

REPEATED TIME TO EVENT MODEL OF NAUSEA AND VOMITING INDUCED BY EFPEGLENATIDE

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Introduction

Obesity has become an increasingly prevalent condition in modern society, significantly impacting both health and overall quality of life. Among the most widely used pharmacological interventions are **glucagon-like peptide-1 (GLP-1) receptor agonists**, which have demonstrated substantial efficacy in promoting weight loss. However, despite their therapeutic benefits, clinical trials have consistently reported gastrointestinal adverse effects associated with this drug class, including nausea, vomiting, diarrhea, and constipation. Consequently, a comprehensive safety evaluation is crucial in the development of novel GLP-1 receptor agonists to ensure both efficacy and tolerability.

Objectives

Efpeglenatide is a novel GLP-1 receptor agonist administered as a once-weekly subcutaneous injection, with demonstrated efficacy in reducing glycated hemoglobin levels and body weight across multiple clinical trials. To assess the safety profile of efpeglenatide, we conducted a pharmacokinetic and pharmacodynamic analysis of adverse events using pooled data from six clinical trials. Given that nausea and vomiting are among the most frequently reported adverse effects of GLP-1 receptor agonists, our analysis specifically focused on characterizing the impact of efpeglenatide on these gastrointestinal symptoms.

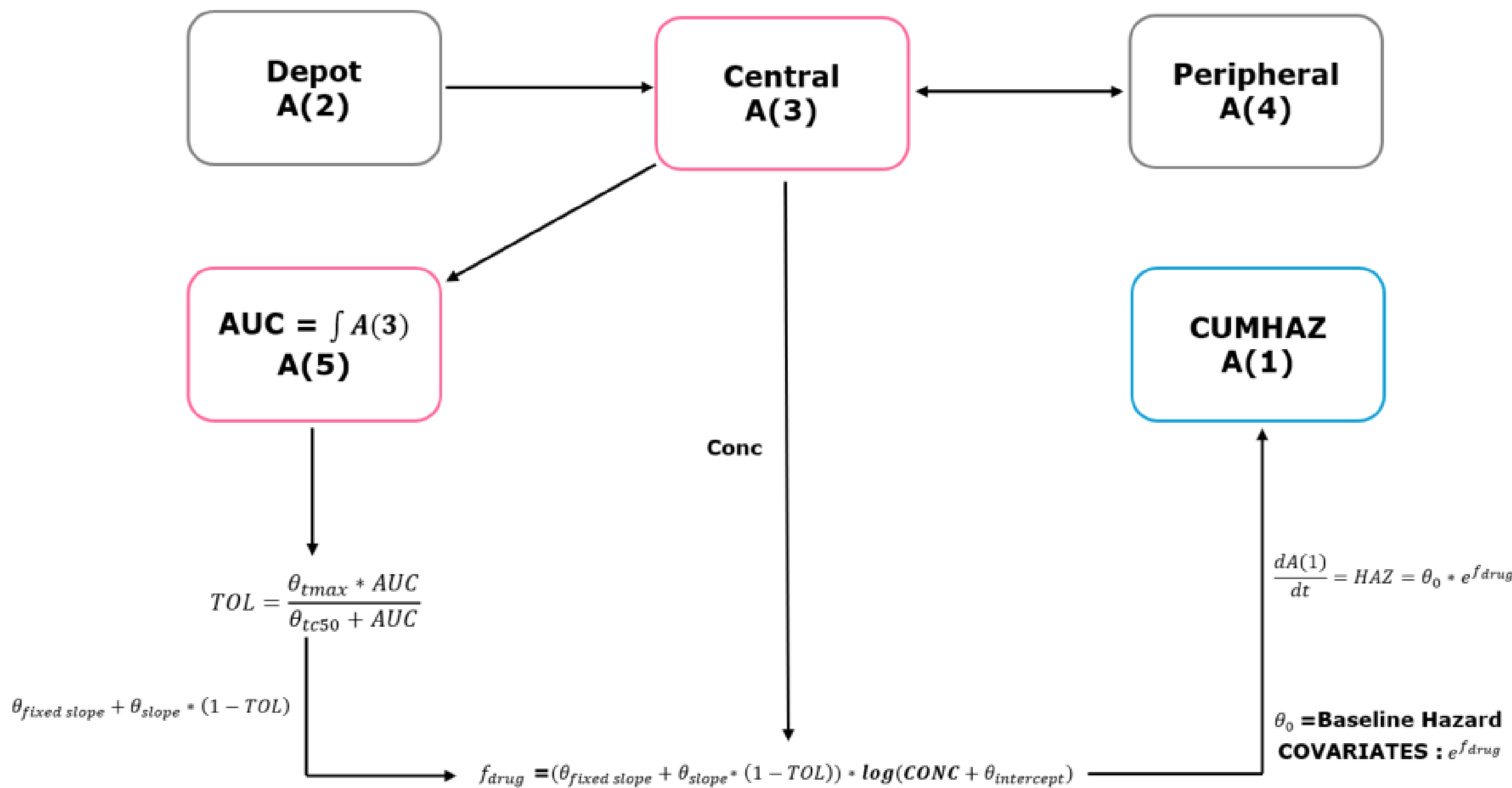
Method

This analysis incorporates pharmacokinetic data and nausea/vomiting events from six clinical trials, including five conducted in diabetic patients and one in obese patients. Repeated time-to-event modeling was performed using NONMEM (version 7.5) to evaluate nausea and vomiting in a total of **917 participants**, including **295 obese individuals**. The final model employed an exponential model with multiple covariates. Two distinct models were developed: one incorporating data from all six studies and another exclusively utilizing data from the obesity-focused trial (Study 205), the latter of which was used for predicting nausea and vomiting in obese patients. Among the 917 patients assigned to the treatment group, **678 patients** were included in the analysis after excluding those without available PK profile. Among **the 678 subjects** analyzed, **247 (36%)** reported at least one occurrence of nausea or vomiting.

Table1. Summary of subjects in 6 clinical trials

Study	Type of subjects	Number of subjects			
		Total	Efpeglenatide	Placebo	Liraglutide
102	Type 2 Diabetic Mellitus	47	26	8	13
201	Type 2 Diabetic Mellitus	48	40	8	-
202	Type 2 Diabetic Mellitus	68	51	17	-
203	Type 2 Diabetic Mellitus	252	179	37	36
204	Type 2 Diabetic Mellitus	207	157	50	-
205	Obesity	295	235	60	-
Total	-	917	688	180	49

Figure1. Schemic of Nausea And Vomiting model [205 Study]



Results

The model demonstrated a reasonable fit to the observed data for both the overall patient population and the obese subgroup. Given that Efpeglenatide is intended for obesity treatment, this abstract focuses solely on the obesity-specific model. The concentration-dependent adverse event rate was best described by a **log-linear** model.

The estimated first-order rate constant governing the decline of the non-drug effect over time was **0.0208 hr⁻¹**, corresponding to a half-life of **33.32 hours (approximately 1.5 days)**. This indicates that the non-drug effect diminishes by half within this period and returns to the baseline hazard approximately **7 days** after treatment initiation. The **rate of change in drug effect on the log-hazard** (θ_{slope}) was estimated at **0.627 1/(hr*ng/mL)**, with an **intercept** ($\theta_{intercept}$) of **0.634 ng/mL**. This indicates that for every **1 ng/mL increase in the logarithm of the sum of drug concentration and the intercept**, the log-hazard ratio increases by **0.627 1/(hr*ng/mL)**. The intercept, being **less than 1**, suggests a **fixed reduction in log-hazard** independent of drug concentration when **efpeglenatide is absent**. [$\theta_{slope} * \log(\theta_{intercept}) = -0.286$] Considering both the intercept and drug concentration, the **equivalent drug concentration required to achieve a 1 ng/mL change in log concentration** was estimated at **2.084 ng/mL**. [$e^{1 - \theta_{intercept}} = 2.084 \text{ ng/mL}$] This implies that an increase in **efpeglenatide concentration by 2.084 ng/mL** leads to a **0.627 1/(hr*ng/mL) increase in the log-hazard ratio**.

To characterize tolerance, an **E_{max} model** was applied, using the cumulative **area under the concentration-time curve (AUC)** as the driving factor. The estimated **TC₅₀ (AUC at which 50% tolerance is established)** was **109,872 ng*h/mL**. At a weekly **initial dose without titration**, the time required to reach **TC₅₀** was approximately **four weeks**, indicating rapid tolerance development following initial administration. The maximum tolerance effect on slope was estimated at **0.996**, the determination of the maximum slope reduction is **0.0025** [$\theta_{slope} \cdot (1 - \theta_{TOL_{max+slope}}) = 0.0025$].

In the maximum tolerance state, the slope decreases from **0.627 (hr*ng/mL)⁻¹** to **0.0025 (hr*ng/mL)⁻¹**, indicating a substantial reduction in the impact of drug concentration on log-hazard. In other words, the potency of the drug’s concentration-dependent effect on log-hazard was **significantly reduced—by approximately 251-fold**. The model estimation parameters are shown in Table 2.

REFERENCES

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- Pharmacokinetic and Pharmacodynamic Data Analysis Concepts and Applications (5th Edition)_by Gabrielsson p.221.
- Cheng Cai Tang et al. The Journal of Clinical Pharmacology 2024, 64(2) 215–226.
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Table2. Parameter estimates for the nausea and vomiting model[205 study]

Time to event modeling parameters	Estimates
Base model : Exponential model	
Baseline hazard (205 study)	0.000153 1/hr
Covariates : Concentration [Log-Linear]	
The attenuating rate of change in the drug effect on the log hazard attributed to log(concentration) at time equal zero (Slope)	0.627 1/(hr*ng/mL)
The stationary drug effect modifying the attenuating change rate of the drug effect on the log hazard (Intercept)	0.634 ng/mL
Covariates : Tolerance effect from cumulative concentration (AUC) [E_{max}]	
Maximum tolerance effect	0.996
Cumulative concentration(AUC) at 50% AUC tolerance effect	109,872 hr*ng/mL
Covariates : Placebo effect over time	
The first-order rate constant which governs the rate with which maximum non-drug effect 1 changes with time t	0.0208 1/hr

The visual predictive check (VPC) for the obese subject model shows a sharp increase in nausea and vomiting within the first seven days after drug administration and slight increases thereafter, attributed to both the drug effect and a temporary non-drug effect lasting about a week. The model-estimated TC₅₀ value indicated that 50% tolerance to nausea and vomiting was achieved after approximately **four weeks** with a weekly initial dose of efpeglenatide. Given that the HM-EXC-205 study utilized higher dosing exposure than a weekly initial dosing, TC₅₀ was likely reached earlier than with the weekly initial dose. By **twelve weeks**, 90% tolerance (TC₉₀) is achieved at the higher doses, leading to a further reduction in nausea and vomiting. Beyond **four weeks**, drug concentrations stabilize, and the log-linear model predicts minimal further increases in drug-related effects. Consequently, adverse events become rare, aligning with the plateau observed in the cumulative probability curve. In summary, nausea and vomiting peak in the **first week**, decline significantly after **four weeks** due to rapid tolerance development, and become infrequent after **twelve weeks**. The visual predictive check (VPC) of HM-EXC-205 study is shown in Figure 2.

Figure2. Cumulative probability of patients experiencing nausea and vomiting

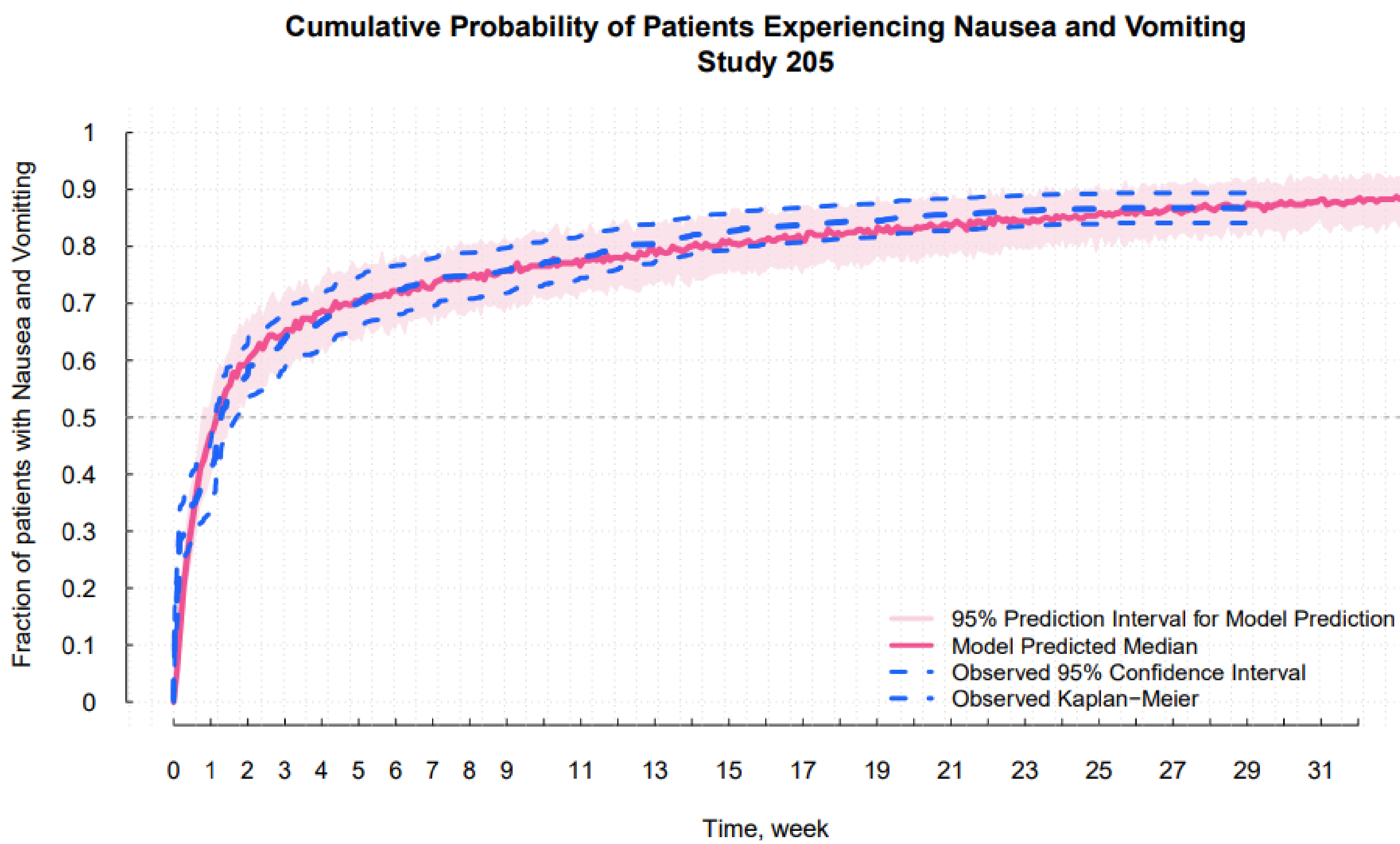


Figure3. Simulation plot following various doing regimens

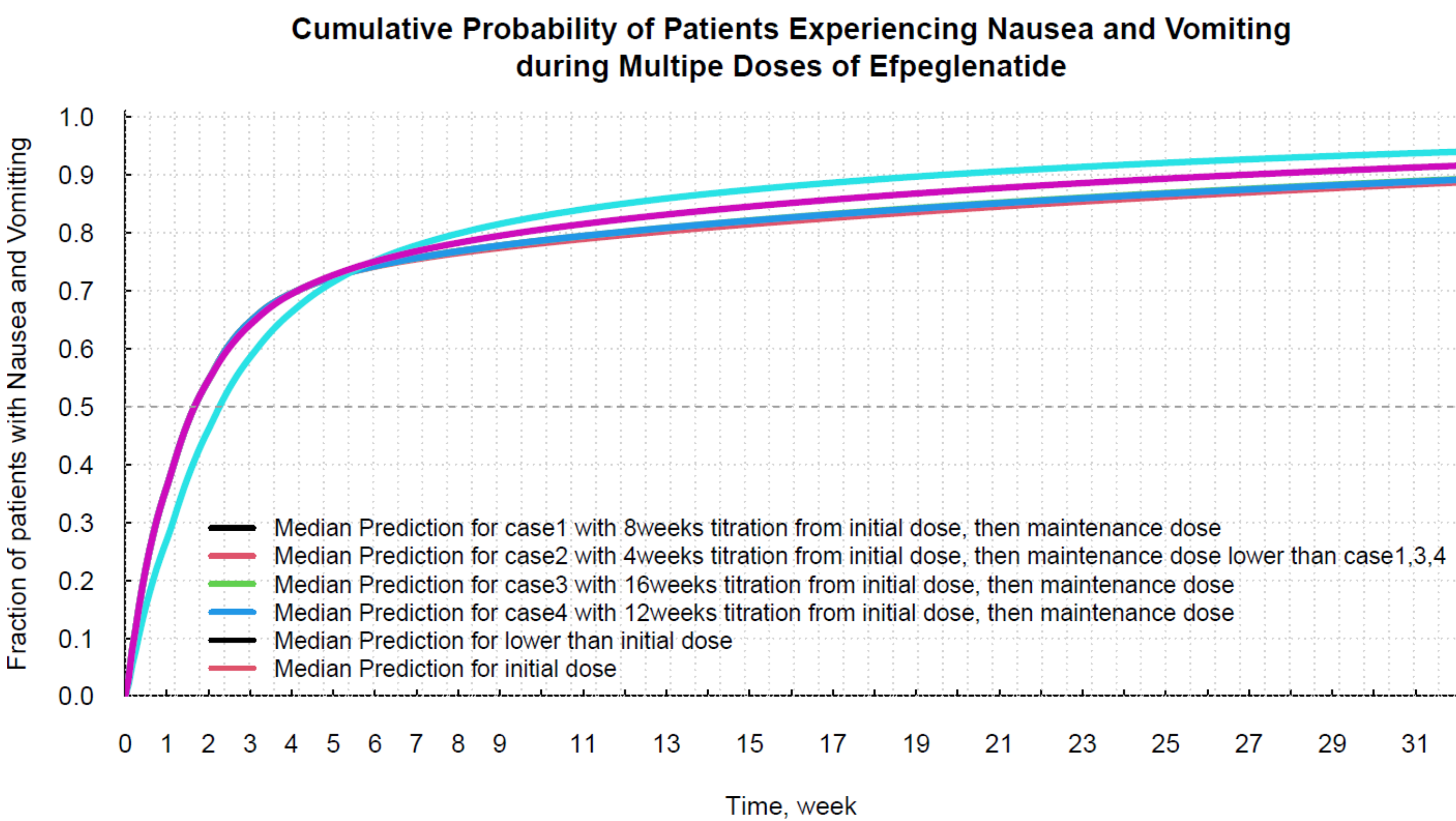


Figure 3 shows simulation plots for different dosing regimen cases. It can be seen that in all the different dosing cases with 8-week titration, there is a sharp increase in adverse events up to week 3, followed by a gradual decrease in the slope of the graph as tolerance is established above 50%. We could see that the cumulative probability flattens out after 8 weeks, regardless of the dose regimen.

Conclusion

The repeated time to event model for nausea and vomiting described and predicted adverse events of efpeglenatide in patients with type 2 diabetes and obesity successfully. The model predicted that efpeglenatide rapidly increases the incidence of nausea and vomiting early after the first dose through approximately **four weeks** after which tolerance is rapidly established with significant drop in the frequency of adverse events. A **simulation study** showed that administering an **initial dose for four weeks** is sufficient to achieve **50% tolerance**, which occurs when the **cumulative AUC** reaches **109,872 hr*ng/mL or higher**. Increasing the dose within the first **four weeks**, rather than maintaining a **weekly dose of initial dose or more**, did not significantly raise the risk of **adverse events** after **four weeks**, with similar outcomes observed across different dosing regimens. Across all simulations, tolerance was almost fully established by **twelve weeks**, after which the incidence of nausea and vomiting became negligible. The results of this modeling study provide useful information about the relationship between PK and major advance event of nausea / vomiting following efpeglenatide. This information will help determine the appropriate efpeglenatide dose regimens with maximal effect and minimal adverse event.

Acknowledgement

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