Research Article

Improper Selection of a Pre-specified Primary Dose–Response Analysis Delays Regulatory Drug Approval

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ABSTRACT. Dose–response analysis is one of the accepted efficacy endpoints to establish effectiveness. The purpose of this research was to inform selection of an appropriate pre-specified primary dose–response analysis to demonstrate drug efficacy in a registration trial. The power and the type I error rate of the placebo-corrected (*i.e.*, simply adjusting the observed treatment value by subtracting the placebo mean) and the placebo-anchored (*i.e.*, including the placebo data as dose 0 in the regression) slope analyses were assessed based on regulatory submission data for two antihypertensive drugs and simulated data from hypothetical clinical trials. In the simulated hypothetical trials, the impact of different dosing strategies (*i.e.*, the fixed dose *versus* the weight-based per kilogram dose), sample size, and scenarios governing the drug exposure–response relationship (*e.g.*, $E_{\max}$, ED_{50} , and SD) was also evaluated. For each scenario, a total 300 replications were simulated. The placebo-anchored slope analysis is always more powerful to demonstrate effectiveness in all plausible scenarios. The difference between the placebo-anchored and the placebo-corrected analyses was maximum when the studied doses were too high. However, the dose–response analysis is not sensitive to the dosing strategies. Furthermore, the type I error rate of these two methods was also found to be comparable. The design of dose–response studies should carefully consider these results to justify the inclusion of placebo and the analysis method. The pharmaceutical industry and the regulatory agencies are equally responsible for using the appropriate methods of primary analysis and providing justification in the protocol.

KEY WORDS: dose–response; power; type I error.

INTRODUCTION

Dose–response analysis is one of the well-accepted endpoints to demonstrate drug efficacy in a registration trial (1,2). The International Conference on Harmonisation (ICH) E4 guidance on Dose–Response Information to Support Drug Registration states that a positive dose–response slope from a randomized trial provides the evidence of a drug effect. The dose–response analysis is arguably more informative in dose recommendation compared with conventional drug and placebo comparison. The use of the dose–response as a primary efficacy endpoint is common in pediatric drug development. The recent examples of National Drug Authority (NDA) submissions to the Food and Drug Administration (FDA) which used a dose–response slope as a primary efficacy endpoint are: Atacand (candesartan) (3), Toprol-XL (metoprolol) (4), Benicar (olmesartan) (5), and Diovan (valsartan) (6) pediatric submissions for the treatment of hypertension (Table I) and rufinamide and oxcarbazepine for the treatment of epilepsy (7–9).

According to the ICH E4 guidance, even though a placebo group is not theoretically necessary in all dose–response studies, inclusion of a placebo group is desirable especially when a study uses doses that are too high and, therefore, cannot demonstrate a significant dose–response slope. In our observation from the submissions we mentioned above and other pediatric cardiovascular trials reported in literatures (10,11), the recommendation has not received enough attention in drug development practice and the implications have not been fully appreciated by clinical trial sponsors. For the NDA submissions mentioned above, most of them either did not include a placebo group or used the placebo-corrected slope analysis (described below) to demonstrate drug efficacy, if placebo was included. The placebo-corrected slope analysis in some of these submissions led to a wrong conclusion about the efficacy of drugs, if other evidence was not considered. Because the results of the primary analysis of efficacy endpoints are of critical importance, without inclusion of a placebo group or improper selection of a pre-specified primary dose–response, slope analysis can sometimes significantly delay a regulatory decision.

The placebo-corrected analysis adjusts the observed individual value in each active treatment group by subtracting the placebo mean value. Therefore, the slope analysis ignores all information from placebo in the study and is the practical

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Table 1. Pediatric Clinical Trial Submissions for the Treatment of Hypertension Based on Dose-Response Efficacy Endpoints

Drug	Study	Population	Treatment	Efficacy	Dose-response endpoint
Atacand (candesartan)	D2451C00261 (study 261A)	Hypertensive subjects 6 to <17 years of age (<i>N</i> =240)	Candesartan: 2, 8, or 16 mg oral tablet for subjects weighing <50 kg Candesartan, 4, 16, or 32 mg oral tablet for subjects weighing ≥50 kg Placebo At 2:2:1 ratio	SiSBP least-square mean change from baseline to week 4/LOCF, -3.7, -8.6, -11.2, and -10.9 mmHg for placebo and candesartan low, medium, and high doses	Placebo-corrected slope for SBP=-0.38 (<i>p</i> =0.0973)
Toprol-XL (metoprolol)	D4020C00033 (study 307A)	Hypertensive subjects 6 to <17 years of age (<i>N</i> =144)	Metoprolol, 0.2, 1.0, and 2.0 mg/kg or placebo at 2:1:2:1 ratio	SiSBP least-square mean change from baseline to week 4/LOCF: -1.9, -5.2, -7.7, and -6.3 mmHg for placebo and metoprolol low, medium, and high doses	Placebo-corrected slope for SBP=-0.11 (<i>p</i> =0.5731)
Benicar (olmesartan)	CS0866-AU301, period II cohorts A and B	Hypertensive subject 6 to <17 years (<i>N</i> =300)	Olmesartan, 2.5 or 20 mg for subject weighing <35 kg Olmesartan, 5 or 40 mg for subject weighing ≥35 kg At 1:1 ratio	SiSBP mean change from baseline to week 3/LOCF, -6.63 and -11.87 mmHg for placebo and olmesartan low and high doses	Slope for SBP=-0.75 (<i>p</i> <0.0001)
Diovan (valsartan)	CVAL489A 2307, phase 1	Hypertensive subject 1 to <6 years (<i>N</i> =90)	Valsartan, 5, 20, or 40 mg oral tablet for subjects weighing <18 kg Valsartan, 10, 40, or 80 mg oral tablet for subjects weighing ≥50 kg At 2:1:2 ratio	SiSBP mean change from baseline to week 2/LOCF, -8.4, -8.3, and -8.6 mmHg for valsartan low, medium, and high doses	Slope for SBP=-0.10 (<i>p</i> =0.7162)

SiSBP sitting systolic blood pressure, LOCF last observation carried forward. SBP systolic blood pressure

equivalent of not including a placebo arm in the study. On the other hand, the placebo-anchored slope analysis includes the data from the placebo group in the regression by treating placebo as dose 0 (Fig. 1). Therefore, the placebo-anchored analysis includes more data points and a wider dose-range and in general will provide more power in demonstrating drug efficacy.

This manuscript focuses on the appropriate selection of a pre-specified primary dose-response slope analysis for evidence of efficacy. Toward that end, we assessed the power and type I error of the placebo-anchored slope analysis compared with the placebo-corrected slope analysis in detecting a significant dose-response slope to demonstrate evidence of efficacy in a registration trial. Our primary intent is to bring clinical trial sponsors' attention to the selection of an appropriate pre-specified primary dose-response analysis for efficacy and the provision of adequate justification in the protocol for a registration trial.

METHODS

Case Study: Candesartan and Metoprolol Pediatric Data

The observed clinical results from candesartan (3) and metoprolol (4) pediatric trials were used to compare the placebo-anchored slope analysis *versus* placebo-corrected slope analysis.

Candesartan Trial

Pediatric hypertensive subjects 6 to <17 years of age were randomized into a placebo control and three dose levels (2/4, 8/16, and 16/32 mg once daily for body weight <50/≥50 kg) with a 1:2:2:2 ratio (35:69:68:68 subjects for placebo/low dose/medium dose/high dose). The pre-specified primary efficacy endpoint was the slope of linear regression for the change in trough sitting SBP (sitting systolic blood pressure (SiSBP)) from placebo to week4/last-observation-carried-forward (LOCF) as a function of candesartan dose ratio (1:4:8). The least-square mean of SiSBP change from baseline was -3.7, -8.6, -11.2, and -10.9 mmHg for placebo, low dose, medium dose, and high dose, respectively, which supported the antihypertensive effect of candesartan at all tested doses (by ANOVA test). The observed standard deviation of SiSBP change from baseline was approximately 10 mmHg for each treatment group. To retrospectively assess the power of the placebo-anchored slope analysis *versus* placebo-corrected slope analysis, a total of 300 replications were simulated according to the sample size of each treatment group, the population means of treatment effects, and variability observed in the candesartan trial.

medium dose, and high dose, respectively, which supported the antihypertensive effect of candesartan at all tested doses (by ANOVA test). The observed standard deviation of SiSBP change from baseline was approximately 10 mmHg for each treatment group. To retrospectively assess the power of the placebo-anchored slope analysis *versus* placebo-corrected slope analysis, a total of 300 replications were simulated with SAS 9.2 according to the sample size of each treatment group, the population means of treatment effects, and variability observed in the candesartan trial.

Metoprolol Trials

Similar to the design of candesartan trial, pediatric hypertensive subjects 6 to <17 years of age were randomized into a placebo control and three dose levels (0.2, 1.0, and 2.0 mg/kg) with a 1:2:1:2 ratio (23:45:23:49 subjects for placebo/low dose/medium dose/high dose). The pre-specified primary efficacy endpoint was the slope of linear regression for the change in trough sitting SBP (SiSBP) from placebo to week4/LOCF as a function of metoprolol dose ratio (1:5:10). The least-square mean of SiSBP change from baseline was -1.9, -5.2, -7.7, and -6.3 mmHg for placebo, low dose, medium dose, and high dose, respectively, which supported the antihypertensive effect of metoprolol at medium and high doses (by ANOVA test). The observed standard deviation of SiSBP change from baseline was approximately 8.9 mmHg for each treatment group. To retrospectively assess the power of the placebo-anchored slope analysis *versus* placebo-corrected slope analysis, a total of 300 replications were simulated according to the sample size of each treatment group, the population means of treatment effects, and variability observed in the metoprolol trial.

Clinical Trial Simulation

The trial design was derived from candesartan and metoprolol pediatric trial experience (3,4). It was a placebo-controlled, parallel group, dose-ranging study. A total of three drug dose groups and a placebo were administered in patients with a 1:1:1:1 ratio. The simulations were conducted using SAS 9.2.

Fig. 1. Illustrating the placebo-corrected *versus* the placebo-anchored slope analysis for the candesartan clinical trial

Exposure–Response Model

The drug response data were simulated through a simple $E_{\max}$ model based on area under the curve (AUC) at steady state:

$$E_i = \left(E_{\text{Placebo}} + \frac{E_{\max} \times \text{AUC}_i}{\text{ED}_{50} + \text{AUC}_i} \right) + \varepsilon_i \quad \text{with } \varepsilon_i \text{ i.i.d. } N(0, \sigma^2) \quad (1)$$

Where E_i represents the pharmacodynamic effect for the i^{th} subject. E_{Placebo} is the typical placebo effect. $E_{\max}$ is the maximum effect of the drug. ED_{50} is the AUC producing half of the maximum effect. ε_i represents the residual error and follows normal distribution with zero mean and σ^2 of variance.

In pediatric trials, the weight-based dose strategy is widely used. However, for adolescents and adults, the fixed-dose strategy is commonly adopted. The dosing strategy is determined to minimize the between-subject variability in drug exposure and the complexity of the dosing regimen. To investigate the impact of the different dosing strategies on the power, two typical dosing strategies were evaluated: the fixed dose strategy and the weight-based per kilogram dose strategy targeting the same AUC exposure for the median weight subject in a trial. Therefore, AUC at steady state is simulated according to the following equations.

For fixed-dose strategy:

$$\begin{aligned} \text{AUC}_i &= \frac{D_i}{\text{CL}_i} = \frac{D_i}{\text{CL}_{\text{TV}} \times \left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{\lambda}} = \frac{D_i / \text{CL}_{\text{TV}}}{\left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{\lambda}} \\ &= D'_i \times \left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{-\lambda} \quad \text{with } D'_i = D_i / \text{CL}_{\text{TV}} \end{aligned} \quad (2)$$

For per kilogram dose strategy:

$$\begin{aligned} \text{AUC}_i &= \frac{D_i \times \frac{W_{t_i}}{W_{t_{\text{ref}}}}}{\text{CL}_i} = \frac{D_i \times \frac{W_{t_i}}{W_{t_{\text{ref}}}}}{\text{CL}_{\text{TV}} \times \left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{\lambda}} \\ &= D'_i \times \left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{1-\lambda} \quad \text{with } D'_i = D_i / \text{CL}_{\text{TV}} \end{aligned} \quad (3)$$

Where W_{t_i} represents the body weight for the i^{th} subject. $W_{t_{\text{ref}}}$ represents the median body weight (reference subject) in the simulated trial. λ is the power factor of body weight on the individual clearance. D_i represents the dose administered to the reference subject. D'_i represents the AUC achieved by the reference subject. $D_i / W_{t_{\text{ref}}}$ is the per kilogram dose amount for the per kilogram dose strategy. Therefore, the dose–response relationship can be further described as:

For fixed-dose strategy:

$$E_i = \left(E_{\text{Placebo}} + \frac{E_{\max} \times D'_i \times \left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{-\lambda}}{\text{ED}_{50} + D'_i \times \left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{-\lambda}} \right) + \varepsilon_i \quad \text{with } \varepsilon_i \text{ i.i.d. } N(0, \sigma^2) \quad (4)$$

For per kilogram dose strategy:

$$E_i = \left(E_{\text{Placebo}} + \frac{E_{\max} \times D'_i \times \left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{1-\lambda}}{\text{ED}_{50} + D'_i \times \left(\frac{W_{t_i}}{W_{t_{\text{ref}}}} \right)^{1-\lambda}} \right) + \varepsilon_i \quad \text{with } \varepsilon_i \text{ i.i.d. } N(0, \sigma^2) \quad (5)$$

To generate a relative wide range of body weight, a pediatric trial with ages uniformly distributed from 6 to 18 years of age was simulated. The body weight of each subject was simulated according to US Centers for Disease Control (CDC) Growth Chart with the least-mean square (LMS) technique (12). In the US CDC Weight–Age table, three estimated parameters for weight are provided at each age level: the median (M), the generalized coefficient of variation (S), and the power in the Box–Cox transformation (L). The L reflects the degree of skewness. The LMS transformation equation for weight is:

$$\text{Weight} = M \times (1 + L \times S \times Z)^{1/L} \quad \text{if } L \neq 0 \quad (6)$$

or

$$\text{Weight} = M \times \exp(S \times Z) \quad \text{if } L = 0 \quad (7)$$

where Z is the z-score that corresponds to the percentile which can be randomly generated from a standard normal distribution.

Trial Simulation

A total of three drug dose groups (with dose ratio of 1:4:8) and a placebo were administered in patients with a 1:1:1:1 ratio. The typical placebo effect in the simulated pediatric hypertension trial was assumed to be -3 mmHg. The simulation method was Monte Carlo. Four levels of the residual error were assessed (*i.e.*, with the standard deviation 4, 7, 10, or 13). For each treatment group, four sample size levels per group were evaluated (*i.e.*, 20, 40, 60, or 80 subjects per group). Different scenarios governing the drug exposure–response relationship in the pediatric hypertension trial were also evaluated (Table II). Four levels of ED_{50} (*i.e.*, 0.5, 2, 8, or 16) were selected relative to the lowest D'_i which was set as 1. When ED_{50} is set as 0.5, the simulation represents a scenario commonly observed in pediatric antihypertensive drug trials (10,11) in which all three tested doses (*i.e.*, 1:4:8) are relatively high compared with the ED_{50} . When ED_{50} is set as 16, the simulation represents a situation rarely seen in pediatric registration trials in which all three tested doses (*i.e.*, 1:4:8) are relatively low compared with the ED_{50} . λ was chosen from 0 to 1 where 0 represented there was no weight effect on clearance (so ideally the fixed-dose strategy should be applied in this case) and 1 represented that clearance increased linearly with body weight (so ideally per kilogram dose should be chosen in this case). There were total of 960 combinations of scenarios.

To assess the type I error rate, scenarios based on the exposure–response relationship, assuming no drug effect were also evaluated, *i.e.*, $E_{\max} = 0$:

$$E_i = (E_{\text{Placebo}} + 0 \times D'_i) + \varepsilon_i = E_{\text{Placebo}} + \varepsilon_i \quad \text{with } \varepsilon_i \text{ i.i.d. } N(0, \sigma^2) \quad (8)$$

Table II. Simulation Scenarios for Hypothetical Clinical Trials

Placebo effect	−3				
Treatment dose (D')	Placebo/low dose/medium dose/high dose=0:1:4:8				
Lamda_wt	0	0.25	0.5	0.75	1
$E_{\max}$	−5	−10	−15		
ED ₅₀	0.5	2	8	16	
SD	4	7	10	13	
No. of subjects	20	40	60	80	

SD standard deviation

For each scenario, a total of 300 replications were simulated. Data were analyzed to assess the power of the placebo-anchored and placebo-corrected slope analyses under different scenarios.

Statistic Analysis: Power and Type I Error Calculation

For empirical data based on the metoprolol and candesartan trials and simulated data from hypothetical clinical trials, a simple linear regression analysis was implemented in SAS 9.2. For each scenario, the power was defined as the proportion of positive trials (with a statistically significant dose–response slope from 0 at $\alpha=0.05$) out of 300 replications. The null hypothesis was that the drug treatment has no effect (the dose–response slope equals 0). The false-positive rate (type I error rate) of an analysis was calculated as the proportion of false-positive trials (with a statistically significant dose–response slope from 0 for a scenario assuming no drug effect) out of 300 replications. If the underlining true power is 80% or the true type I error rate is 5%, the standard error is 0.023 for the estimated power or 0.013 for the estimated type I error rate (based on the normal approximation to the binomial distribution). The simulation results should provide valid direction for the trial analysis under this variability.

RESULTS

In candesartan and metoprolol clinical trials, the placebo-corrected dose–response slope as the pre-specified primary efficacy endpoint failed to demonstrate efficacy of the drugs. As shown in Fig. 2, the power for the placebo-corrected analysis to detect a significant dose–response slope was 41% for candesartan and 9% for metoprolol trials.

However, the power was more than twofold higher with the use of the placebo-anchored analysis (*i.e.*, 90% for candesartan and 30% for metoprolol).

For the simulated hypothetical clinical trials, the power of the placebo-anchored slope analysis to detect a significant dose–response relationship was consistently higher than that of the placebo-corrected slope analysis at each of the simulated scenarios irrespective of dosing strategies. Figure 3 illustrates the probability of rejecting the null hypothesis (H_0 , the slope of dose–response equals to 0) *versus* sample size per group for different scenarios with fixed or per kilogram dosing for the placebo-anchored slope analysis and the placebo-corrected slope analysis. As expected, the power for the dose–response analysis was sensitive to the sample size, the residual variability (SD), the maximal drug effect size ($E_{\max}$), and the studied dose range relative to the dose–response parameter ED₅₀. Generally, the power decreased drastically if the population was assumed to be less responsive to the test drug (*i.e.*, $E_{\max}$ is small) and less sensitive to the test dose range (*i.e.*, ED₅₀ is large). The power also decreased as the residual variability increased. On the other hand, the power was not sensitive to the dosing strategies. The placebo-anchored slope analysis was always superior in power compared with the placebo-corrected slope analysis no matter whether a fixed-dose strategy or a weight-based dosing strategy was used in a clinical trial. The simulation results also showed that a dosing strategy regardless of the relationship between body weight and drug clearance did not seem to substantially affect the power of a dose–response analysis. For both the placebo-anchored slope analysis and the placebo-corrected slope analysis, the power to detect a significant dose–response relationship with a fixed-dose strategy was always similar to that with a per-kilogram strategy irrespective of the relationship between body weight and clearance (*e.g.*, $\lambda=0$ or $\lambda=1$). However, these results should not be interpreted to mean that selection of a dosing strategy is irrelevant to the clinical outcome. Although the statistical power of a dose–response analysis may be similar between the two tested dosing strategies, the between-subject variability in drug exposure will be different as we explained in the “Methods” section. An appropriate dosing strategy should be selected to minimize the between-subject variability in drug exposure and the complexity of the dosing regimen.

The largest difference in power between the placebo-anchored slope analysis and the placebo-corrected slope analysis was observed under the scenarios where the studied

Fig. 2. The estimated power of a dose–response-based efficacy analysis for the candesartan and metoprolol clinical trials

Fig. 3. The power of a dose–response-based efficacy analysis *versus* sample size per group with fixed or per kilogram dosing for different scenarios (by ED_{50} , E_{max} , SD, and Lamda_wt)

dose range was relatively high compared with the dose–response parameter ED_{50} (e.g., when ED_{50} was 0.5) because, in those cases, a plateau drug effect was achieved over the studied dose range. As shown in Fig. 3, the power for placebo-corrected slope analysis was <20% compared with the 80% power with the placebo-anchored analysis under a scenario where the ED_{50} was half of the lowest studied dose. The superiority in power with the placebo-anchored slope analysis compared with that of the placebo-corrected analysis was consistent under all scenarios irrespective of the studied dose range relative to ED_{50} , although the magnitude of the difference became smaller when the studied dose range was not relatively high compared with ED_{50} . As shown in Fig. 3, when ED_{50} is set as 16, the simulation represents a situation in which all three tested doses (*i.e.*, 1:4:8) are relatively low compared with the ED_{50} . However, such low-dose scenarios are rarely seen in clinical registration trials because dose-finding studies of a drug in earlier phases will generally recommend doses providing maximal drug effect. Therefore, our following discussion focuses primarily on the high-dose scenarios.

In the simulation scenarios where the null hypothesis was true (*i.e.*, there is no drug effect, $E_{\text{max}}=0$ and the slope of dose–response equals to 0), the type I error was well

controlled around 5% for both the placebo-anchored slope analysis and the placebo-corrected slope analysis at alpha of 0.05. The type I error was insensitive to the treatment sample size and the residual variability (Fig. 4).

DISCUSSION

There are multiple reasons which can cause failure of a registration trial. For example, we had previously found inadequate dose-selection, lack of acknowledgement of differences between adult and pediatric populations, and lack of pediatric formulations were associated with failures of pediatric antihypertensive trials (10,11). However, based on recent submissions across different therapeutic areas, we observed inadequate attention was paid by some clinical trial sponsors in selection of an appropriate pre-specified primary dose–response analysis for evidence of efficacy. The simulation results presented here clearly showed that the placebo-anchored slope analysis is always more powerful to detect a significant dose–response relationship and establish drug efficacy in all plausible scenarios. Yet, several clinical trials protocols have used the placebo-corrected slope analysis. The difference between the placebo-anchored and the placebo-corrected analyses was maximum when the studied doses

Fig. 4. The false-positive rate of a dose-response-based efficacy analysis *versus* sample size per group for different scenarios (by SD)

were too high. However, the dose-response-based analysis is not sensitive to the dosing strategies regardless of the relationship between body weight and drug clearance. Furthermore, the type I error rate of these two methods was also found to be comparable. Therefore, direct drug development implications of our finding are:

1. For providing the clinical evidence of efficacy, the placebo-anchored slope analysis rather than the placebo-corrected slope analysis should be used as the primary dose-response analysis for the efficacy endpoint.
2. Where possible, placebo should be included in dose response studies to maximize the power to establish the evidence of efficacy.

The approvals of candesartan and metoprolol pediatric NDA submissions were delayed due to the failure of the unwisely pre-specified primary efficacy endpoint based on the placebo-corrected slope analysis. The pharmacometric analysis of those two submissions by the FDA were critical to bridge information from multiple available resources (*e.g.*, placebo-anchored dose-response slope analysis, ANCOVA analysis, mixed-model repeated-measures analysis, exposure-response analysis, cross-trial comparison between pediatrics and adults) to demonstrate drug efficacy and support approval (3,4). The power of 30% for metoprolol using the placebo-anchored analysis to detect a significant dose-response slope may still be too low to demonstrate adequate evidence of efficacy. This may be due to inadequate dose-selection (all three tested doses seem high relative to ED_{50}) and other trial design issues (*e.g.*, smaller sample size compared with candesartan trial). Therefore, the pediatric indication of metoprolol was not issued. However, the

increased power from the placebo-anchored analysis combined with other sensitivity analyses mentioned above together provided sufficient confidence to the agency to give a dose recommendation in the label. The olmesartan (5) and valsartan (6) pediatric NDA submissions failed regulatory approval at least in part because the trials failed to demonstrate adequate dose-response relationships with a likely reason that the studied doses were too high.

One concern regarding the placebo-anchored analysis is that the slope from the placebo-anchored analysis may less precisely reflect the dose-response relationship over the tested dose range compared with the placebo-corrected analysis. However, drug developers need to separate the evidence of efficacy and precise characterization of dose-response relationship. For the primary evidence of efficacy, the focus is to provide evidence that the drug is better than placebo. We contend that the placebo-anchored slope analysis is superior to achieve the primary purpose of demonstrating drug efficacy. To derive dosing recommendations to target a specific effect size after drug efficacy is established, several analyses such as exposure-response analysis, pairwise comparison, etc., are commonly used (13).

CONCLUSION

While we used two case studies involving antihypertensive drugs, the results of our research could be applied to other therapeutic areas. The placebo-anchored slope analysis is superior in demonstrating drug efficacy compared with the placebo-corrected slope analysis. The design of dose-response studies should carefully consider these results to justify the inclusion of placebo and the analysis method. In the cases presented here, the pharmaceutical industry and the

regulatory agencies are equally responsible for using the appropriate methods of analysis and providing justification in the protocol.

Disclaimer The contents of the manuscript represent the authors' personal opinion and do not necessarily reflect any position of the Food and Drug Administration.

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Conflict of Interest None

REFERENCES

- Guideline for industry: dose–response information to support drug registration, ICH-E41994: [(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073115.pdf) p.].
- Guidance for industry providing clinical evidence of effectiveness for human drug and biological products: [(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryinformation/Guidances/ucm078749.pdf) p.].
- Candesartan clinical pharmacology review 2009: [(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM189128.pdf) p.].
- Metoprolol clinical pharmacology review summary 2006: [(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM164065.pdf) p.].
- Olmесartan clinical pharmacology review 2010: [(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM201697.pdf) p.].
- Valsartan clinical pharmacology review 2007: [(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm072894.pdf) p.].
- Oxcarbazepine approval package: [(http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-014_Trileptol.cfm) pp.].
- Rufinamide approval package: [(http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021911s000_TOC.cfm) p.].
- Lee JY, Garnett CE, Gobburu JV, Bhattaram VA, Brar S, Earp JC, *et al.* Impact of pharmacometric analyses on new drug approval and labelling decisions: a review of 198 submissions between 2000 and 2008. *Clin Pharmacokinet.* 2011;50(10):627–35.
- Benjamin DK, Smith PB, Jadhav P, Gobburu JV, Murphy MD, Hasselblad V, *et al.* Pediatric antihypertensive trial failures: analysis of end points and dose range. *Hypertension.* 2008;51(4):834–40.
- Li JS, Cohen-Wolkowicz M, Pasquali SK. Pediatric cardiovascular drug trials, lessons learned. *J Cardiovasc Pharmacol.* 2011;58(1):4–8.
- 2000 CDC growth charts for the United States: methods and development: [(http://www.cdc.gov/nchs/data/series/sr_11/sr_246.pdf) p.].
- Guidance for industry: exposure–response relationships—study design, data analysis, and regulatory applications 2003: [(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf) p.].