Validation of Clinical Response Rates Extrapolated With Dose-Response Estimation Methods in Chronic Hepatitis Delta

CO91

Barinder Singh[1], Shubhram Pandey[2], Sumeet Attri[2], Marvin Rock[3], Chong Kim[3]

[1]Pharmacoevidence, London, UK; [2]Pharmacoevidence, Mohali, India; [3]Gilead Sciences, Foster City, CA, USA

CONCLUSIONS

- Non-linear regression models can be effective alternatives to conventional linear and expected maximum effect model (EMAX) models for estimating long-term responder rates, particularly in clinical trials with limited participants
- This study supports the wider use of advanced nonlinear regression models to estimate long-term response rates, offering robust evidence for HTA submissions to demonstrate the cost-benefit of treatments over extended periods. This approach enhances decision-making and planning for effective long-term patient management

PLAIN LANGUAGE SUMMARY

- Responder data from MYR301 was limited to week 48, necessitating extrapolation beyond this period to assess the full benefit of each treatment arm
- To predict responder rates at weeks 96 and 144, several methods were used, including Time-series analysis, the expected maximum effect model (EMAX), and nonlinear least squares estimation (NLSE). The best method was chosen by comparing Akaike Information Criterion (AIC) scores and visual inspection
- The NLSE method gave the best results, with its predictions confirmed by follow-up data from MYR301. These methods are especially effective for small sample sizes or low proportions, offering potentially more accurate predictions than traditional approaches

INTRODUCTION

- MYR 301 clinical study (NCT03852719) is a multicentre, open-label, randomized, phase 3 clinical study assessing the efficacy and safety of bulevirtide (BLV) in patients with chronic hepatitis delta (CHD)[1]
- To date, interim week 48 data has been used in health technology assessment (HTA) submissions to the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC)
- Due to limited follow-up data, it was necessary to extrapolate the clinical data beyond week 48 to obtain an estimate of the full benefit associated with each of the treatment arms
- Extrapolation is important in clinical research to predict long-term outcomes from short-term data when follow-up is limited[2]

OBJECTIVE

- The current research aims to explore if dose-response extrapolation methods are more viable for predicting long-term data with a small sample size and to validate the accuracy of these predictions by comparing extrapolation results with actual data

METHODS

- Individual patient-level data (IPD) for BLV 2mg and 10mg treatments from the MYR301 trial was divided into training (baseline to week 40) and testing (week 40 to week 48) data sets
- Several dose-response estimation methods were employed to predict the proportion of responders (complete, virologic, and alanine aminotransferase (ALT) normalization response) at weeks 96, 108, and 144 for both BLV doses. The definitions of different types of responders are summarized in **Table 1**
- Extrapolation methods included standard (time-series analysis and expected maximum effect model [EMAX])[3] and non-standard (nonlinear least squares estimation [NLSE] and NLSE with Box-Cox transformation using log-logistic and Weibull distributions) techniques[4,5]
- The best-fit model was selected based on the Akaike Information Criterion (AIC) and visual inspection[6]
- Extrapolations from all models were compared with actual data at weeks 96, 108, and 144, using mean square error (MSE) to assess the accuracy and visual inspection

Table 1. Responder definitions

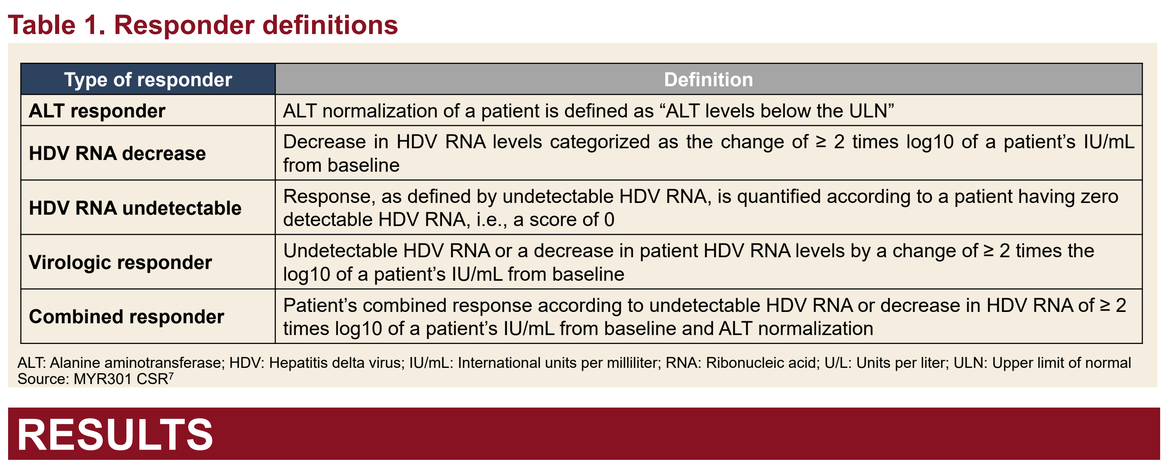
Type of responder	Definition
ALT responder	ALT normalization of a patient is defined as "ALT levels below the ULN"
HDV RNA decrease	Decrease in HDV RNA levels categorized as the change of ≥ 2 times log10 of a patient's IU/mL from baseline
HDV RNA undetectable	Response, as defined by undetectable HDV RNA, is quantified according to a patient having zero detectable HDV RNA, i.e., a score of 0
Virologic responder	Undetectable HDV RNA or a decrease in patient HDV RNA levels by a change of ≥ 2 times the log10 of a patient's IU/mL from baseline
Combined responder	Patient's combined response according to undetectable HDV RNA or decrease in HDV RNA of ≥ 2 times log10 of a patient's IU/mL from baseline and ALT normalization

ALT: Alanine aminotransferase; HDV: Hepatitis delta virus; IU/mL: International units per milliliter; RNA: Ribonucleic acid; U/L: Units per liter; ULN: Upper limit of normal
Source: MYR301 CSR[7]

RESULTS

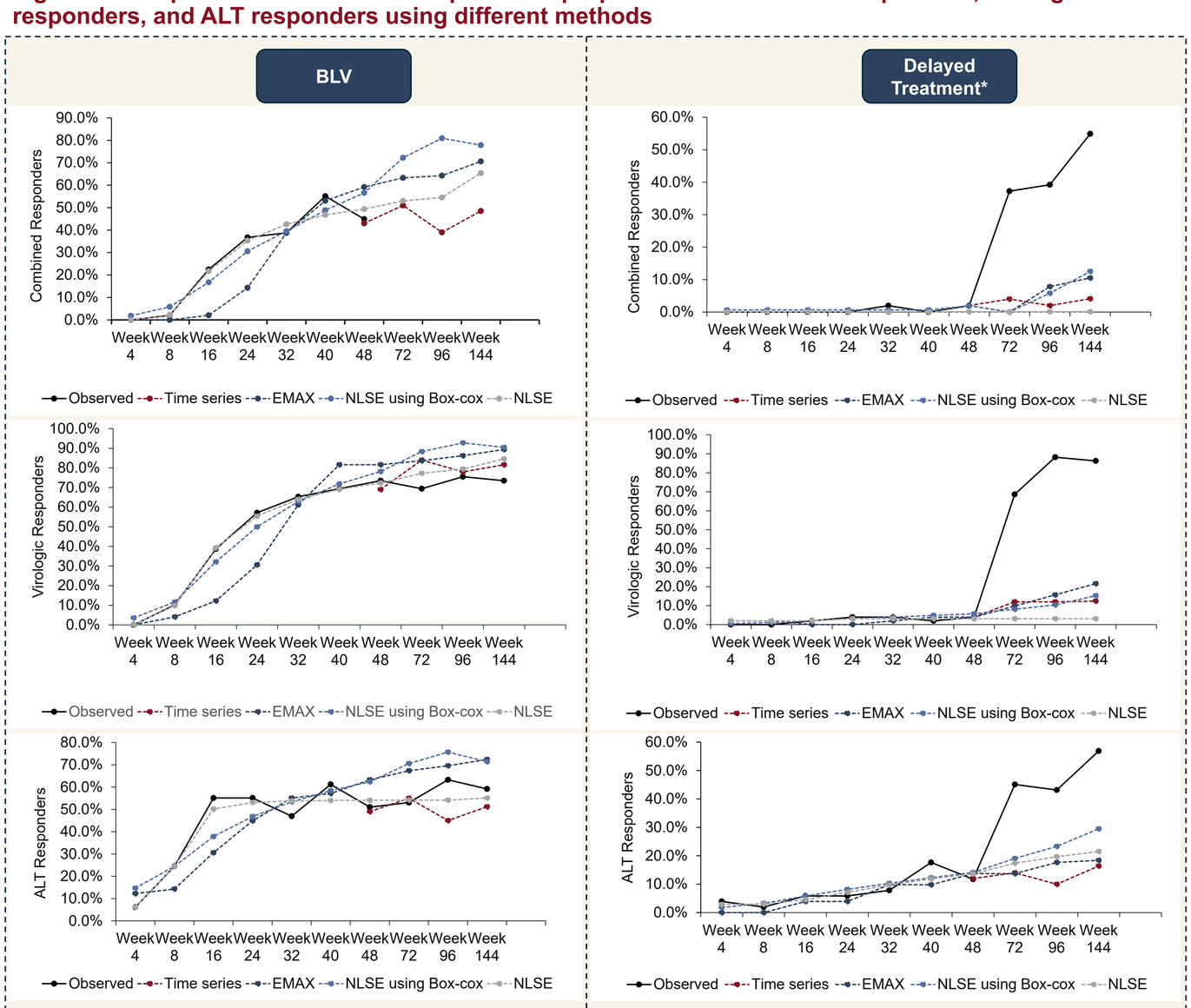
- The NLSE with Box-Cox transformation using log-logistic distribution was selected as the best-fit model based on the minimum AIC and visual inspection **(Figure 1)**
- Comparisons of predictions from the best-fitted model with actual data at weeks 96, 108, and 144 showed the lowest MSE for all endpoints, indicating that the selected model provided the most accurate extrapolated values **(Figure 2)**
- **Figure 3** depicts the prediction of combined responders, virologic responders, and ALT responders for validation

Figure 1: AIC of ALT, combined and virologic responders from NLSE and NLSE box-cox transformation model: BLV (a), Delayed treatment (b)



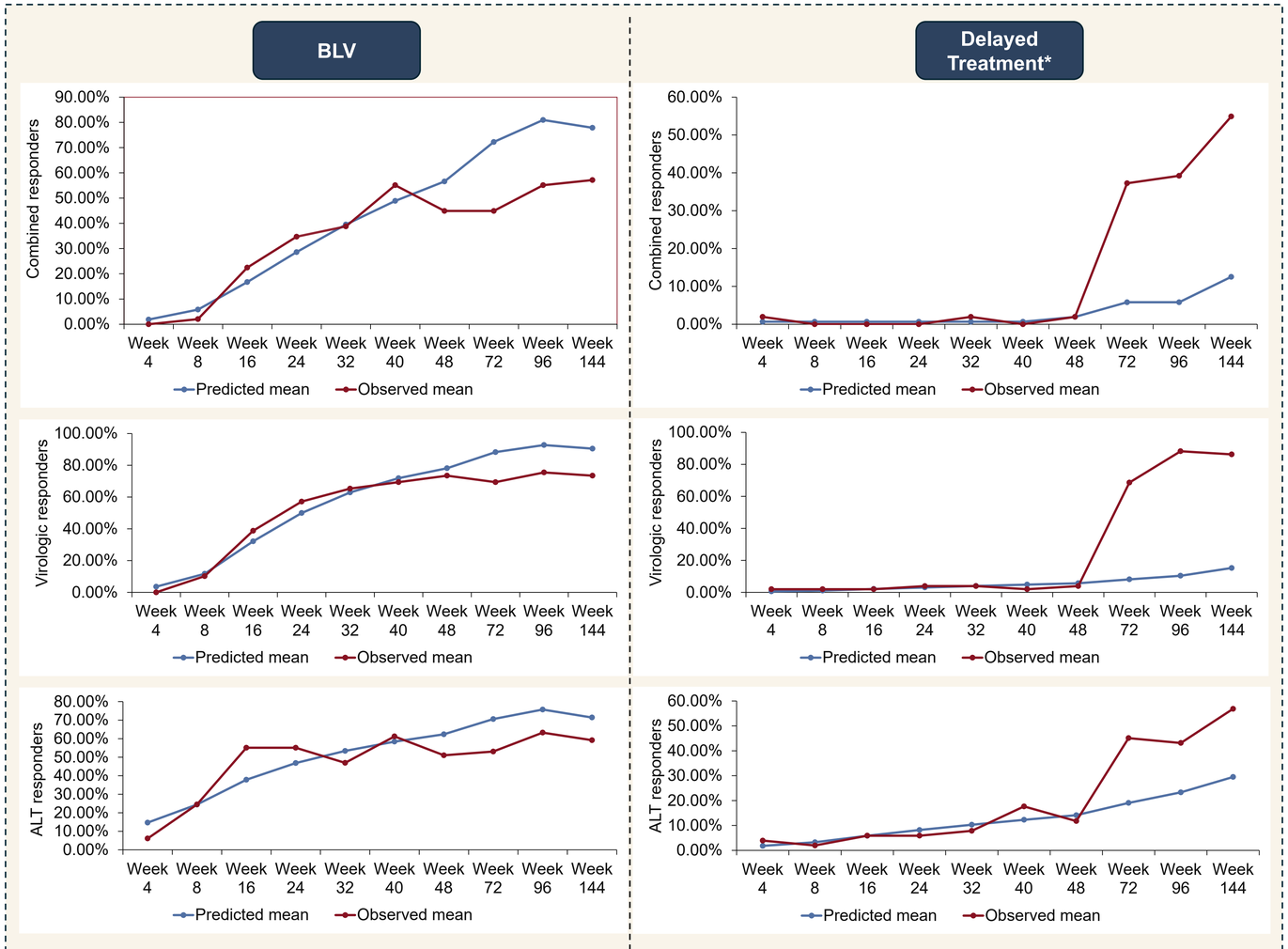
AIC: Akaike Information Criterion; ALT: Alanine aminotransferase; BLV: Bulevirtide; NLSE: Nonlinear least squares estimation

Figure 2: Comparison of observed and predicted proportions of combined responders, virologic responders, and ALT responders using different methods



ALT: Alanine aminotransferase; BLV: Bulevirtide; EMAX: Expected Maximum Effect Model; NLSE: Nonlinear Least Square Estimation
*Participants in the delayed treatment group were switched to bulevirtide 10 mg once daily for an additional 96 weeks

Figure 3: Prediction of combined responders, virologic responders, and ALT responders



ALT: Alanine aminotransferase; BLV: Bulevirtide
*Participants in the delayed treatment group were switched to bulevirtide 10 mg once daily for an additional 96 weeks

LIMITATIONS

- A key limitation of NLSE estimation is that over longer follow-up periods, the projected maximum response may exceed 100%, particularly for endpoints with high initial response rates

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