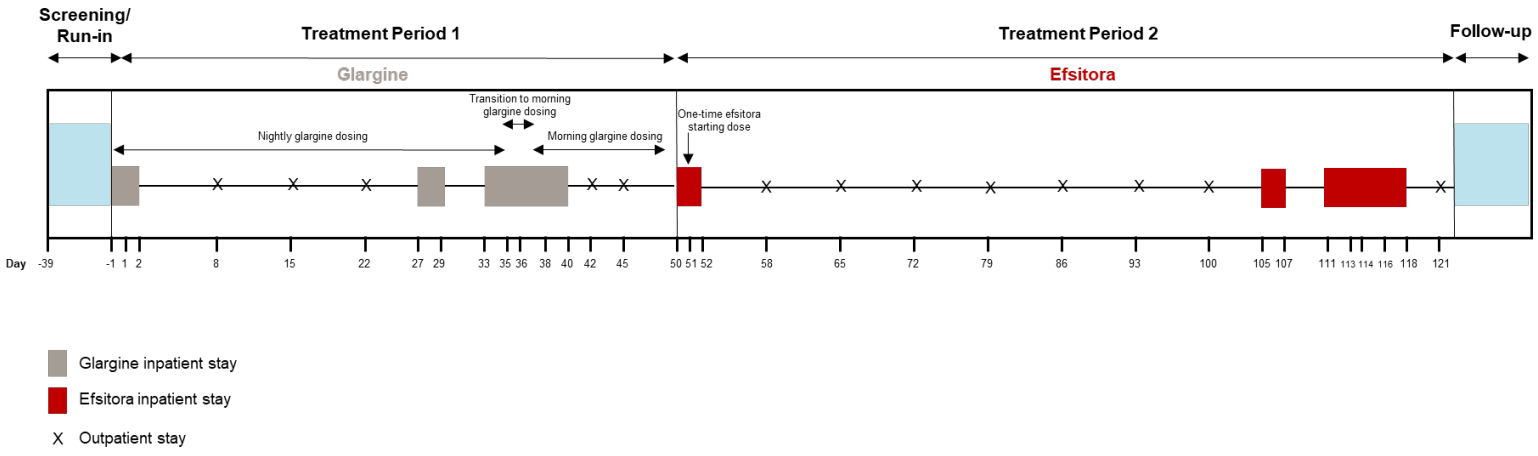
	Efsitora		Glargine		
	Proportion of participants with hypoglycemic event n/N (%)	Number of hypoglycemic events	Proportion of participants with hypoglycemic event n/N (%)	Number of hypoglycemic events	Difference in proportions (efsitora - glargine) (95% CI)
Sensitivity Analysis 1[a]					
Level 1 hypoglycemia (<70 and ≥54 mg/dL)					
Prolonged Fasting	16/31 (51.6)	31	17/31 (54.8)	35	-3.2% (-27.4%, 20.9%)
Prolonged Fasting with Exercise	19/29 (65.5)	36	15/29 (51.7)	26	13.8% (-8.1%, 35.7%)
Double Dosing					
Between 0 and 48h	17/31 (54.8)	57	21/31 (67.7)	46	-12.9% (-39.3%, 13.5%)
Between 0 and 96h	21/31 (67.7)	151	-	-	-
Between 48 and 96h	20/31 (64.5)	94	-	-	-
Level 2 hypoglycemia (<54 mg/dL)					
Prolonged Fasting	5/31 (16.1)	5	0/31 (0.0)	0	16.1% (0.0%, 32.3%)
Prolonged Fasting with Exercise	2/29 (6.9)	2	0/29 (0.0)	0	6.9% (-5.8%, 19.6%)
Double Dosing					
Between 0 and 48h	3/31 (9.7)	3	5/31 (16.1)	5	-6.5% (-25.0%, 12.1%)
Between 0 and 96h	5/31 (16.1)	9	-	-	-
Between 48 and 96h	4/31 (12.9)	6	-	-	-
Sensitivity Analysis 2[b]					
Level 1 hypoglycemia (<70 and ≥54 mg/dL)					

Double Dosing					
Between 0 and 48h	13/19 (68.4)	44	15/19 (79.0)	34	-
Between 0 and 96h	15/19 (79.0)	105	-	-	-
Between 48 and 96h	14/19 (73.7)	61	-	-	-
Level 2 hypoglycemia (<54 mg/dL)					
Double Dosing					
Between 0 and 48h	1/19 (5.3)	1	4/19 (21.1)	4	-
Between 0 and 96h	4/19 (21.1)	6	-	-	-
Between 48 and 96h	3/19 (15.8)	5	-	-	-

[a] Sensitivity analysis 1 calculated the incidence and number of hypoglycemia events for participants who achieved a stable fasting plasma glucose of 80 to 120 mg/dL.

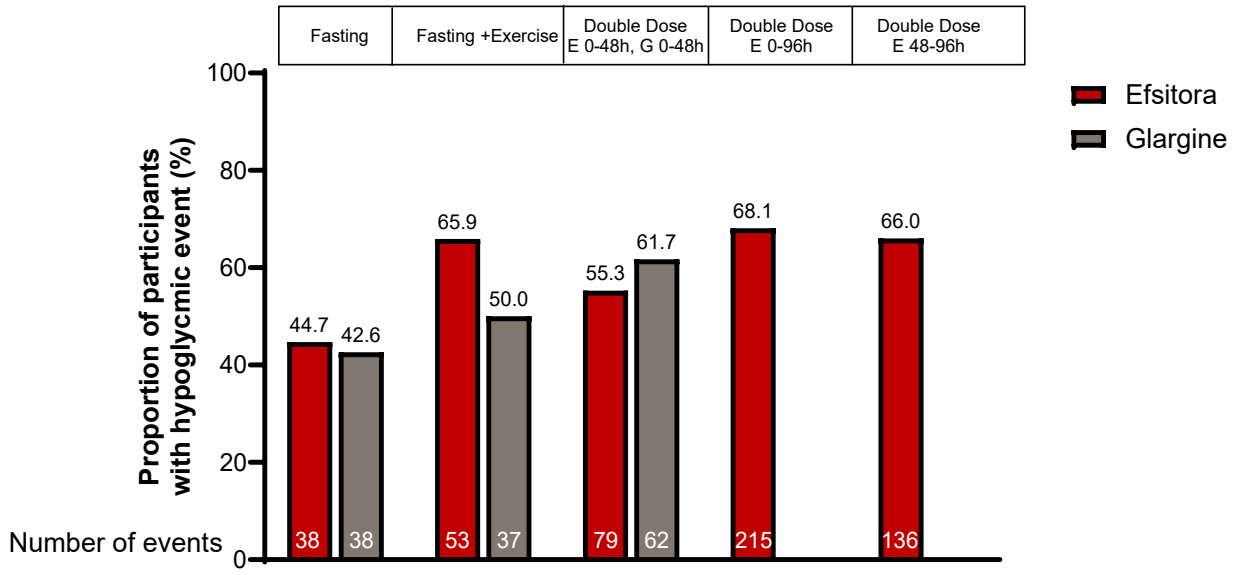
[b] Sensitivity analysis 2 calculated the incidence and number of hypoglycemia events in the double dosing provocation period in participants with T2D who had similar FPG prior to the double dosing in both treatment periods.

Supplemental Figure 1. Study Design



Supplemental Figure 2. Incidence of Hypoglycemic Events During Provocation Periods

A



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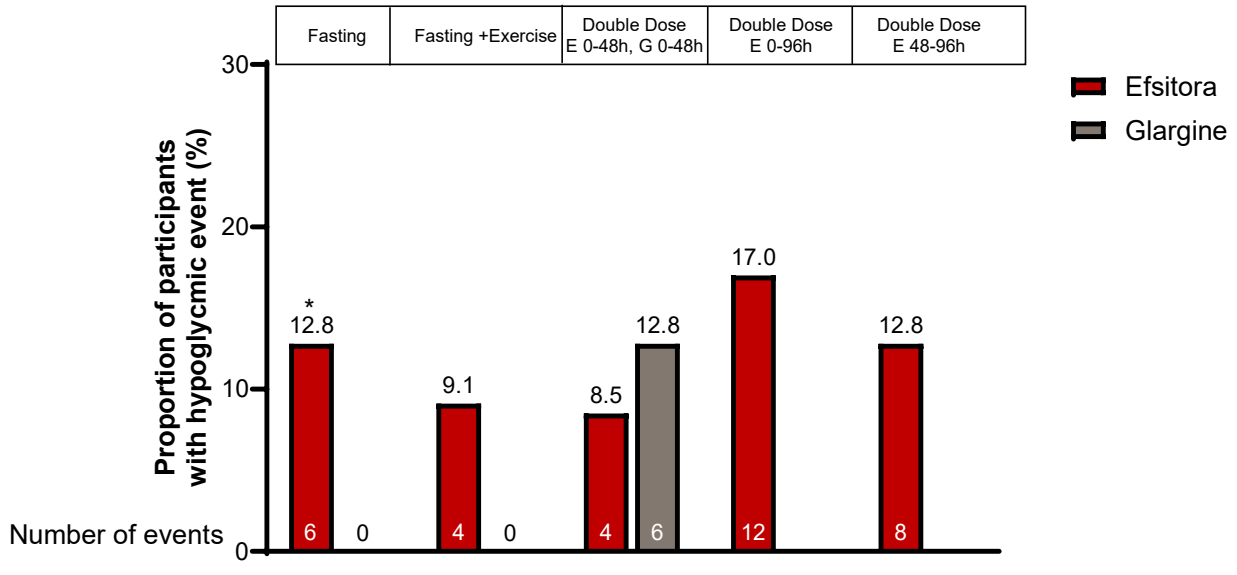
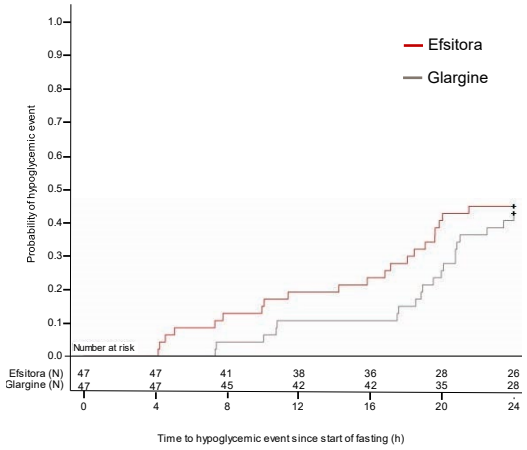


Supplemental Figure 3. Kaplain-Meier Curves of Time to Level 1 Hypoglycemia

A



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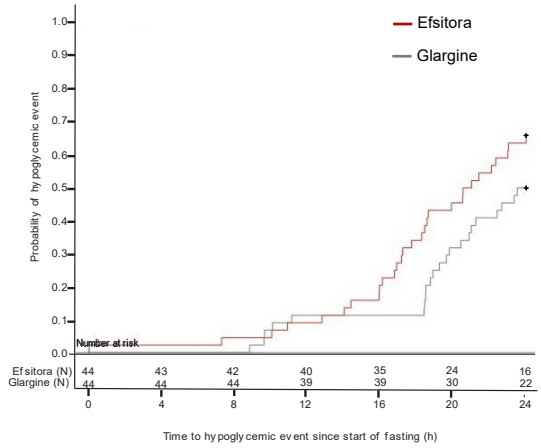

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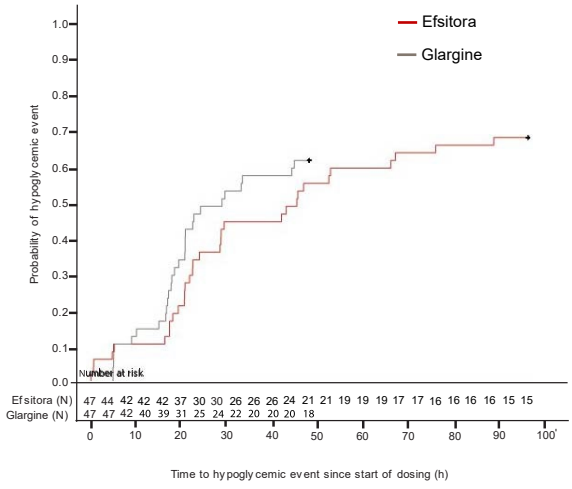
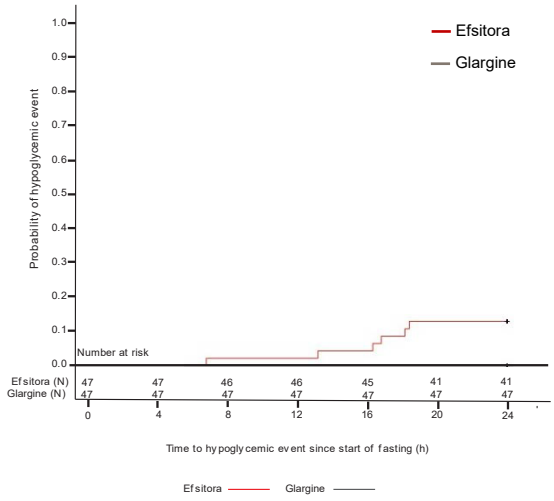


Supplemental Figure 4. Kaplain-Meier Curves of Time to Level 2 Hypoglycemia

A



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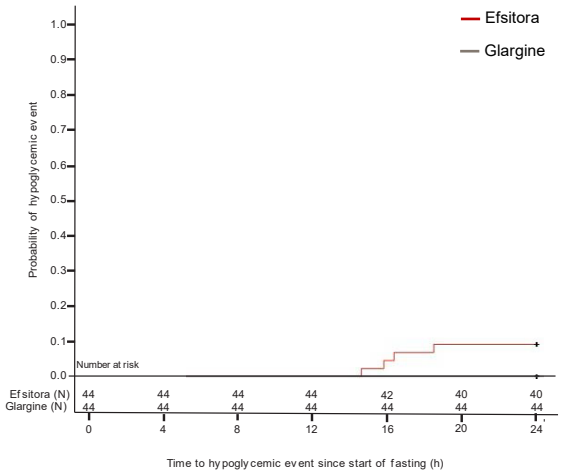

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