CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-723

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-723	Submission Date(s): 10/31/2003, 08/12/04
Brand Name	Lyrica
Generic Name	Pregabalin
Pharmacometrician	He Sun, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Sponsor	Pfizer
Relevant IND(s)	53,763;
Submission Type; Code	1S
Formulation; Strength(s)	Capsules, 25/50/75/100/150/200/225/300 mg
Proposed Indications	Treatment of postherpetic neuralgia
Proposed Dosage Regimen	Starting dose: 75 mg BID (150 mg/day) Optimal dose: 150 mg BID (for most patients) Maximum dose: 300 mg BID

Background:

This review is an addendum to the primary review completed by Dr. Sue Chih Lee on 03/22/04 for this NDA. Pregabelin was originally developed for thrice daily dosing. To enhance patient compliance, twice daily dosing was later pursued and is the currently proposed regimen. Pfizer attempted to link the TID and BID regimens through modeling and simulations. However, in those analyses, data from both DPN and PHN trials were combined and the posterior check indicated that the 300-mg dose was not well predicted. An information request seeking additional analyses was originally sent to Pfizer on 07/14/04 and the elements of this request were further clarified 08/02/04. Specifically, the 07/14/04 communication requested;

> The Division recommends that Pfizer conduct additional modeling and simulation analyses for the PHN indication as follows:
>
> A. Model the TID trials (Studies 30, 45, 127) to predict the BID outcome for trial 196 at Week 8.
>
> B. Model the BID trial (Study 196) to predict the TID outcome for trials 45 and 127.
>
> Explore modeling by treating the pain score as categorical outcome as well as continuous outcome.

Pfizer submitted the response on 08/12/04 with additional analyses concluding that total daily dose is predictive of the pain score response independent of the regimen (TID or BID). Pfizer noted that due to time constraints the cross-validation exercise for the TID trials alone (leave-one-study-out) was not performed and that the predictions were summarized differently from graphical and tabular presentations requested by the Agency.

Summary of the Analyses

Additional analyses were performed in the PHN alone population to further assess the predictive performance of the model for both BID and TID regimens. The exposure-response model was based on a pooled analysis of four PHN studies (1008-030, -045, -127, -196), treating the daily pain scores as an ordered categorical response. Details of the model development, internal posterior predictive check, external (cross-validation) posterior predictive check can be found in Addendum 1. Model fit to the TID trials (studies 1008-030, -045, and -127) was used to predict the outcome in the BID trial (study 1008-196), and conversely, a model fit to the BID trial was used to predict outcomes for the three TID trials. Details of modeling TID data and predicting BID data and modeling BID data and predicting TID data can be found in Addendum 2.

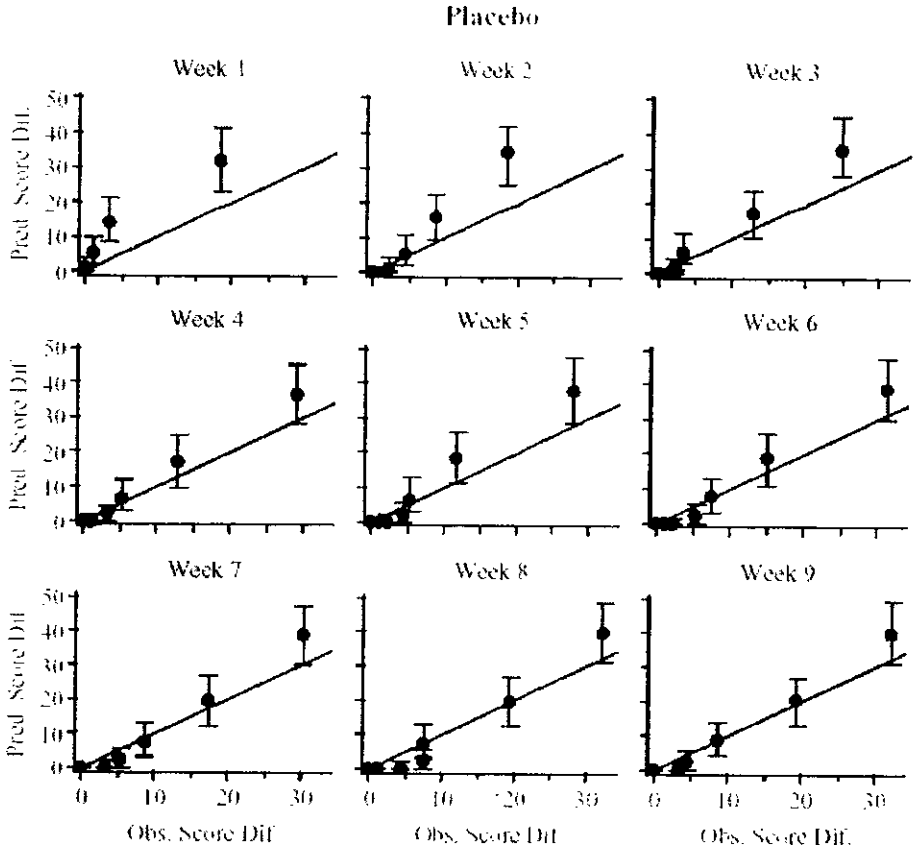
The BID data alone did not contain sufficient information (study 196) to adequately characterize the curvature of the dose-effect or placebo-time profiles. The estimates of the parameters used to model these profiles were highly correlated and a reduced model employing linear does-effect and placebo-time sub-models was subsequently used to predict outcomes of TID regimen.

Model developed using TID data adequately predicted outcome of BID regimen. In most of the external, cross dose regimen prediction checks, outcome for the placebo group was predicted poorly and high dose at later time was predicted better (see figures 1 and 2), although the overall predictions are no worse than those from BID to BID or BID+TID to BID or TID internal predictions. This implies that; (1) TID and BID tend to have similar dose-response, (2) dose (not dose regimen) is the major determinant for pain score value (not the pain score changes from placebo arm, see item 3), and (3) pain score change from baseline for placebo groups has the largest variability among trials.

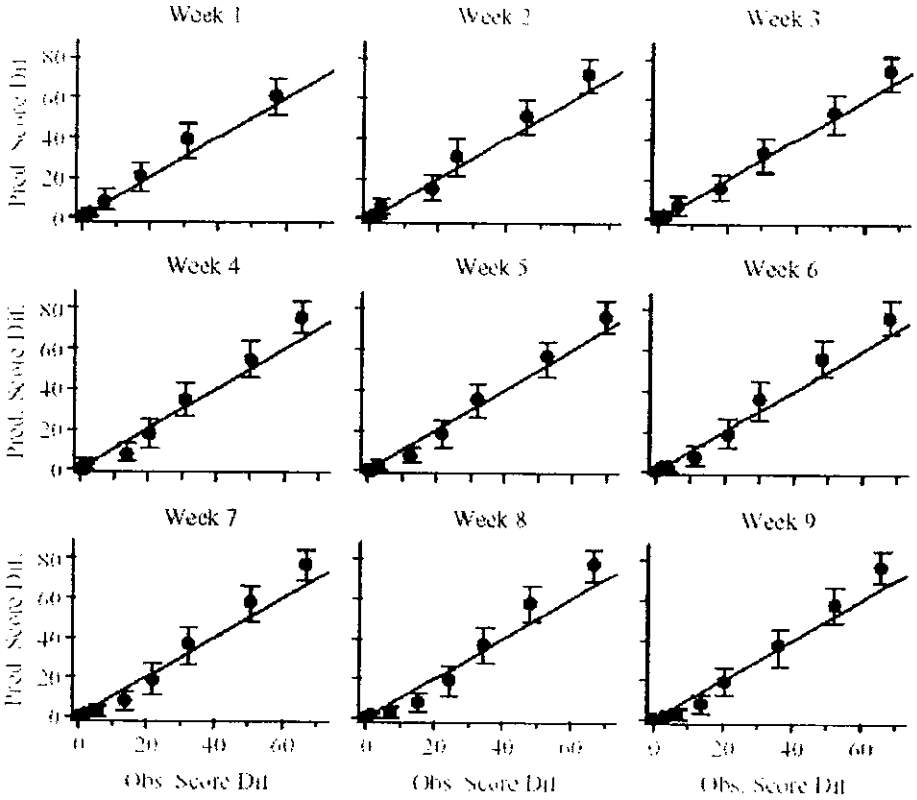
When sponsor used the means of placebo pain scores as reference, the dose-response curve appeared nicely for all trials and cross trials. If the placebo pain score for each trial was used separately, the rank order of dose-response (delta from placebo) is less than typical dose-response curve across trials.

The deviation in prediction is in the 0.25-0.34 point range (the net change in pain score from baseline at 300/600mg dose is about 2 to 2.5 points, for placebo it is about 0.7 to 1 points).

Overall, the cross regimen predictions are acceptable. This means that the BID regimen is equally effective as TID and has on the same dose-response relationship as TID (but this does not mean the BID trial itself is confirmed).


Placebo
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Pred. Score Dif.
Obs. Score Dif.
0
10
20
30
40
50

300/600 mg/Day BID



Addendum 1
Results of Proposed Analyses as Per NDA 21-723 Submission, Dated July 20, 2004

BACKGROUND

A pregabalin exposure-response analysis in patients with postherpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN) was previously reported (RR 754-00011). The analysis was based on pooled data from 8 patient studies (1008-014, -029, -030, -045, -127, -131, -132). For 7 of these studies pregabalin was administered TID with the exception of PHN study 1008-132 where pregabalin was administered BID. The final model indicated that response in neuropathic pain was a function of total daily dose independent of frequency of administration.

The final model (RR 754-00011) was used to perform a posterior predictive check (PPC) of the weekly mean pain scores for pregabalin given BID in a PHN population from an independent study (1008-196) that was not used in the development of the final model as previously reported (RR 754-00019). The PPC confirmed that improvement in weekly mean pain scores was a function of total daily dose independent of BID or TID administration.

At the Agency's request, additional analyses have now been performed in the PHN alone population to further assess the predictive performance of the model for both BID and TID regimens.

The following sections provide details regarding the methods, results and conclusions from these additional analyses.

METHODS

Model Development

A pregabalin exposure-response model has been developed for the PHN alone population based on a pooled analysis of four PHN studies (1008-030, -045, -127, -196), treating the daily pain scores as an ordered categorical response since daily pain scores were measured as integral, ordinal values on an 11-point numerical rating scale. A similar

model building procedure was followed to that described for the pregabalin exposure-response model in the combined PHN and DPN populations (RR 754-00011).

A base model was developed postulating several parametric forms for the drug model including: Emax-type, power, and linear dose-response models. The final base model was selected based on likelihood ratio tests (LRTs), where the difference in the minimum objective function (ΔMOF) values between two hierarchical models is approximately distributed as chi-square with the number of degrees of freedom equal to the difference in the number of parameters estimated between the two hierarchical models. A ΔMOF>10.8 for 1 degree of freedom corresponding to a significance level of α=0.001 to reject the null hypothesis (i.e., the fixed parameter in question has no influence) was used to guide base model development.

It should be noted that no additional modeling was performed to investigate alternative placebo models. The final parametric form of the placebo model including study-dependent placebo effects as described for the combined PHN and DPN exposure-response model (RR 754-00011) was employed for the PHN alone model development.

A full model was developed simultaneously fitting all covariate parameters investigated on both the placebo and drug components of the final base model. Wald's approximation method (WAM) was employed to rank all 2^k possible submodels derived from the presence or absence of each of the k covariate parameters in the full model. The top 15 models based on the WAM rankings were then fit using the NONMEM software and the final model was selected as the one with the largest value of Schwarz Bayesian criterion (SBC).

Internal Posterior Predictive Check

To assess the predictive performance of the final model an internal posterior predictive check (PPC) was performed simulating 300 hypothetical datasets of daily pain scores conditioning on the design, observed covariates, and dropouts for each of the four studies used in the development of the final model (i.e., 1008-030, -045, -127, -196). Parameter uncertainty was taken into account in the simulations by sampling a different set of population estimates for each of the 300 hypothetical trials from a multivariate normal distribution using the population mean estimates and covariance matrix of the estimates from the final model fit. Weekly mean pain scores were calculated within a patient from the daily pain scores for the observed data and for each of the 300 hypothetical datasets for each study design. For each individual, the mean of the last 7 daily pain scores

(observed or simulated) were carried forward (LOCF) to impute the missing observations after dropout. These weekly mean pain scores were then averaged across patients to obtain population means. Key order statistics (percentiles) of the weekly population mean pain scores for each treatment group from the 300 simulated trials for each study were calculated. These statistics were compared to the weekly population mean pain scores obtained from the observed data for each study (i.e., 1008-030, -045, -127, -196). The model was considered to be consistent with the data to the extent that the observed population means were contained within the distribution of the simulated population means and no systematic biases were observed.

External (Cross-Validation) Posterior Predictive Check

To further assess the predictive performance of the model, cross-validation was performed using a 'leave-one-study-out' strategy. This strategy entailed fitting the final model to three of the four PHN studies. An external PPC was performed using these cross-validation fits to predict the weekly population mean pain scores on the study that was excluded. The external PPC was performed in a similar fashion as described above for the internal PPC. This external PPC was performed for each of the 4 PHN studies excluded individually:

1. Fit the final model to the PHN data for studies 1008-030 (TID), -045 (TID), and –127 (TID) and perform a PPC on study 1008-196 (BID).

2. Fit the final model to the PHN data for studies 1008-045 (TID), -127 (TID), and –196 (BID) and perform a PPC on study 1008-030 (TID).

3. Fit the final model to the PHN data for studies 1008-030 (TID), -127 (TID), and –196 (BID) and perform a PPC on study 1008-045 (TID).

4. Fit the final model to the PHN data for studies 1008-030 (TID), -045 (TID), and –196 (BID) and perform a PPC on study 1008-127 (TID).

To the extent that the internal and external (cross-validation) PPC results provide adequate predictive performance, they would suggest that the final exposure-response model using total daily dose as a measure of exposure, is predictive of the pain score response, regardless of regimen (i.e., BID or TID).

RESULTS

BASE MODEL DEVELOPMENT

Daily pain scores were collected as integral, ordinal values on an 11-point numerical rating scale from 0 to 10. In the analysis, the pain score (PS) was treated as an ordered categorical variable. The mean of the 7 most recent available baseline pain scores observed during the baseline study phase was used for each patient's baseline.

The general form of the population pharmacodynamic (PD) model is given by the following expression:

$$\text{logit}\left[P\left(PS_{ij} \le m\right)\right] = \sum_{k=0}^{m} \beta_k + \theta_{base}\left(\overline{PS}_{i0} - 6.5\right) + f_p\left(t_j, X_i\right) + f_d\left(D_{ij}, t_j, X_i\right) + \eta_i$$

where logit(p) = log(p)-log(1-p), $P(PS_{ij} \le m)$ denotes the probability that the daily pain score, PS_{ij}, for patient i at time t_j is less than or equal to some score m, $\overline{PS}_{i0}$ denotes the average baseline PS for patient i, f_p denotes the placebo-time effect, f_d denotes the drug effect where D_{ij} denotes the pregabalin dose, X_i denotes a vector of patient covariates that may influence the placebo-time and/or drug effects, and η_i denotes an interindividual random effect with zero mean and variance ω^2. θ_{base} is a regression parameter that adjusts the population mean baseline logit probabilities (β_k, k = 0,...,9) for the individual's observed average baseline pain score.

The parametric form for the placebo-time effects (f_p) including study-dependent placebo effects is given by the following expression:

$$f_p\left(t_j\right) = Pmax_k\left(1 - e^{-k_{plc} t_j}\right)$$

where $Pmax_k$ is the asymptotic maximum placebo effect (for study k), and k_{plc} is a constant that governs the rate at which the placebo effect reaches this maximum.

Three classes of drug models (f_d) were considered: Emax-type, linear, and power model dose-response. For all three classes, a time-dependent exposure effect was included to investigate the time of onset of the drug effect.

The sigmoid-Emax model with the time-dependent exposure effect is given by the following expression:

$$f_d\left(D_{ij},t_j\right)=\frac{E\,max\left[D_{ij}\left(1-e^{-k_{eq}t_j}\right)\right]^{\gamma}}{ED_{50}^{\gamma}+\left[D_{ij}\left(1-e^{-k_{eq}t_j}\right)\right]^{\gamma}}$$

where Emax denotes the maximum drug effect (on the logit scale), ED_{50} denotes the dose corresponding to 50% of the maximum effect, γdenotes the sigmoidicity parameter (i.e., Hill coefficient) governing the steepness of the dose-response, and k_{eq} is an equilibration rate constant governing the rate of onset of the drug effect.

The power dose-response model with the time-dependent exposure effect is given by the following expression:

$$f_d(D_{ij},t_j)=\alpha\left[D_{ij}\left(1-e^{-k_{eq}t_j}\right)\right]^{\gamma}$$

where α denotes the slope parameter for the power model, and k_{eq} is as previously defined. With γ=1, the power dose-response model with the time-dependent exposure effect collapses to the linear dose-response model with the time-dependent exposure effect given by the expression:

$$f_d\left(D_{ij},t_j\right)=\theta_{drg}\left[D_{ij}\left(1-e^{-k_{eq}t_j}\right)\right].$$

The base model development process started with the sigmoid-Emax model with the time-dependent exposure effect. The sigmoid-Emax model was considered the reference model from which reduced models were considered to test the sigmoidicity (γ= 1), instantaneous onset of drug effect (ie, k_{eq} = ∞), and the absence of a drug effect (ie, f_d = 0). The changes in the minimum objective function values relative to the reference model are shown in Table 1.

Table 1. Base Model Selection – Emax-Type Models

Base Model Description	MOF	ΔMOF
Sigmoid-Emax w/ Time-Dependent Exposure (Reference)	155043.988	
Emax w/ Time-Dependent Exposure (ie, $\gamma = 1$)	155053.169	9.18
Emax w/ Instantaneous Exposure (ie, $\gamma = 1$, $k_{eq} = \infty$)	155060.279	16.29
No Drug Effect Model (ie, $f_d = 0$)	155548.928	504.94

MOF = Minimum objective function value.
ΔMOF = Change in MOF relative to reference model.

It was noted that in all of the Emax-type models, ED_{50} estimates were higher than the maximum dose studied (i.e., >600 mg/day), and the population estimates of Emax and ED_{50} were highly correlated (ρ>0.95). This suggests that the range of doses studied does not provide sufficient information to precisely estimate these parameters and a model with less curvature than the Emax model (i.e., a model that does not have an asymptote) is appropriate. Therefore, power dose-response models were tested as alternatives to Emax models. The power model with time-dependent exposure ($\alpha(D(1-e^{-keqt})^{\gamma}$) was considered the new reference model and reduced models were evaluated to test the curvature ($\gamma = 1$), instantaneous onset of drug effect (i.e., $k_{eq} = \infty$), and the absence of a drug effect (i.e., $f_d = 0$). The changes in the minimum objective function values relative to the new reference model are shown in Table 2. When γ is equal to 1, the new reference model collapses to the linear exposure-response model.

In fitting the power models, high correlations between the estimates of α and γ were observed (ρ>0.95). To reduce this correlation, dose was scaled such that α represents the drug effect at 300 mg/day, which resulted in a more stable model fit (ρ=0.85).

Table 2. Base Model Selection – Power/Linear Models

Base Model Description	MOF	ΔMOF
Power Model w/Time-Dependent Exposure (Reference) ($\alpha(D(1-e^{-keqt}))^{\gamma}$)	155043.845	
Linear w/ Time-Dependent Exposure (γ=1, $\alpha D(1-e^{-keqt})$)	155062.670	18.825
Instantaneous Exposure (k_{eq}=∞, αD^{γ})	155052.526	8.681
Instantaneous Exposure with Scaled Dose (k_{eq}=∞, $\alpha(D/300)^{\gamma}$)	155052.525	8.680
No Drug Effect Model (i.e., $f_d = 0$)	155548.928	505.063

MOF = Minimum objective function value.
ΔMOF = Change in MOF relative to reference model

These base model results indicate the following:

- When only PHN studies are combined, dose-related drug effects do not support Emax-type models. The maximum dose studied does not appear to have reached a plateau on the dose-response curve.
- Power models describe the drug effect as well as Emax models (similar MOF between reference models in Tables 1 and 2). A power dose-response model with instantaneous onset of drug effect appears to be parsimonious. Scaling the dose reduces the correlation between parameter estimates leading to a more numerically stable model.
- Dose-related drug effects are statistically significant (ΔMOF > 500, $p < 0.001$).
- The curvature parameter γ in the power model ($\alpha(D(1-e^{-kt})^{\gamma}$) is statistically significant (ΔMOF = 18.83, $p < 0.001$) suggesting there is departure from a linear (γ=1) dose-response model.
- A time-dependence of the drug exposure is not statistically significant (ΔMOF = 8.68, $p = 0.003$).

On the basis of these results, the power model without a time-dependent exposure effect was considered the final base model used for subsequent model development.

The NONMEM control stream and output for the final base model with study-dependent placebo effects are provided in the Appendix.

Full Model Development

A full model was developed building on the final base model discussed in the previous section.

Covariates were investigated on the maximum placebo effect (Pmax) including: gender (SEX_i =0 for females, SEX_i=1 for males), age (AGE_i), body weight (WT_i), and average baseline pain score ($\overline{PS_{i0}}$). Regimen (TID vs BID) was not included as a covariate since this effect was confounded with the study-dependent placebo parameters. The placebo

covariate parameters were included in the model in multiplicative form given by the expression:

$$P\max_i = P\max_k \left(1+\theta_{sex}^{(plc)}\right)^{SEX_i} \left(\frac{AGE_i}{70\ \text{yrs}}\right)^{\theta_{age}^{(plc)}} \left(\frac{WT_i}{80\ \text{kg}}\right)^{\theta_{wt}^{(plc)}} \left(\frac{\overline{PS}_{i0}}{6.5}\right)^{\theta_{base}^{(plc)}}$$

where $Pmax_k$ denotes the typical $Pmax$ for study k (k = 1,...,4) for a 70-year-old, 80 kg, female having an average baseline pain score of 6.5. For the categorical covariates the covariate parameters (eg, $\theta_{sex}^{(plc)}$) represent the fractional change in $Pmax$. For the continuous covariates the scaled covariate raised to a power (ie, the covariate parameter value) represents the fractional change in $Pmax$ for patients at a given value of the covariate relative to the scaled value. For example, the scaled continuous covariate, AGE_i/70 yrs, raised to the power, $\theta_{age}^{(plc)}$, denotes the fractional change in $Pmax$ for a patient of AGE_i relative to a 70-year-old patient. For the continuous covariate parameters, a value of one indicates that $Pmax$ is directly proportional with the covariate.

Covariates were investigated on both the scaling parameter (α) and the curvature parameter (γ) including: gender, age, body weight, and average baseline pain score. A multiplicative model was employed given by the expressions:

$$\alpha_i = \alpha_o \left(1+\theta_{sex}^{(\alpha)}\right)^{SEX_i} \left(\frac{AGE_i}{70\ yrs}\right)^{\theta_{age}^{(\alpha)}} \left(\frac{WT_i}{80\ kg}\right)^{\theta_{wt}^{(\alpha)}} \left(\frac{\overline{PS}_{i0}}{6.5}\right)^{\theta_{base}^{(\alpha)}}$$

$$\gamma_i = \gamma_o \left(1+\theta_{sex}^{(\gamma)}\right)^{SEX_i} \left(\frac{AGE_i}{70\ yrs}\right)^{\theta_{age}^{(\gamma)}} \left(\frac{WT_i}{80\ kg}\right)^{\theta_{wt}^{(\gamma)}} \left(\frac{\overline{PS}_{i0}}{6.5}\right)^{\theta_{base}^{(\gamma)}}$$

where α_o and γ_o denote the typical α and γ, respectively, in a 70-year-old, 80 kg, female having an average baseline pain score of 6.5.

In addition, CLcr and regimen were investigated as covariates on drug exposure since pregabalin is renally cleared, and regimen differences (BID vs TID) may result in different peak-to-trough concentration fluctuations. The covariate-adjusted drug exposure, denoted D_{ij}^*, substituted for dose (D_{ij}) in the drug model is given by the expression:

$$D_{ij}^{*} = D_{ij}\left(\frac{CLcr_i}{80\ ml/min}\right)^{\theta_{clcr}^{(D)}}\left(1+\theta_{regi}^{(D)}\right)^{REGI_i}$$

It should be noted that these drug exposure covariate parameters are equivalent to a reparameterization of their effects on α. This choice of parameterization was selected to infer that these covariates' influences were on drug exposure rather than a pharmacodynamic property of the drug. It should also be noted that for the original exposure-response model developed for both the PHN and DPN populations, preliminary modeling using average steady-state pregabalin plasma concentrations derived from a population PK model and the individual patient's estimated CLcr showed no advantage compared to dose as a measure of drug exposure (RR 754-00011). Therefore, a decision was made to use the CLcr-adjusted dose (D_{ij}^{*}) as described above so that formal testing of the CLcr effect could be assessed.

The full model was fit to the daily pain scores and resulted in a decrease in MOF = 484.359 ($p < 0.001$) relative to the final base model with the study-dependent placebo effects. Therefore, combination of these parameter effects have a significant influence on the placebo and/or drug parameters.

The NONMEM control stream and output for the full model are provided in the Appendix.

Covariate Model Reduction

The WAM algorithm was applied to the full model fit described in the previous section and the top 15 ranked models based on Wald's approximation to the SBC were fit using NONMEM. The WAM results comparing the Wald-based approximations and the actual NONMEM-based LRT and SBC statistics are given in Table 3.

Table 3. WAM Results

Wald Rank	Covariates Included*				LRT (ΔMOF)		SBC		NONMEM Rank
	Pmax	α	γ	Exposure	Wald	NONMEM	Wald	NONMEM	
5	A,B	A,B,G	A,W		26.394	20.125	-154.44	-151.31	1
2	A,B	A,B,G	W		35.663	31.905	-153.65	-151.77	2
7	A,B	W,B,G		R	39.471	32.701	-155.55	-152.16	3
4	A,B	A,W,B,G	A		26.365	22.597	-154.43	-152.54	4
1	A,B	A,W,B,G	A	R	13.408	13.361	-153.38	-153.36	5
8	A,B	A,W,B,G	A,W		18.311	13.512	-155.83	-153.43	6
3	A,B	B,S	A,W	R	25.608	24.825	-154.05	-153.66	7
6	A,B	W,B,G	A	R	27.211	26.898	-154.85	-154.70	8
9	A,B	A,B,G	A,W	R	18.812	16.545	-156.08	-154.95	9
12	A,B	B,G	A,W,G		30.790	28.203	-156.64	-155.35	10
15	A,B	W,B,G	A,W		31.985	28.354	-157.24	-155.42	11
10	A,B	A,W,B,G	A,W	R	8.014	7.279	-156.12	-155.75	12
11	A,B	W,B,G	A,W	R	19.202	18.629	-156.28	-155.99	13
13	A,B	A,W,B,G	A	R	9.293	9.197	-156.76	-156.71	14
14	A,B	B,G	A,W,G	R	20.695	20.831	-157.03	-157.09	15

* A = Age, B = Base, C = CLcr, G = Gender, R = Regimen, W = Weight.

The Wald-based SBCs are in good rank order correlation with the actual SBCs obtained from fitting these models in NONMEM (ρ=0.818). These results suggested that the WAM algorithm performed well in finding a subset of good fitting models. The final parsimonious model, based on the maximum conditionally ranked NONMEM-based SBC, was obtained by including covariate effects for age and baseline pain score on Pmax; age, baseline pain score and gender on α; and age and weight on γ (ie, the first entry in Table 3 corresponding to NONMEM rank = 1). Moreover, neither CLcr nor regimen effects on exposure were selected for inclusion in the final model. The final model resulted in a ΔMOF = 20.125 for 7 covariate parameter restrictions (degrees of freedom) relative to the full model suggesting little loss in explanatory power. The final model resulted in a MOF considerably closer to the full model than the base model indicating a high degree of parsimony.

The NONMEM control stream and output for the final model are provided in the Appendix.

Parameter Estimates

The parameter estimates for the base, full, and final models are shown in Table 4.

Table 4. Parameter Estimates ± SE

Parameter	Base	Full	Final
MOF	155,052.525	154,568.166	154,588.291
ω^2	8.57 ± 0.39	8.22 ± 0.38	8.25 ± 0.38
Baseline			
β_0	-9.53 ± 0.15	-9.65 ± 0.14	-9.58 ± 0.13
β_1	1.95 ± 0.04	1.95 ± 0.04	1.95 ± 0.04
β_2	1.63 ± 0.02	1.63 ± 0.02	1.63 ± 0.02
β_3	1.58 ± 0.02	1.58 ± 0.02	1.58 ± 0.02
β_4	1.46 ± 0.02	1.46 ± 0.02	1.46 ± 0.02
β_5	1.57 ± 0.02	1.57 ± 0.02	1.57 ± 0.02
β_6	1.65 ± 0.02	1.66 ± 0.02	1.66 ± 0.02
β_7	1.90 ± 0.02	1.91 ± 0.02	1.91 ± 0.02
β_8	2.70 ± 0.03	2.73 ± 0.03	2.73 ± 0.03
β_9	2.71 ± 0.06	2.74 ± 0.06	2.73 ± 0.06
θ_{base}	-1.71 ± 0.06	-2.07 ± 0.08	-2.09 ± 0.07
Placebo			
Pmax 30	1.51 ± 0.245	1.18 ± 0.198	1.32 ± 0.219
Pmax 45	1.29 ± 0.162	1.20 ± 0.140	1.23 ± 0.145
Pmax 127	1.74 ± 0.196	1.58 ± 0.158	1.68 ± 0.182
Pmax 196	0.827 ± 0.069	1.16 ± 0.085	1.08 ± 0.083
k_{plc} (Days^{-1})	0.0217 ±0.0046	0.0213 ± 0.0036	0.0189 ± 0.0035
$t_{1/2}$ (Days)	32.0	32.5	36.7
Drug			
α	1.86 ± 0.156	2.92 ± 0.311	2.27 ± 0.163
γ	0.652 ± 0.0638	0.662 ± 0.0920	0.756 ± 0.056
Exposure			
CRCL	0	0.257 ± 0.526	0
Regimen	0	-0.318 ± 0.096	0
Gender Effect			
Pmax	0	-0.0722 ± 0.0822	0
α	0	-0.483 ± 0.00621	-0.492 ± 0.043
γ	0	-0.197 ± 0.124	0
Age Effect			
Pmax	0	-2.04 ± 0.0940	-1.97 ± 0.08
α	0	1.14 ± 0.421	1.06 ± 0.33
γ	0	-1.28 ± 0.260	-1.50 ± 0.25
Weight Effect			
Pmax	0	0.370 ± 0.178	0
α	0	0.532 ± 0.282	0
γ	0	0.622 ± 0.406	1.18 ± 0.20
Baseline Effect			
Pmax	0	0.924 ± 0.176	0.886 ± 0.144
α	0	1.91 ± 0.243	1.97 ± 0.20
γ	0	0.579 ± 0.485	0

For the final model, the onset of the placebo effect was slow with a half-life of approximately 32 days. The curvature parameter, γ, was estimated less than 1 indicating

that the dose-response was less than dose-proportional. Thus, although the range of doses studied does not provide sufficient information to estimate the ED_{50} and Emax, there is sufficient information to suggest that some curvature is present in the dose-response. It is noted that the regimen effect was not selected in the final model suggesting that the decrease in pain score response is correlated with increasing total daily dose as the measure of exposure, independent of regimen (TID vs BID). This finding will be further evaluated in the following sections based on the internal and external (cross-validation) PPCs.

Internal Posterior Predictive Check

The internal PPC results are presented as plots of the weekly population mean (LOCF) pain scores for each treatment group for each of the four PHN studies (1008-030, -045, -127, -196) as shown in Figures 1-4. The observed weekly population mean pain scores appear to be contained within the distribution of the simulated means predicted by the model. It is noted that the model underpredicts the treatment effect for the 300/600 mg/day TID regimen for Study 1008-127 (Figure 3). For this regimen it is noted that patients were stratified to doses of 300 or 600 mg/day TID based on estimated CLcr below or above 60 ml/min, respectively. The endpoint mean pain score at 13 weeks for this regimen in Study 1008-127 was approximately 0.34 points lower than that predicted by the final model. It is difficult to interpret this discrepancy as evidence of a regimen effect given that discrepancies between regimens at the 150 and 300 mg/day doses were minimal (Figures 2 and 4). Nevertheless, since the final model did not include renal or regimen effects on exposure, it is of interest to assess whether a model that includes such effects may result in improved predictive performance for the 300/600 mg/day TID regimen for Study 1008-127. To this end, additional simulations were performed using the full model where renal and regimen effects on exposure were included in the model.

The internal PPC results for the full model shown as plots of the weekly population mean (LOCF) pain scores for each treatment for each of the four PHN studies are given in Figures 5-8. Comparing these plots with Figures 1-4 for the final model show very little difference in the predictive performance between the full and final models. However, it is noted that the underprediction of the treatment effect for the 300/600 mg/day TID regimen for Study 1008-127 is less (Figure 7), resulting in a discrepancy of only 0.22 points between the observed and full model prediction of the endpoint mean pain score at 13 weeks. Therefore, the full model, which incorporates renal and regimen effects on

exposure, only improves the underprediction of the final model by 0.12 points (0.34 vs 0.22 points).

External (Cross-Validation) Posterior Predictive Check

The external PPC results for the final model are presented as plots of the weekly population mean (LOCF) pain scores for each treatment group for each of the four PHN studies (1008-030, -045, -127, -196) as shown in Figures 9-12. For each figure, the indicated study was excluded when fitting the final model so as to provide a more independent assessment of the predictive performance of the model. As expected, the predictive performance is reduced relative to the internal PPC where all of the data were used to estimate the parameters of the model (Figures 1-4). Nevertheless, with the exception of the 300/600 mg/day TID regimen for Study 1008-127 (Figure 11), the observed weekly population mean (LOCF) pain scores appear to be contained within the distribution of the simulated means predicted by the final model. Moreover, for the cross-validation exercise in which the BID study (1008-196) was predicted based on the model fit from the 3 TID studies (1008-030, -045, -127), less than a 0.25 point difference in the endpoint mean pain scores at 13 weeks was observed (Figure 12). These results suggest that the final model provides adequate predictive performance for the BID regimens even when the model parameters are estimated solely based on data from the TID regimens.

CONCLUSIONS

- Decrease in daily pain score is correlated with increasing pregabalin total daily dose as the measure of exposure, independent of regimen (TID vs BID).

- The range of doses studied in the PHN population does not support precise estimation of the Emax and ED_{50}; however, there is sufficient information to suggest some curvature and departure from a linear dose-response model. The curvature parameter, γ, was estimated to be <1, suggesting that the decrease in pain response at a higher dose is less than that predicted by a linear dose-response model.

- Covariate effects for baseline pain score and age on Pmax (maximum placebo effect), baseline pain score and gender on α (slope parameter of the power model), and age and weight on γ (curvature parameter) included in the final model explained the majority of the change in MOF (approximately 464 out of 484 points) between the base and full models.

- The final (parsimonious) model selected based on the WAM algorithm did not include CLcr and regimen effects on exposure.

- Results of the internal and external (cross-validation) PPCs suggest that the final model using total daily dose as a measure of exposure independent of regimen provides adequate predictive performance of the pain score response for both TID and BID regimens. Furthermore, the final model provides adequate predictive performance for the BID regimens even when the model parameters are estimated solely based on data from the TID regimens.

- Some discrepancies in the model predictions were observed (in the range of 0.25-0.34 points), however, these discrepancies were not observed in a systematic fashion across the dose range, making it difficult to discern if they reflect a deficiency of the model or some anomaly of the data.

FIGURES

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Figure 1. Internal PPC to Predict Study 30 using the Final Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials.

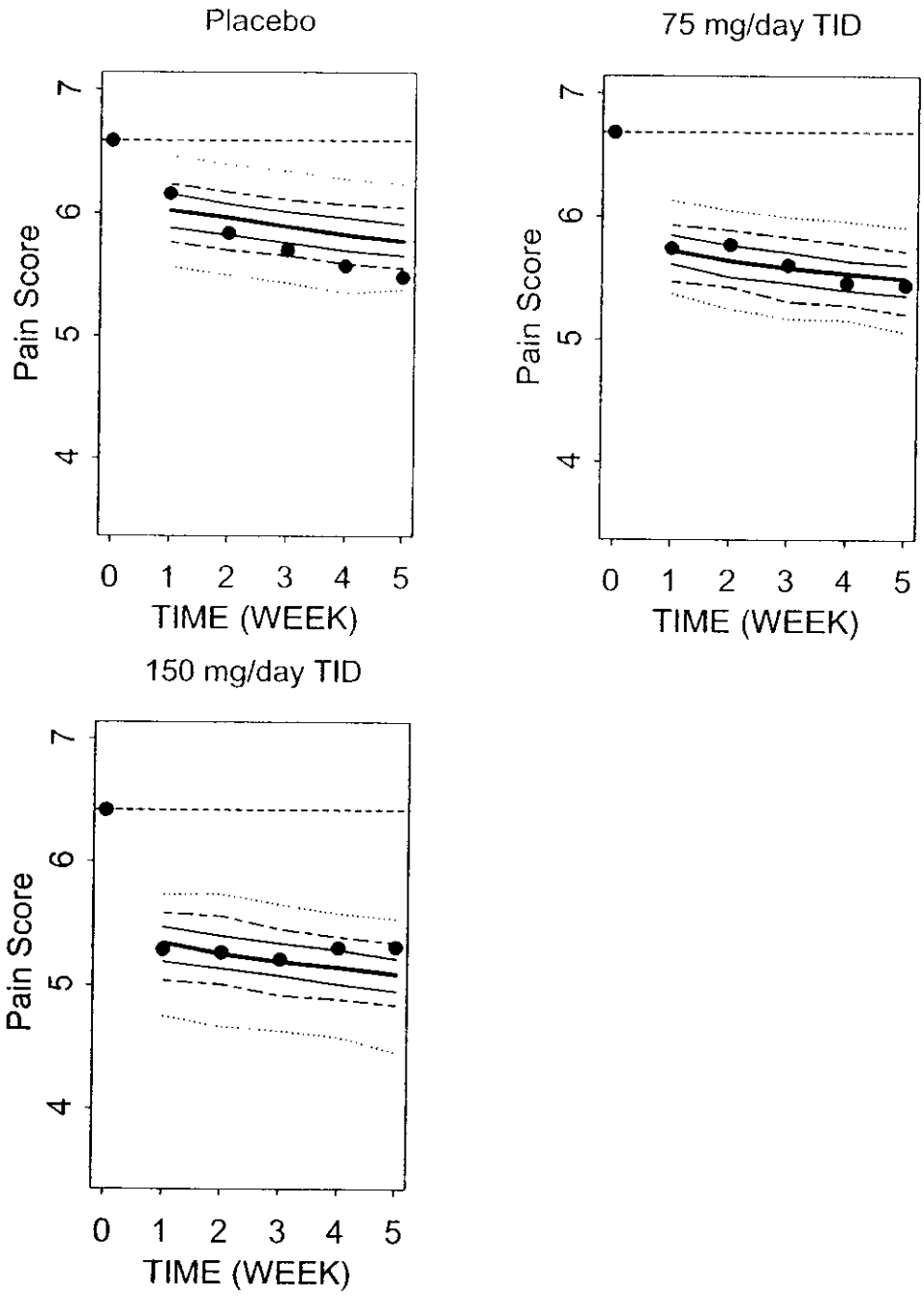


Figure 2. Internal PPC to Predict Study 45 using the Final Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials.

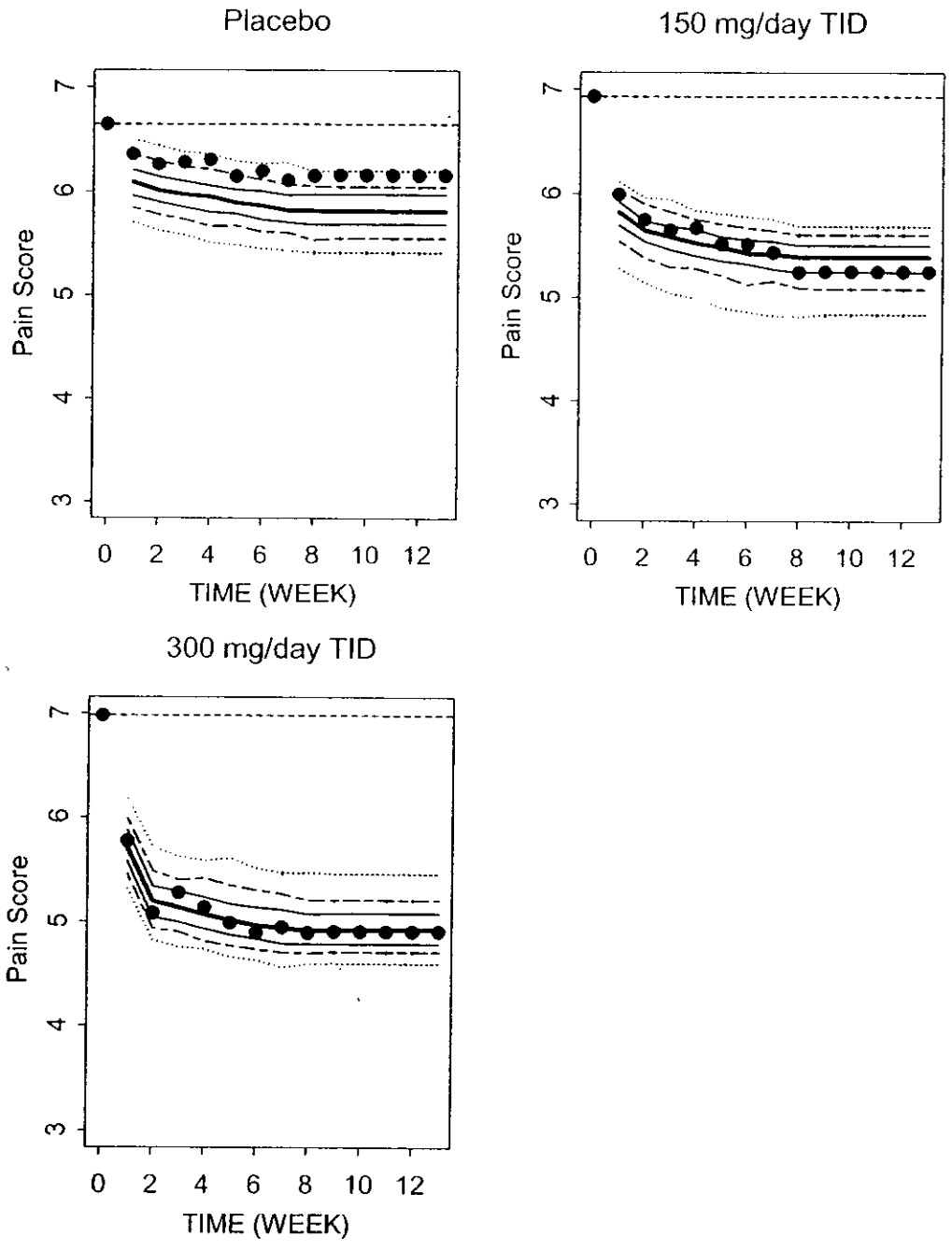


Figure 3. Internal PPC to Predict Study 127 using the Final Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials. Note the 300/600 mg/day TID regimen denotes 300 and 600 mg/day TID doses stratified based on the patient's individual CLcr estimate below and above 60 ml/min, respectively.

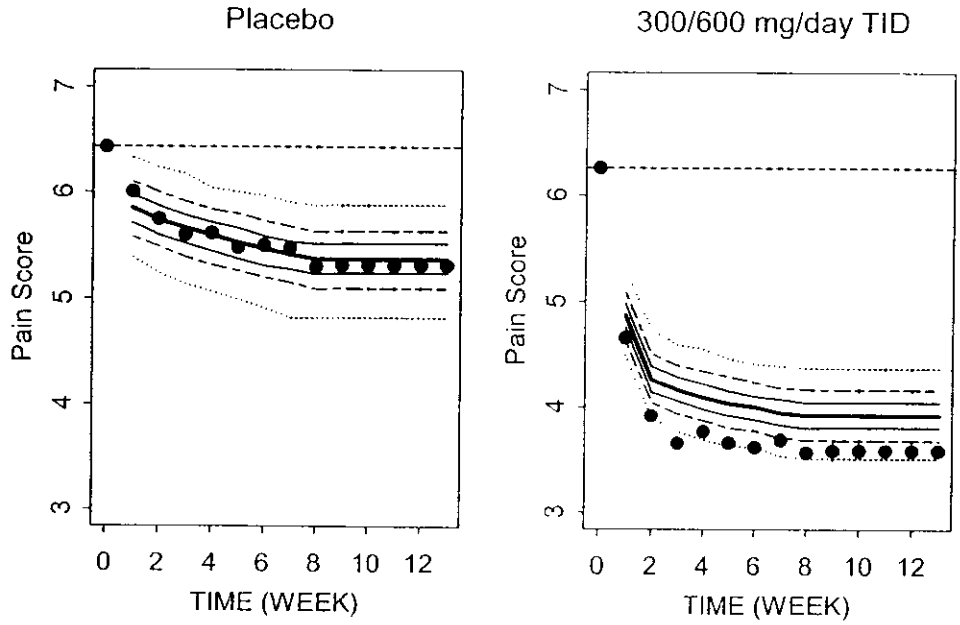


Figure 4. Internal PPC to Predict Study 196 using the Final Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials. Note the 300/600 mg/day BID regimen denotes 300 and 600 mg/day BID doses stratified based on the patient's individual CLcr estimate below and above 60 ml/min, respectively.

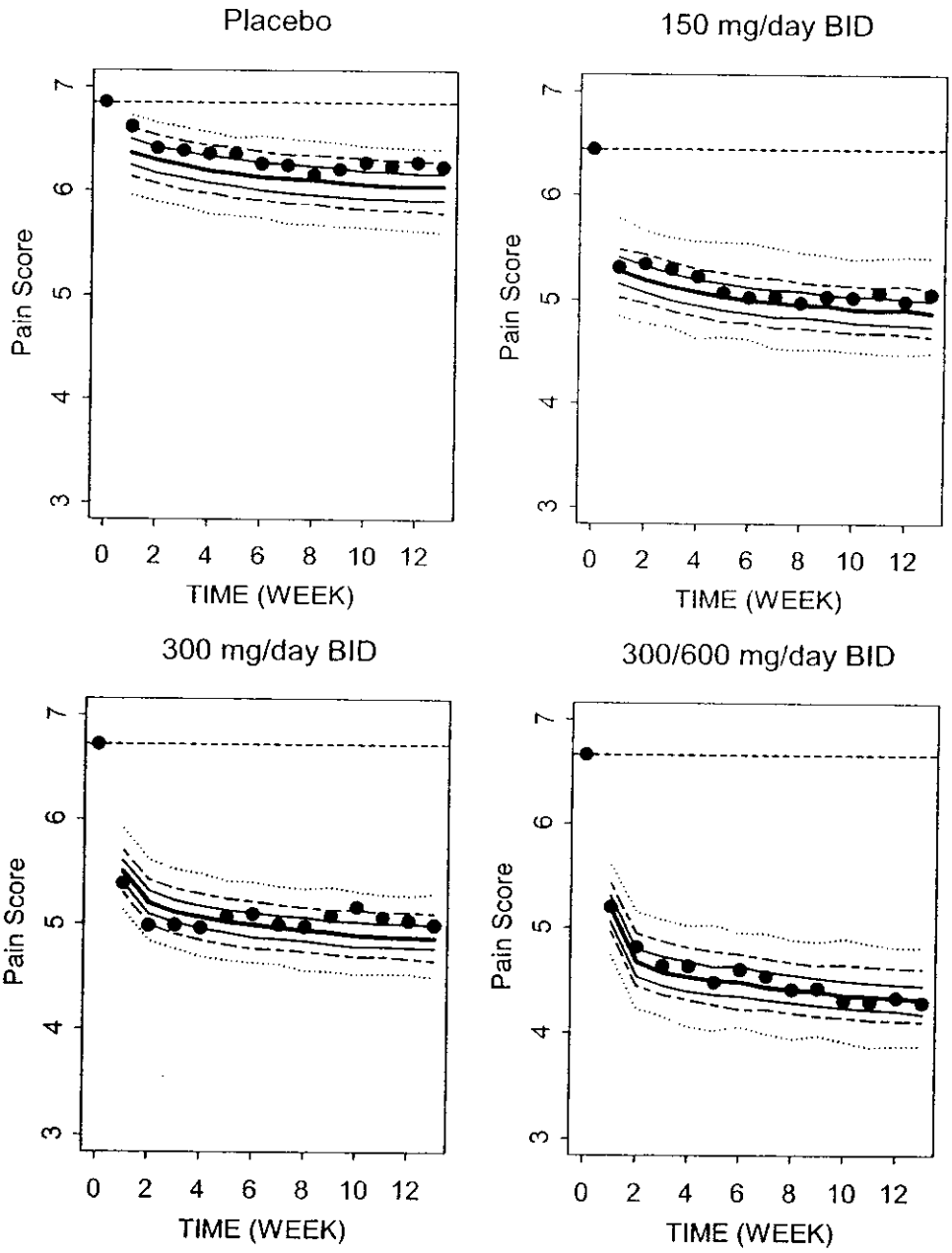


Figure 5. Internal PPC to Predict Study 30 using the Full Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials.

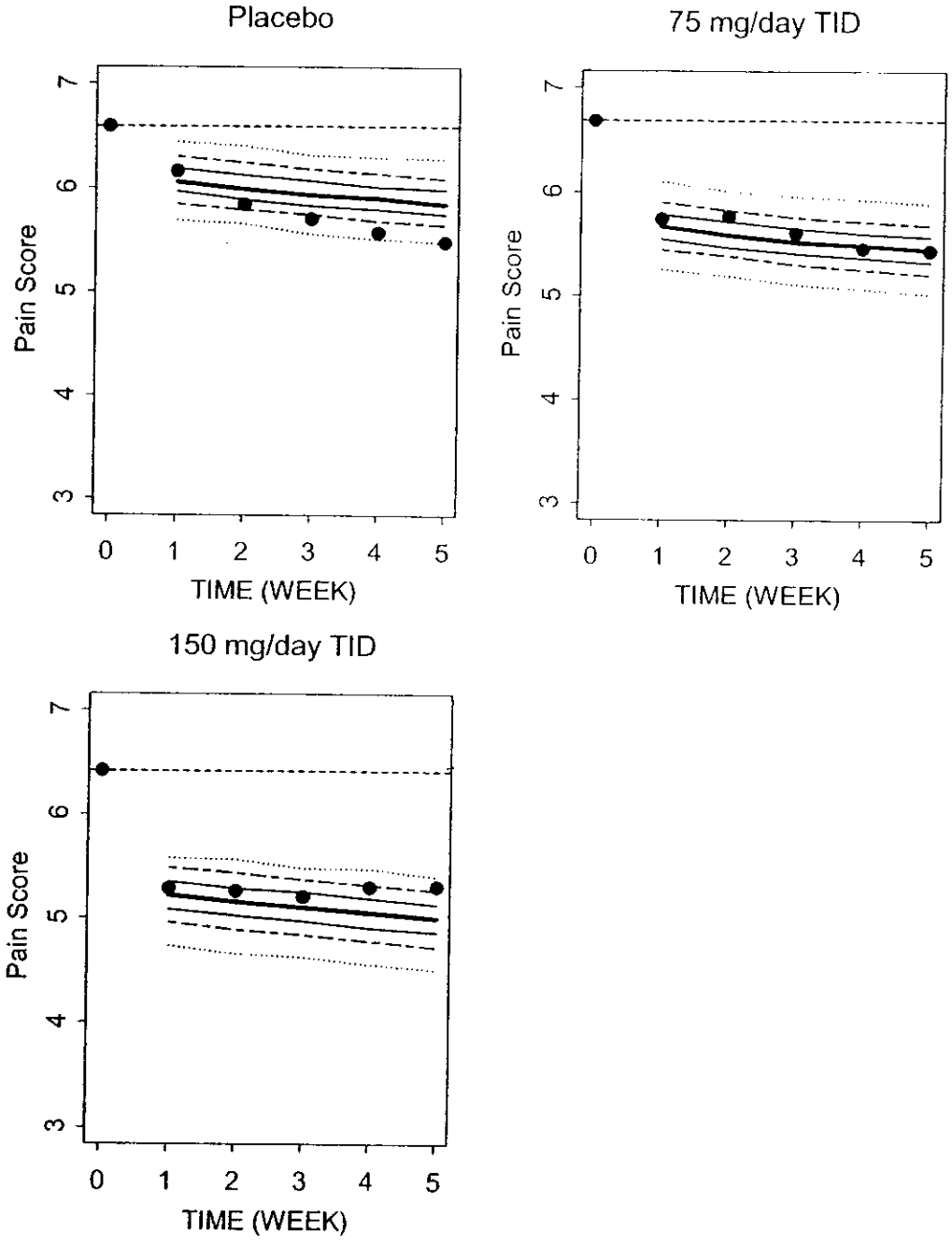


Figure 6. Internal PPC to Predict Study 45 using the Full Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials.

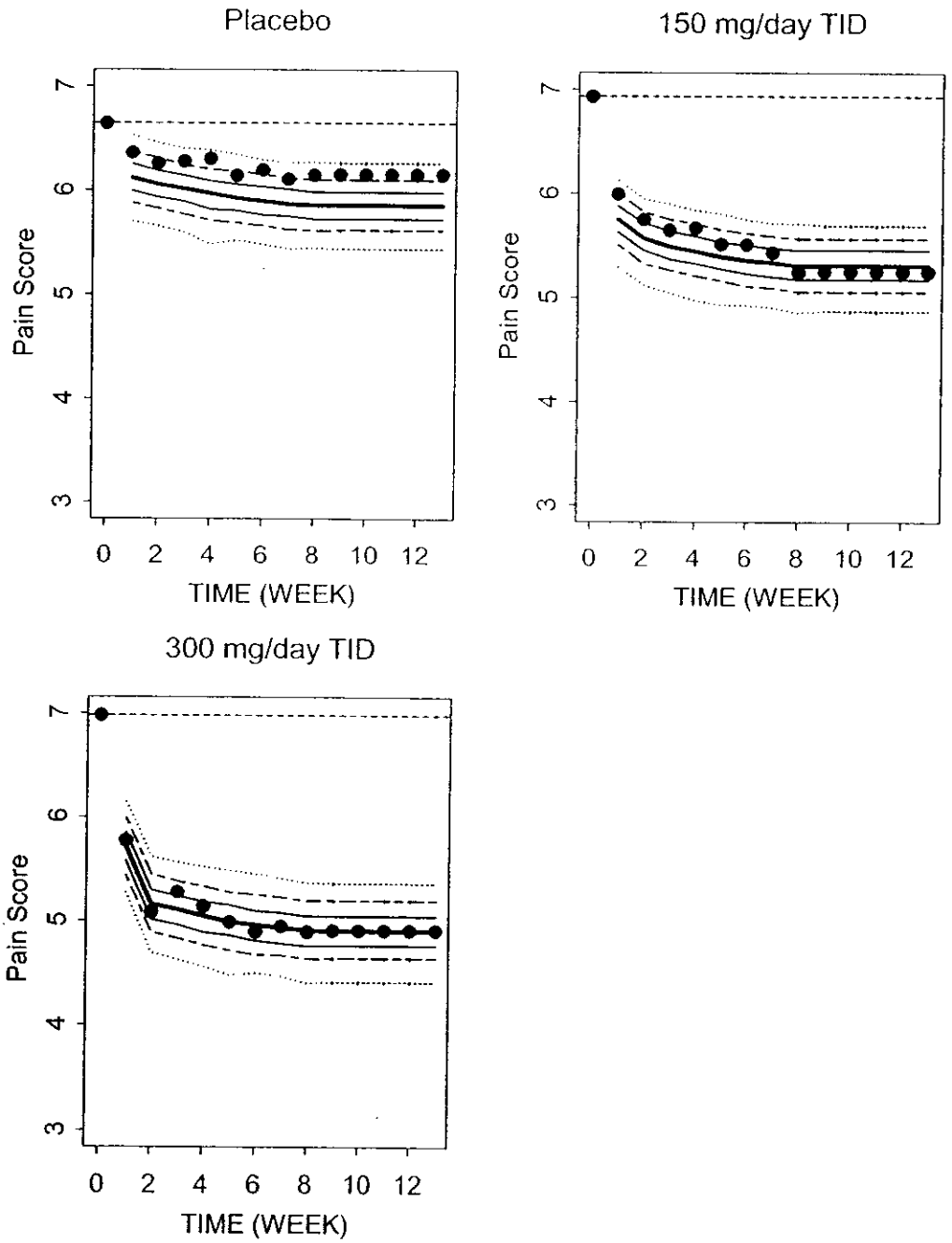


Figure 7. Internal PPC to Predict Study 127 using the Full Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials. Note the 300/600 mg/day TID regimen denotes 300 and 600 mg/day TID doses stratified based on the patient's individual CLcr estimate below and above 60 ml/min, respectively.

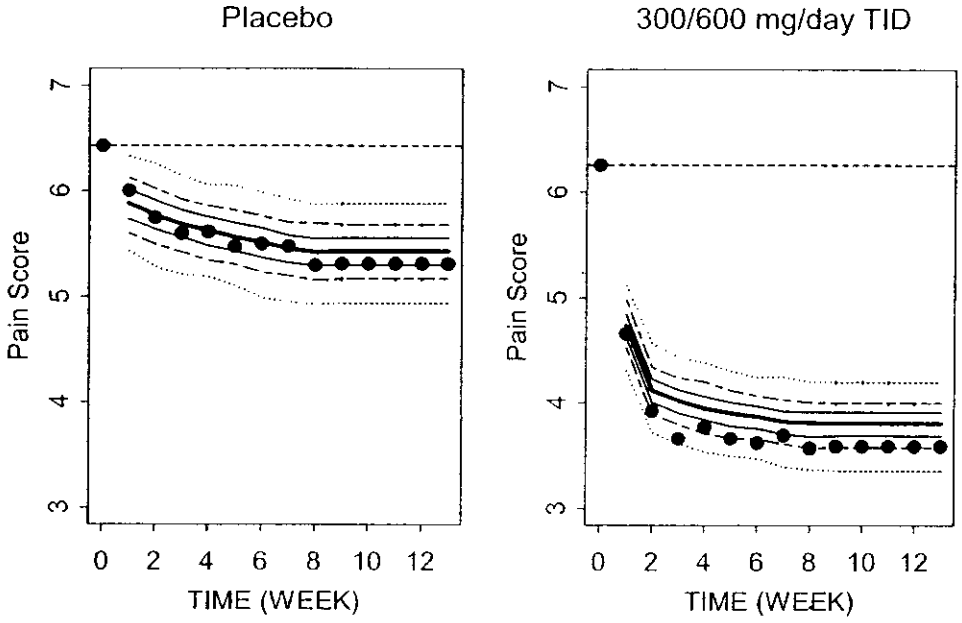


Figure 8. Internal PPC to Predict Study 196 using the Full Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials. Note the 300/600 mg/day BID regimen denotes 300 and 600 mg/day BID doses stratified based on the patient's individual CLcr estimate below and above 60 ml/min, respectively.

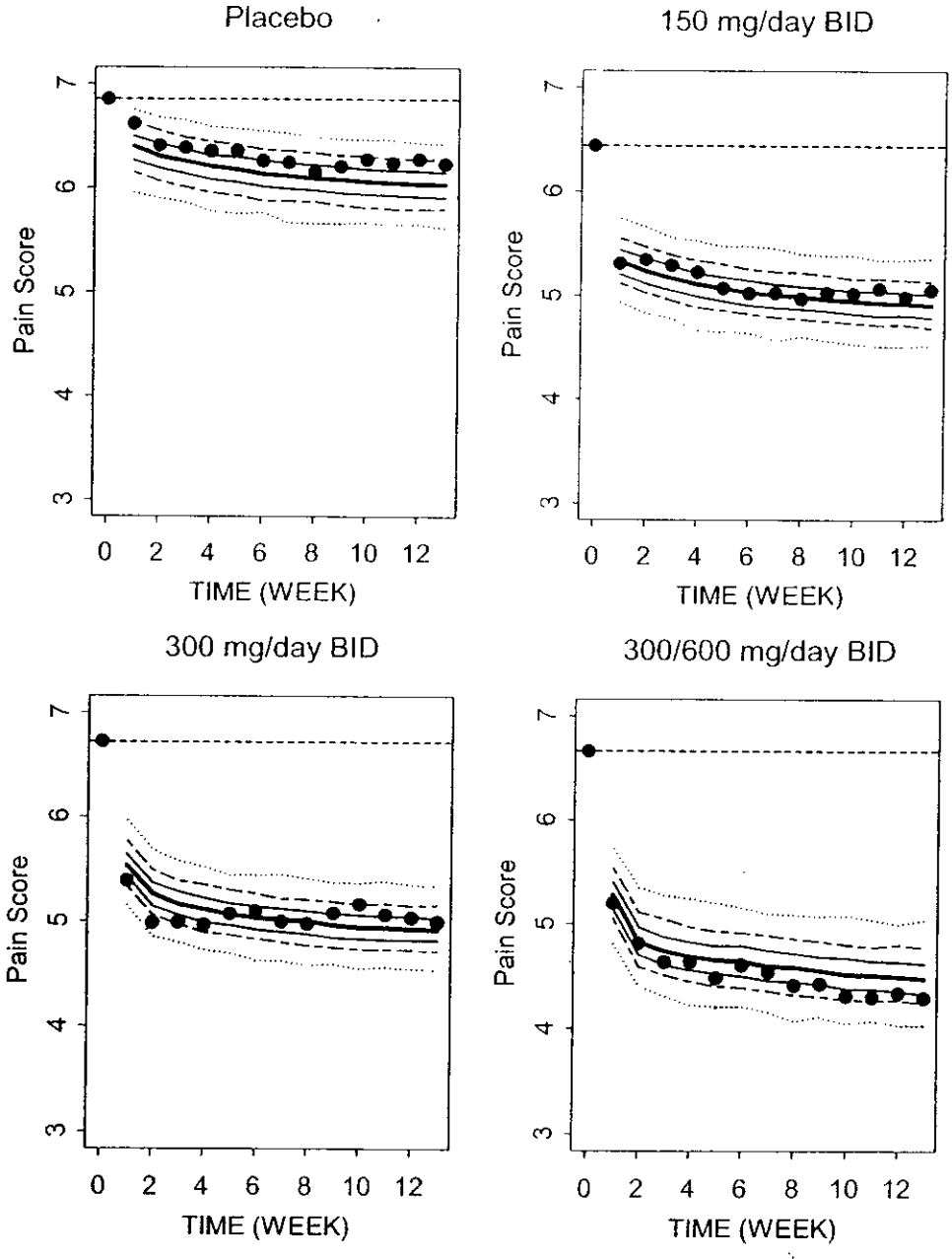


Figure 9. Cross-Validation to Predict Study 30 using the Final Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials.

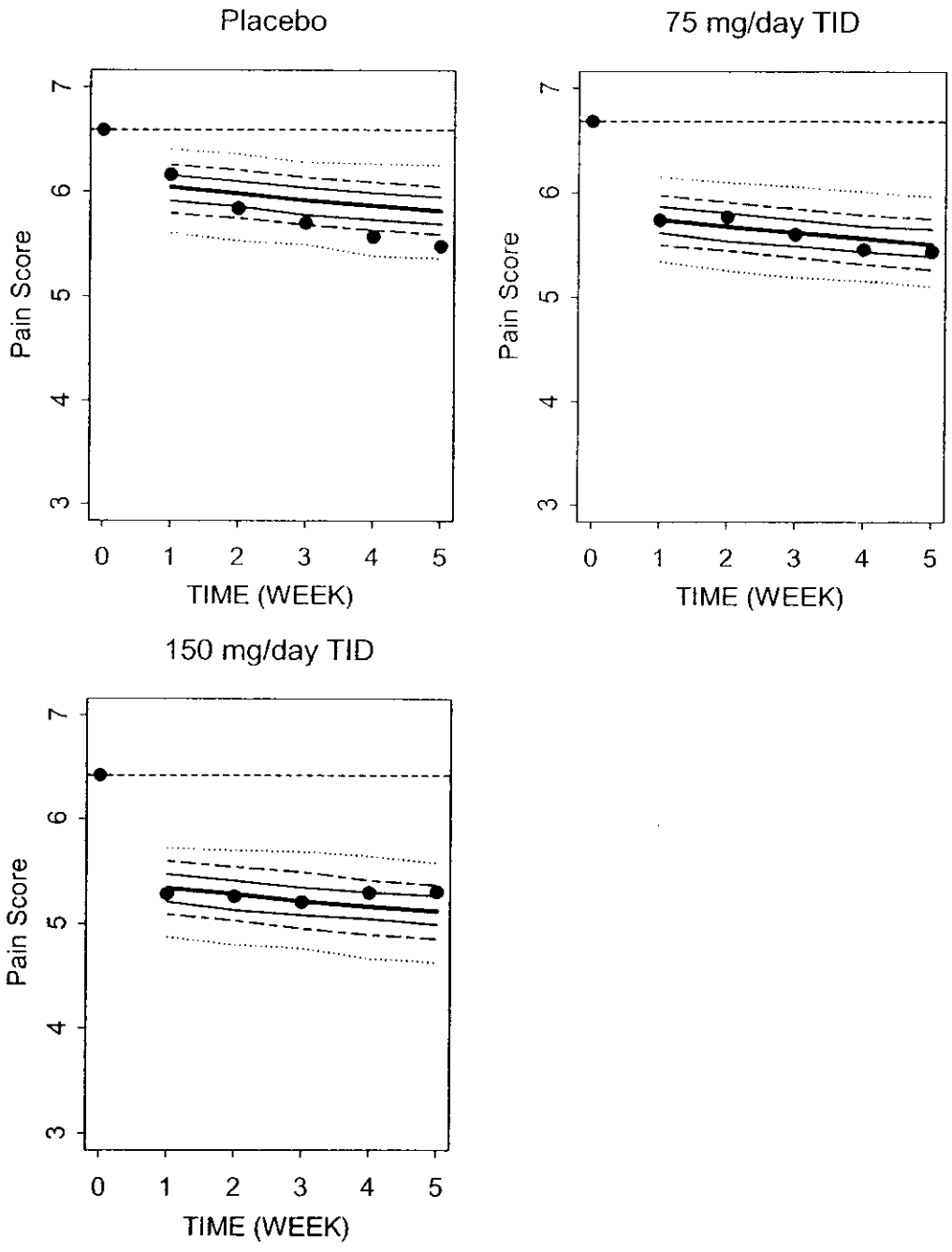


Figure 10. Cross-Validation to Predict Study 45 using the Final Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials.

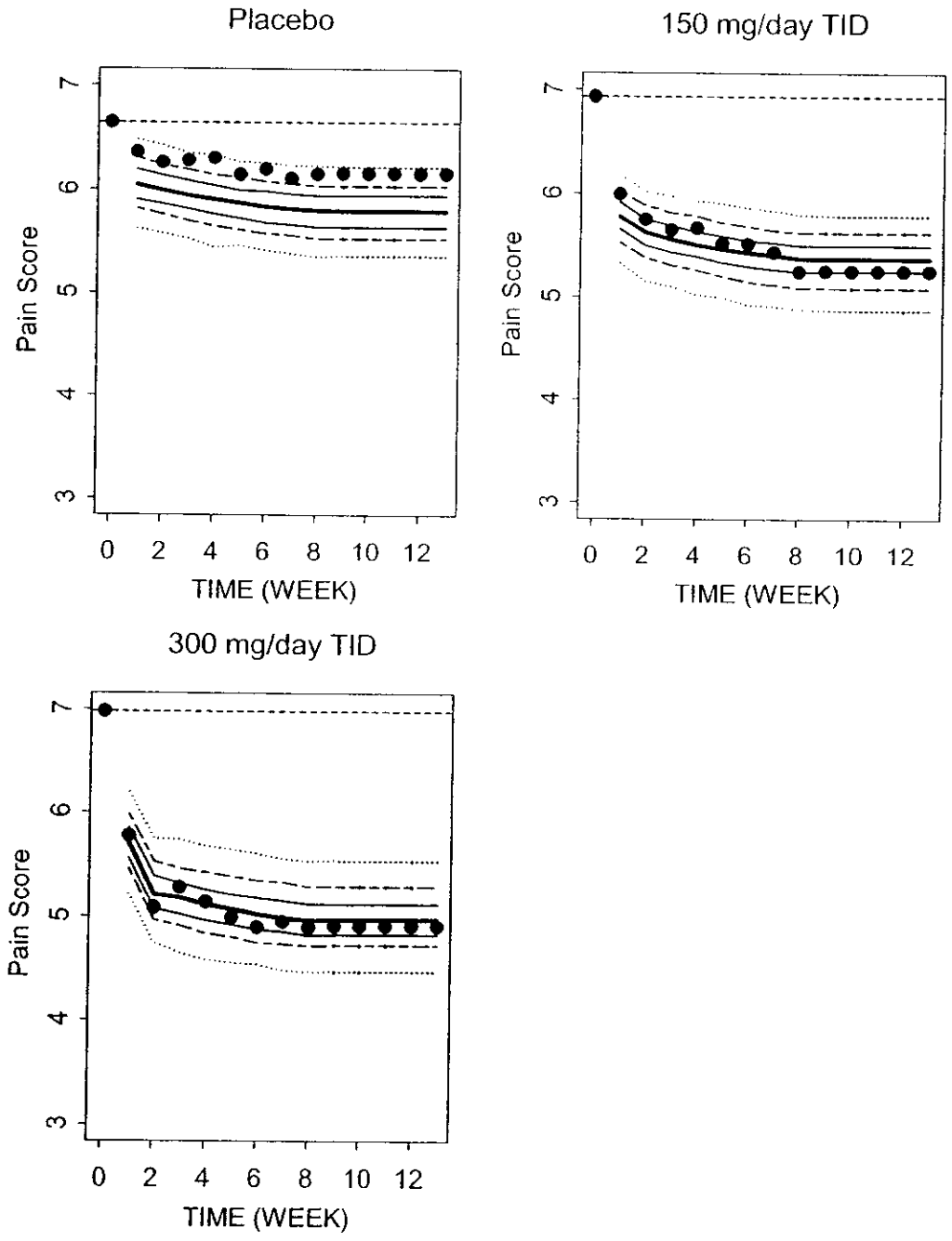


Figure 11. Cross-Validation to Predict Study 127 using the Final Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials. Note the 300/600 mg/day TID regimen denotes 300 and 600 mg/day TID doses stratified based on the patient's individual CLcr estimate below and above 60 ml/min, respectively.

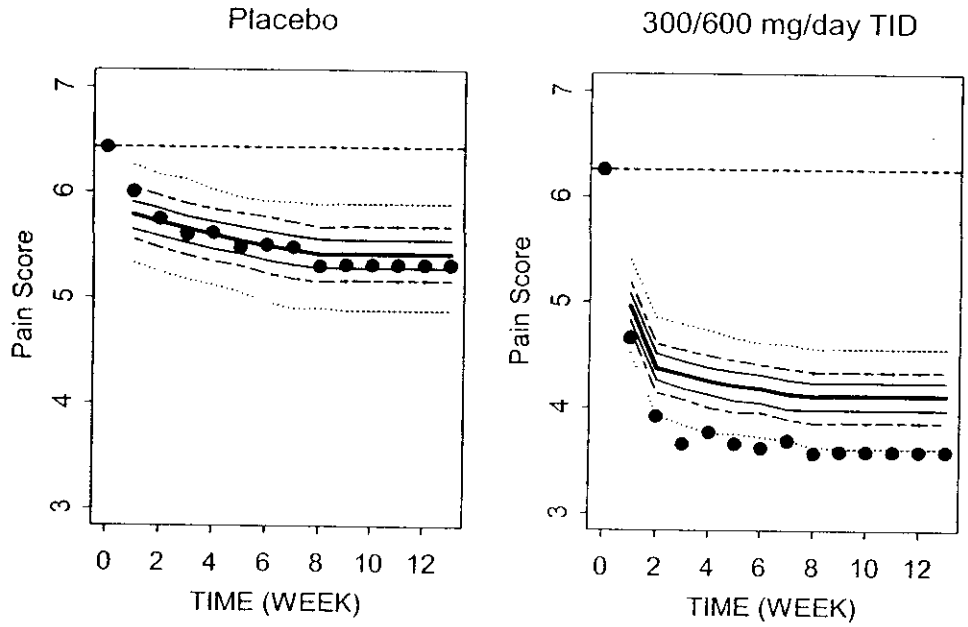
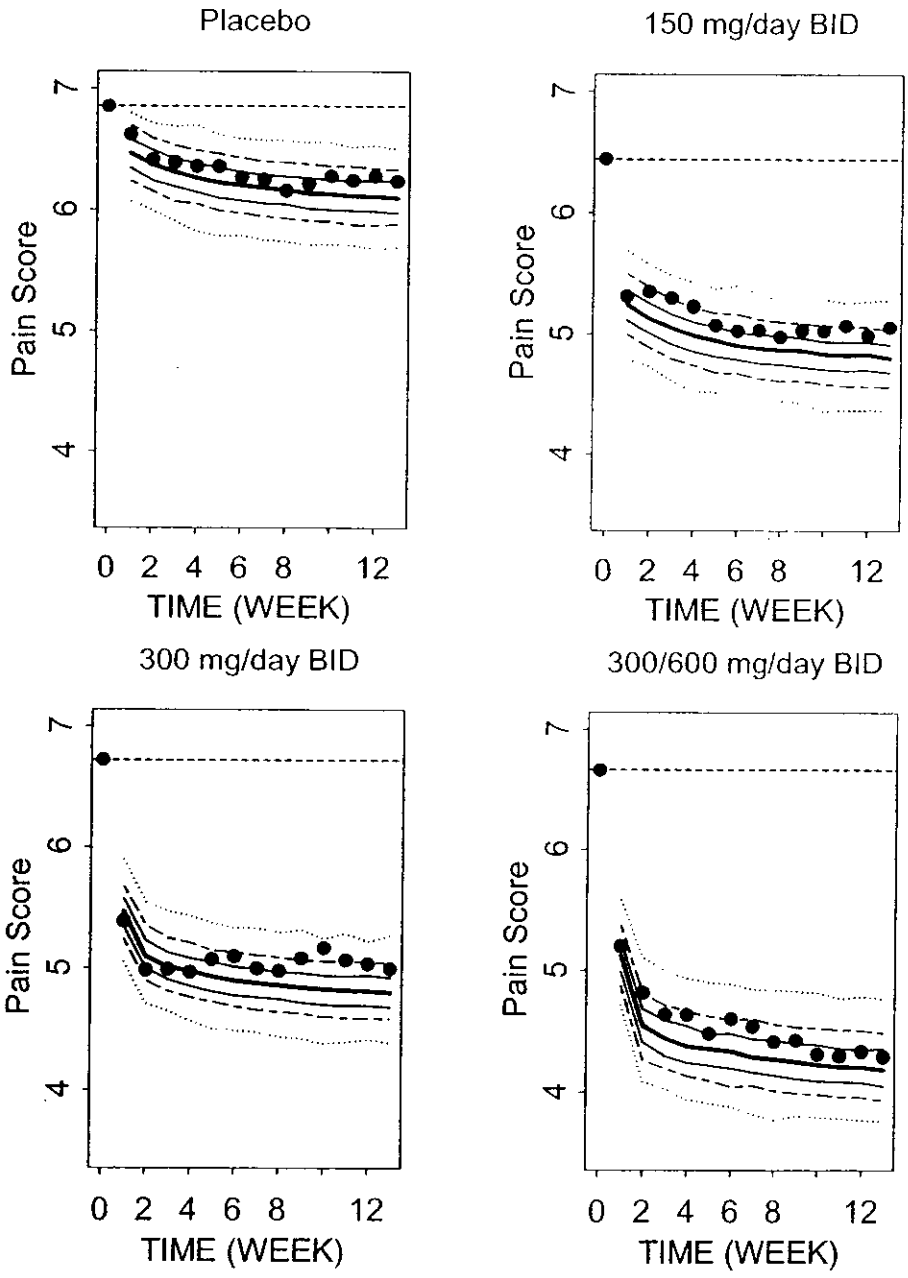


Figure 12. Cross-Validation to Predict Study 196 using the Final Model. Observed (•) weekly mean pain scores with LOCF imputation and comparisons with selected percentiles (median = bold line, 1st and 3rd quartiles = solid line, 10th and 90th percentiles = dashed line, 1st and 99th percentiles = dotted line) of the simulated weekly means from 300 simulated trials. Note the 300/600 mg/day BID regimen denotes 300 and 600 mg/day BID doses stratified based on the patient's individual CLcr estimate below and above 60 ml/min, respectively.



Addendum 2
Response to the FDA Request Regarding NDA 21-723, Dated August 2, 2004

INTRODUCTION

This addendum summarizes additional analyses that were performed in response to the Agency's request, dated August 2, 2004. Specifically, a model fit to the TID trials (Studies 1008-030, -045, and -127) was used to predict the outcomes in the BID trial (Study 1008-196), and conversely, a model fit to the BID trial was used to predict outcomes for the three TID trials, noted as Agency recommendations A.2 and A.3, respectively, of the August 2, 2004 request. Moreover, this addendum contains the suggested plots and tables requested by the Agency.

It is noted that Agency recommendation A.1 to perform a 'leave-one-study-out' cross-validation of the three TID studies was not performed, however, cross validation was performed including all four PHN studies (including the BID trial) as discussed in Addendum 1. Moreover, Addendum 1 also contains modeling and simulation results that in part address Agency recommendation A.2.

A response to recommendation A.1 and results of the requested analyses in the suggested tabular and graphical format for recommendations A.2 and A.3 follow. In addition, data files and NONMEM control streams for all model fits will be provided as requested in recommendation A.4.

A.1. CROSS-VALIDATION OF THE TID STUDIES

Lengthy model development (new models) and simulations would be required to address cross-validation of the TID data alone. These models and their cross-validations could not be performed within the time frame allotted for a response. However, as stated in the introduction, this recommendation was addressed, in part, in Addendum 1. The cross-validation was performed in a similar fashion (leave-one-study-out) with the exception that the Sponsor included the BID trial (Study 1008-196) in the model development. We note that inclusion of the BID data provides a more conservative assessment in that if there were BID and TID regimen differences in the response, including the BID data from Study 196 in the model fits would only decrease its predictive performance on the TID data excluded from the model fit.

A.2. MODELING TID DATA AND PREDICTING BID DATA

The final model described in Addendum 1 was fit to the TID studies (1008-030, -045, and -127) and used to predict the BID study data (1008-196). Plots of the observed and predicted patient percentages versus cumulative change from baseline pain scores by study week for Study 196 are provided in Attachment A.2, labeled as Type1A plots. Similar plots for the cumulative percent change from baseline pain scores by study week for Study 196 are provided in Attachment A.2, labeled as Type 2A plots. Concordance plots of the predicted versus observed patient percentages based on change and percent change from baseline pain scores are also provided in Attachment A.2, labeled as Type 1B and 2B plots, respectively. The range bars in these plots indicate 90% prediction intervals. For the Type 1B and 2B plots, the line of unity was added to help discern the concordance between the observed and predicted percentages of patients. Regression statistics (such as R^2) were not performed for these plots. The predicted percentages are highly correlated across the specified absolute or percent changes from baseline due to their cumulative nature (e.g., a patient demonstrating ≥12.5% change would also exhibit a ≥0% change from baseline). The regression statistics would be biased because of this correlation.

The corresponding tables used to generate the plots provided in Attachment A.2 are provided electronically as a SAS listing file.

A.3. MODELING BID DATA AND PREDICTING TID DATA

The asymptotic covariance matrix of the estimates from fitting the final model (Addendum 1) to the Study 196 BID data alone indicated that the model was not stable. The correlations of the slope (α) and curvature (γ) parameter estimates of the drug effect model, and the rate constant (k_{plc}) and maximum (P_{max}) parameter estimates of the placebo-time effect model were –0.922 and –0.993, respectively. These results suggest that the BID data alone did not contain sufficient information to adequately model the curvature in the drug effect and placebo-time effect models. To mitigate this instability, the drug effect model was reduced to a linear dose-response by fixing γ=1 (i.e., αD^{γ} was reduced to αD) and the placebo-time effect model was reduced to a linear time-response (i.e., $k_{plc} \cdot t$).

Since the final model described in Addendum 1 included a weight effect on γ, the weight effect was added to α for the reduced drug effect model to incorporate its influence as given by the expression

$$\alpha_i = \alpha_o \left(1 + \theta_{sex}^{(\alpha)}\right)^{SEX_i} \left(\frac{AGE_i}{70\ \text{yrs}}\right)^{\theta_{age}^{(\alpha)}} \left(\frac{WT_i}{80\ \text{kg}}\right)^{\theta_{wt}^{(\alpha)}} \left(\frac{\overline{PS}_{i0}}{6.5}\right)^{\theta_{base}^{(\alpha)}}.$$

The placebo-time effect was parameterized as

$$f_p(t_j) = k_{plc} \cdot \left(\frac{AGE_i}{70\ \text{yrs}}\right)^{\theta_{age}^{(plc)}} \cdot \left(\frac{\overline{PS}_{i0}}{6.5}\right)^{\theta_{base}^{(plc)}} \cdot t_j .$$

Addendum 1 contains more detailed information on how to interpret these parameters. This reduced exposure-response model fitted to the BID data alone resulted in a more stable model.

Before the Study 196 BID data-model was used to predict the TID study data, an internal posterior predictive check (PPC) was performed to assess the adequacy of the model predictions to the Study 196 outcomes. Plots of the observed and predicted patient percentages versus cumulative change and percent change from baseline pain scores by study week for Study 196 are provided in Attachment A.3, labeled as Type1A and 2A plots, respectively. Concordance plots of the predicted versus observed patient percentages based on change and percent change from baseline pain scores for Study 196 are also provided in Attachment A.3, labeled as Type 1B and 2B plots, respectively.

The Study 196 BID data-model was used to predict the outcomes for each of the three TID studies. The graphical results of these external PPCs for the patient percentages versus cumulative change and percent changes in pain scores (Type 1A and 2A plots) and the concordance plots of the predicted versus observed patient percentages (Type 1B and 2B plots) are also provided in Attachment A.3.

The corresponding tables used to generate the plots provided in Attachment A.3 are provided electronically as a SAS listing file.

A.4. ELECTRONIC DATA FILES AND NONMEM CONTROL STREAMS

The electronic data files and NONMEM control streams will be provided.

CONCLUSIONS

- The model developed using the TID data (studies 030, 045, 127) adequately predicted the percentage of patients for the specified (absolute or percent) changes from baseline pain for patients receiving pregabalin BID (Attachment A.2). The deviations between the observed and predicted percentages of patients were within the prediction error.

- The BID data alone did not contain sufficient information (study 196) to adequately characterize the curvature of the dose-effect or placebo-time profiles. The estimates of the parameters used to model these profiles were highly correlated. To reconcile the correlation, a reduced model employing linear dose-effect and placebo-time sub-models was developed. The internal PPC of the reduced model (using the study 196 data) indicated the model adequately predicted the pregabalin data as the deviations between the observed and predicted percentages of patients were within the prediction error.

- The reduced model developed using the BID data (study 196) adequately predicted the percentage of patients for the specified (absolute or percent) changes from baseline pain for patients receiving pregabalin TID (Attachment A.3). The deviations between the observed and predicted percentages of patients were within the prediction error with the exception of the 300/600 mg/day TID (dose stratified by CLcr below or above 60 ml/min) in Study 127. These deviations (i.e., under-prediction of the response) are consistent with the findings discussed in Addendum 1.

- The cross-validation of the PHN final model (TID model prediction of the BID data and BID model prediction of the TID data) suggested that any response differences due to regimen were generally less than that attributable to prediction error. These results suggest that the final model using total daily dose as a measure of exposure independent of regimen provides adequate predictive performance of the pain score response for both TID and BID regimens.

ATTACHMENTS

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Attachment A.2.

TID Model (Studies 030, 045, 127) Prediction of BID Data (Study 196)

Type 1A: Percentage of Patients Versus ΔScore by Week and Treatment Group

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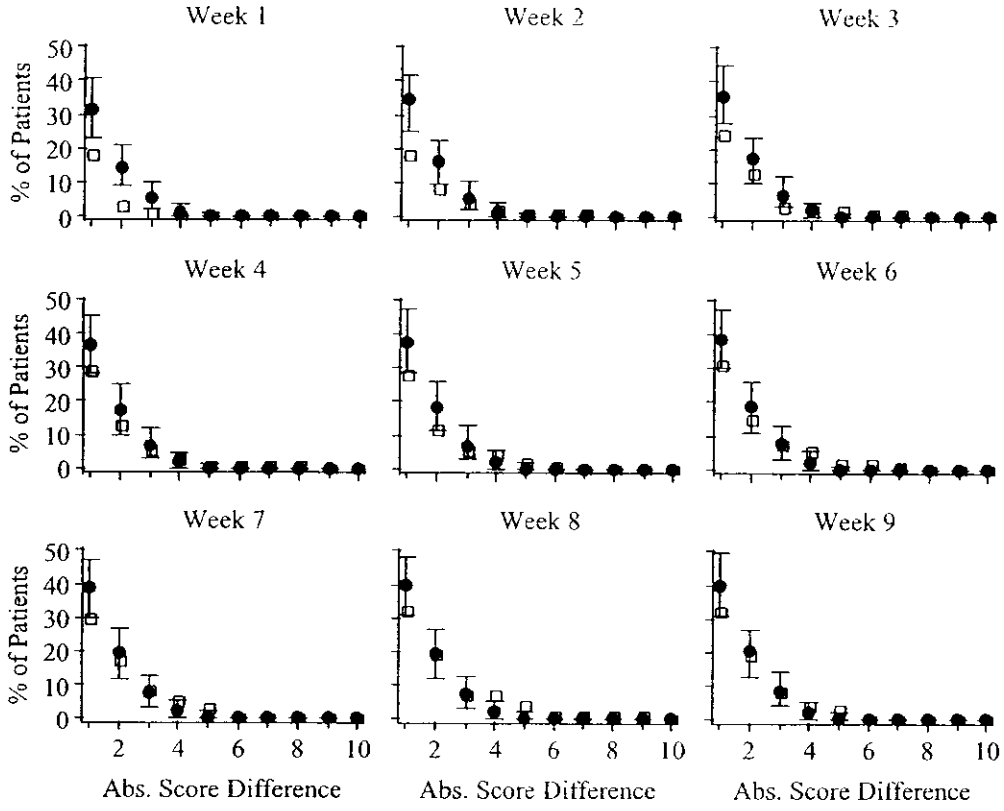
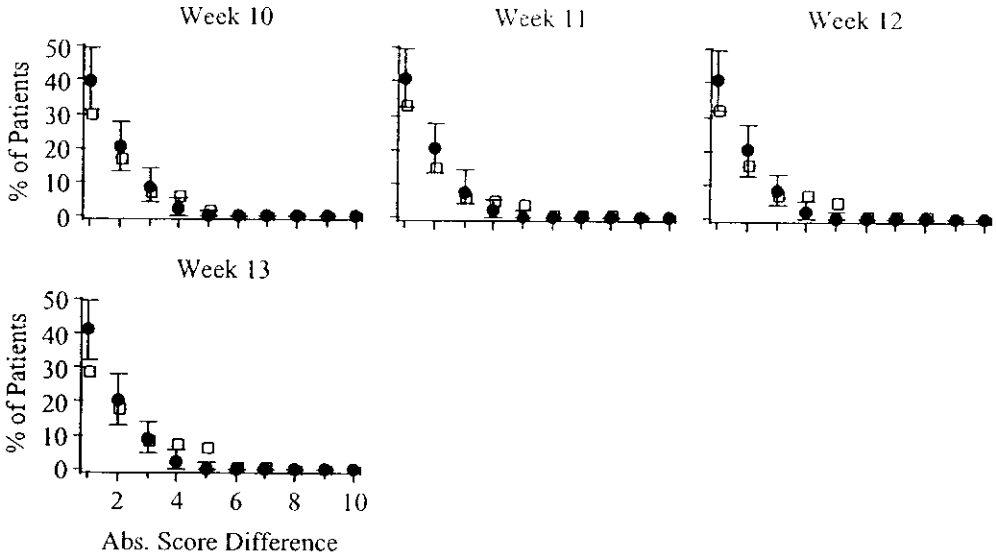
Placebo

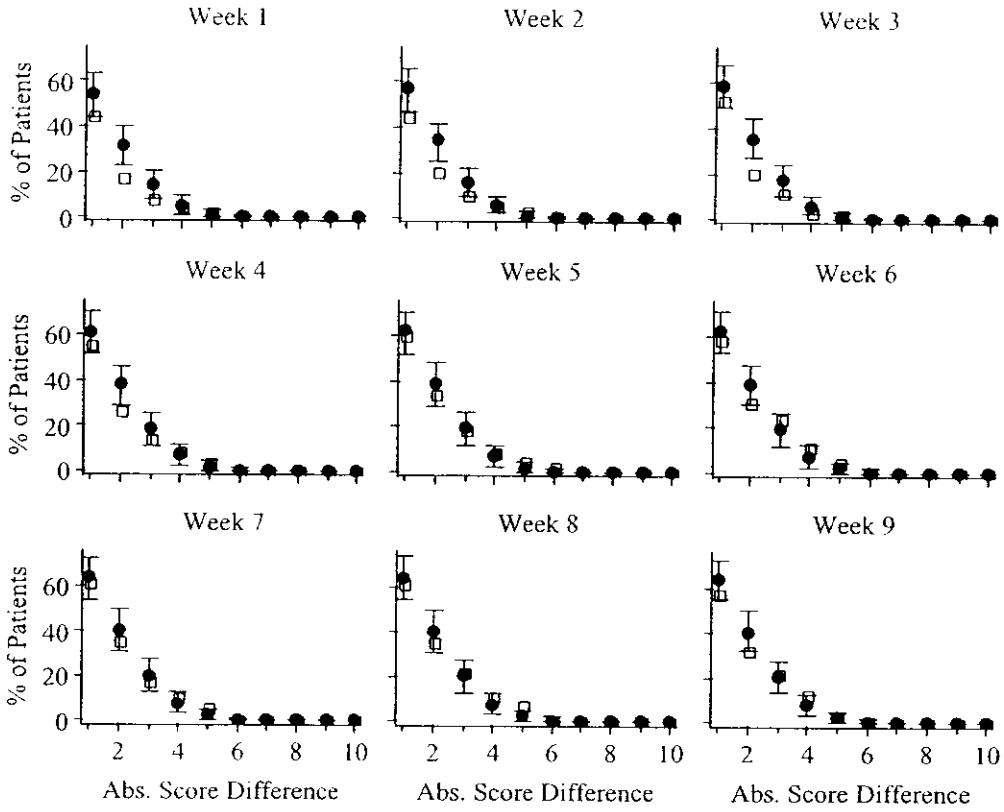

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
10
20
30
40
50
2
4
6
8
10
Abs. Score Difference
Predicted
Observed

Placebo

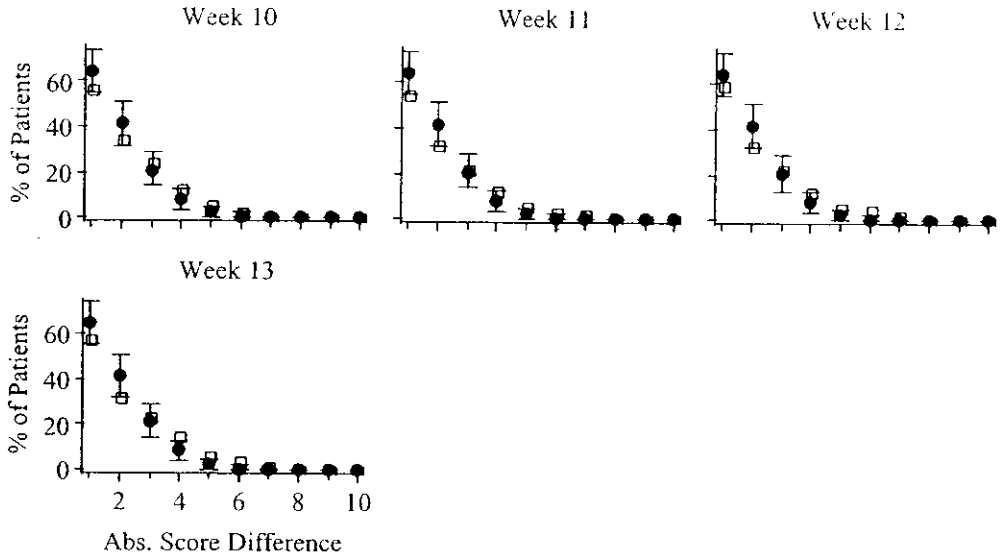


● Predicted
□ Observed

150 mg/Day BID

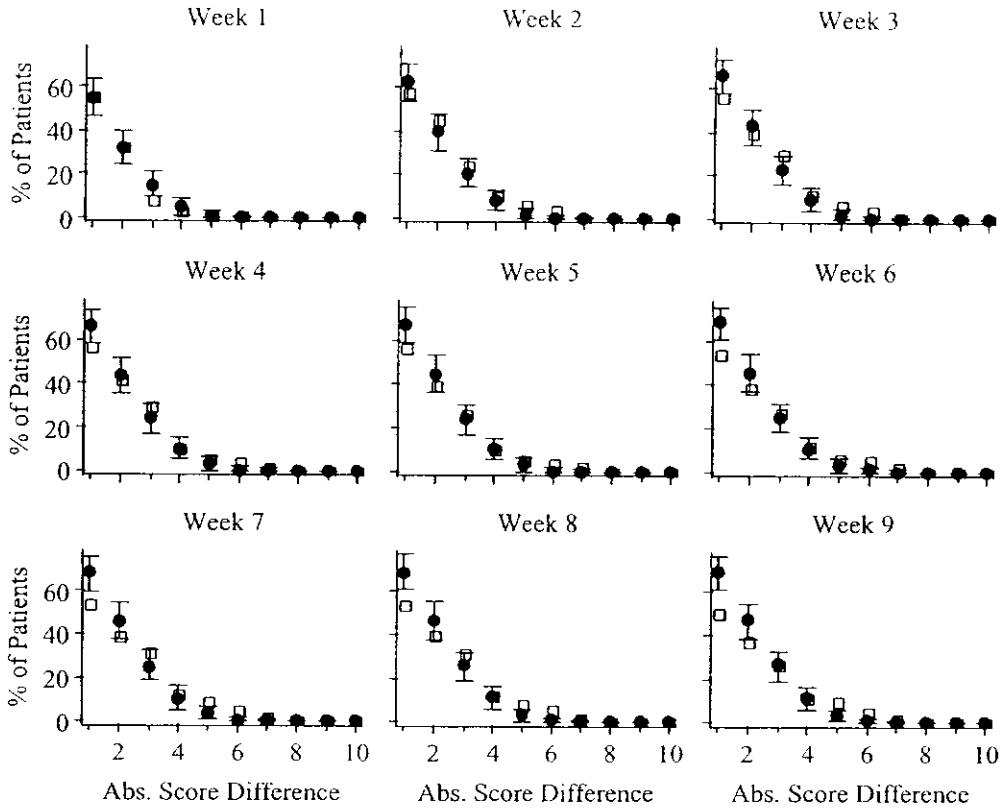


150 mg/Day BID

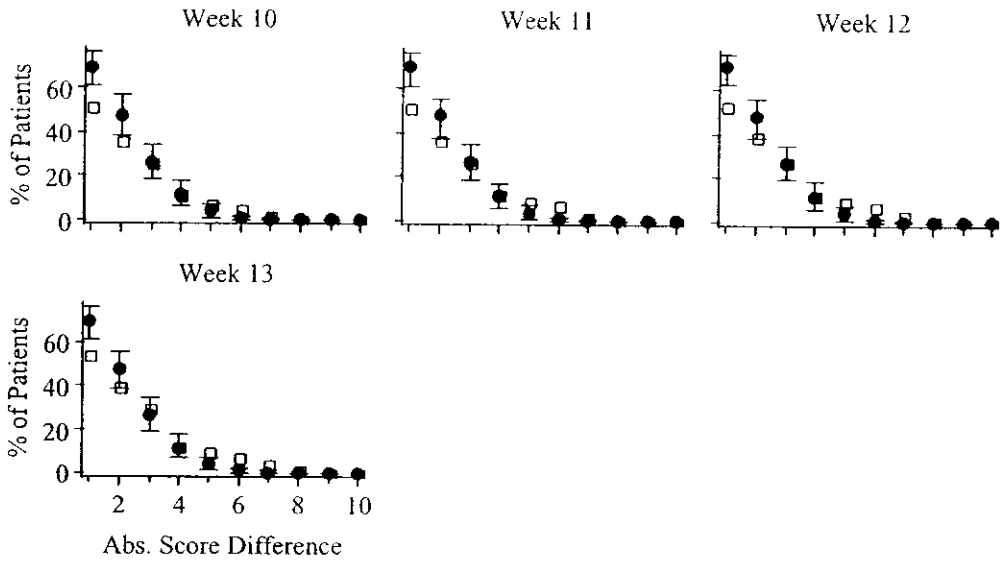


● Predicted
□ Observed

300 mg/DAY BID

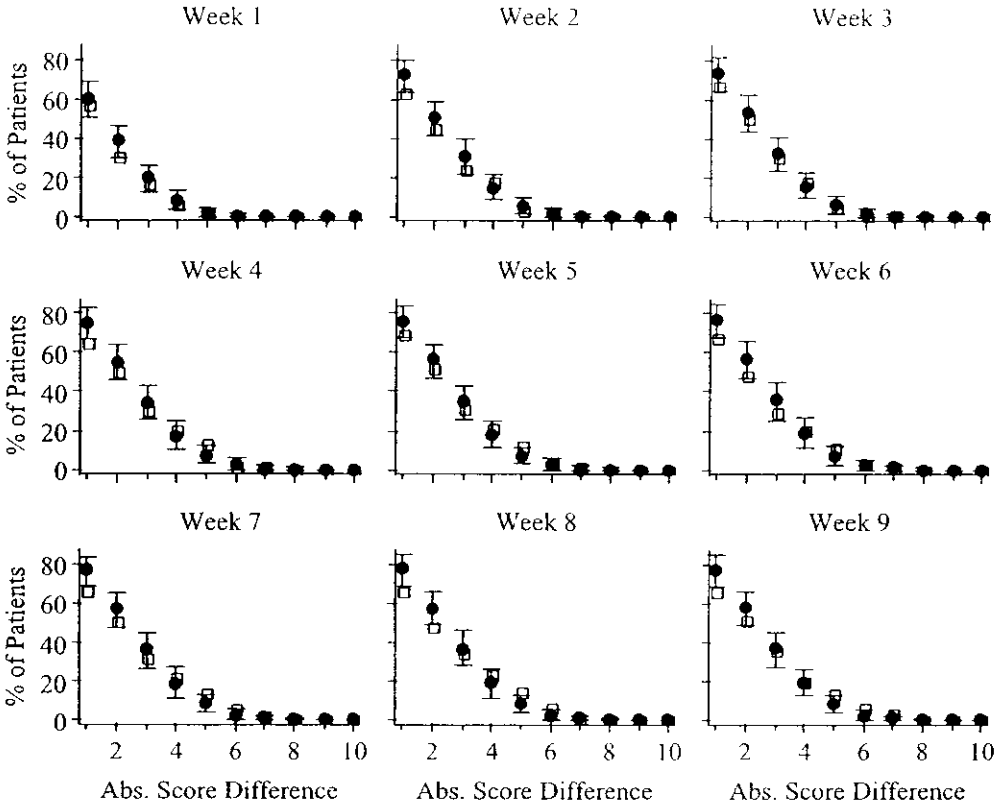


300 mg/DAY BID

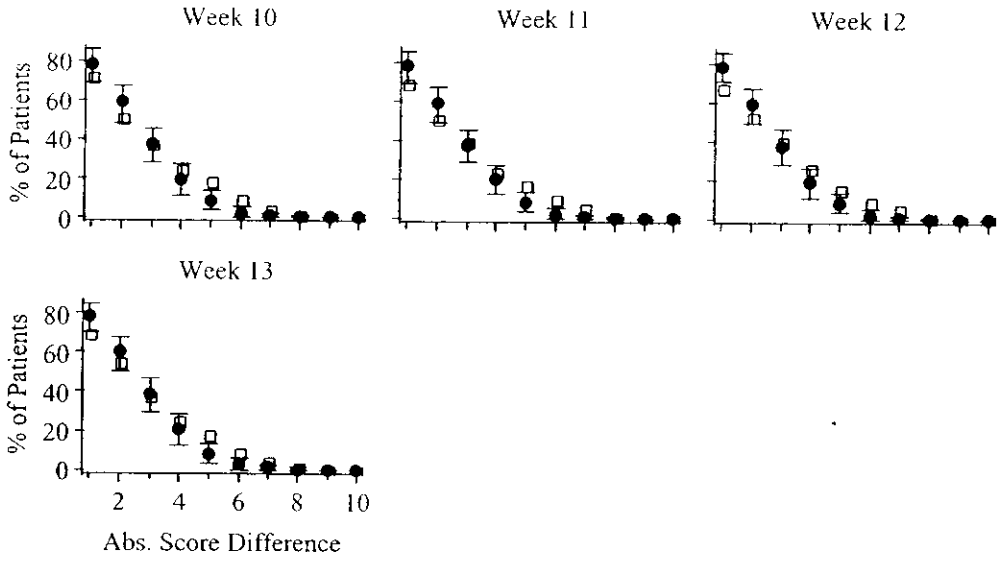


● Predicted
□ Observed

300/600 mg/Day BID



300/600 mg/Day BID



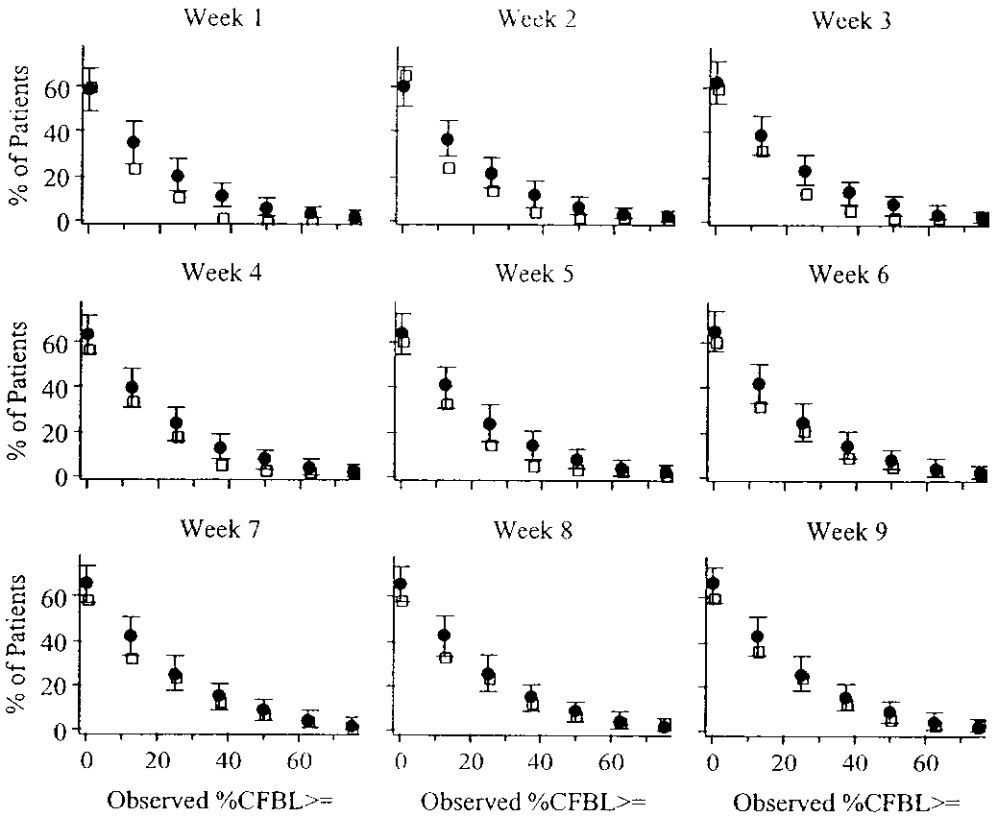
● Predicted
□ Observed

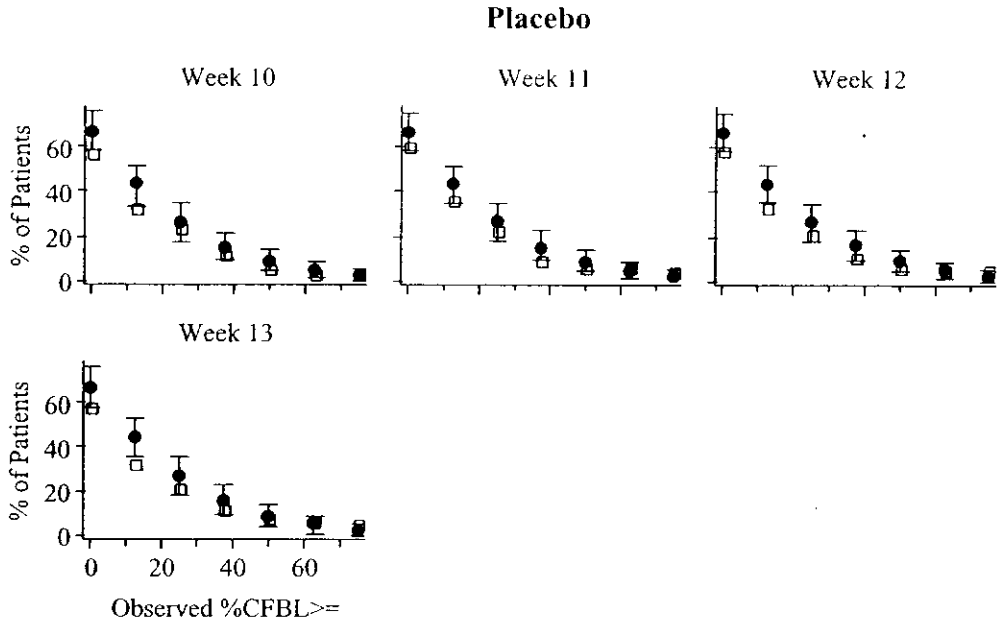
Attachment A.2.

TID Model (Studies 030, 045, 127) Prediction of BID Data (Study 196)

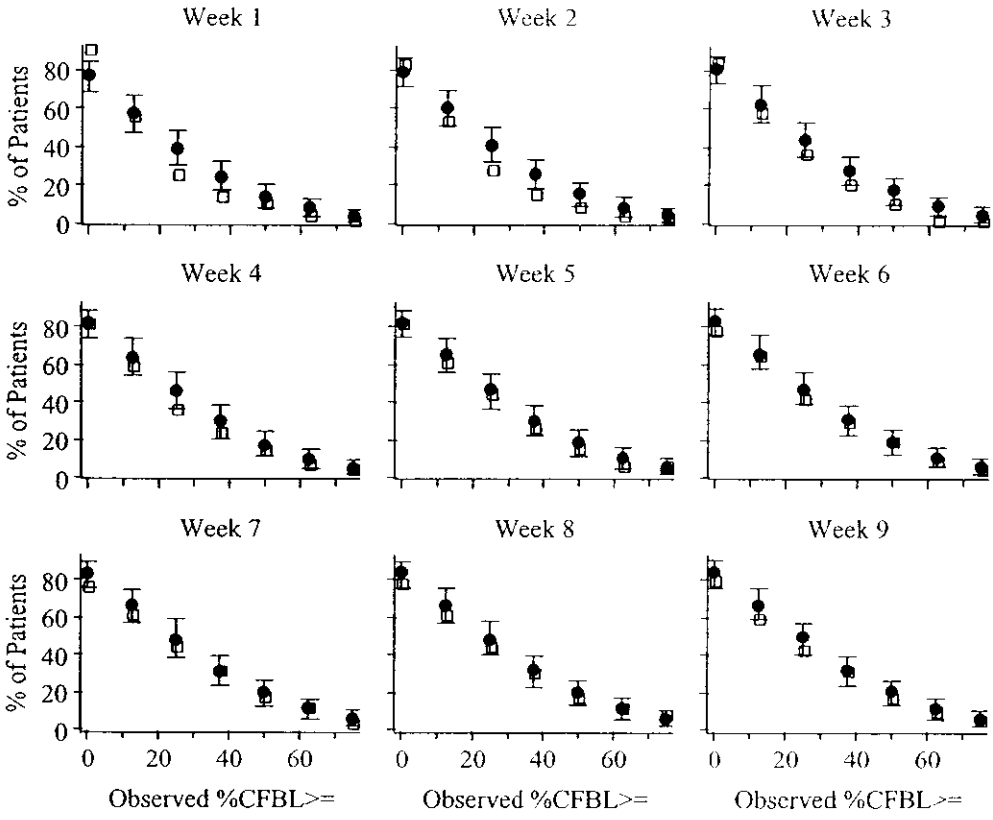
Type 1B: Percentage of Patients Versus %Change in Pain Score by Week and Treatment Group

Placebo

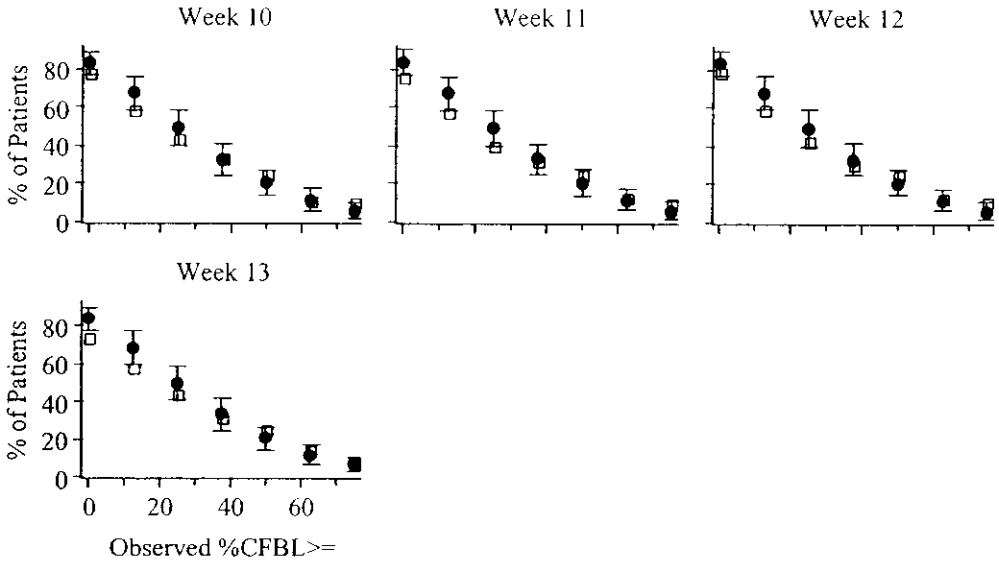

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
Observed %CFBL>=
Predicted
Observed


Placebo
Week 10
Week 11
Week 12
Week 13
% of Patients
0
20
40
60
Observed %CFBL>=
Predicted
Observed

150 mg/Day BID

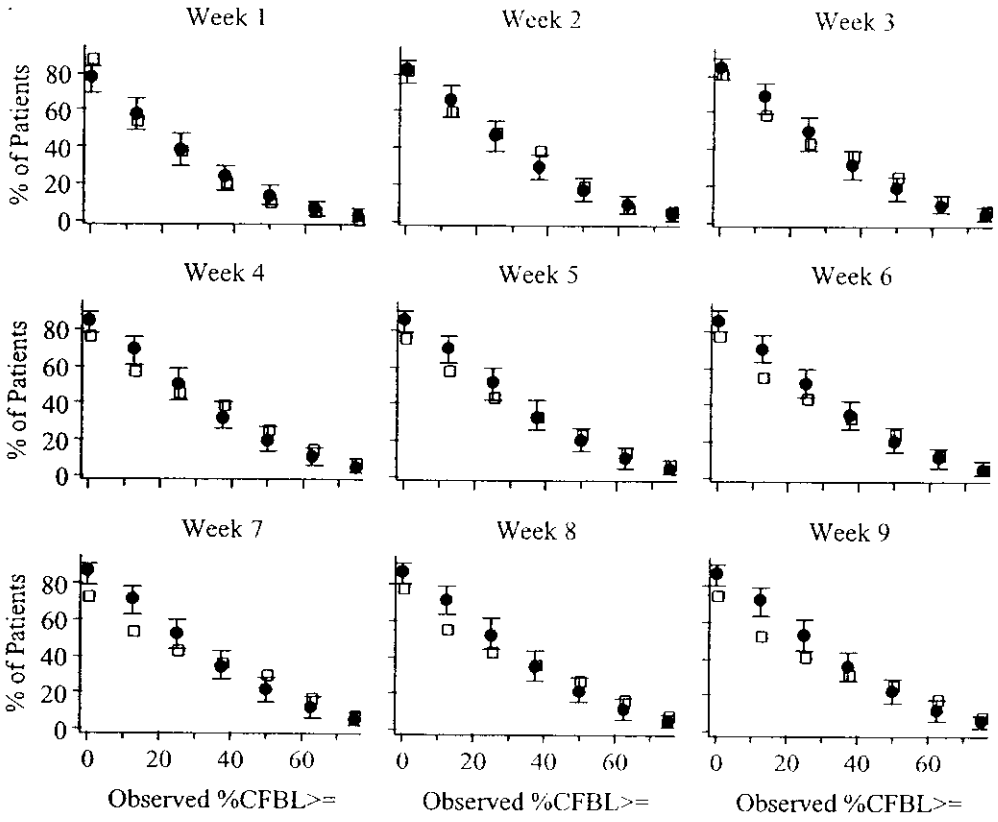


150 mg/Day BID

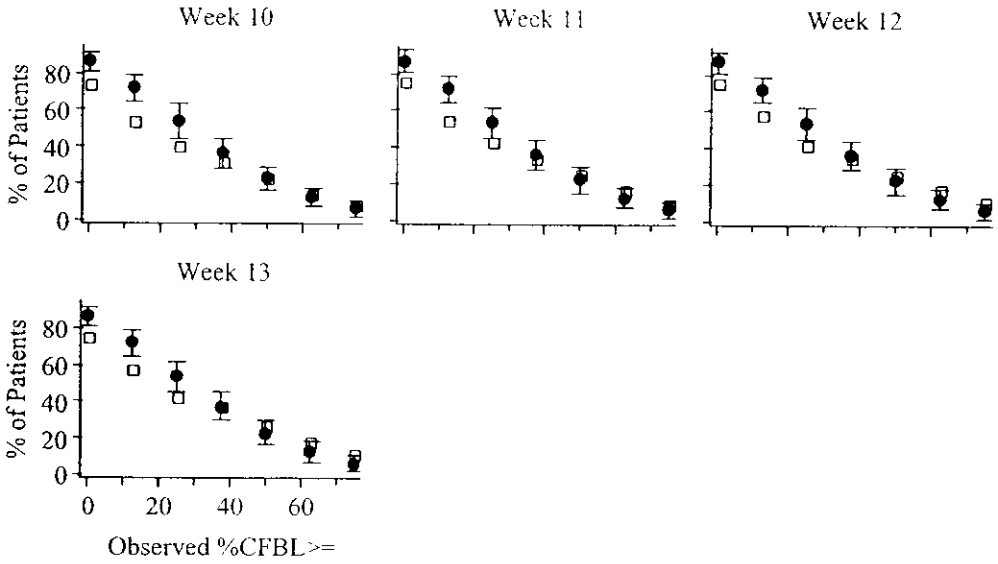


● Predicted
□ Observed

300 mg/Day BID

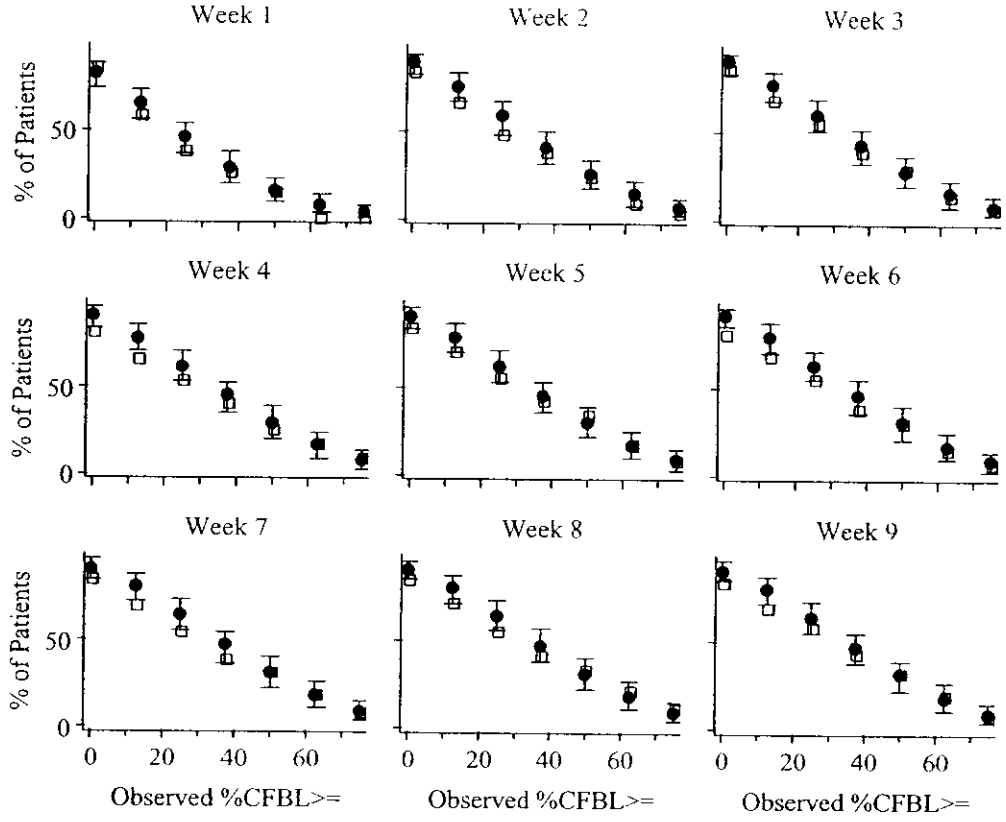


300 mg/Day BID

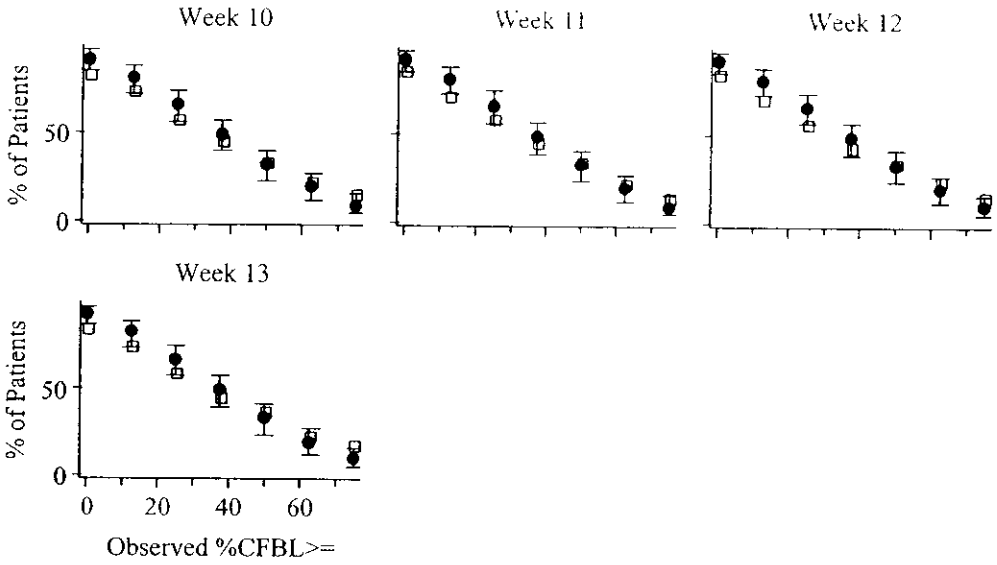


● Predicted
□ Observed

300/600 mg/Day BID



300/600 mg/Day BID



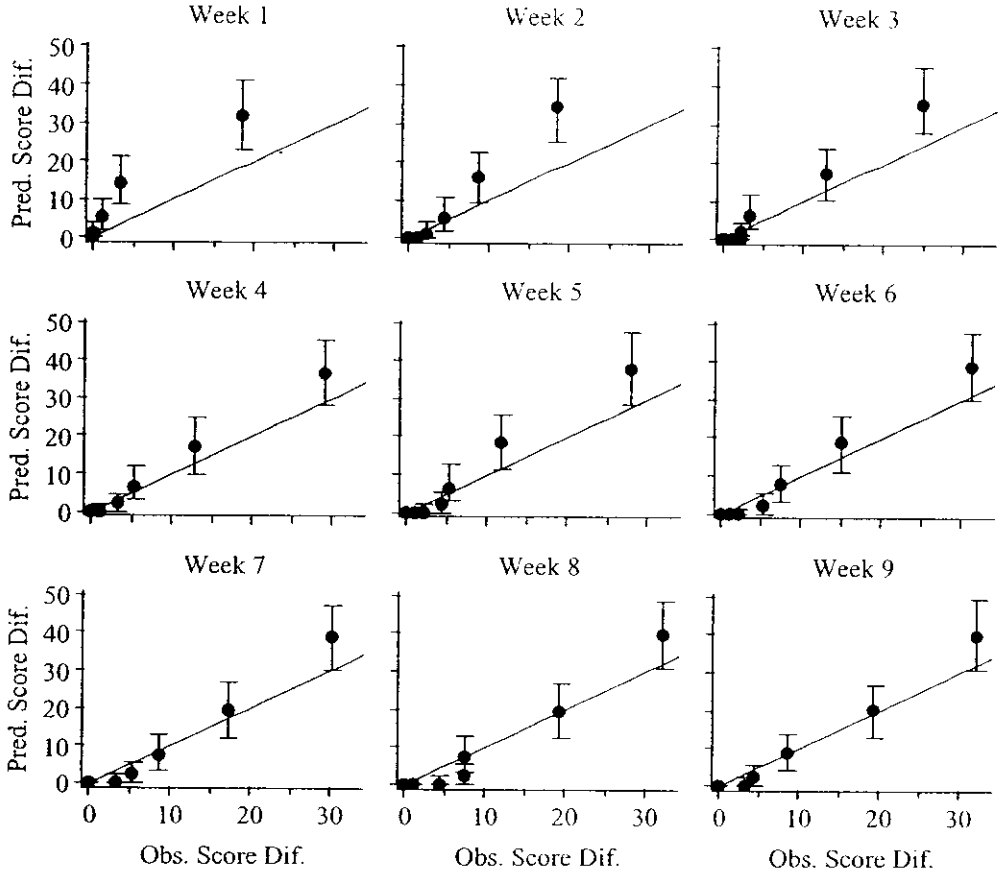
● Predicted
□ Observed

Attachment A.2

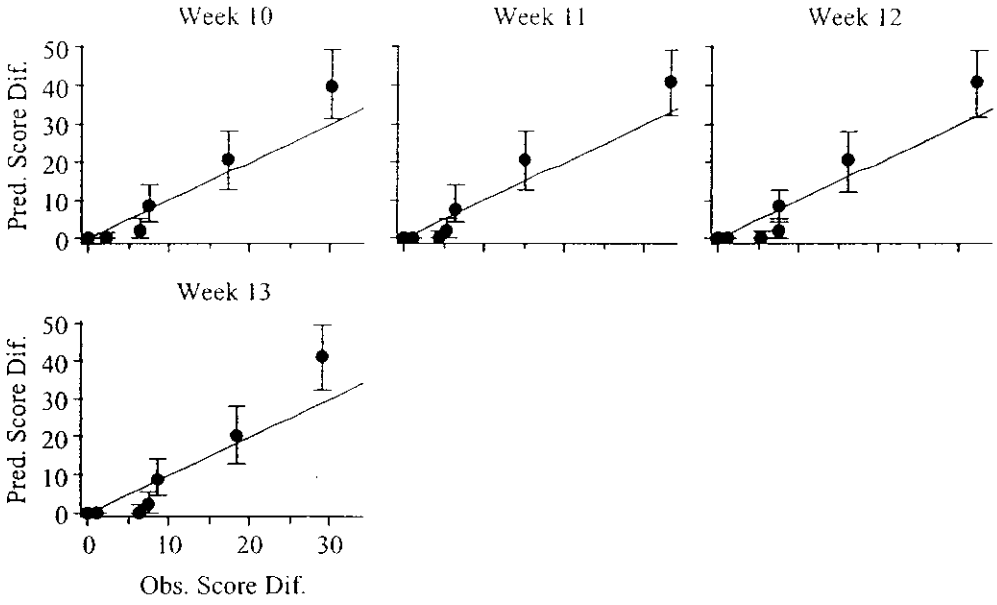
TID Model (Studies 030, 045, 127) Prediction of BID Data (Study 196)

Type 2A: Concordance Plots of Observed and Predicted Percentage of Patients (ΔScore) by Week and Treatment Group

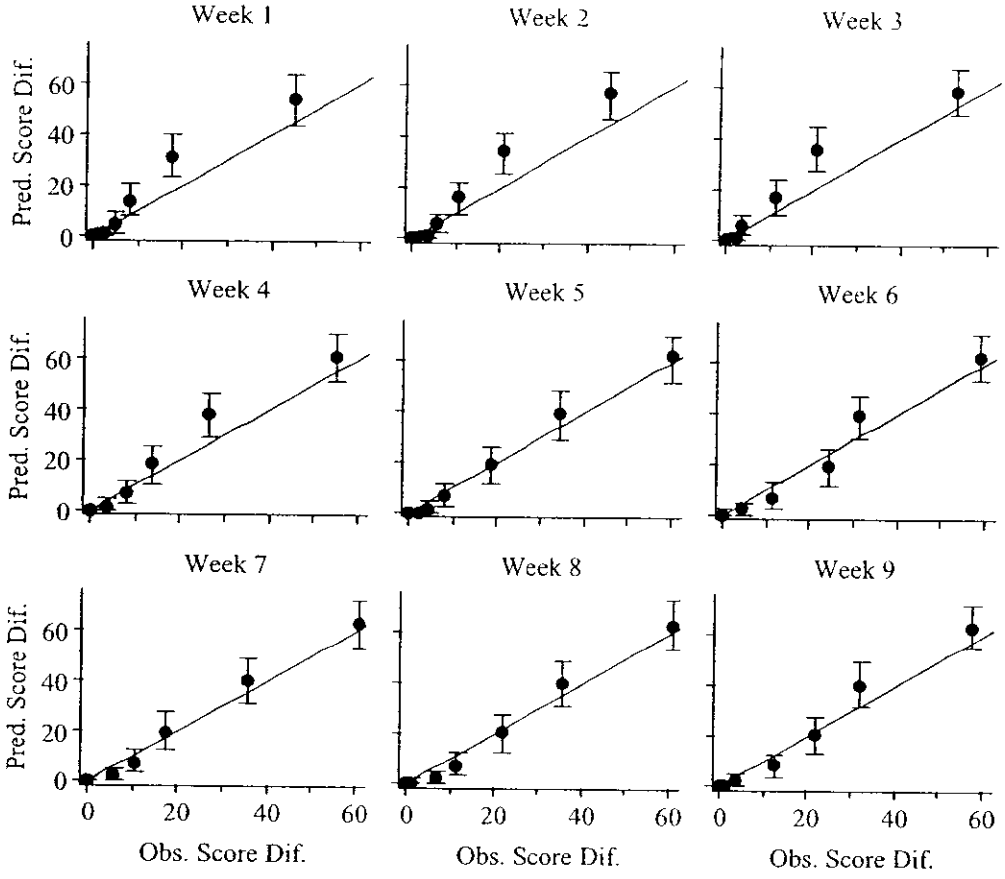
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Pred. Score Dif.
Obs. Score Dif.
0
10
20
30
40
50

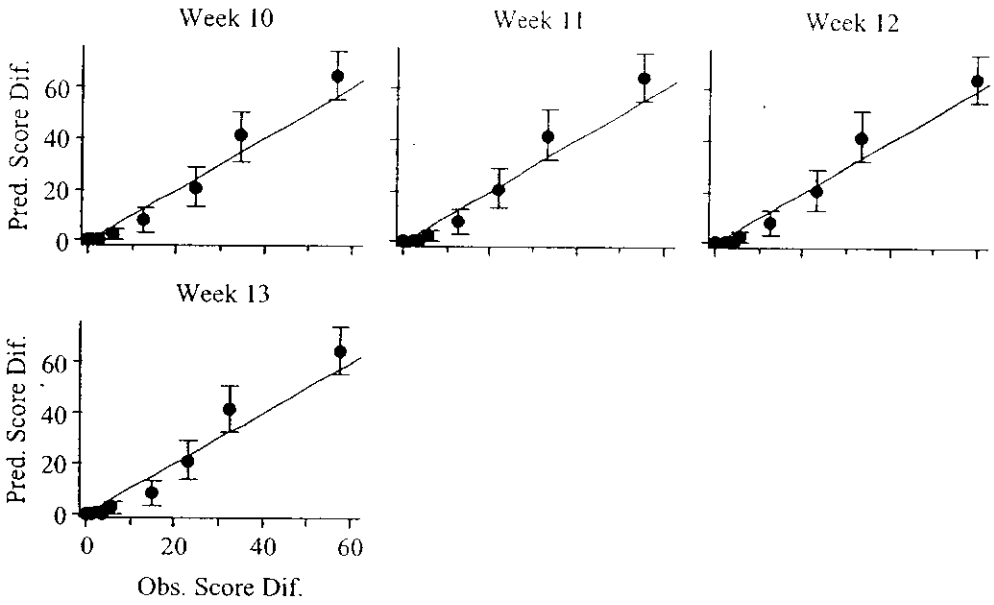
Placebo


Week 10
Week 11
Week 12
Week 13
Pred. Score Dif.
Obs. Score Dif.
0
10
20
30
40
50

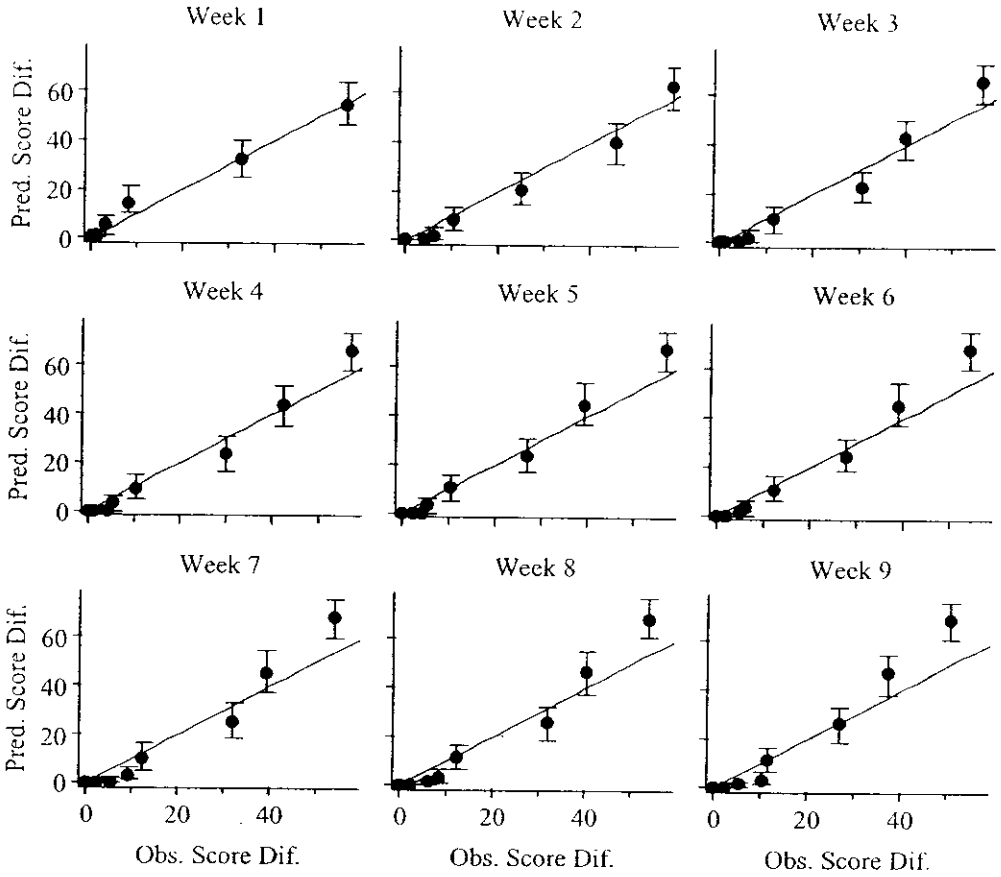
150 mg/Day BID



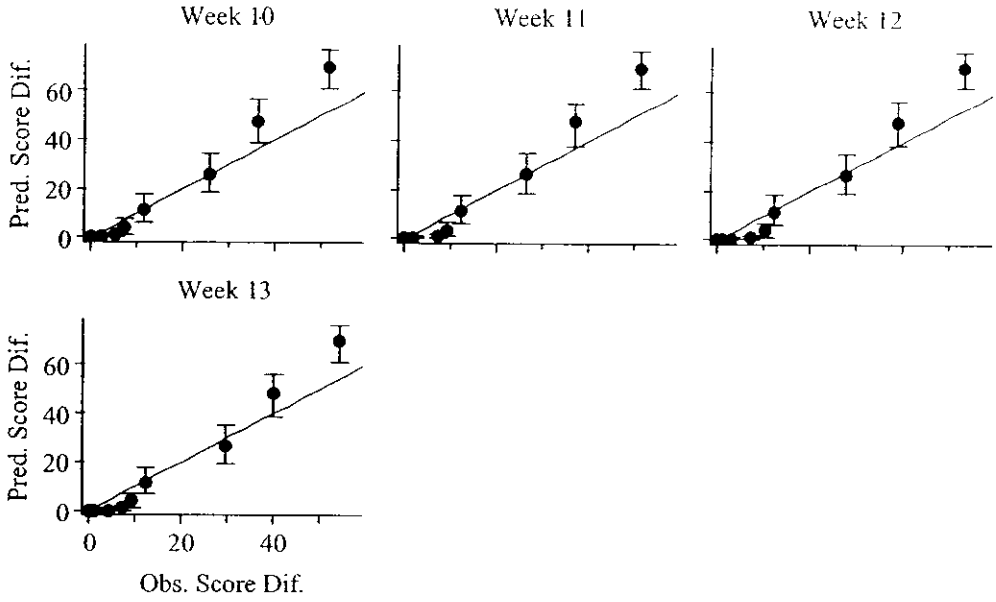
150 mg/Day BID



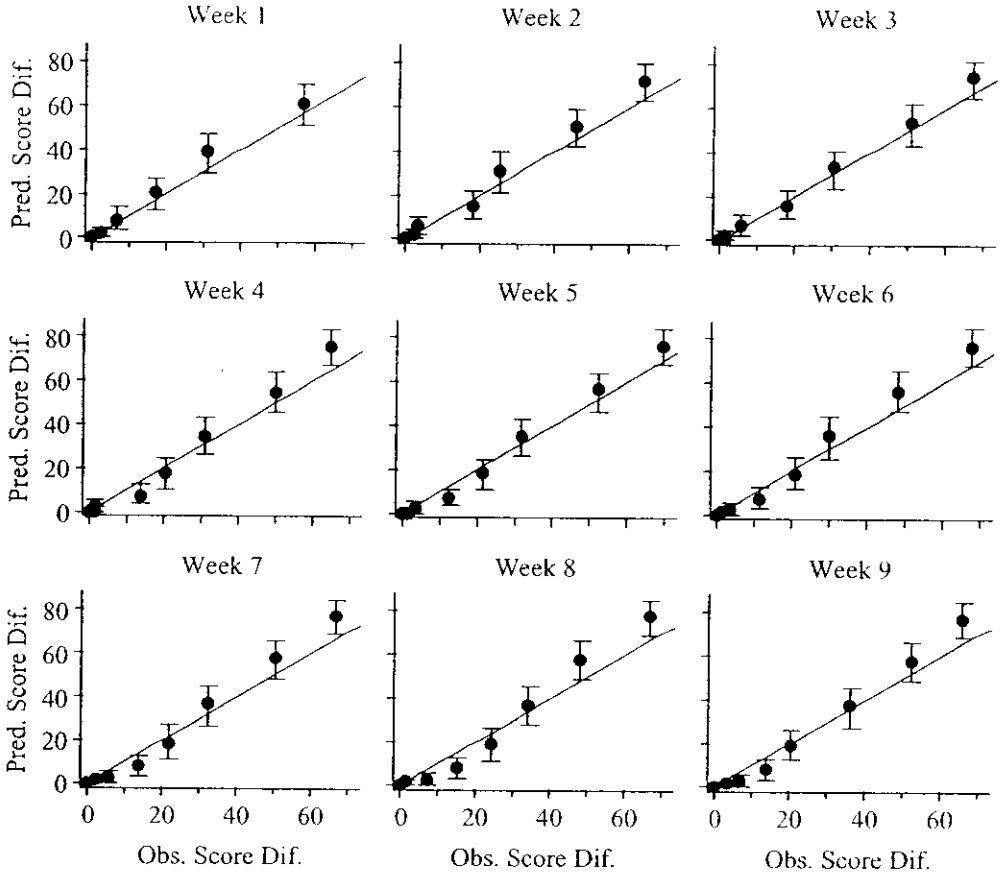
300 mg/DAY BID



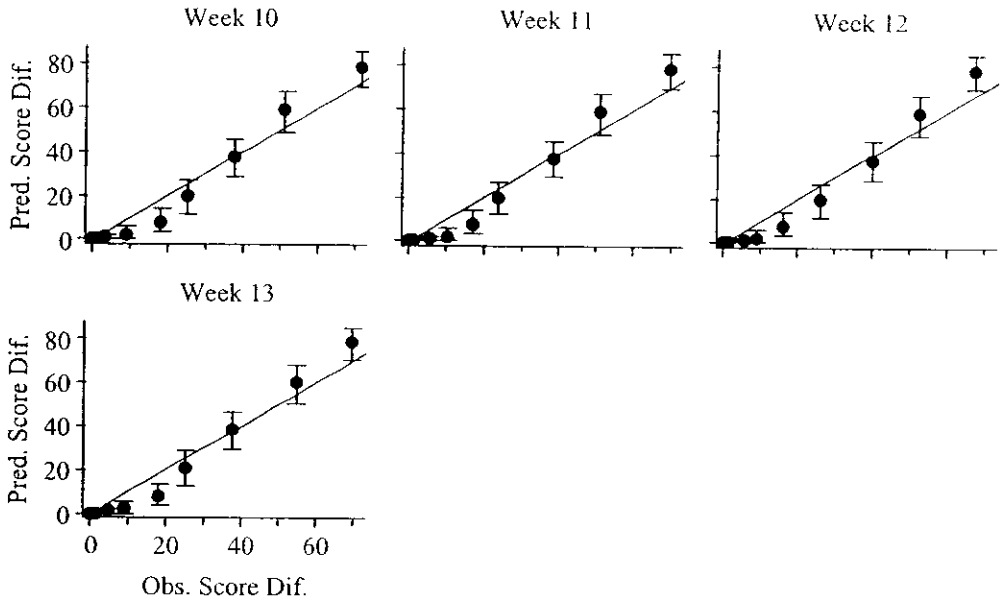
300 mg/DAY BID



300/600 mg/Day BID



300/600 mg/Day BID

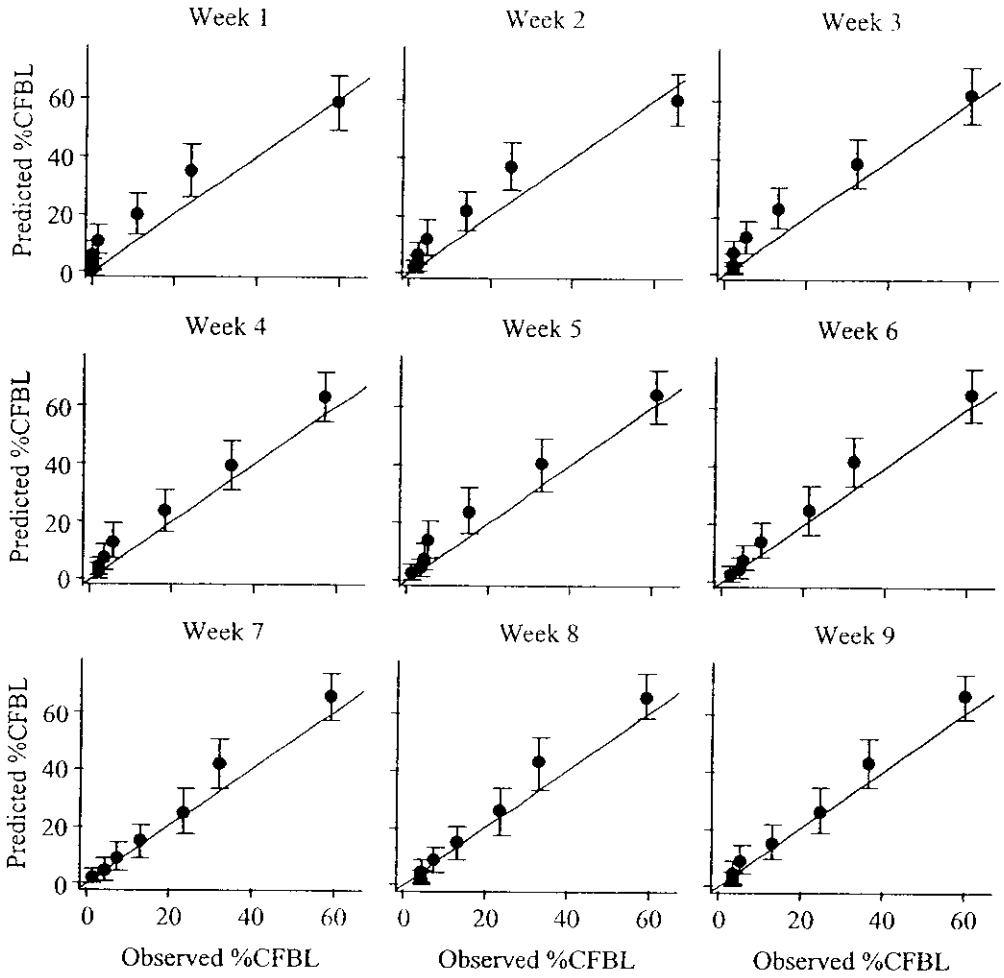


Attachment A.2

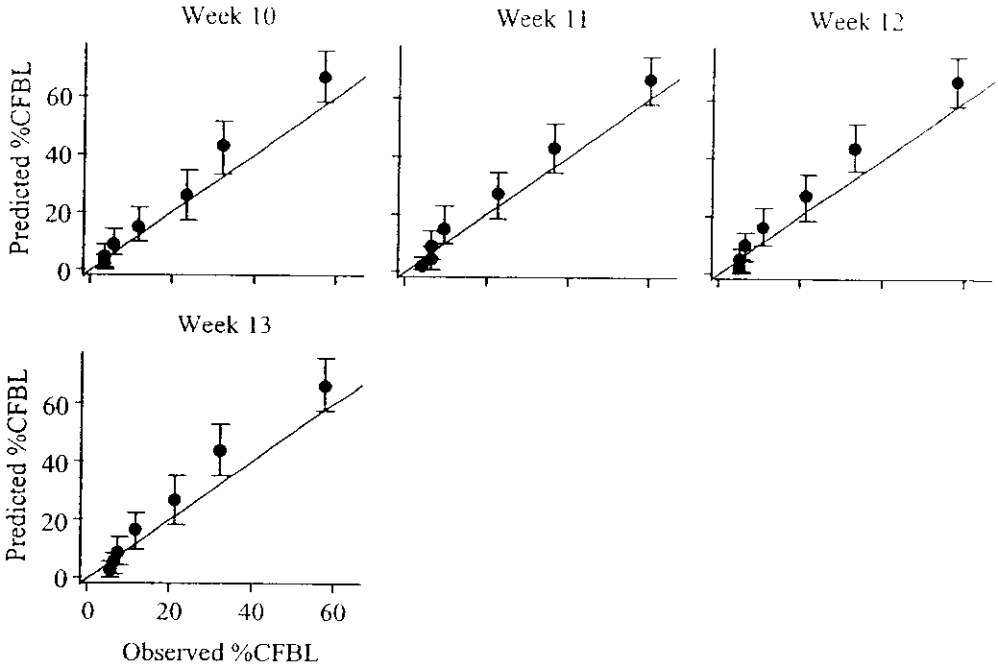
TID Model (Studies 030, 045, 127) Prediction of BID Data (Study 196)

Type 2B: Concordance Plots of Observed and Predicted Percentage of Patients (%Change in Pain Score) by Week and Treatment Group

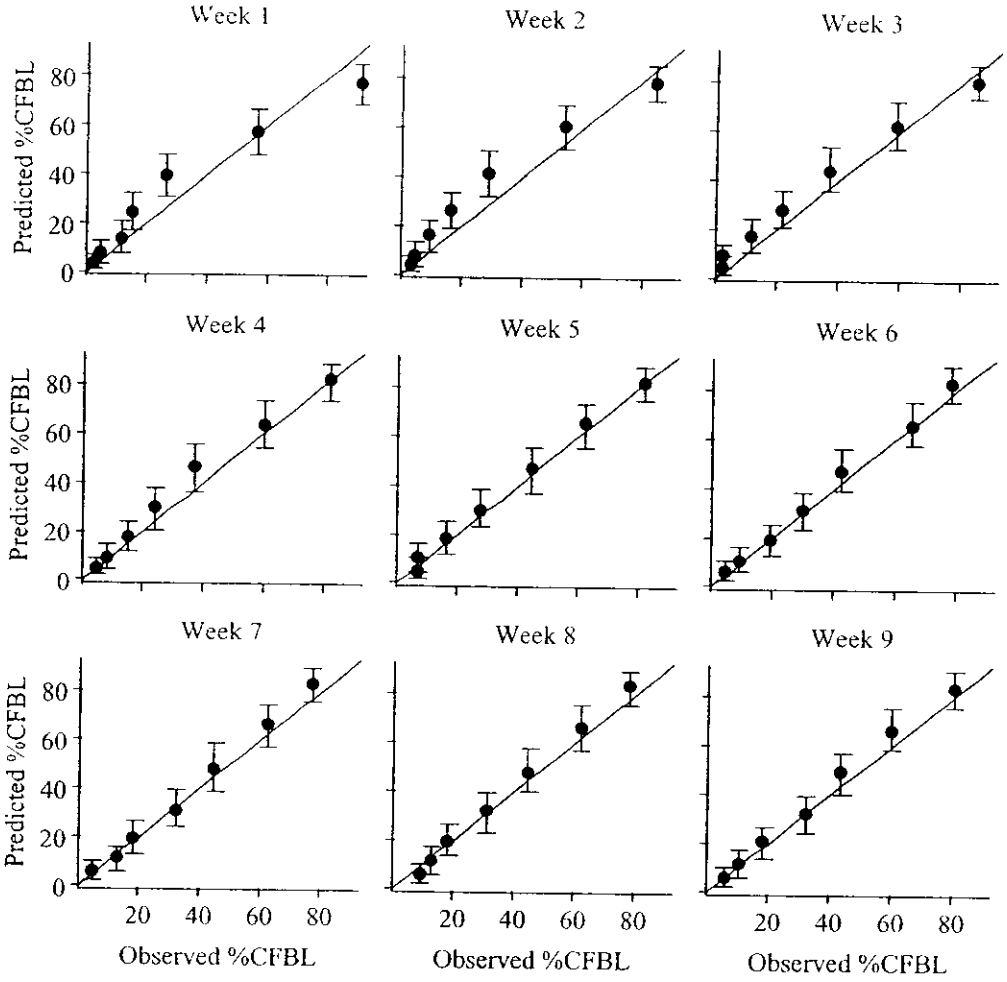
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Predicted %CFBL
Observed %CFBL
0
20
40
60

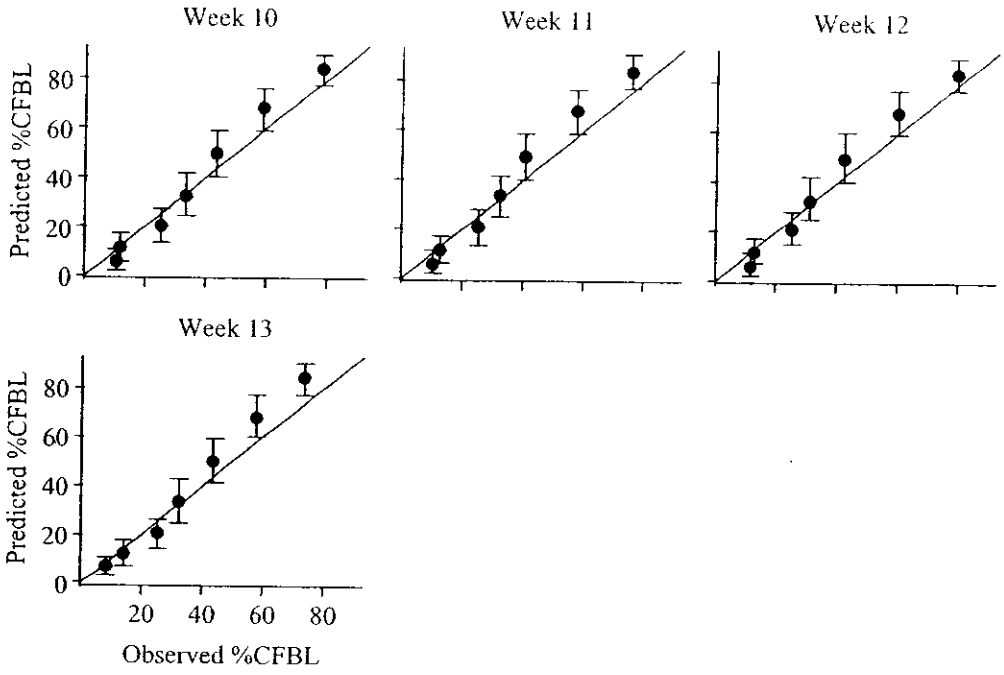
Placebo


Week 10
Week 11
Week 12
Week 13
Predicted %CFBL
Observed %CFBL
0
20
40
60

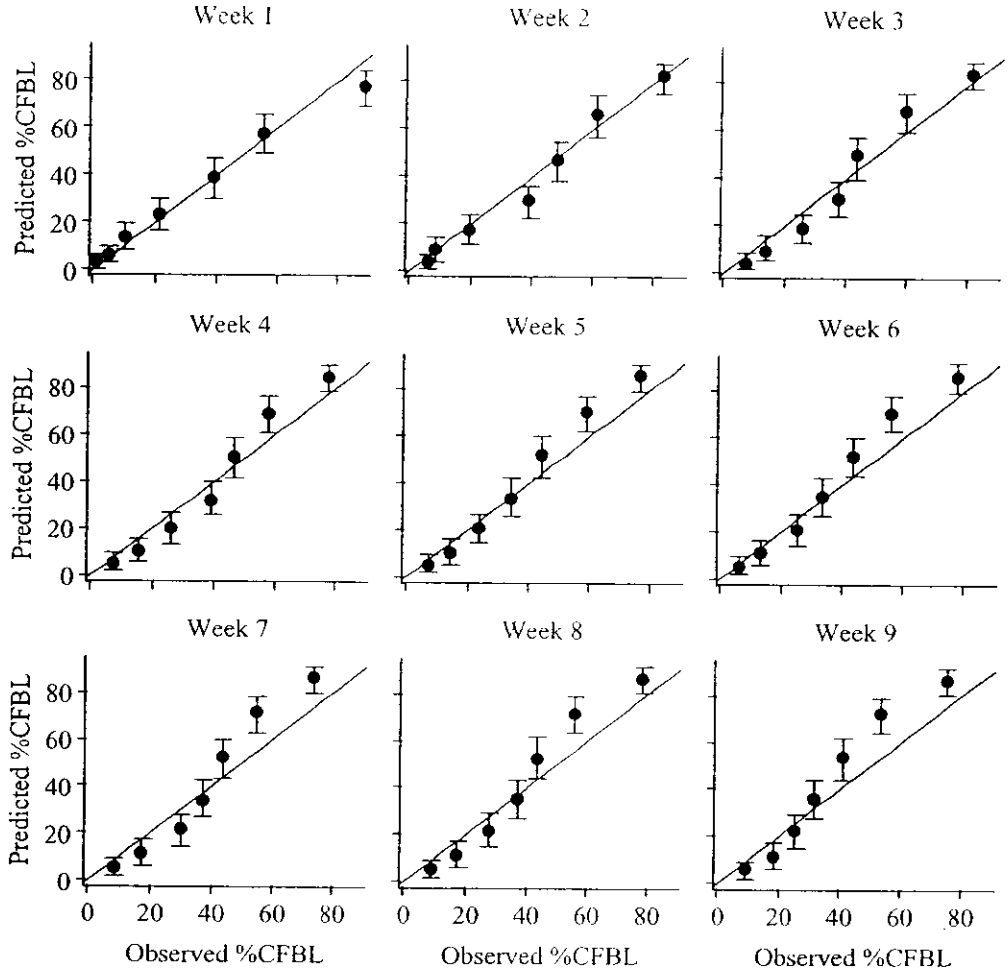
150 mg/Day BID



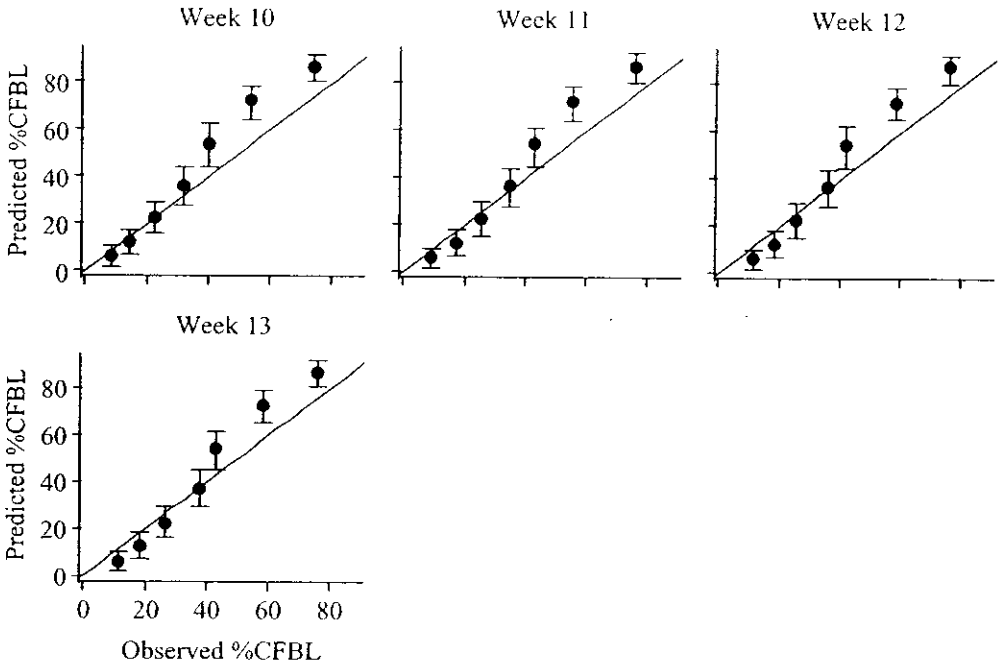
150 mg/Day BID



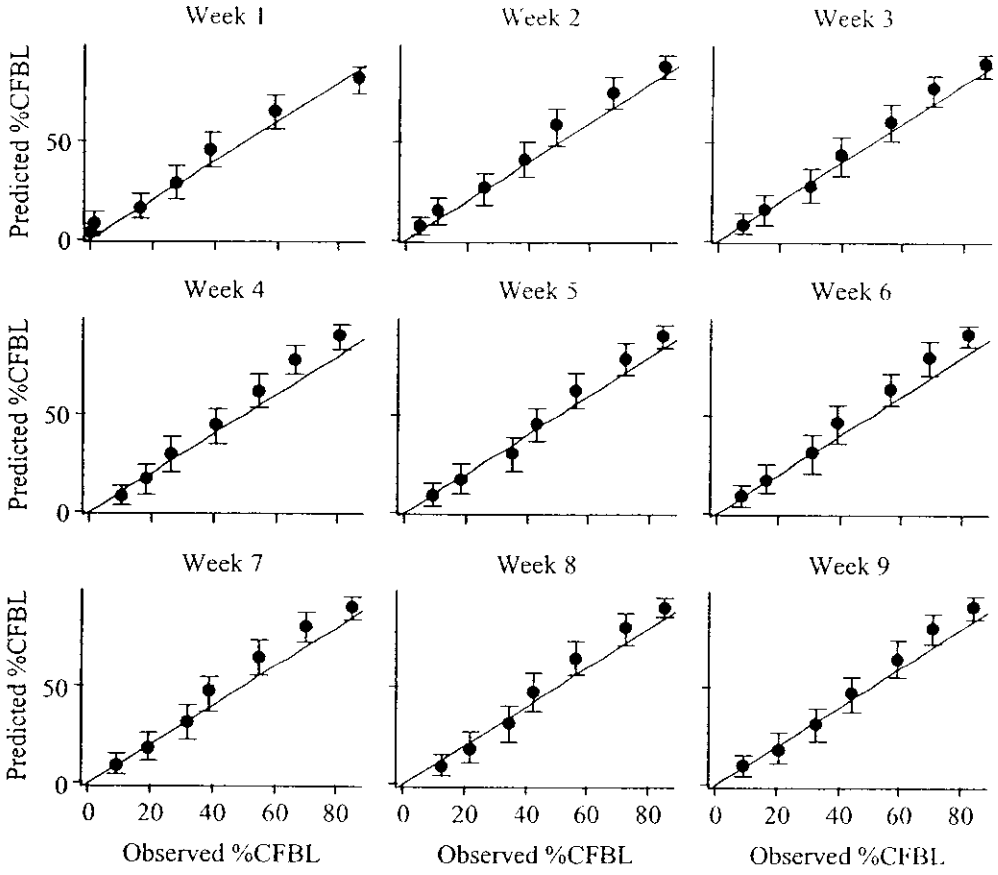
300 mg/Day BID



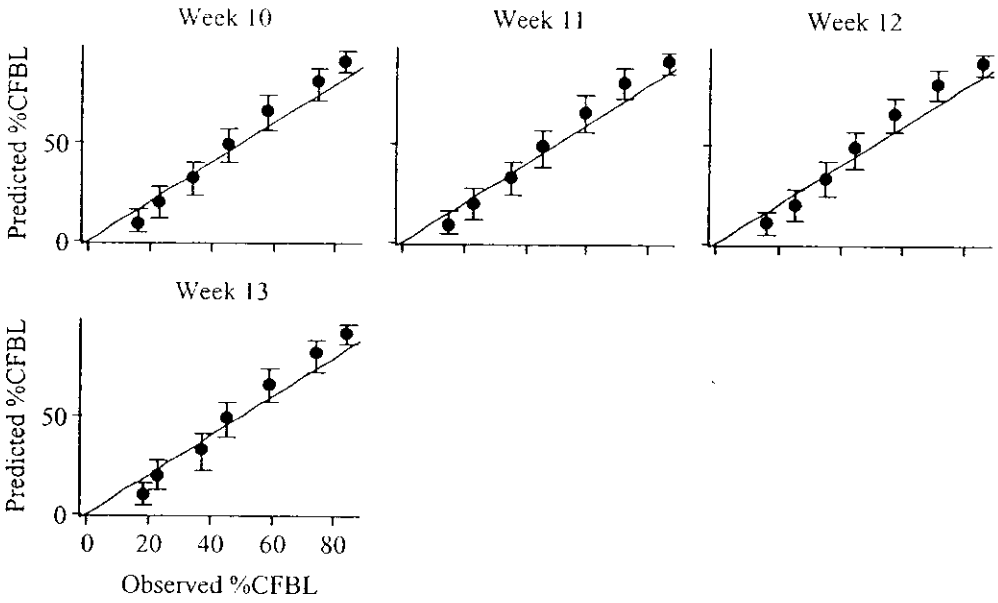
300 mg/Day BID



300/600 mg/Day BID



300/600 mg/Day BID

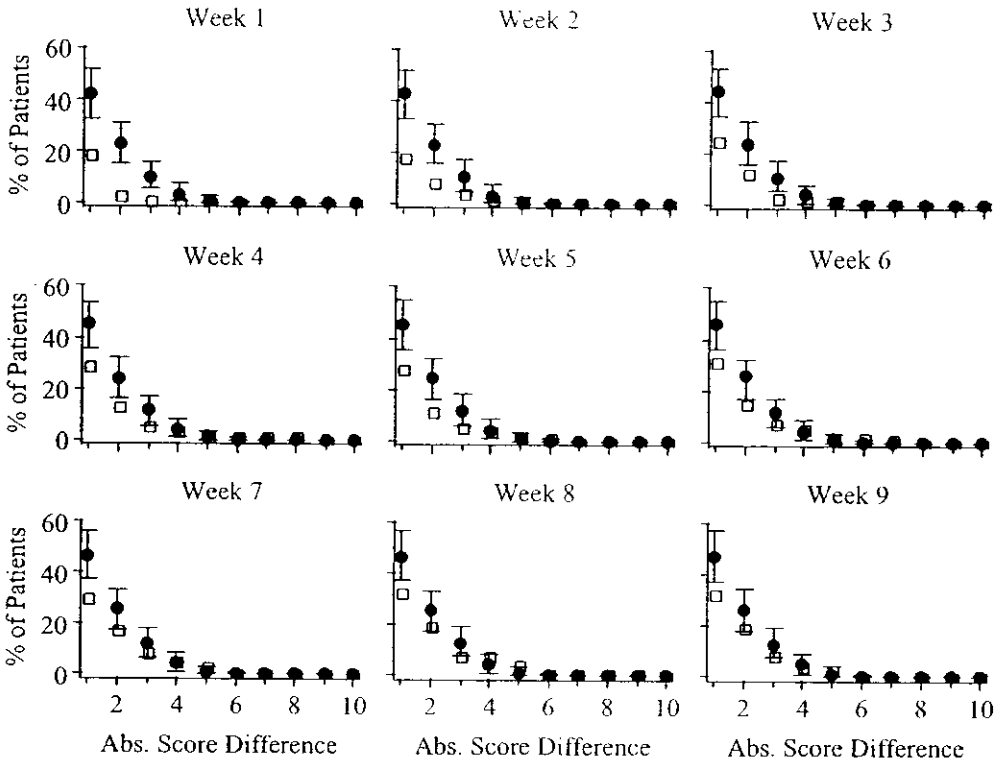


Attachment A.3

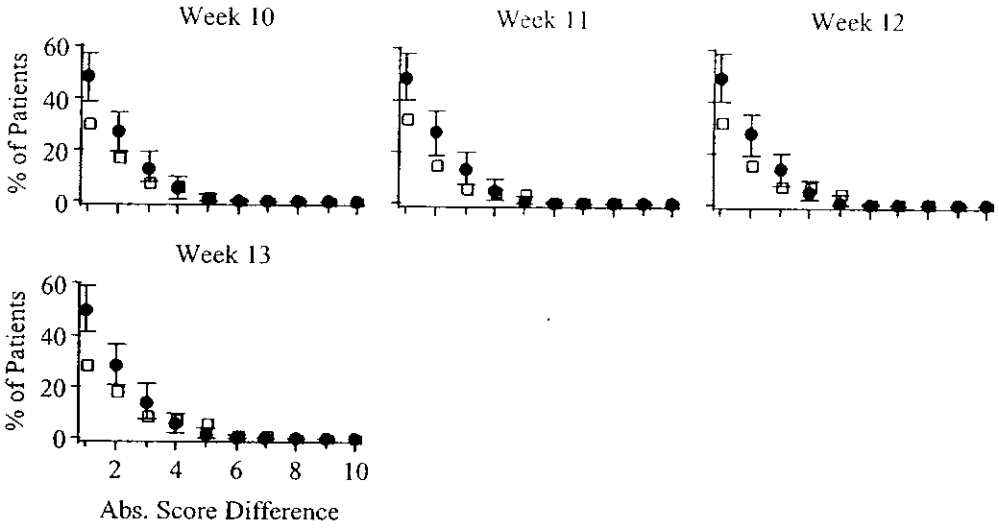
BID Model (Study 196) Prediction of BID Data (Study 196) – Internal PPC

Type 1A: Percentage of Patients Versus ΔScore by Week and Treatment Group

Placebo

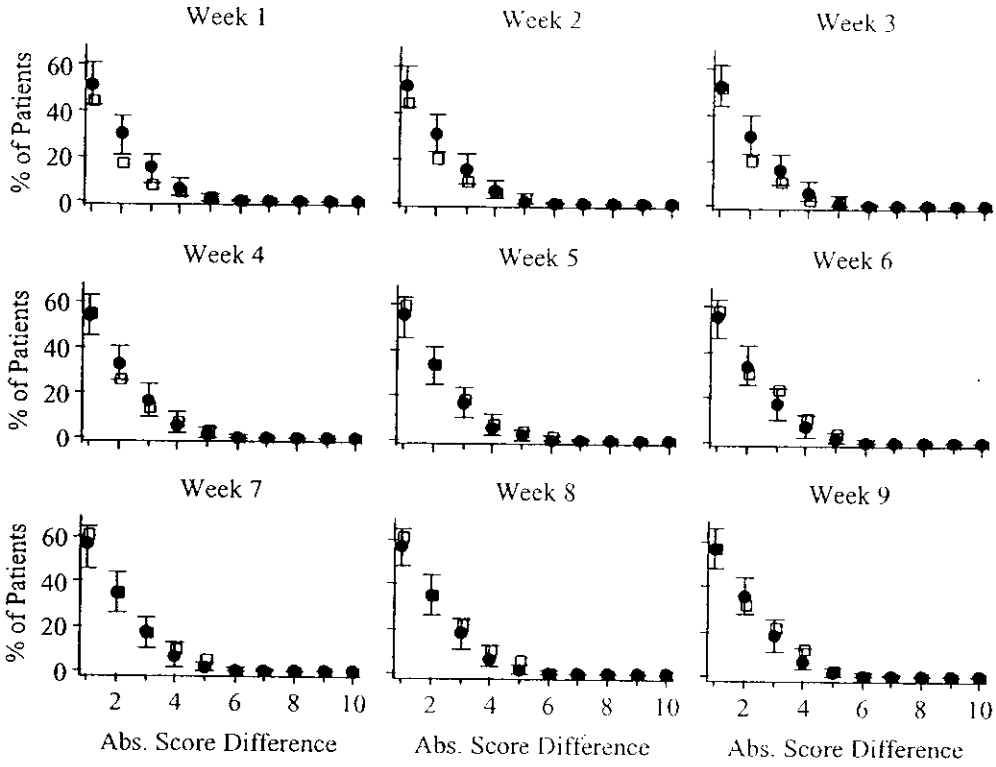

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
60
40
20
0
2
4
6
8
10
Abs. Score Difference
Predicted
Observed

Placebo

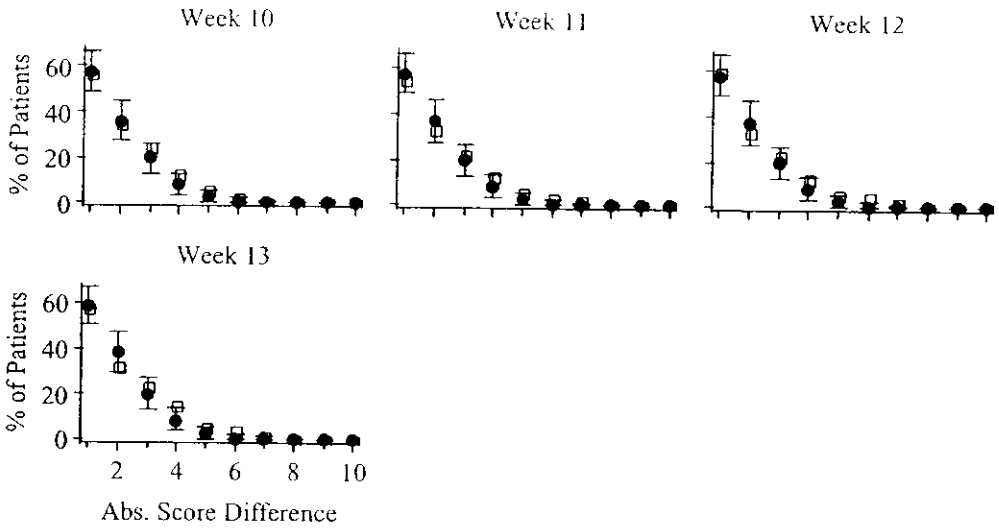


● Predicted
□ Observed

150 mg/Day BID

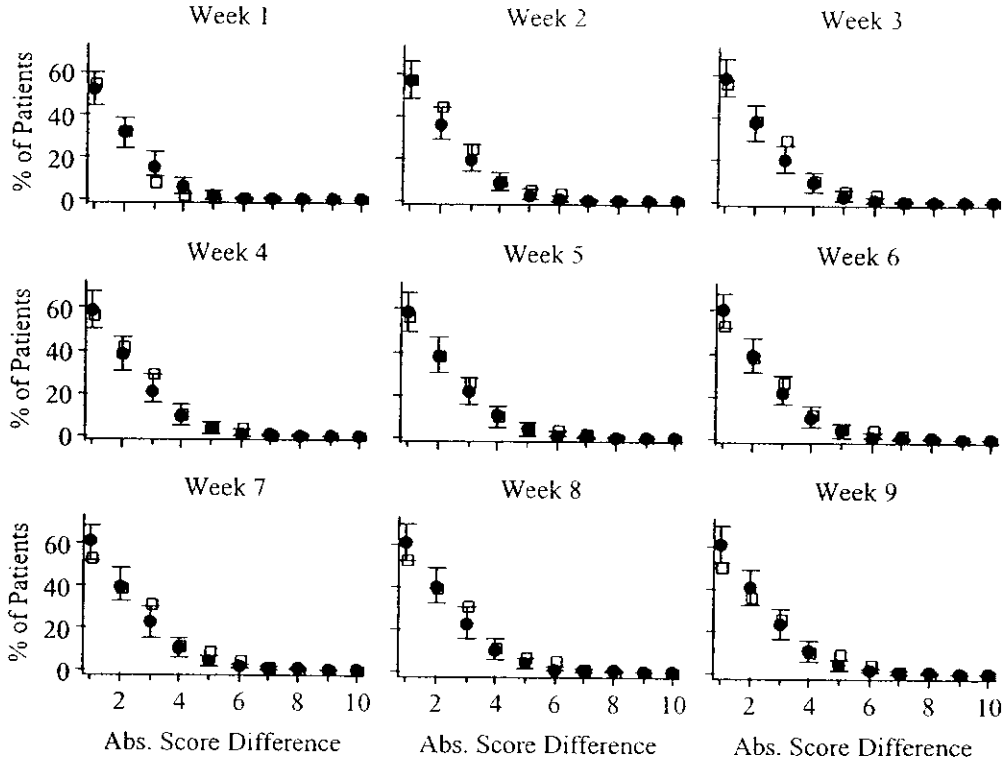


150 mg/Day BID

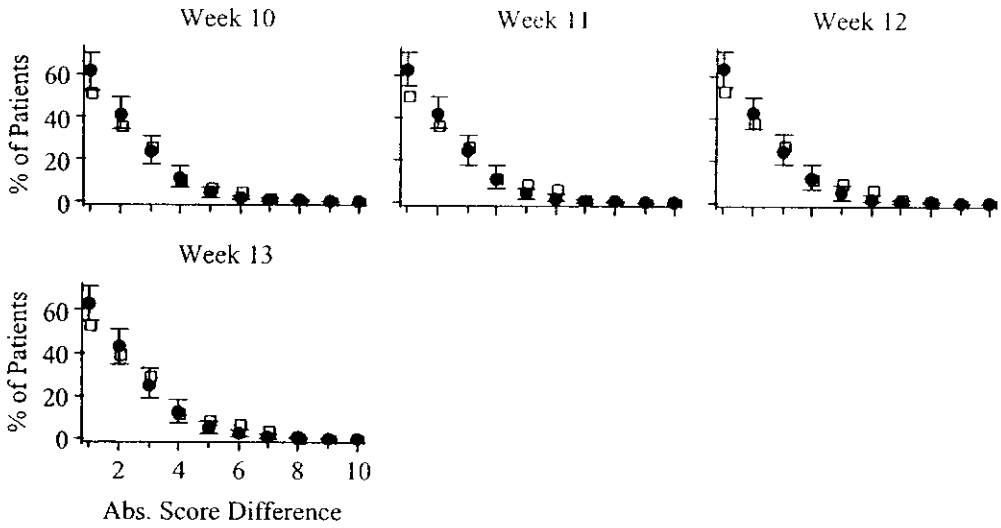


● Predicted
□ Observed

300 mg/DAY BID

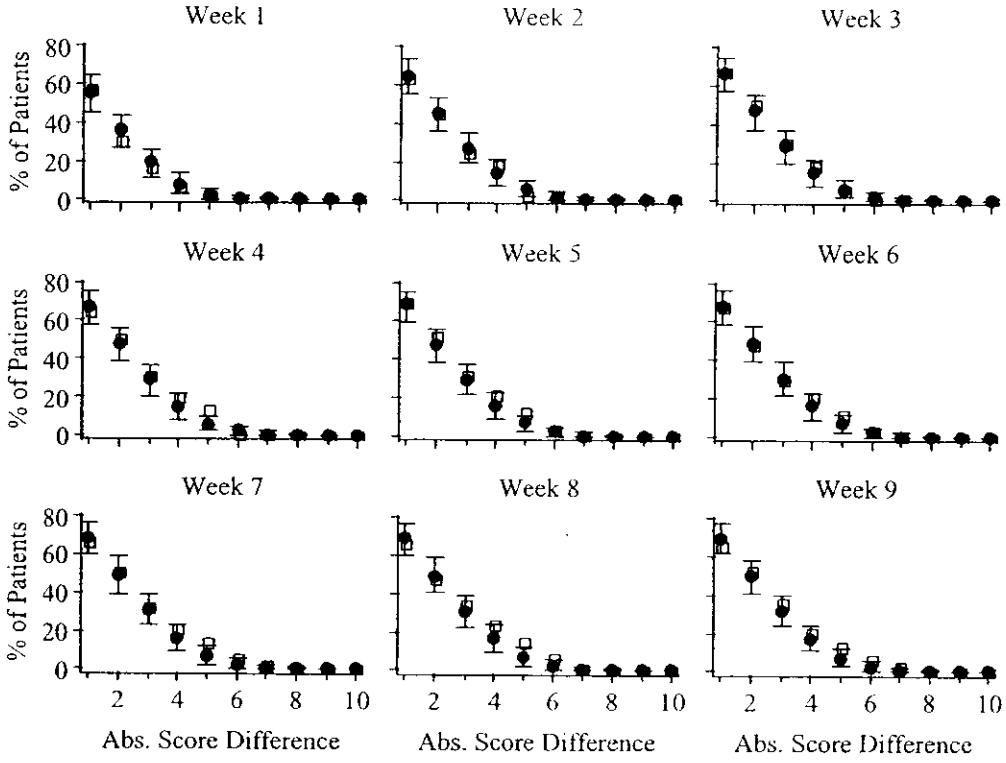


300 mg/DAY BID

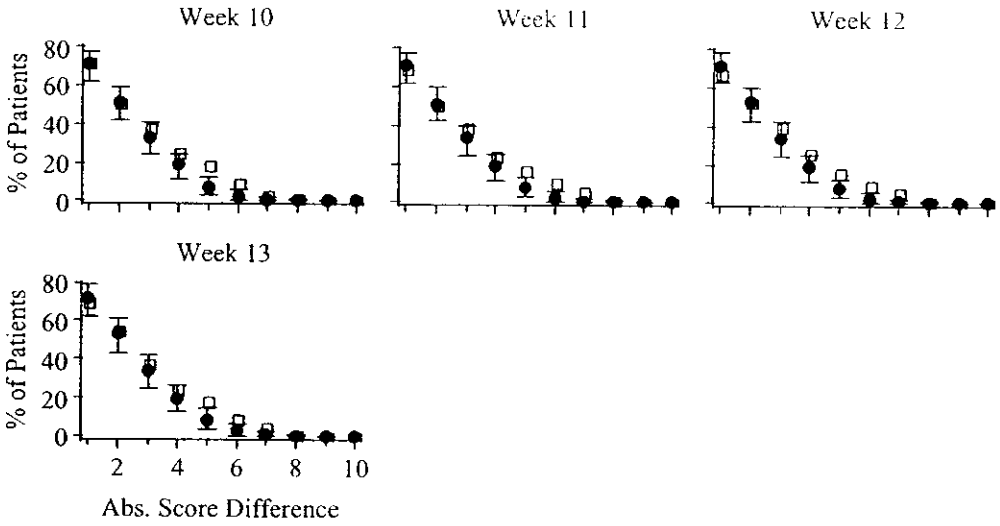


● Predicted
□ Observed

300/600 mg/Day BID



300/600 mg/Day BID



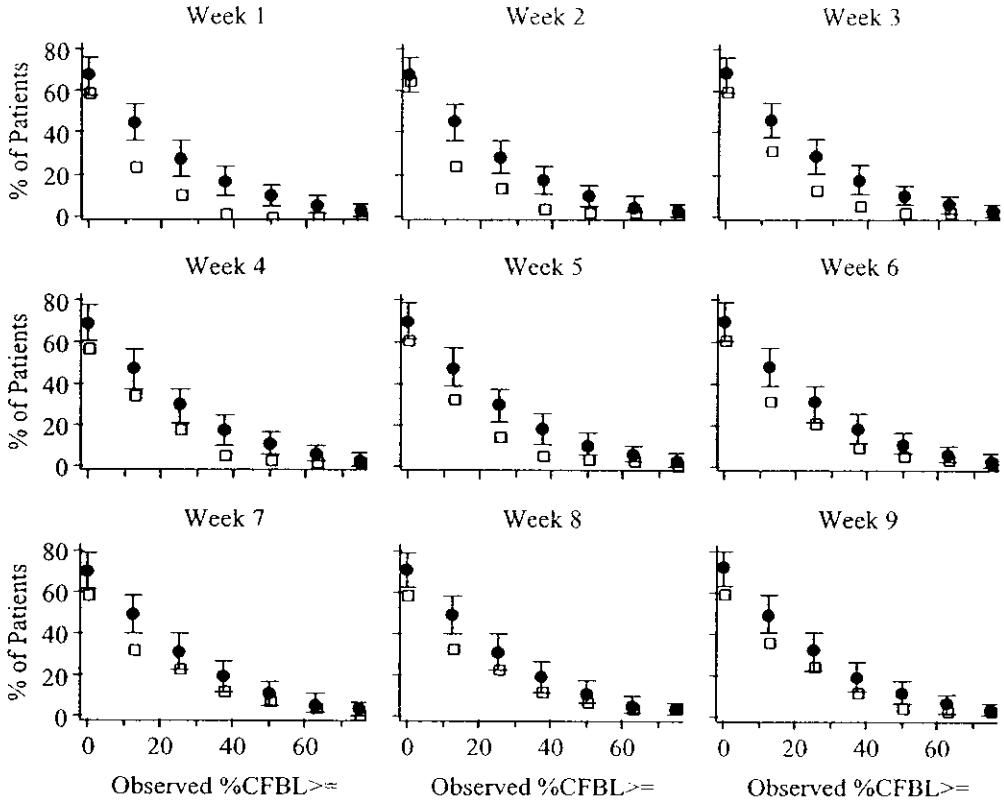
● Predicted
□ Observed

Attachment A.3

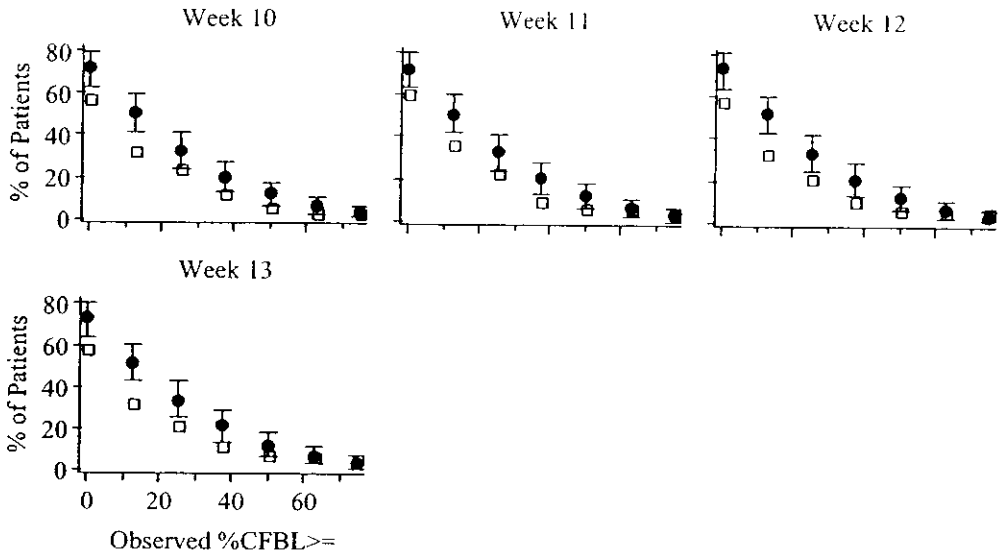
BID Model (Study 196) Prediction of BID Data (Study 196) – Internal PPC

Type 2A: Percentage of Patients Versus %Change in Pain Score by Week and Treatment Group

Placebo

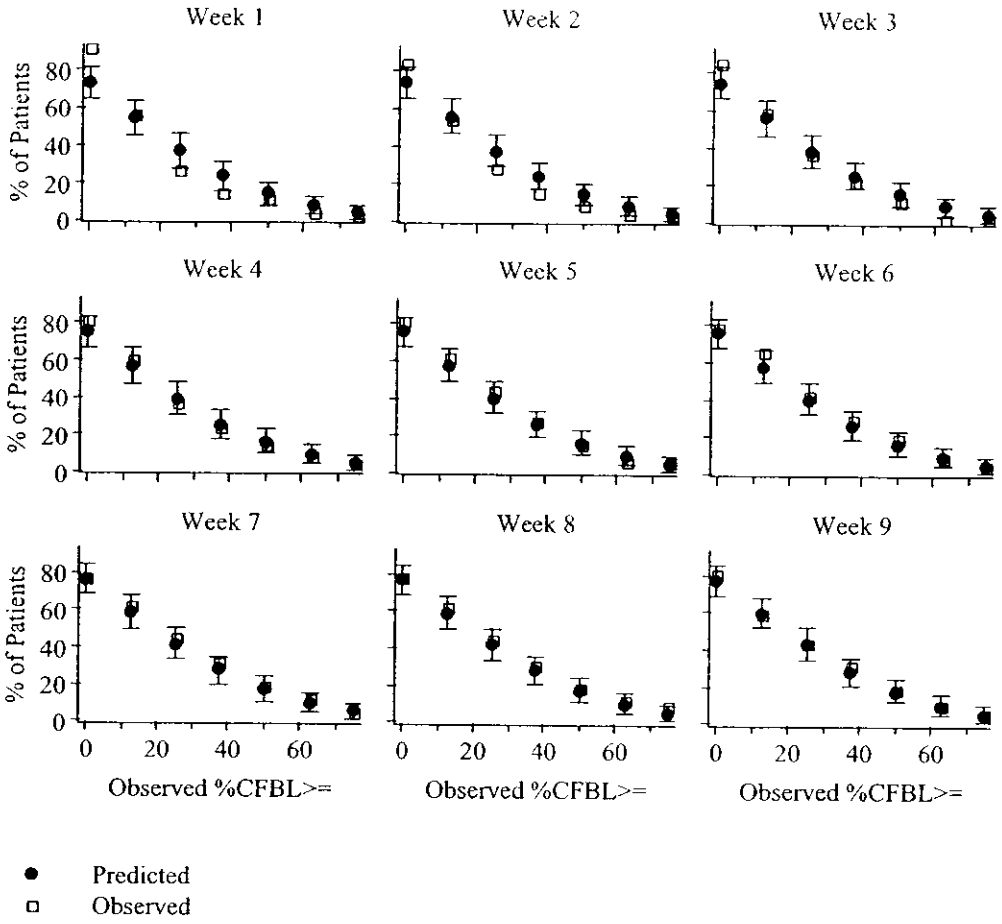

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
80
Observed %CFBL>=
Predicted
Observed

Placebo

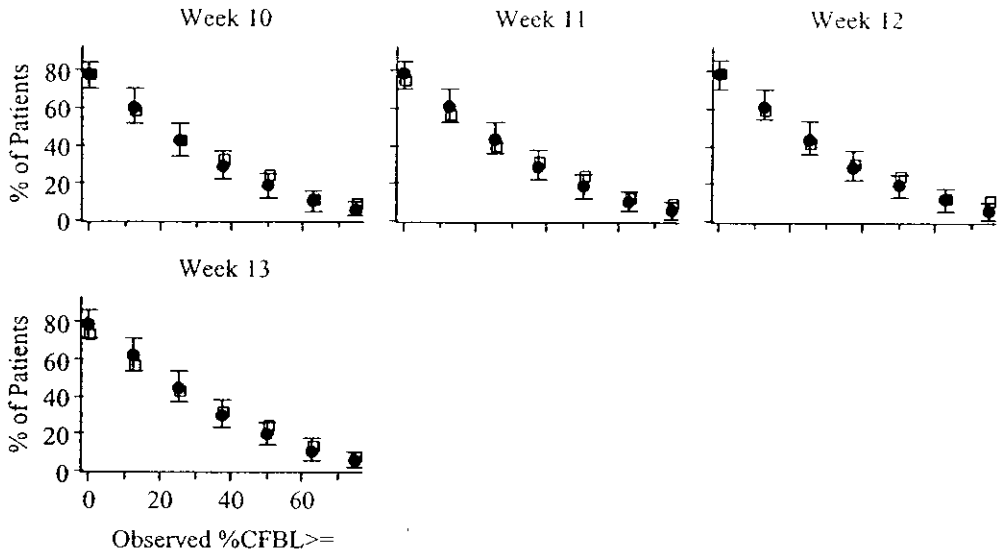


● Predicted
□ Observed

150 mg/Day BID

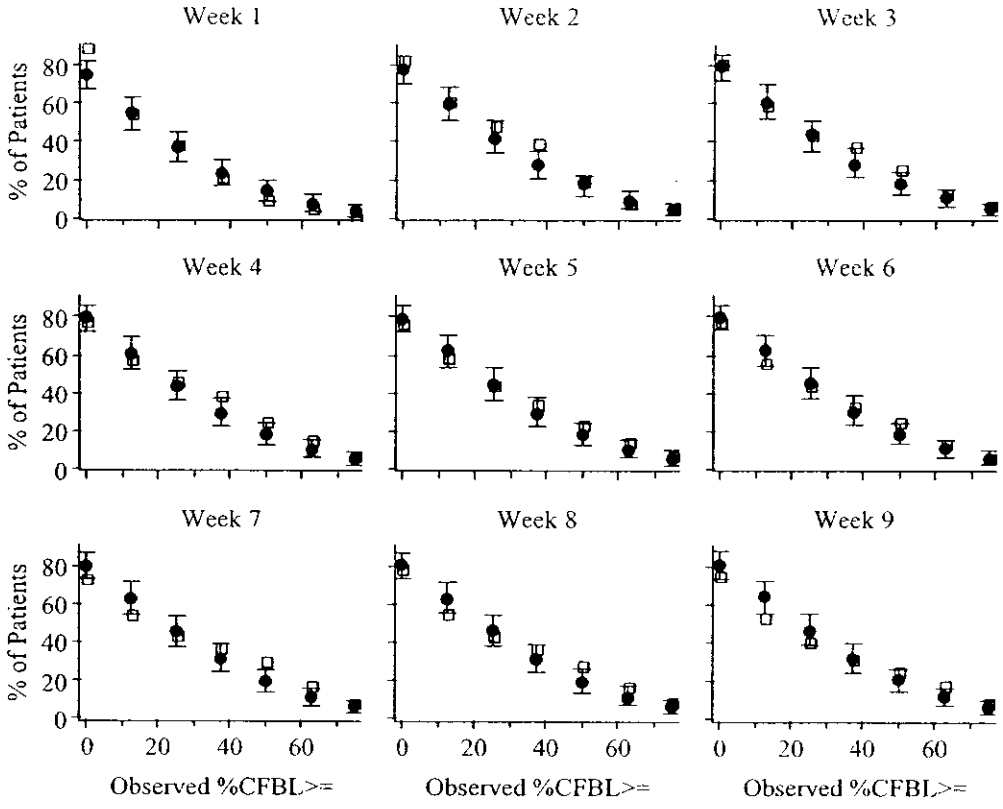


150 mg/Day BID

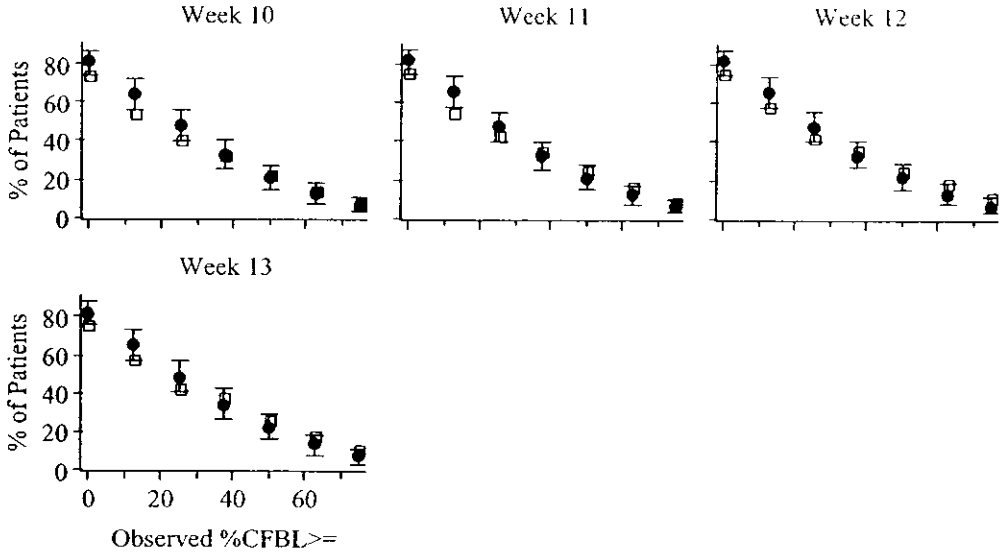


● Predicted
□ Observed

300 mg/DAY BID

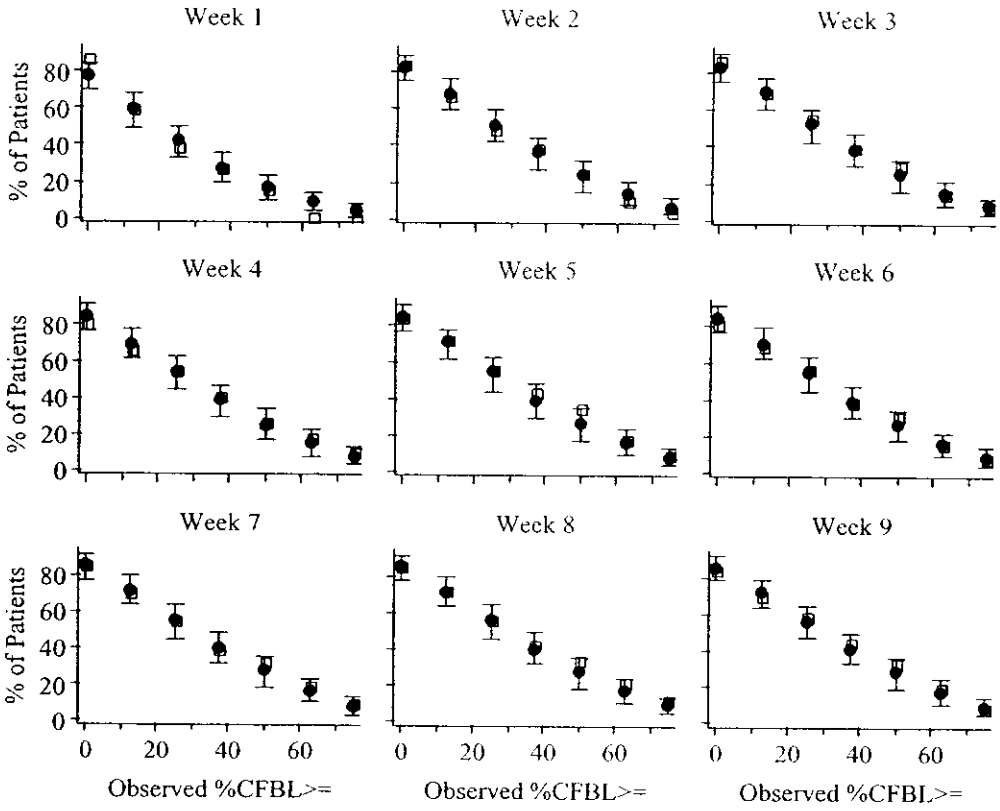


300 mg/DAY BID



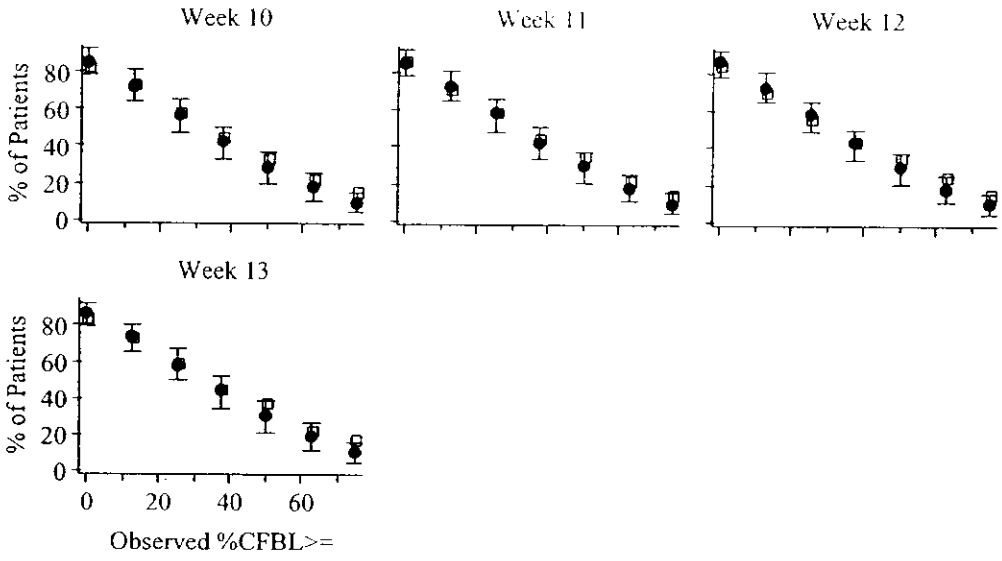
● Predicted
□ Observed

300/600 mg/Day BID



● Predicted
□ Observed

300/600 mg/Day BID



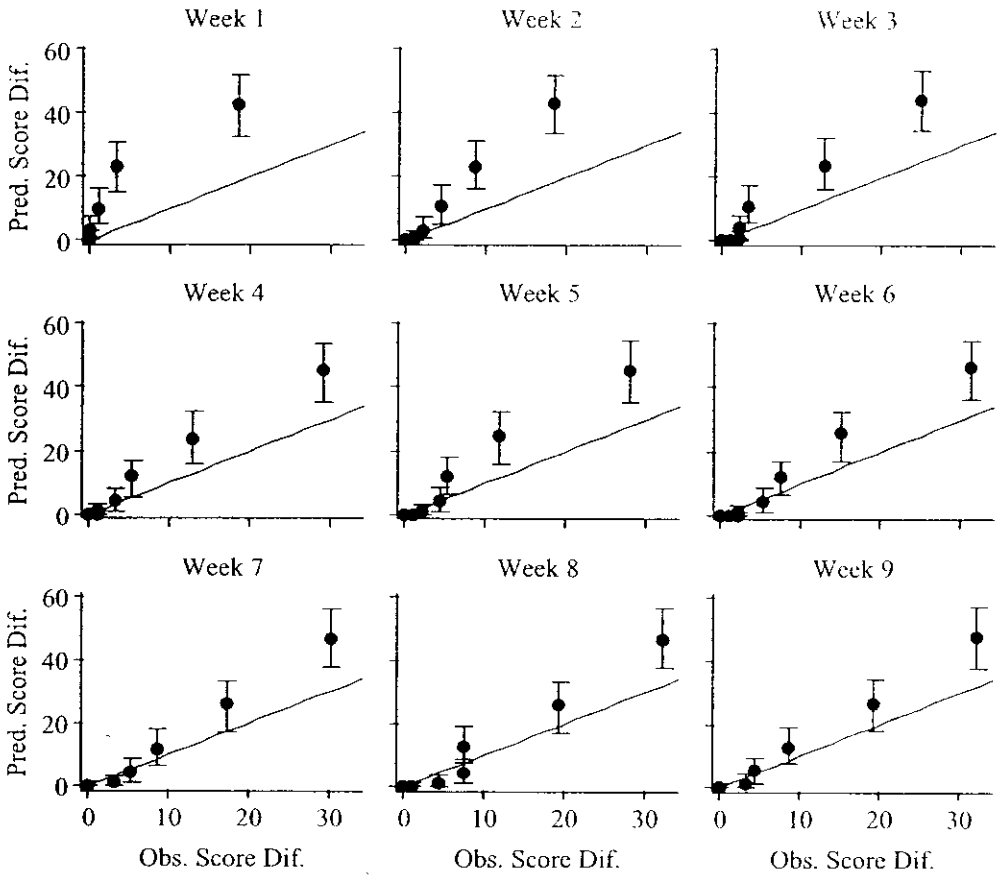
● Predicted
□ Observed

Attachment A.3

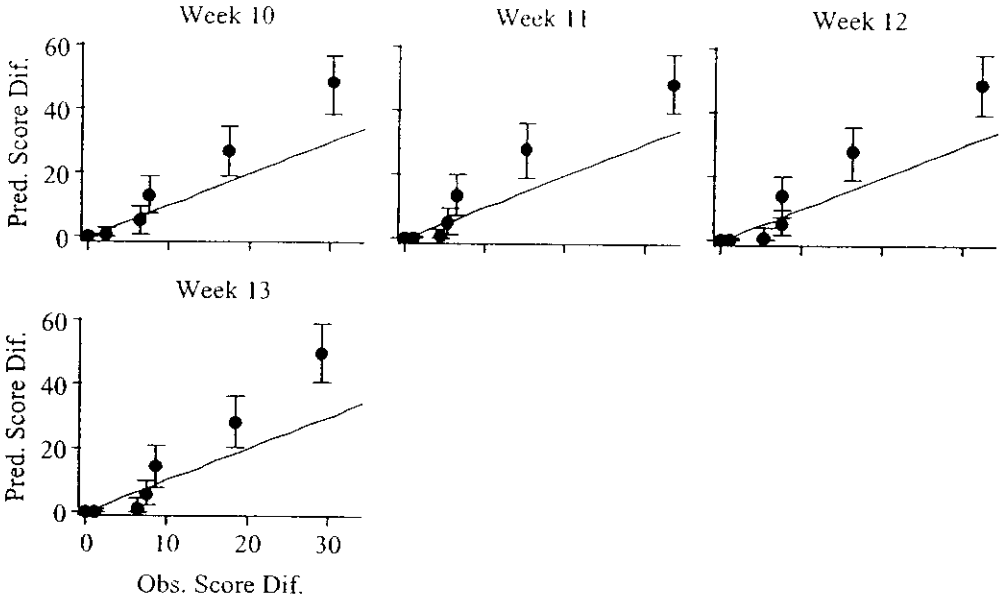
BID MODEL (STUDY 196) PREDICTION OF BID DATA (STUDY 196) – INTERNAL PPC

Type 1B: Concordance Plots of Predicted Versus Observed Percentage of Patients (ΔScore) by Week and Treatment Group

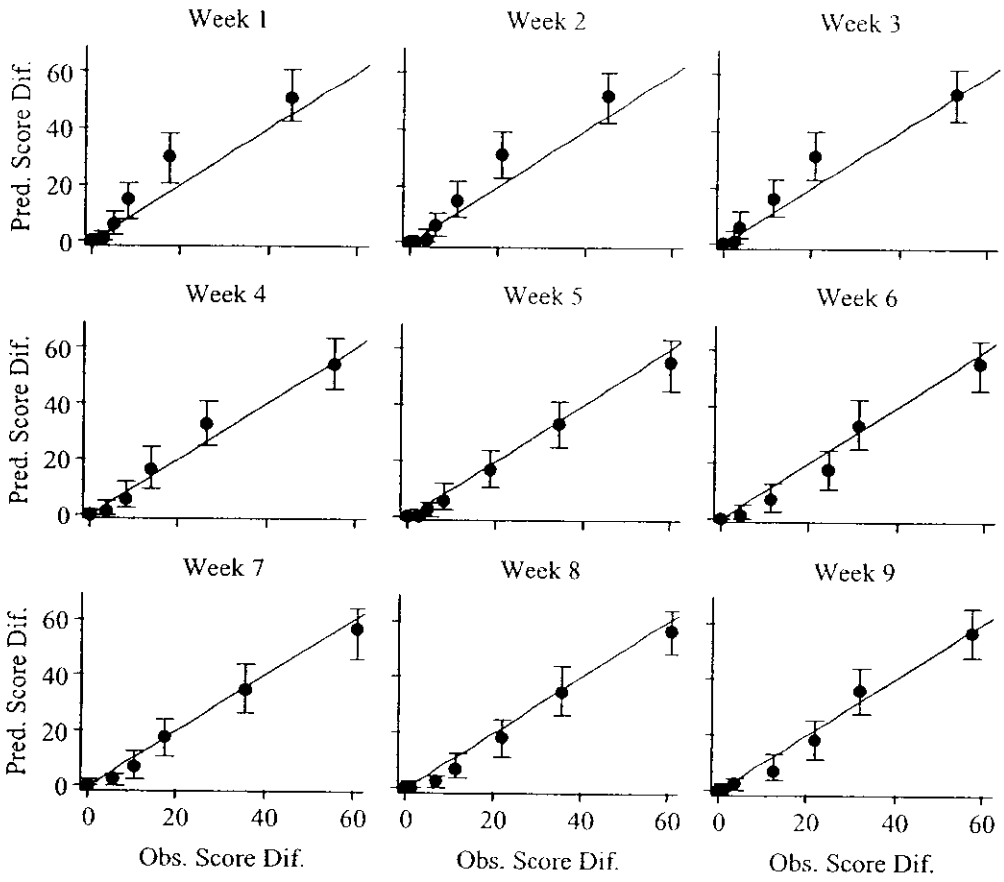
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30

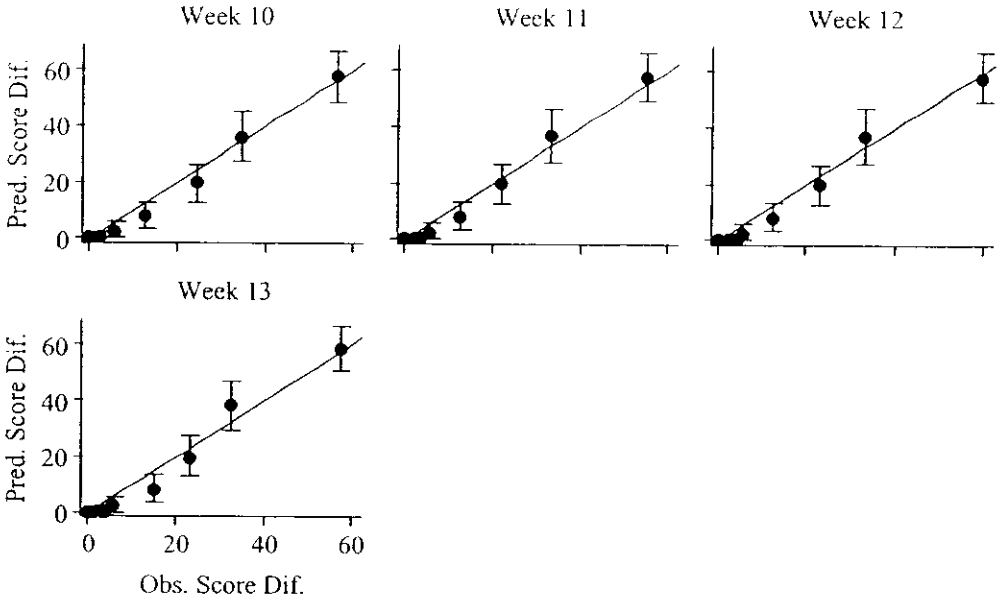
Placebo


Week 10
Week 11
Week 12
Week 13
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30

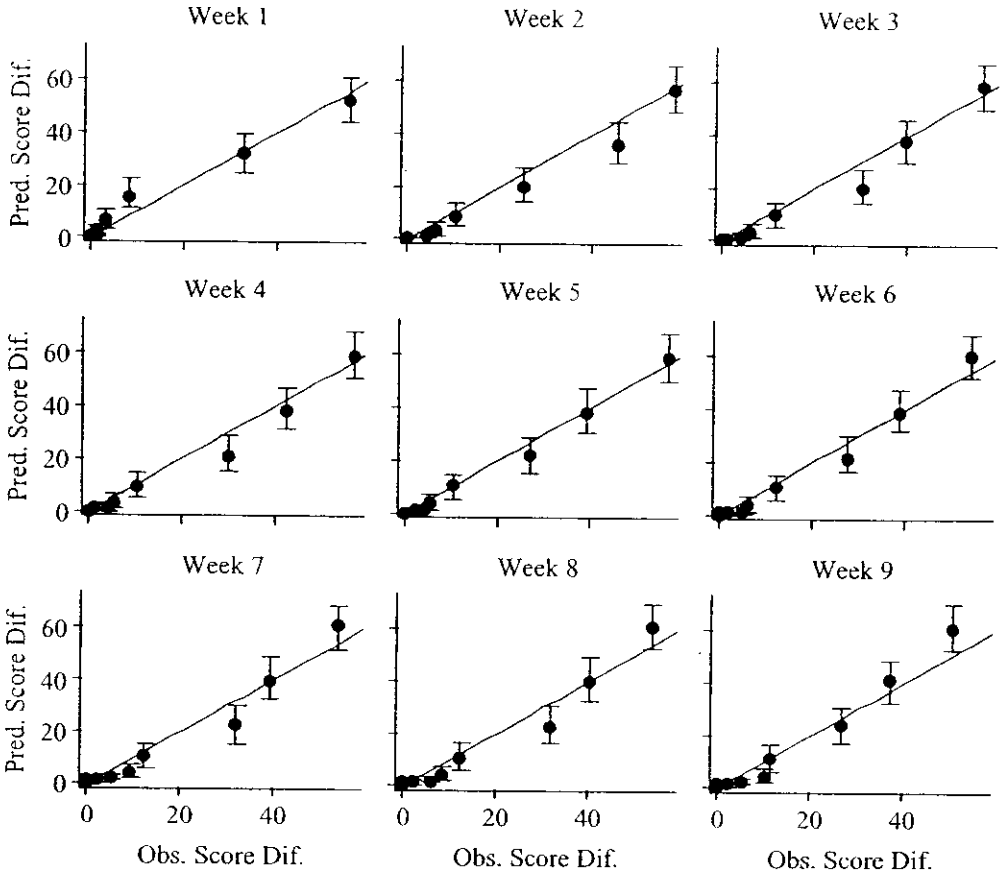
150 mg/Day BID



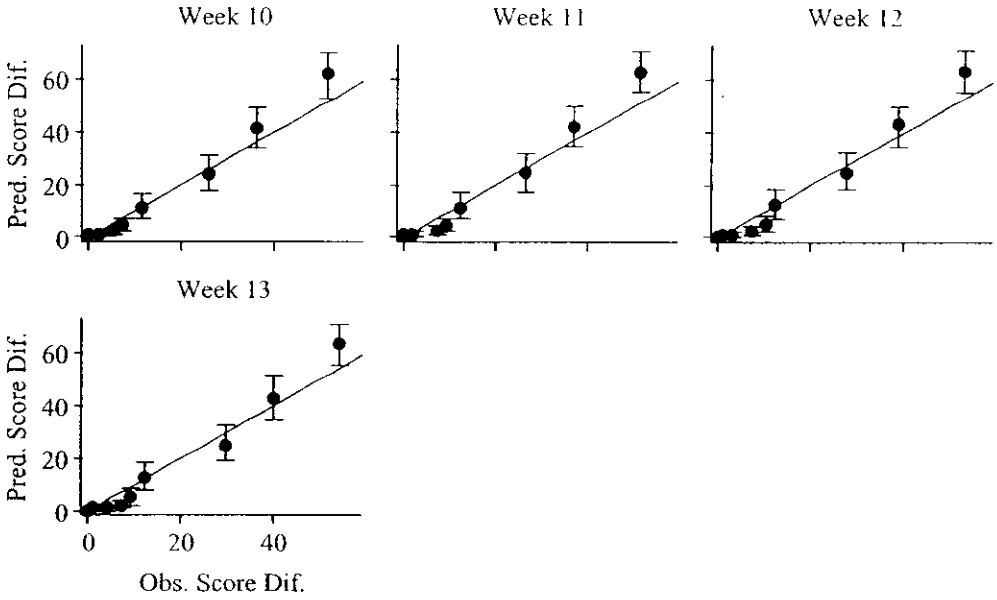
150 mg/Day BID



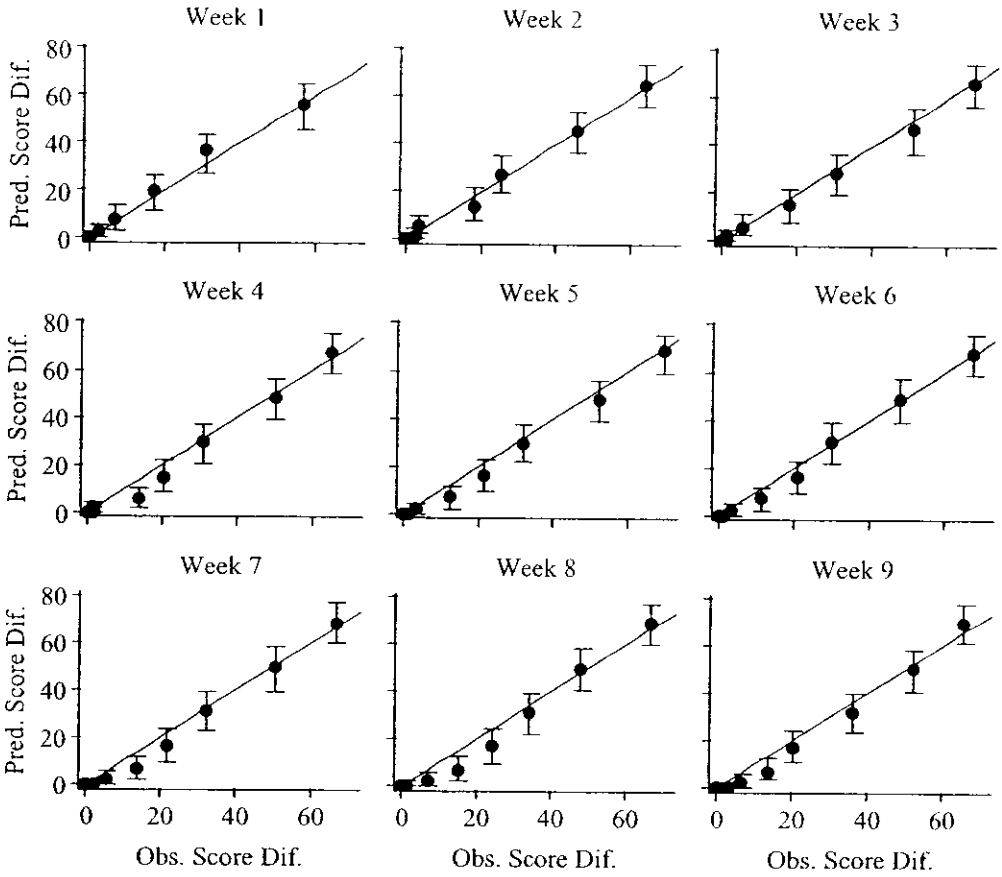
300 mg/Day BID



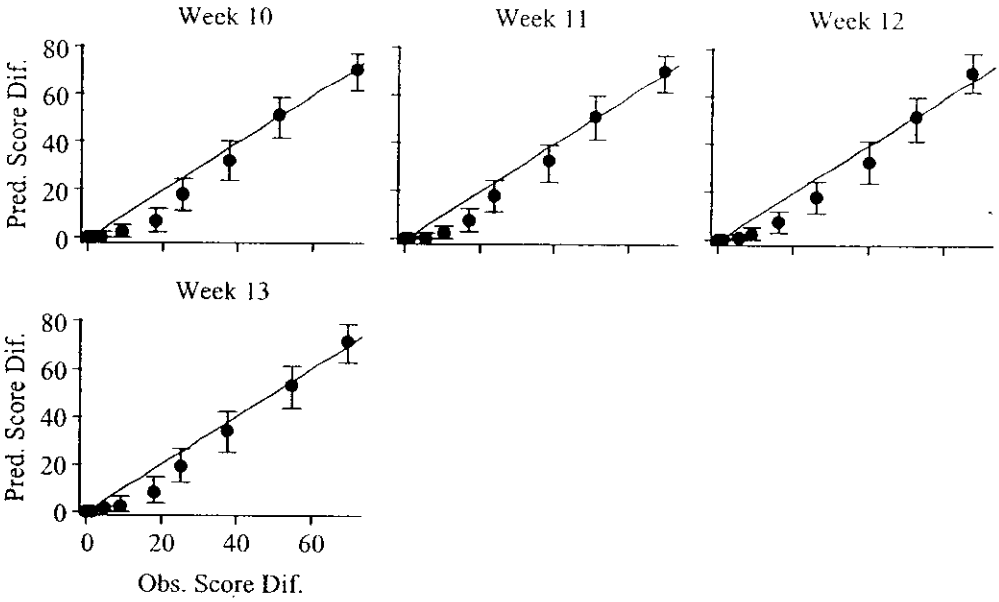
300 mg/Day BID



300/600 mg/Day BID



300/600 mg/Day BID

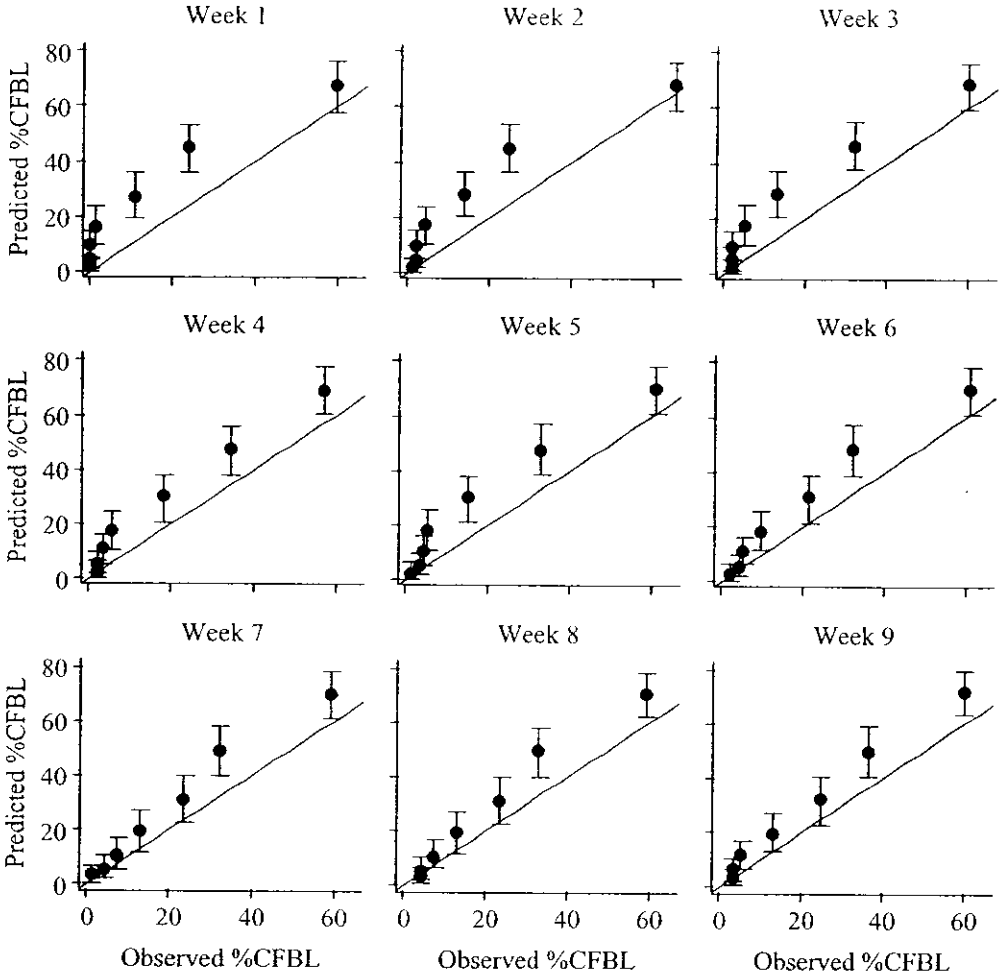


Attachment A.3

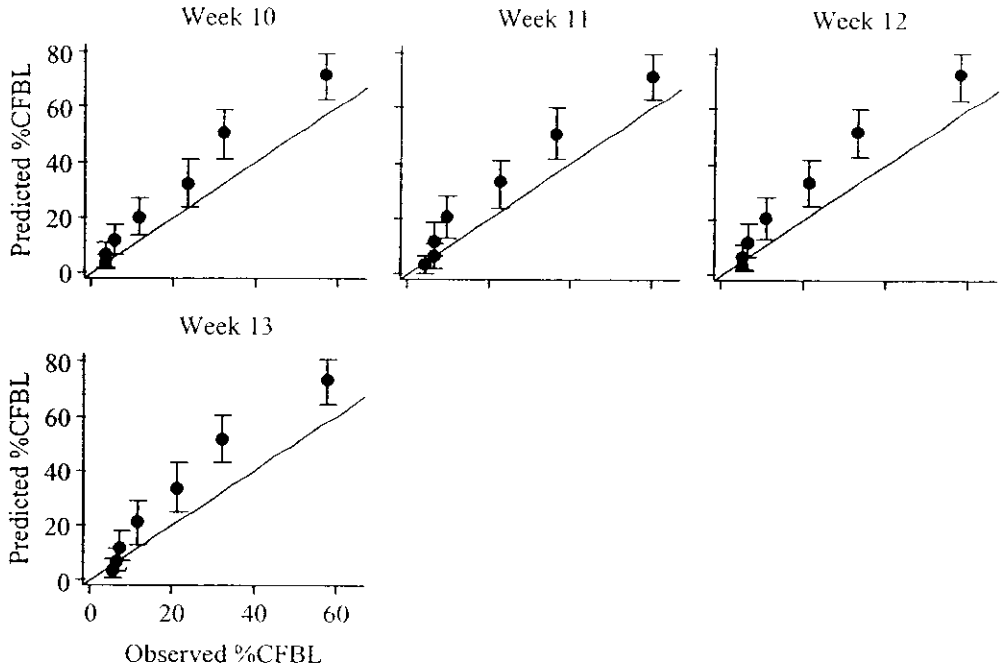
BID MODEL (STUDY 196) PREDICTION OF BID DATA (STUDY 196) – INTERNAL PPC

Type 2B: Concordance Plots of Predicted Versus Observed Percentage of Patients (%Change in Pain Score) by Week and Treatment Group

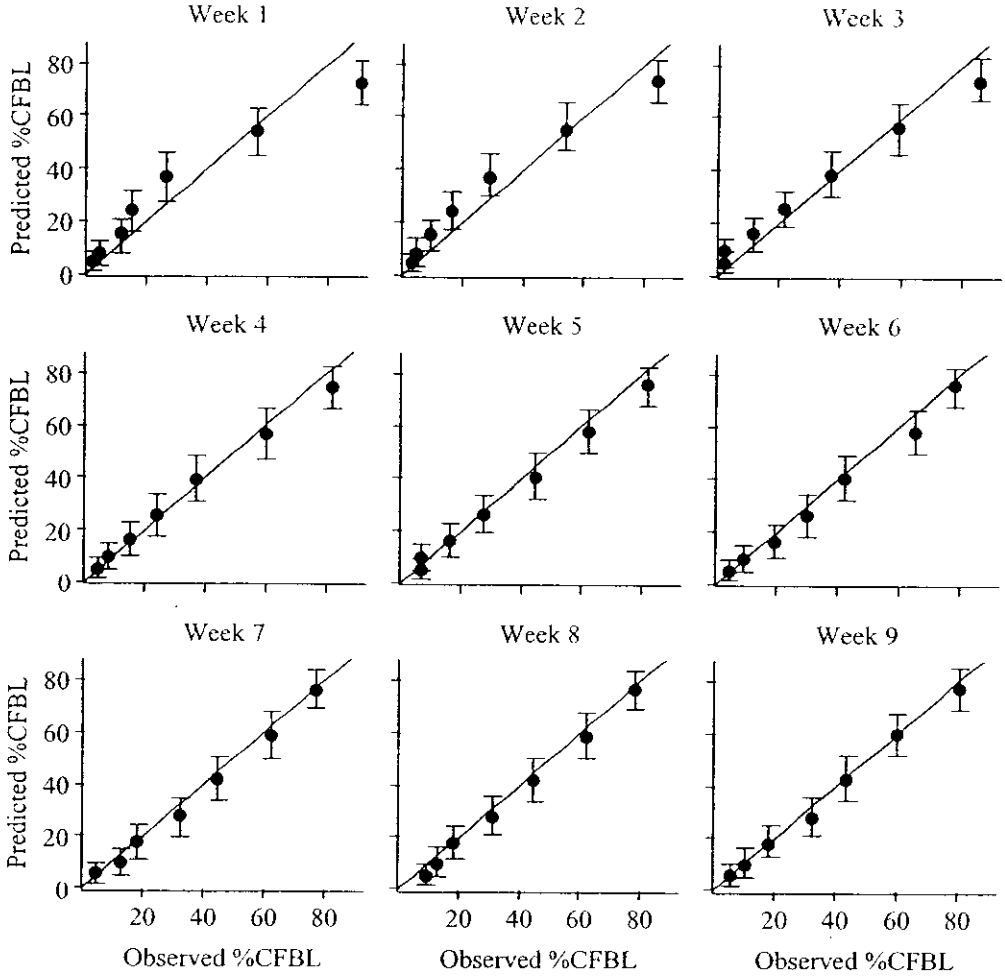
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

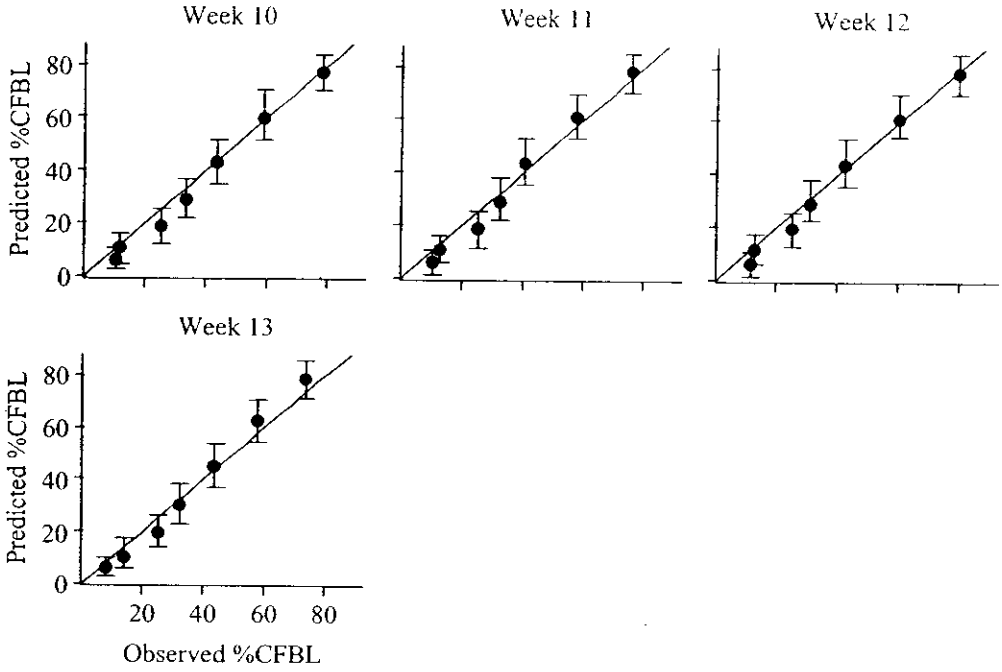
Placebo


Week 10
Week 11
Week 12
Week 13
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

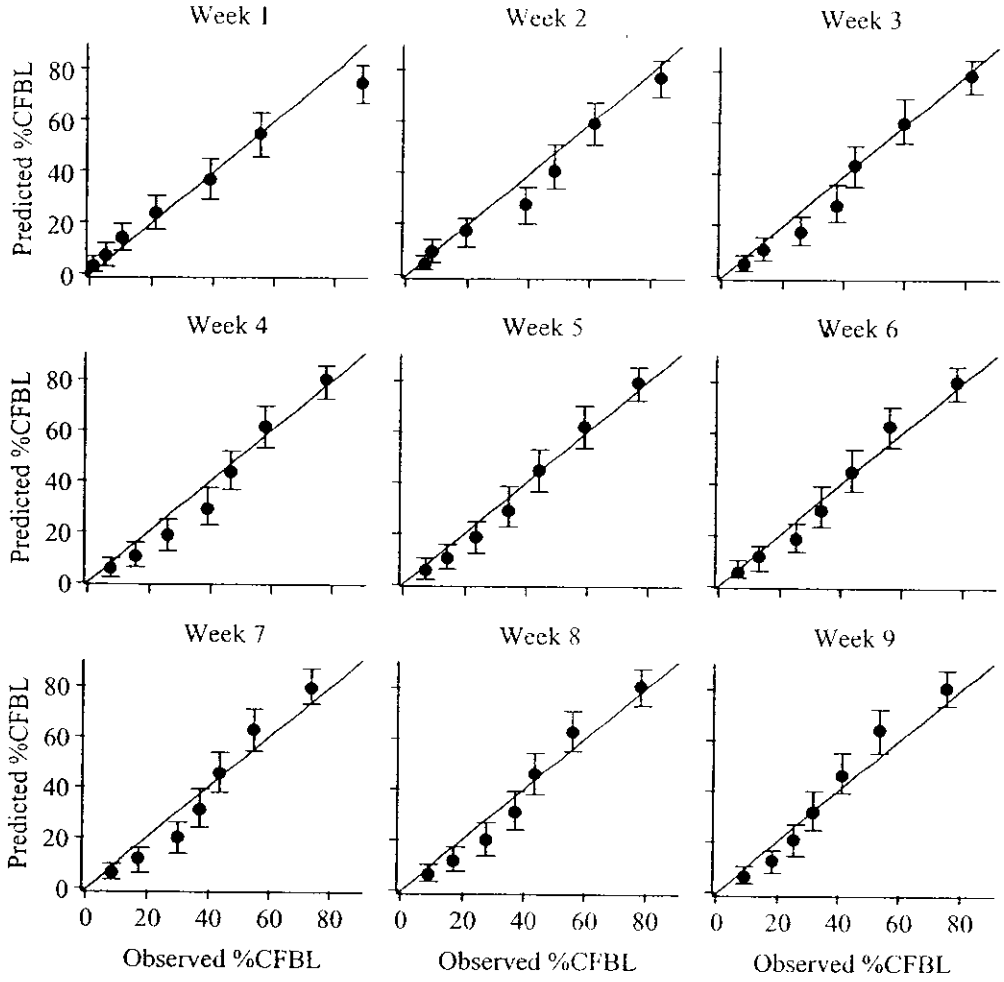
150 mg/Day BID



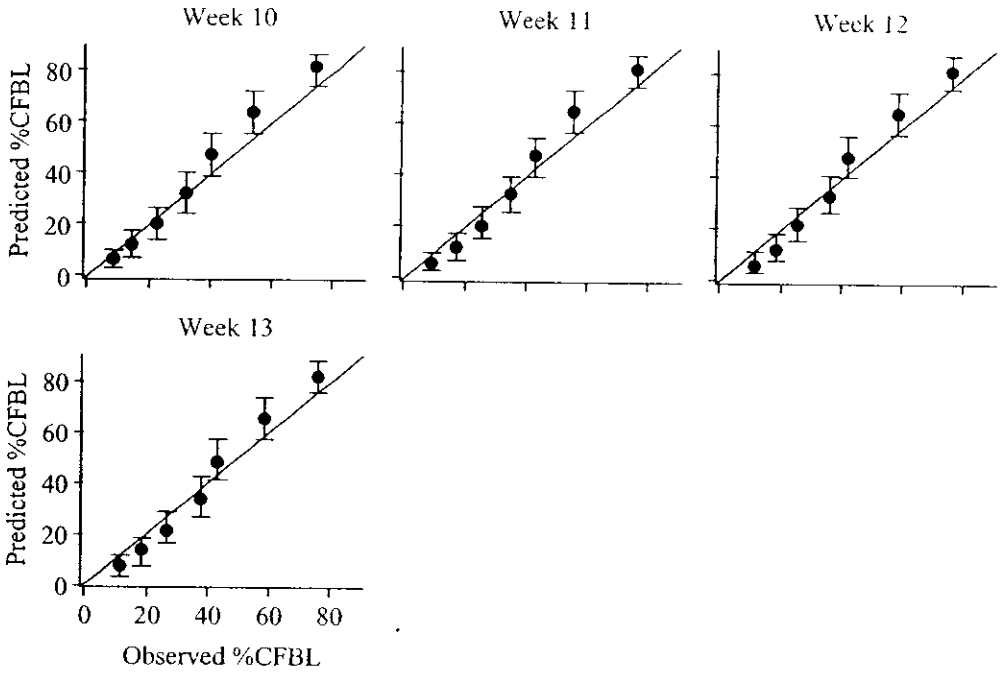
150 mg/Day BID



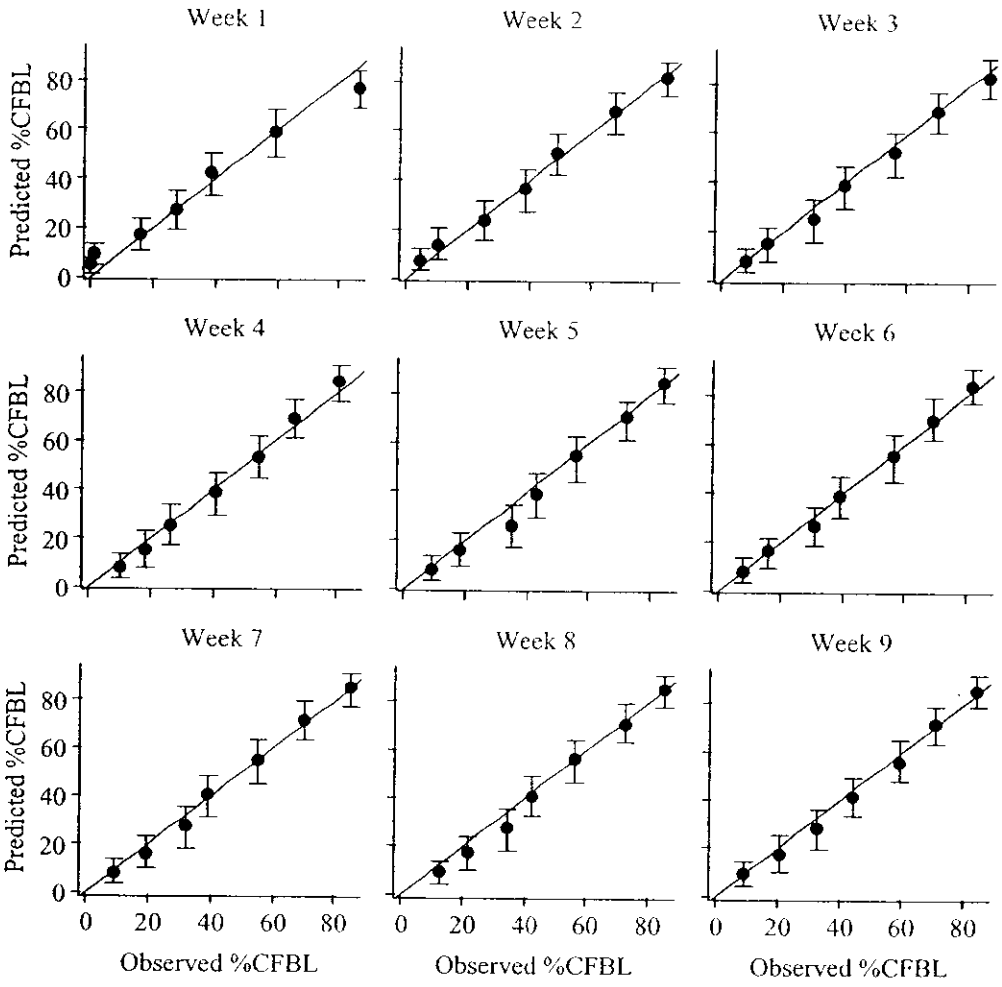
300 mg/Day BID



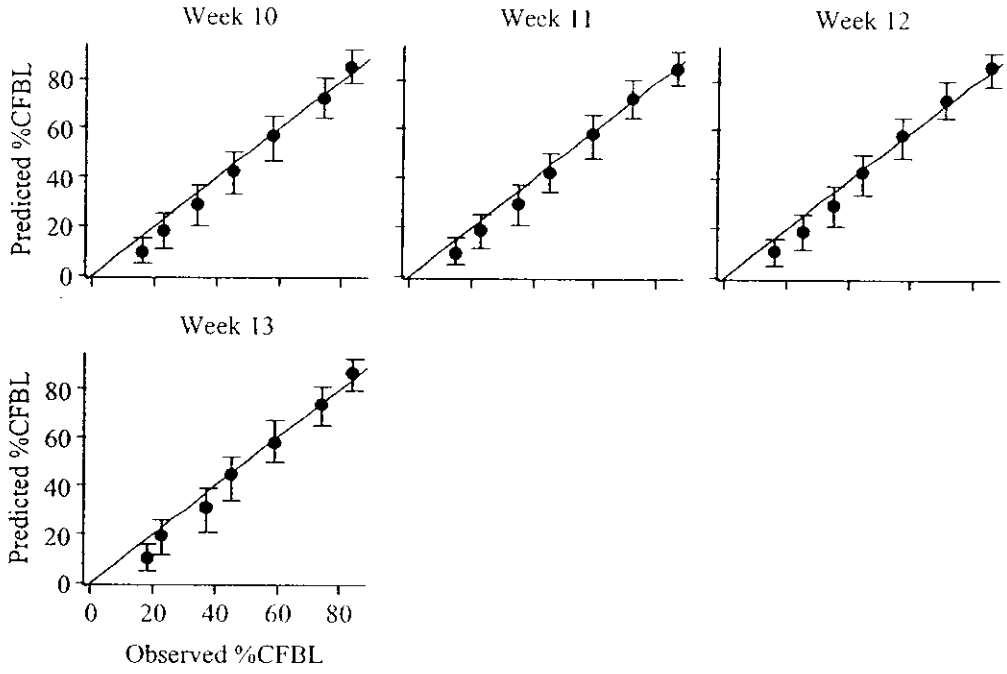
300 mg/Day BID



300/600 mg/Day BID



300/600 mg/Day BID

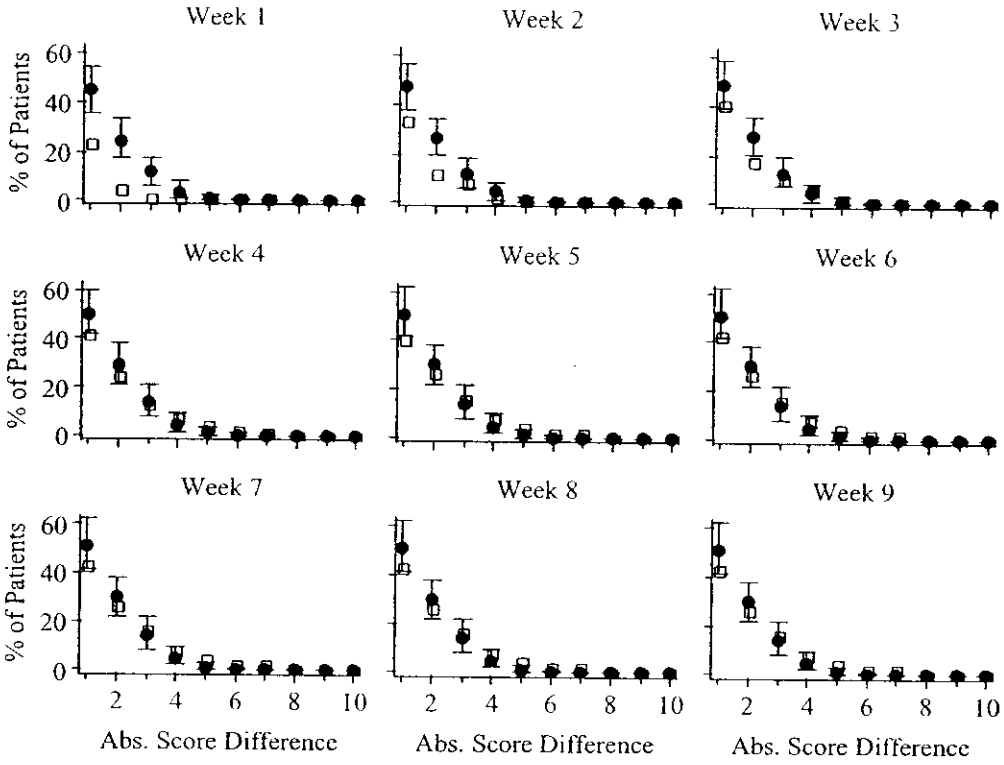


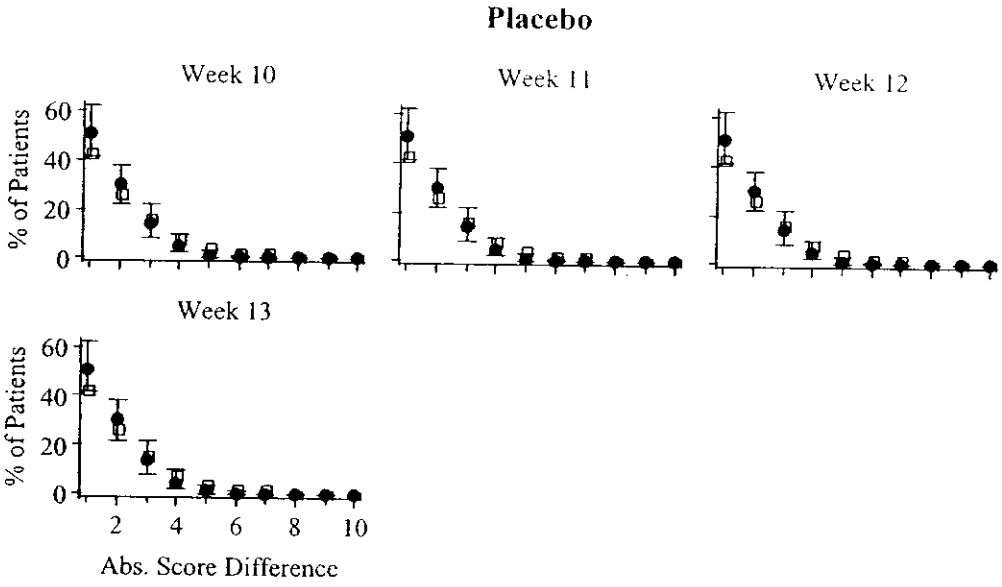
Attachment A.3

BID Model (Study 196) Prediction of TID Data (Study 030) – External PPC

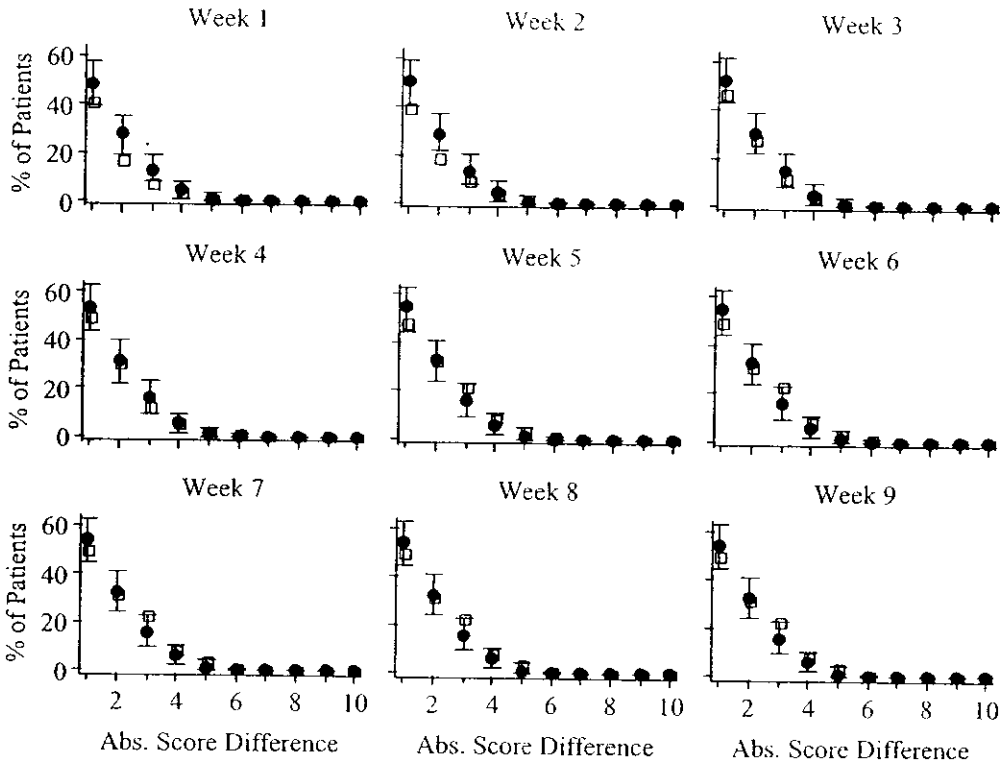
Type 1A: Percentage of Patients Versus ΔScore by Week and Treatment Group

Placebo

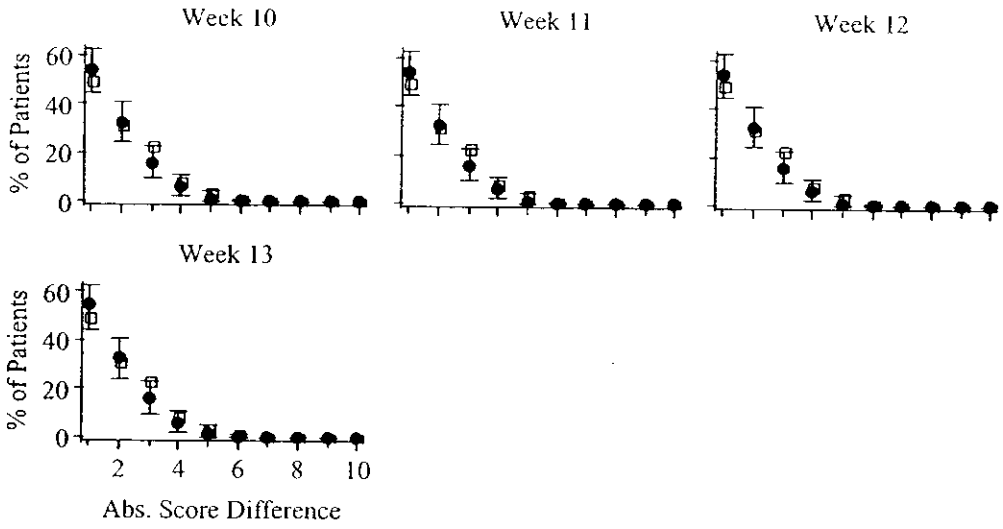

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
2
4
6
8
10
Abs. Score Difference
Predicted
Observed


Placebo
Week 10
Week 11
Week 12
Week 13
% of Patients
60
40
20
0
2
4
6
8
10
Abs. Score Difference
Predicted
Observed

75 mg/Day TID

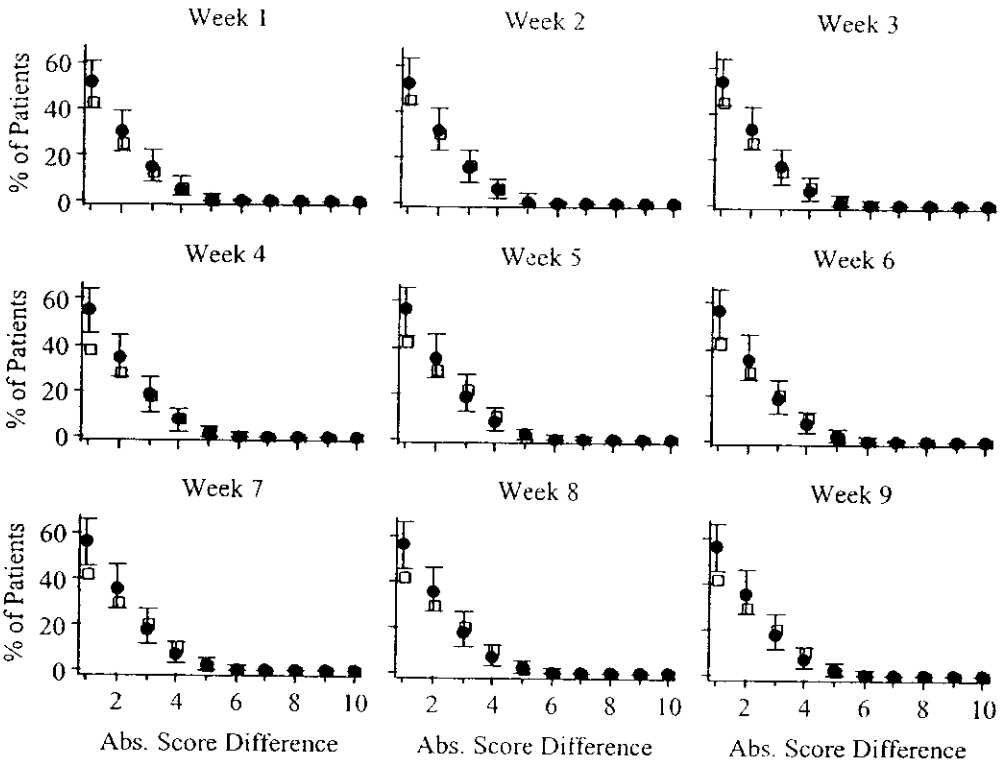

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
60
40
20
0
2
4
6
8
10
Abs. Score Difference
Predicted
Observed

75 mg/Day TID

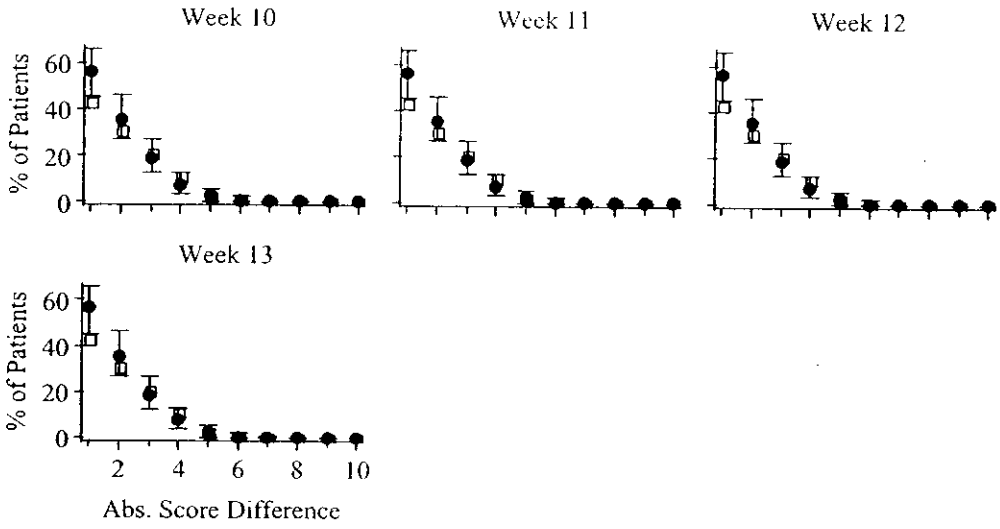


● Predicted
□ Observed

150 mg/Day TID



150 mg/Day TID



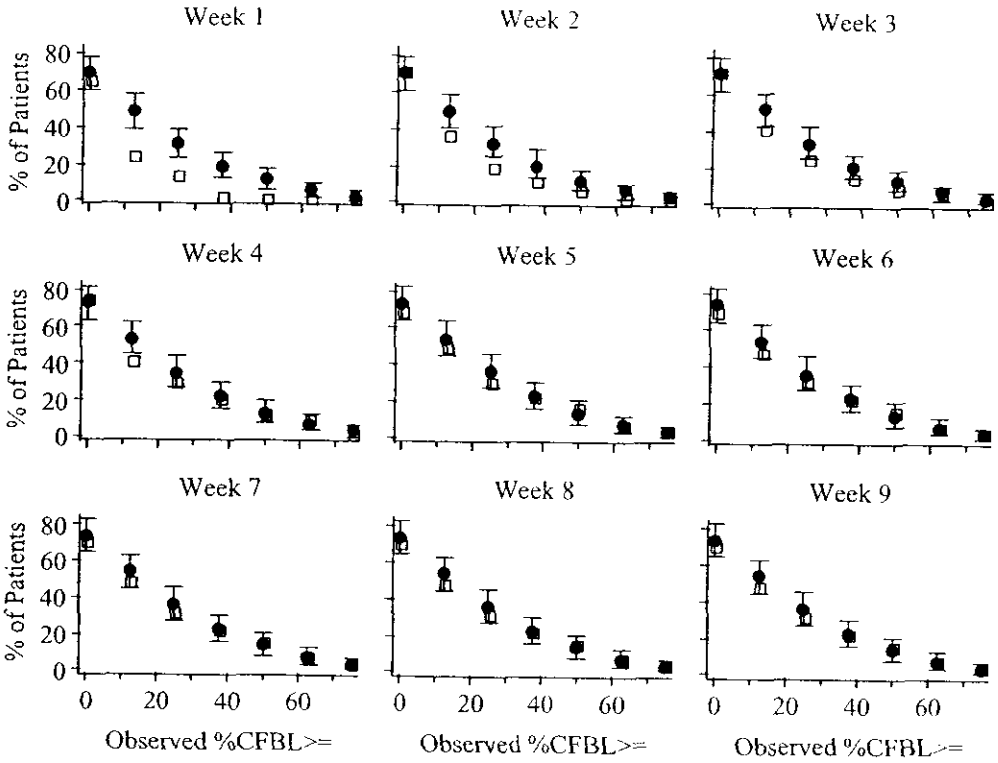
● Predicted
□ Observed

Attachment A.3

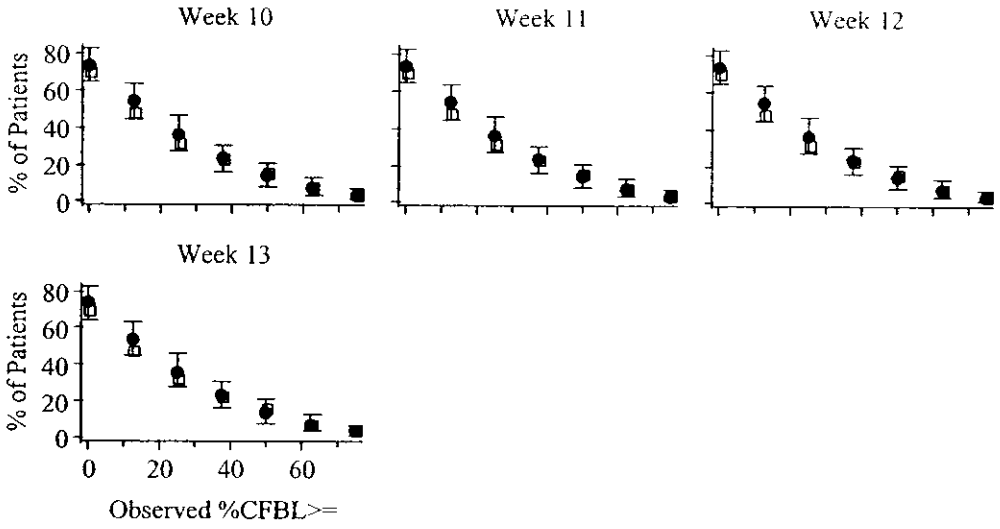
BID Model (Study 196) Prediction of TID Data (Study 030) – External PPC

Type 2A: Percentage of Patients Versus %Change in Pain Score by Week and Treatment Group

Placebo

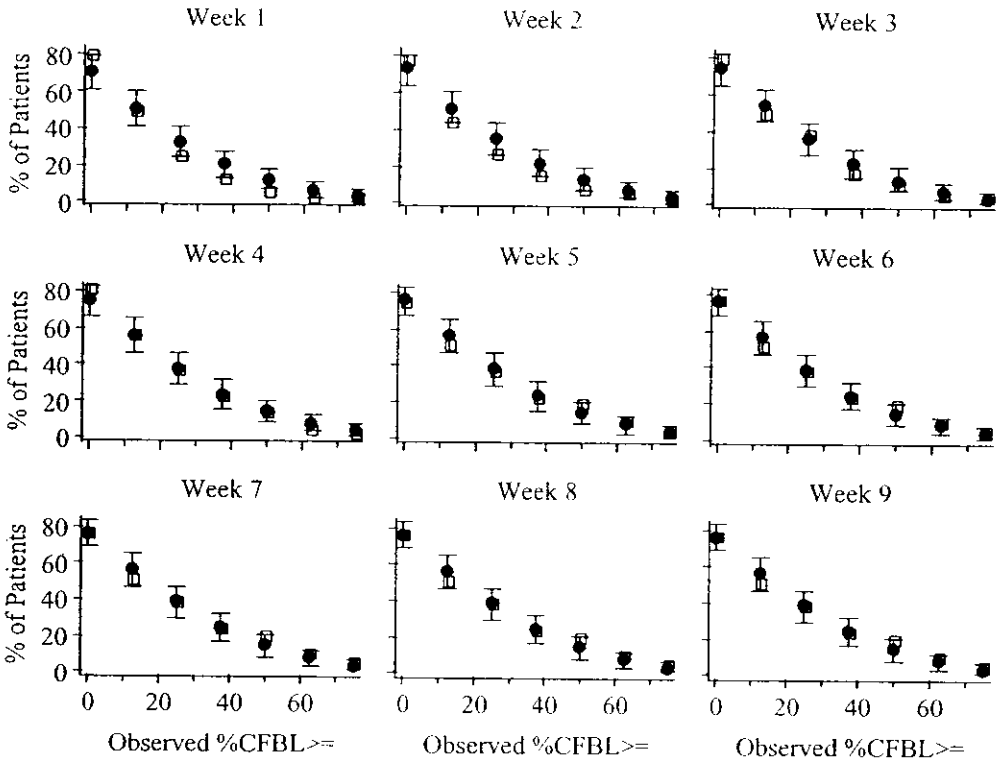

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
80
Observed %CFBL>=
Predicted
Observed

Placebo

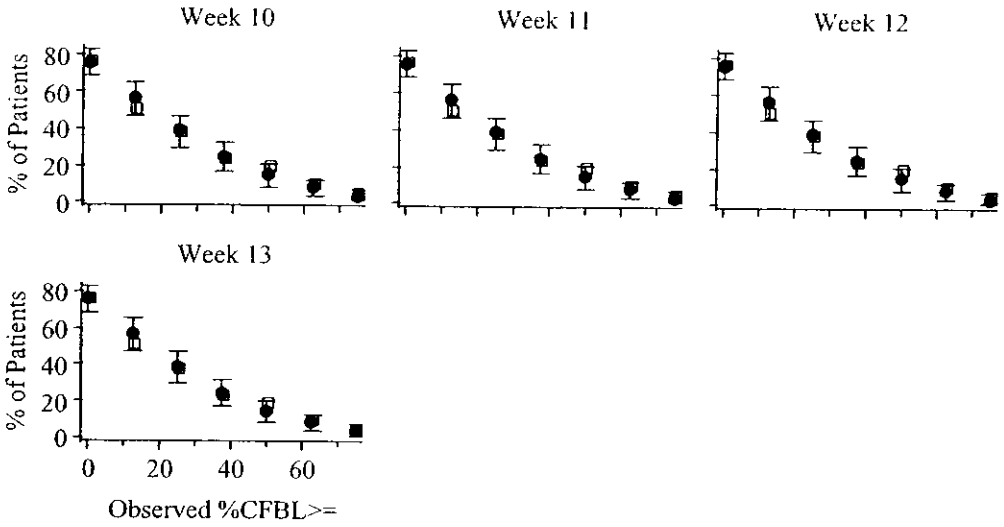


● Predicted
□ Observed

75 mg/Day TID

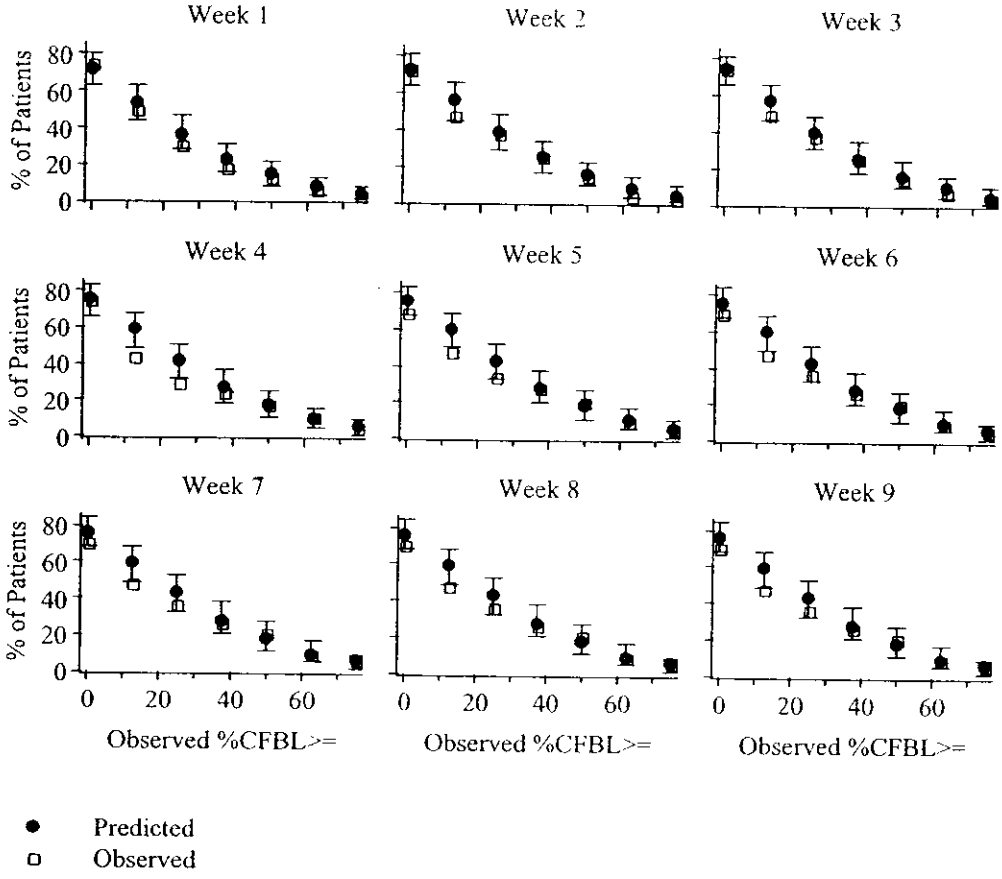

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
80
Observed %CFBL>=
Predicted
Observed

75 mg/Day TID

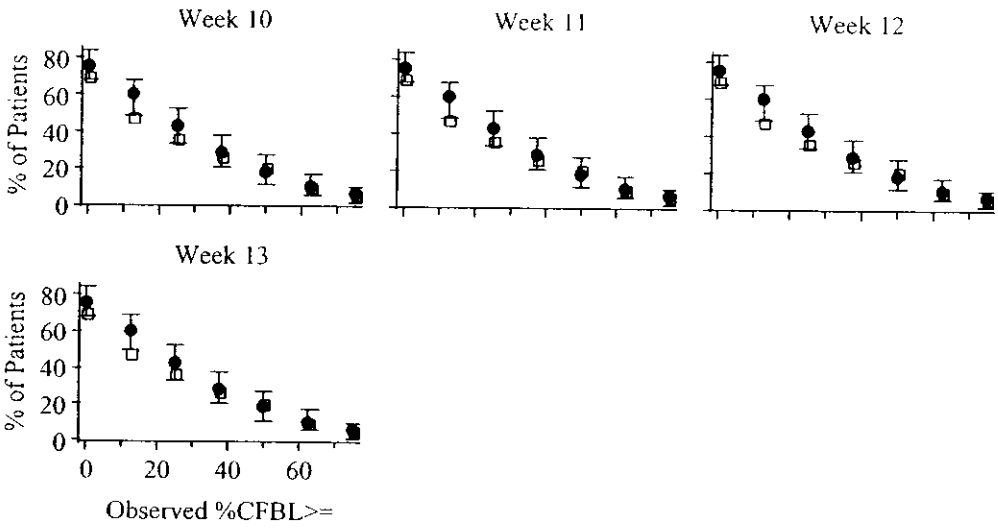


● Predicted
□ Observed

150 mg/Day TID



150 mg/Day TID



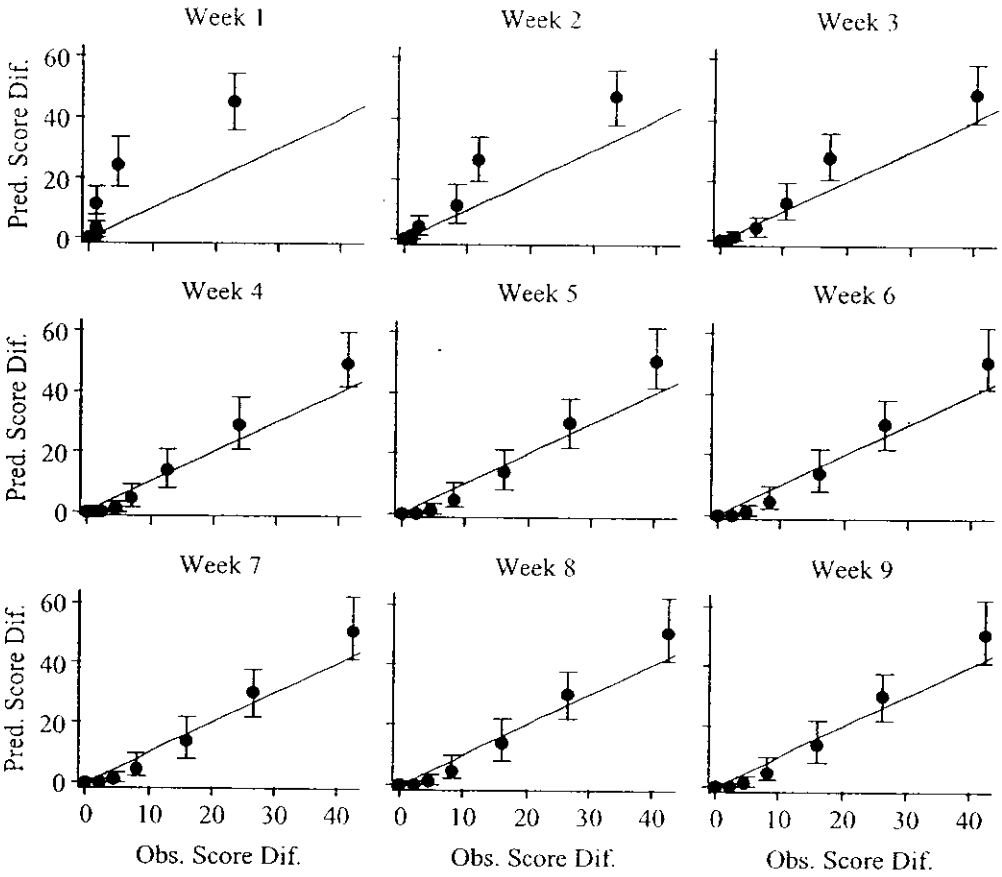
● Predicted
□ Observed

Attachment A.3

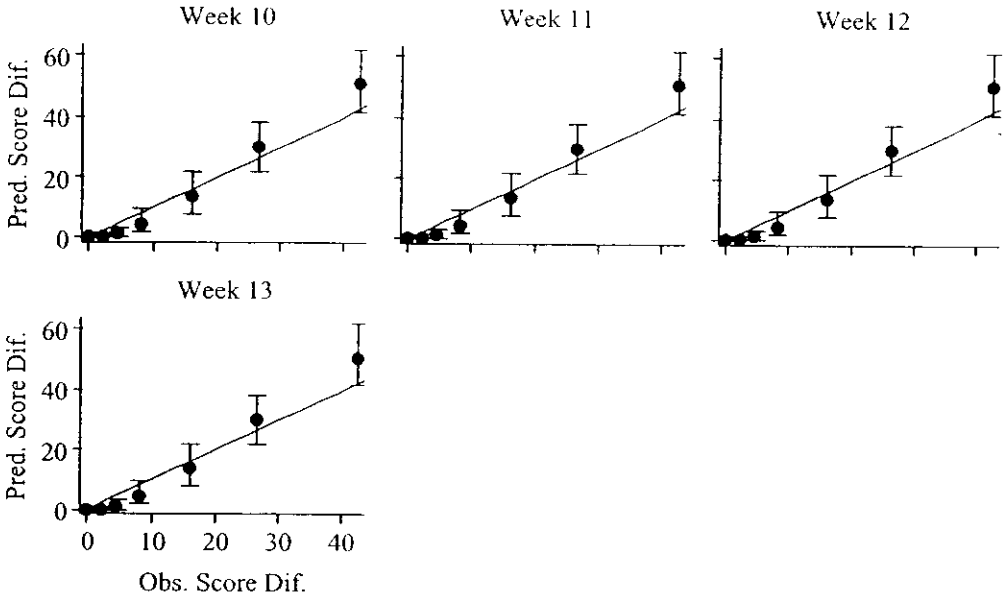
BID Model (Study 196) Prediction of TID Data (Study 030) – External PPC

Type 1B: Concordance Plots of Predicted Versus Observe Percentage of Patients (ΔScore) by Week and Treatment Group

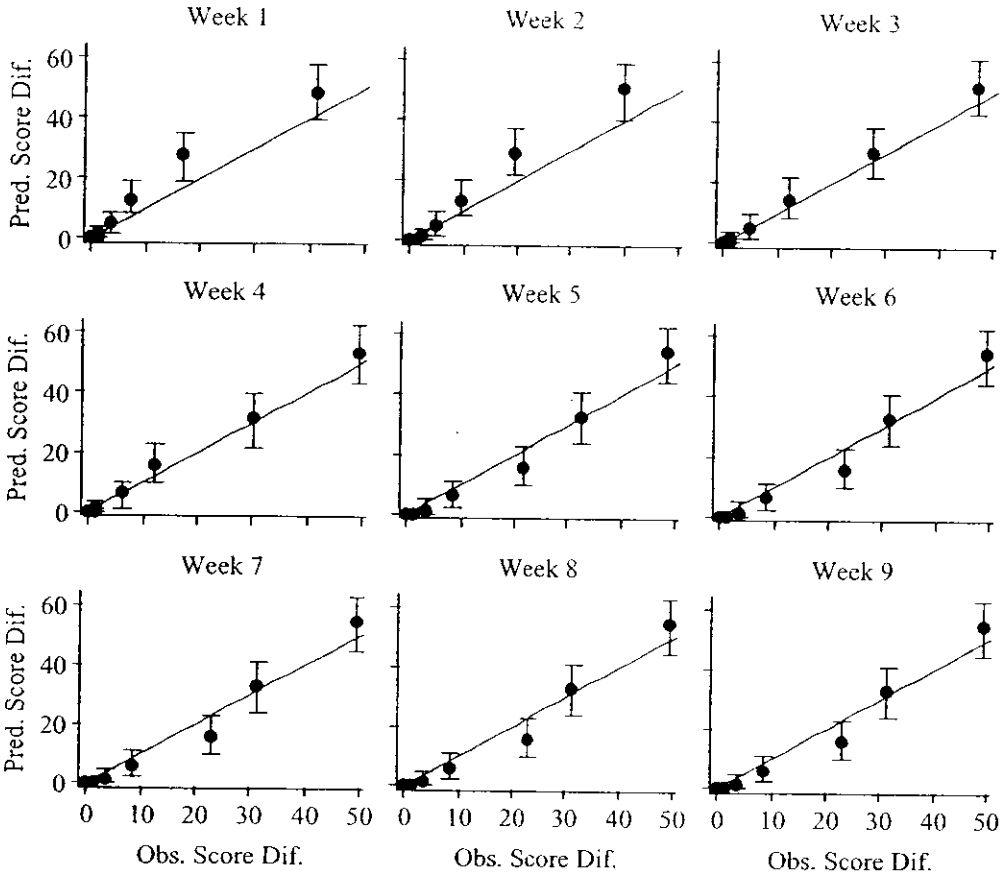
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30
40

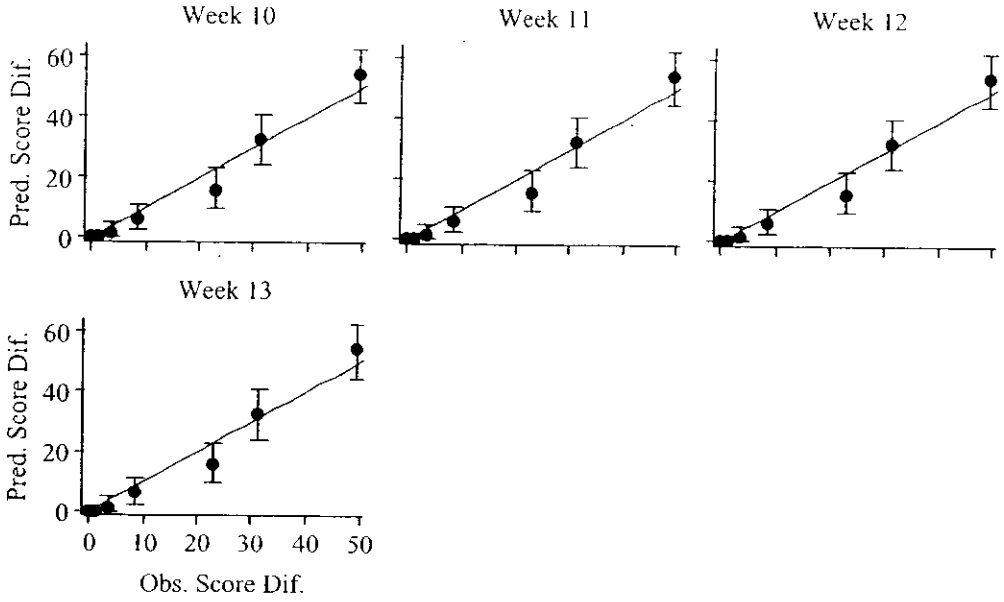
Placebo


Week 10
Week 11
Week 12
Week 13
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30
40

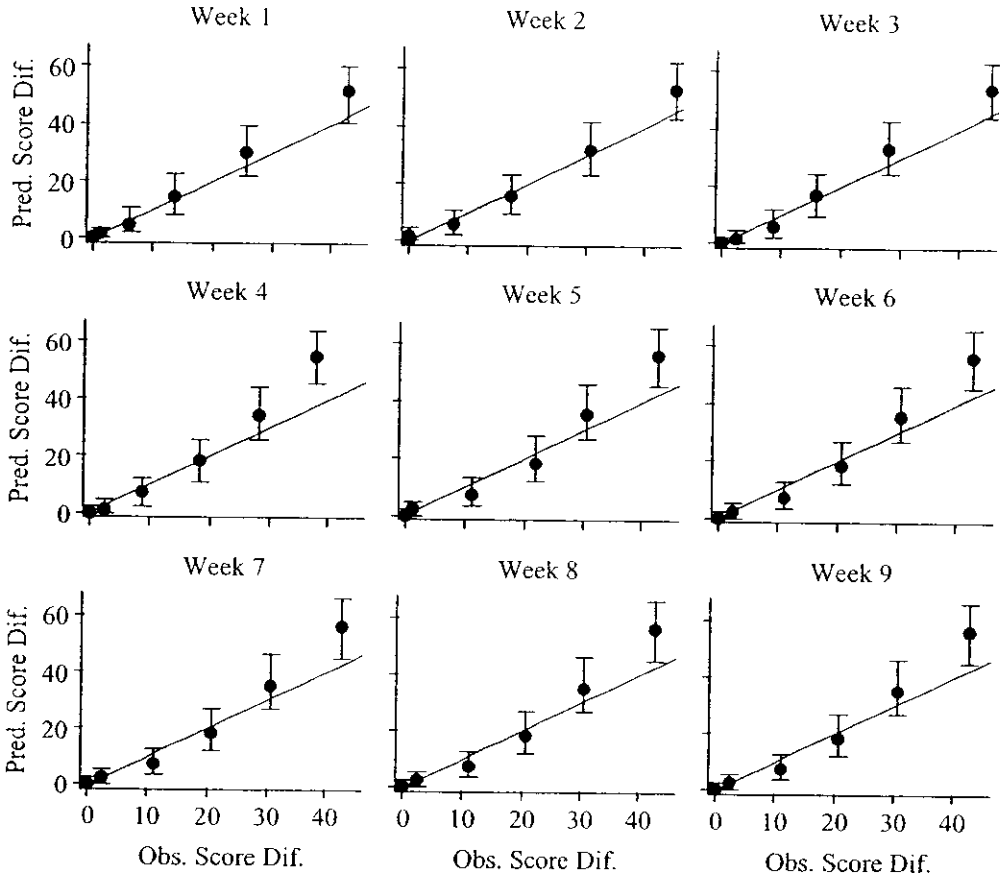
75 mg/Day TID


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Pred. Score Dif.
0
20
40
60
0
10
20
30
40
50
Obs. Score Dif.

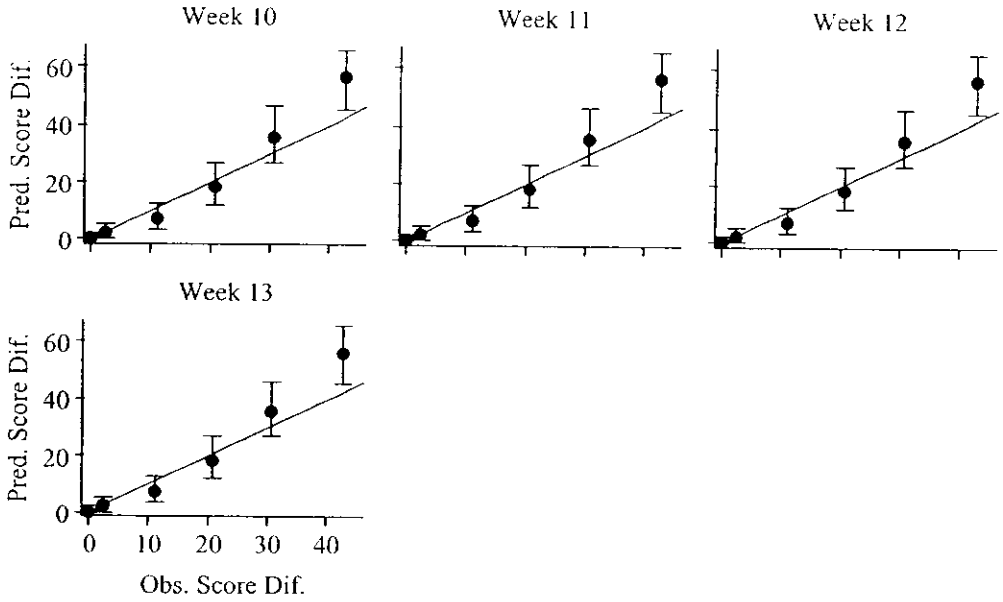
75 mg/Day TID


Week 10
Week 11
Week 12
Week 13
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30
40
50

150 mg/Day TID



150 mg/Day TID

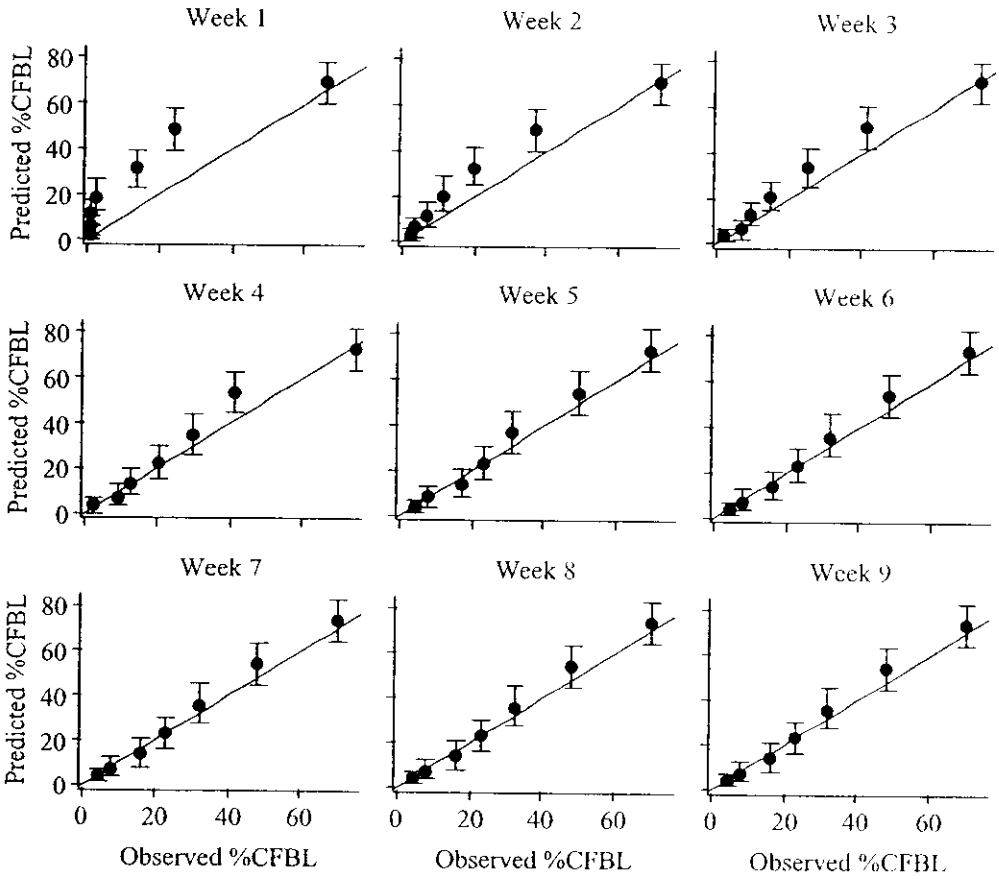


Attachment A.3

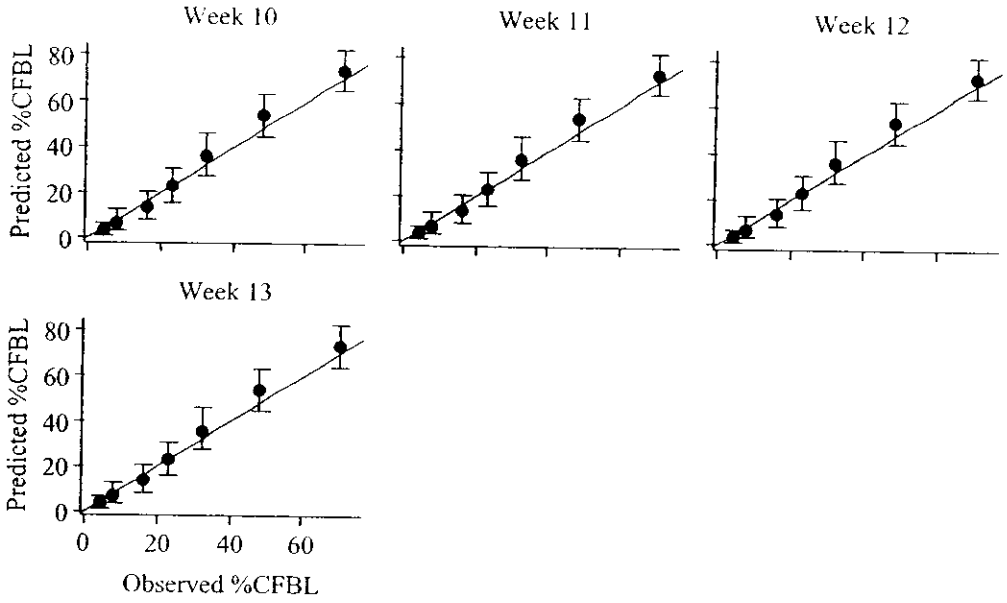
BID Model (Study 196) Prediction of TID Data (Study 030) – External PPC

Type 2B: Concordance Plots of Predicted Versus Observe Percentage of Patients (%Change in Pain Score) by Week and Treatment Group

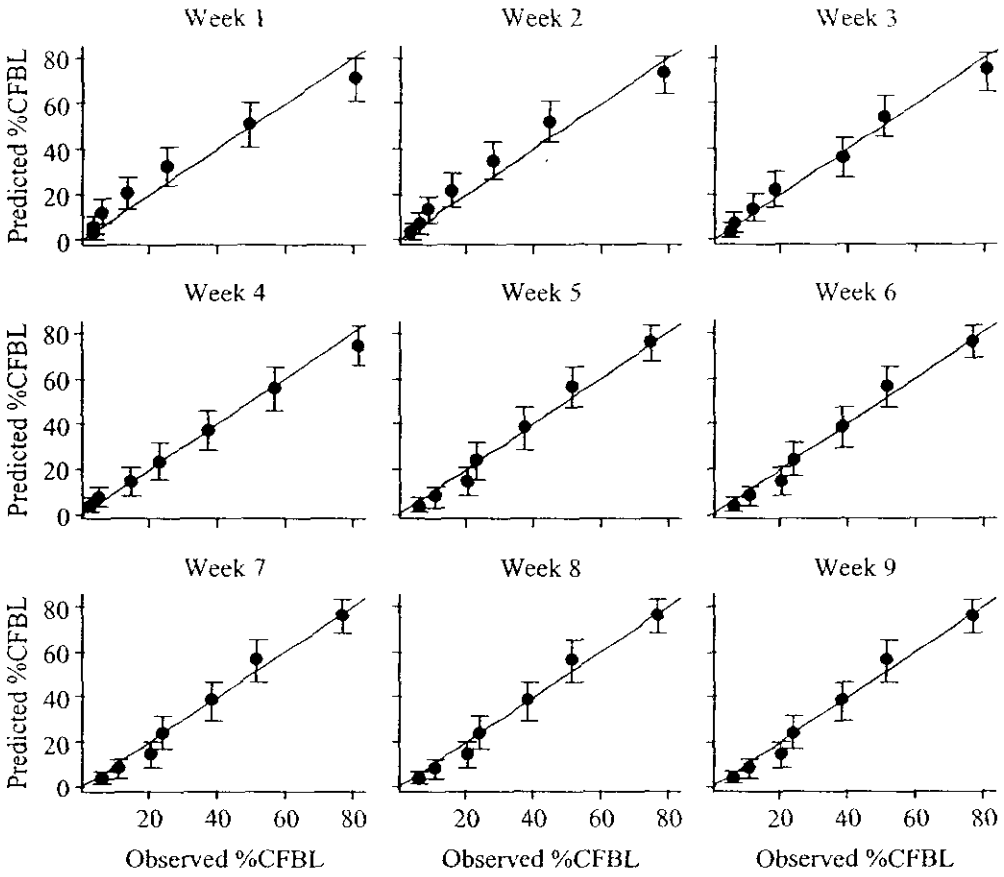
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

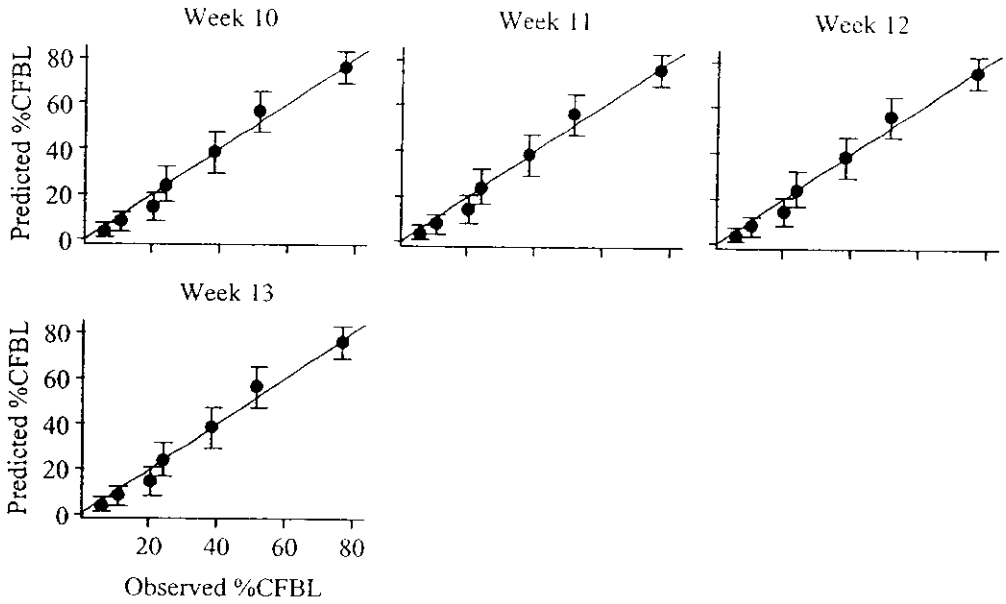
Placebo


Week 10
Week 11
Week 12
Week 13
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

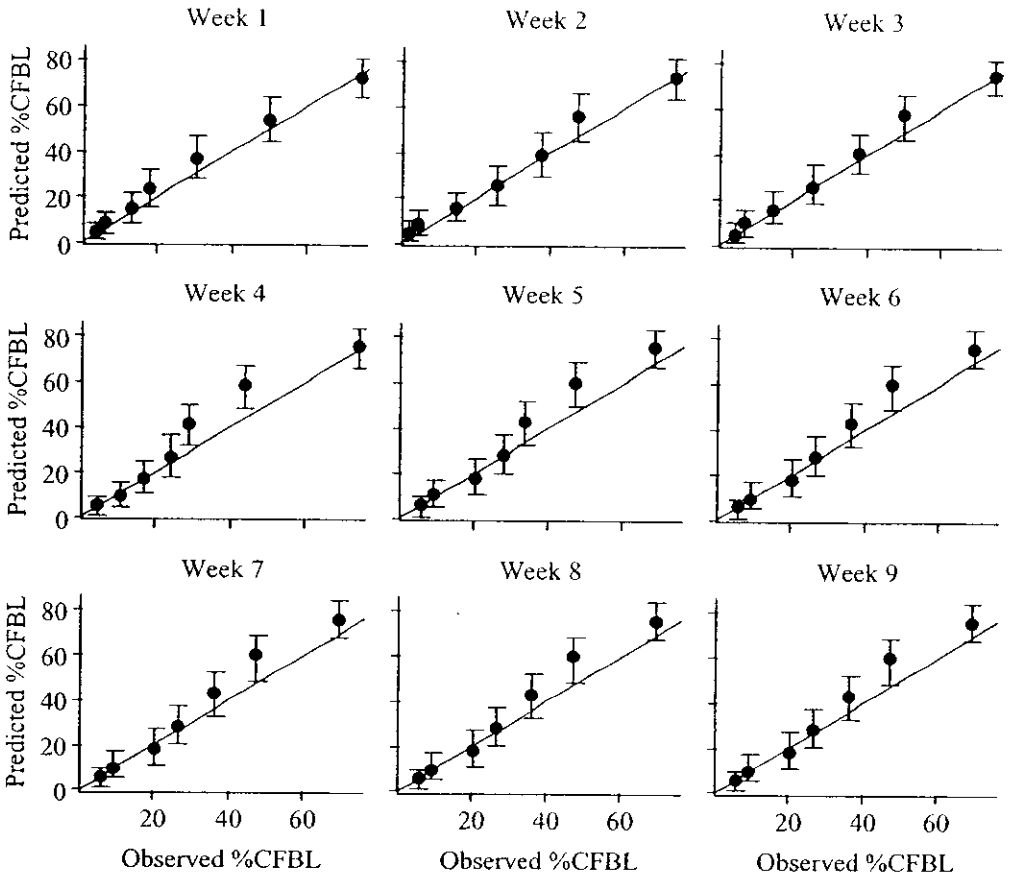
75 mg/Day TID


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

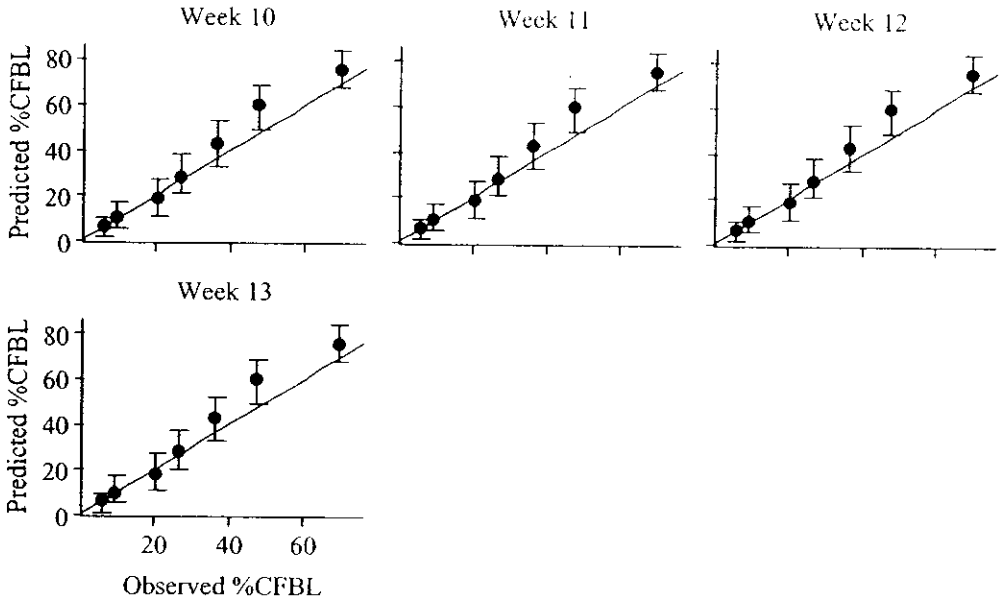
75 mg/Day TID


Week 10
Week 11
Week 12
Week 13
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

150 mg/Day TID



150 mg/Day TID

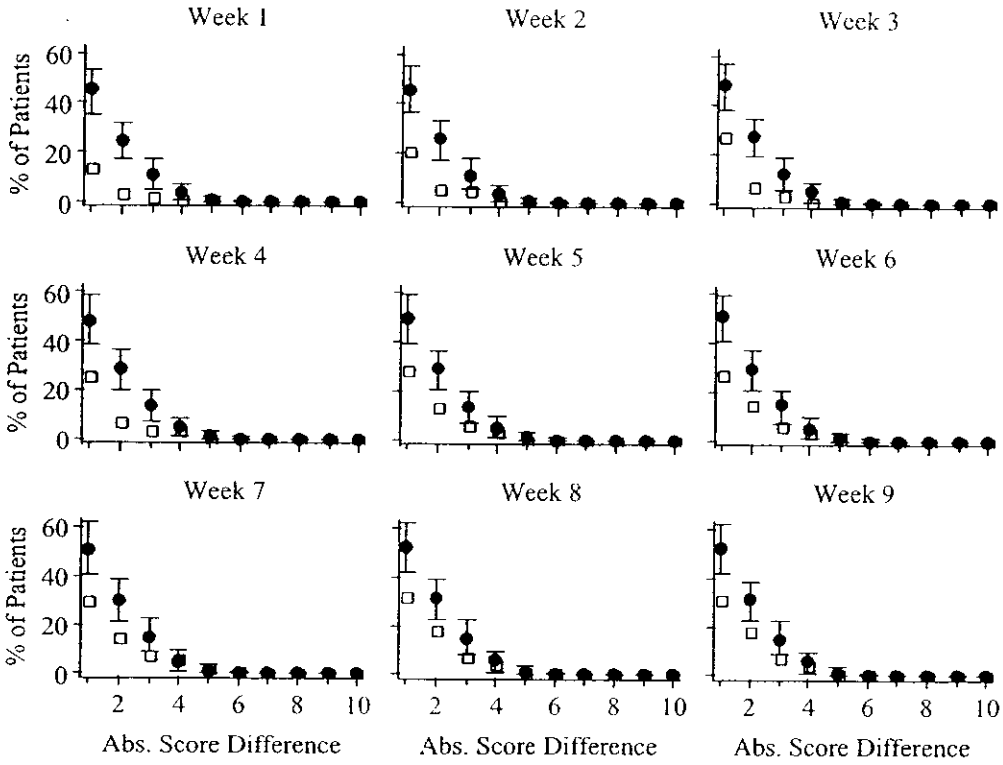


Attachment A.3

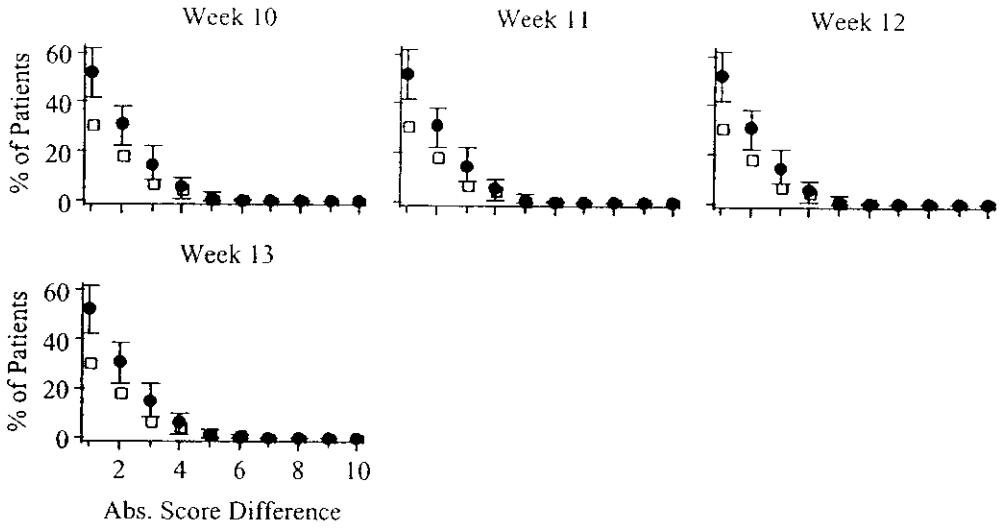
BID Model (Study 196) Prediction of TID Data (Study 045) – External PPC

Type 1A: Percentage of Patients Versus ΔScore by Week and Treatment Group

Placebo

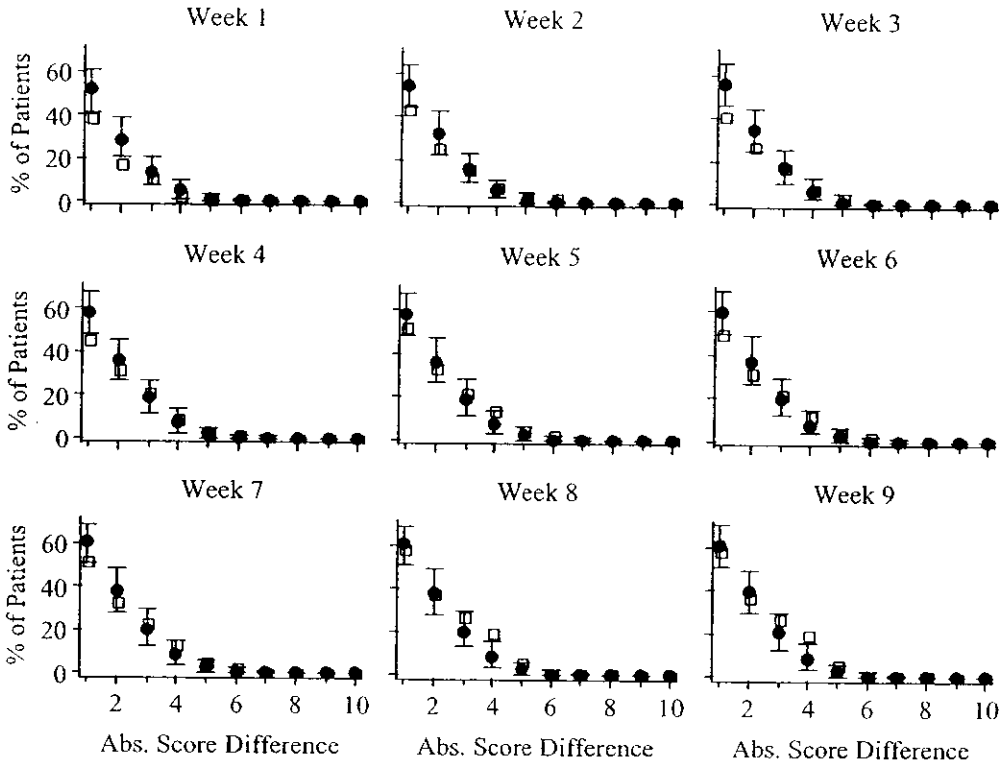

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
2
4
6
8
10
Abs. Score Difference
Predicted
Observed

Placebo

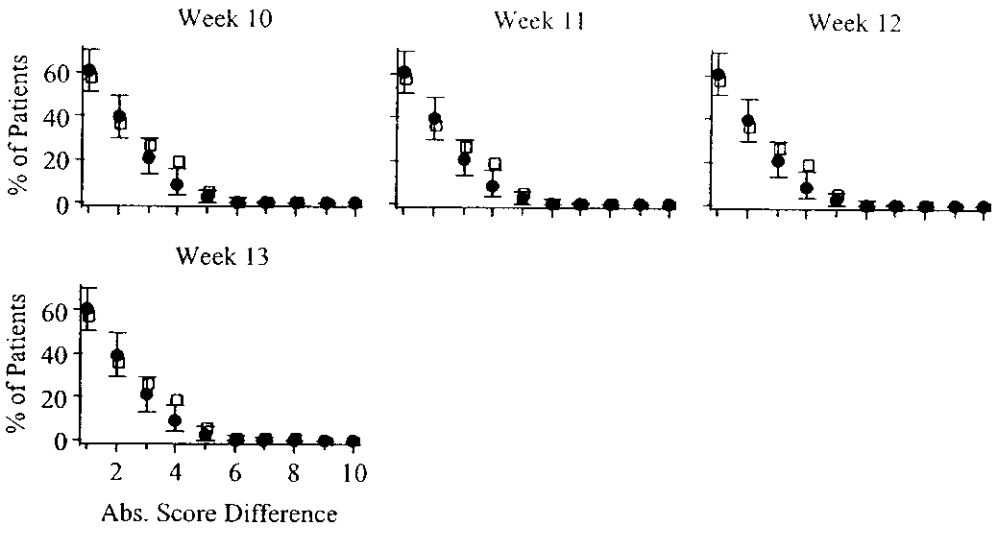


● Predicted
□ Observed

150 mg/Day TID

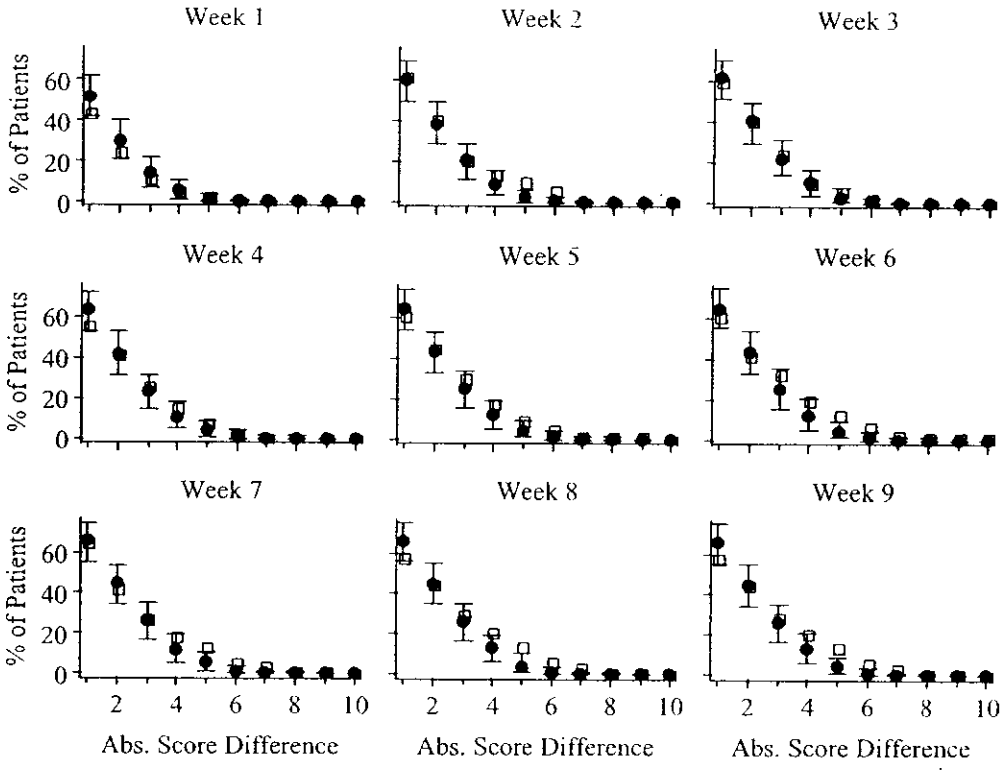


150 mg/Day TID

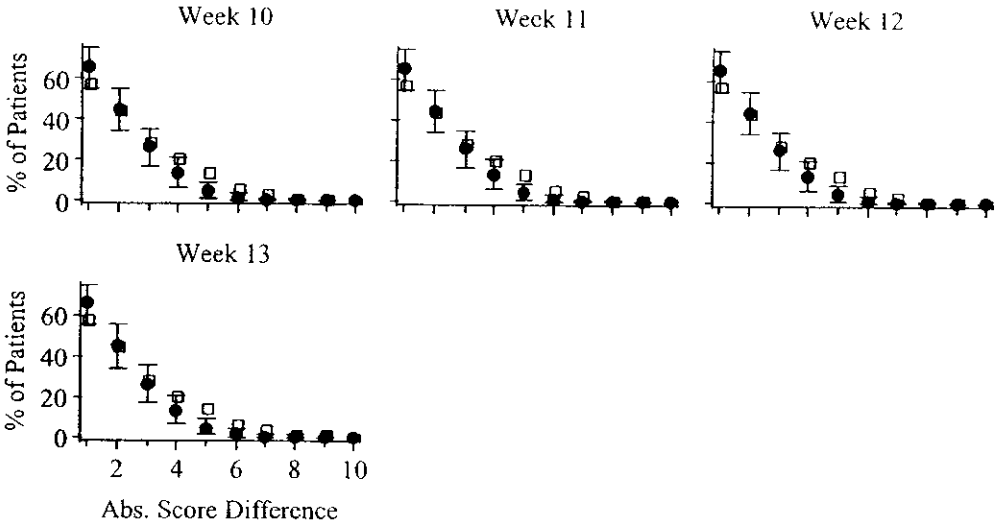


● Predicted
□ Observed

300 mg/Day TID



300 mg/Day TID



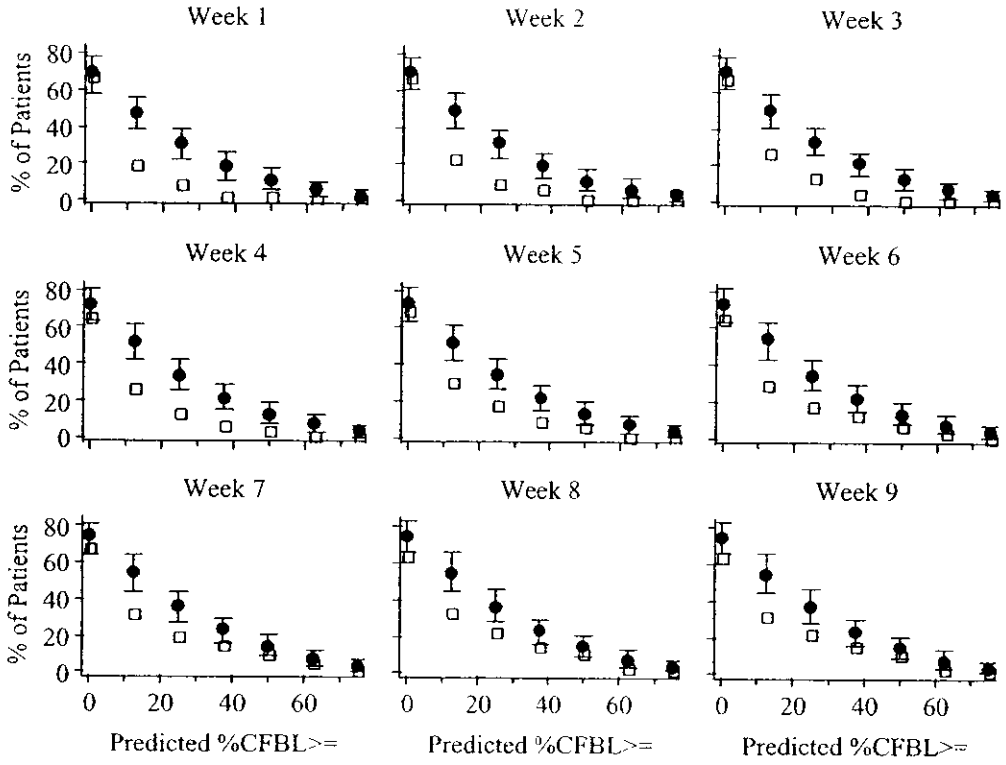
● Predicted
□ Observed

Attachment A.3

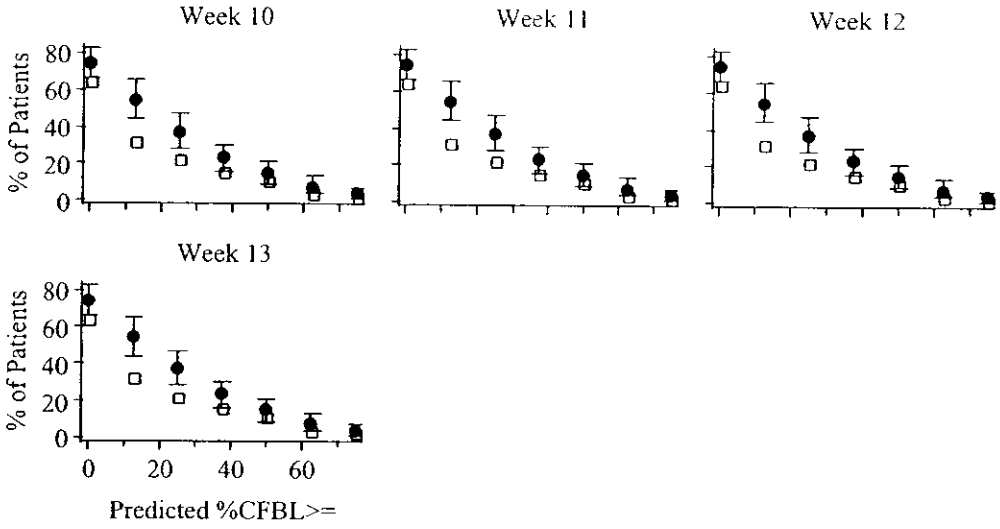
BID Model (Study 196) Prediction of TID Data (Study 045) – External PPC

Type 2A: Percentage of Patients Versus %Change in Pain Score by Week and Treatment Group

Placebo

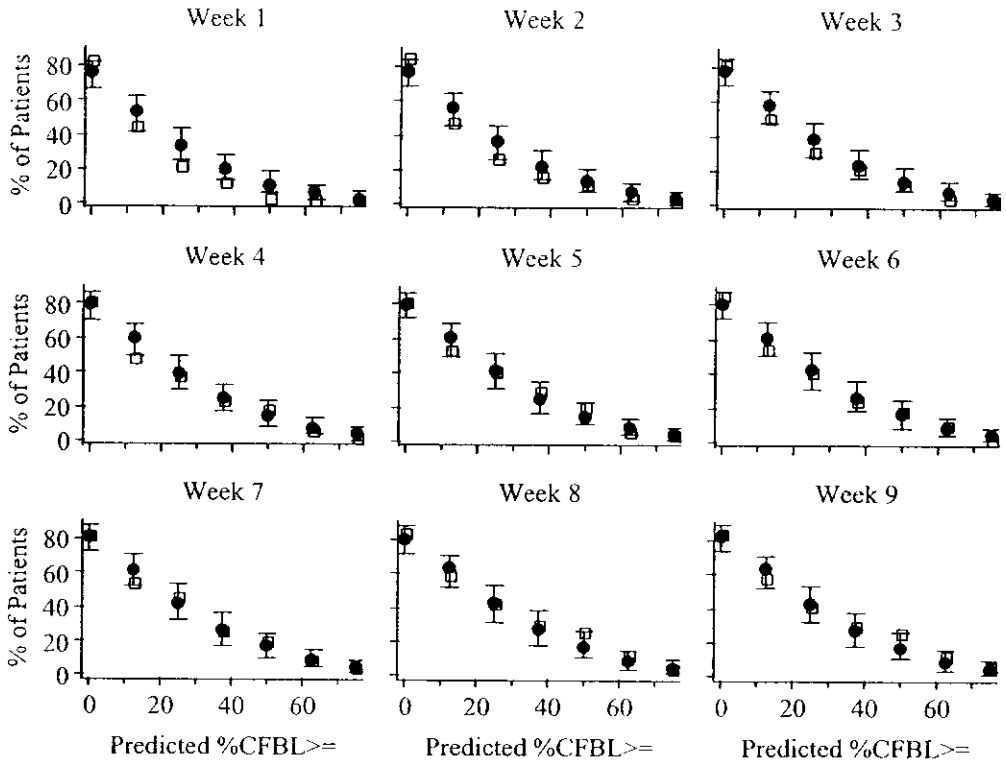

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
80
Predicted %CFBL>=
● Predicted
□ Observed

Placebo

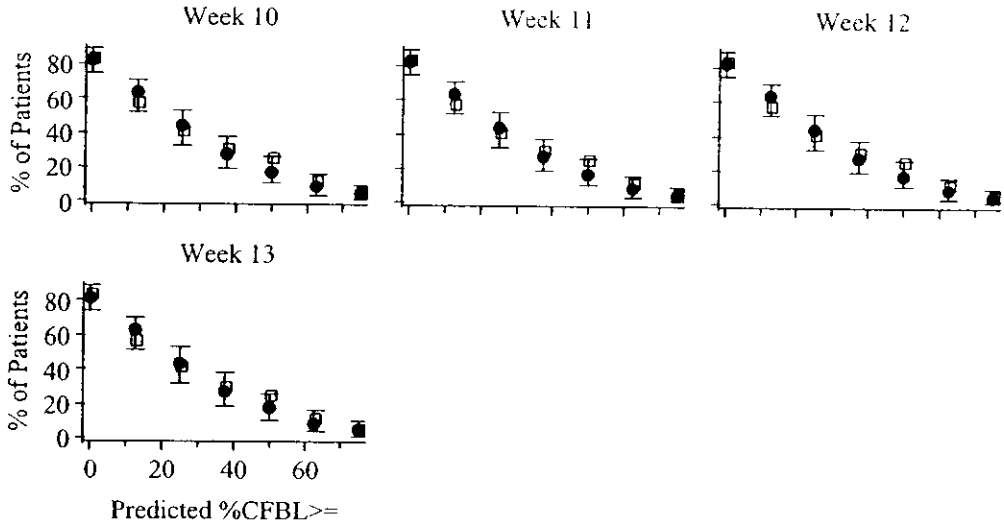


● Predicted
□ Observed

150 mg/Day TID

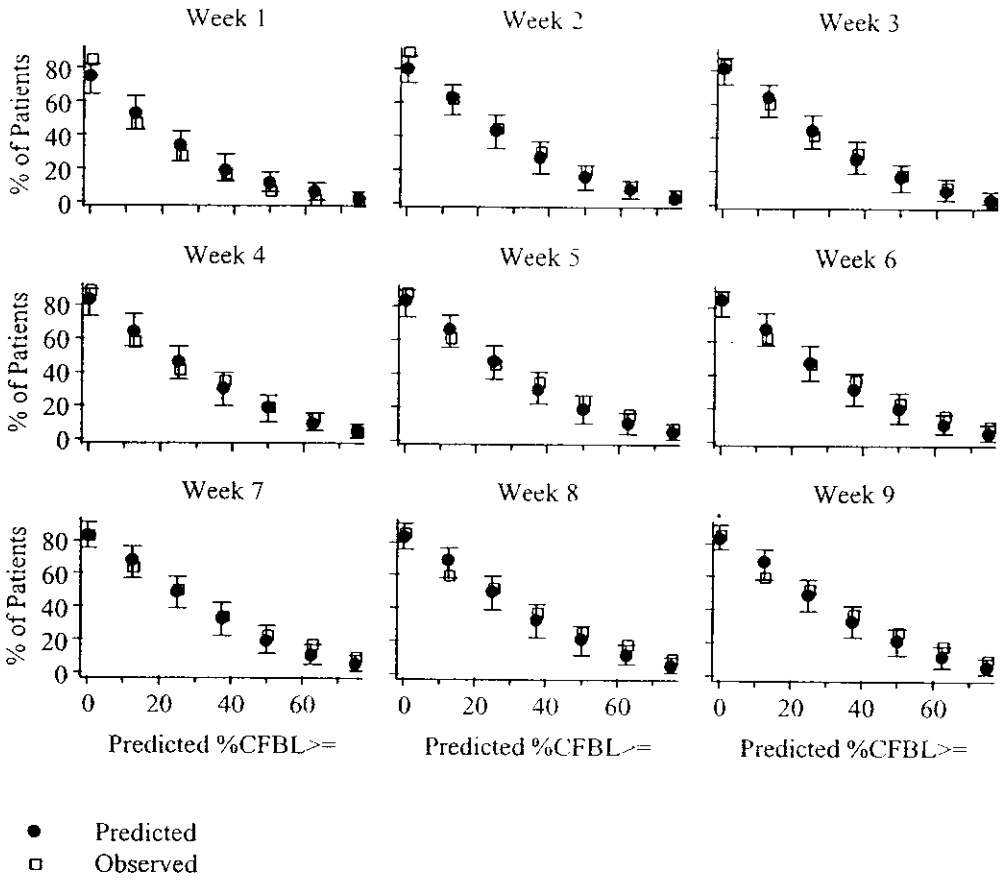


150 mg/Day TID

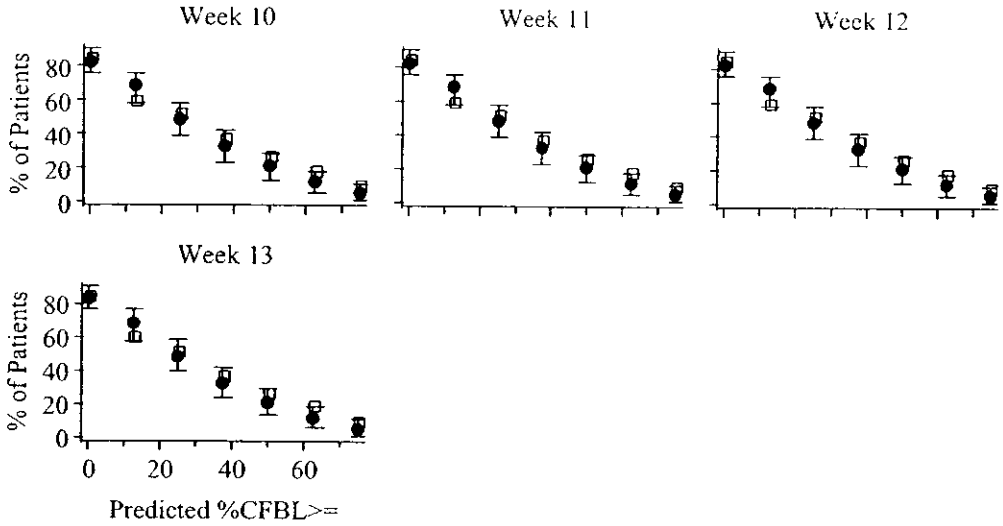


● Predicted
□ Observed

300 mg/Day TID



300 mg/Day TID



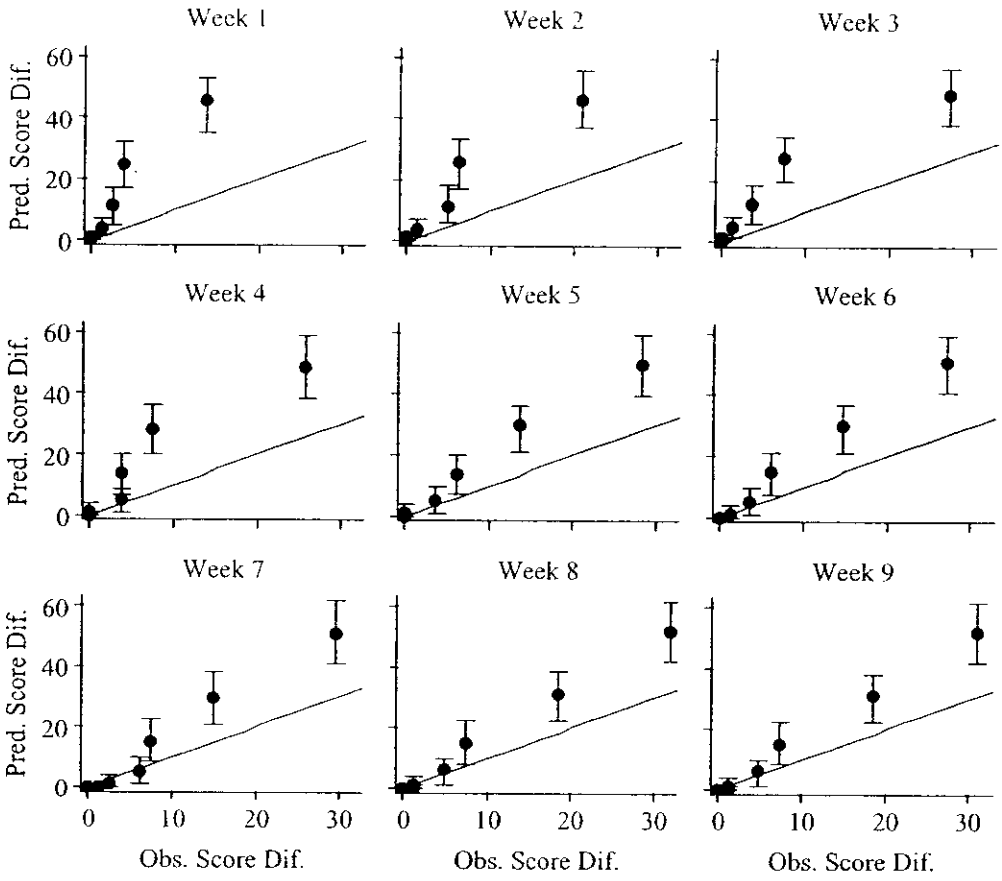
● Predicted
□ Observed

Attachment A.3

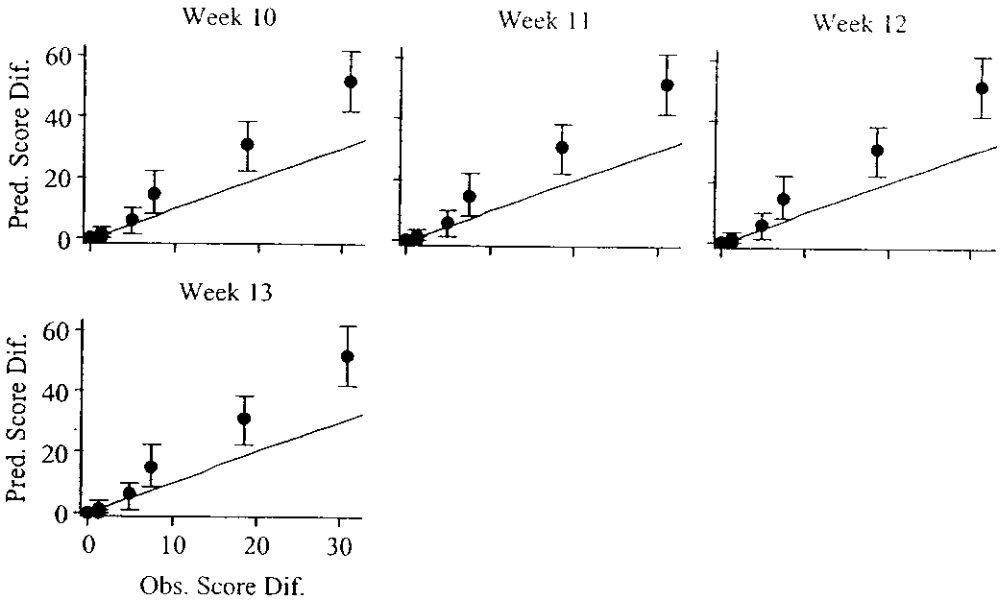
BID Model (Study 196) Prediction of TID Data (Study 045) – External PPC

Type 1B: Concordance Plot of Predicted Versus Observed Percentage of Patients (ΔScore) by Week and Treatment Group

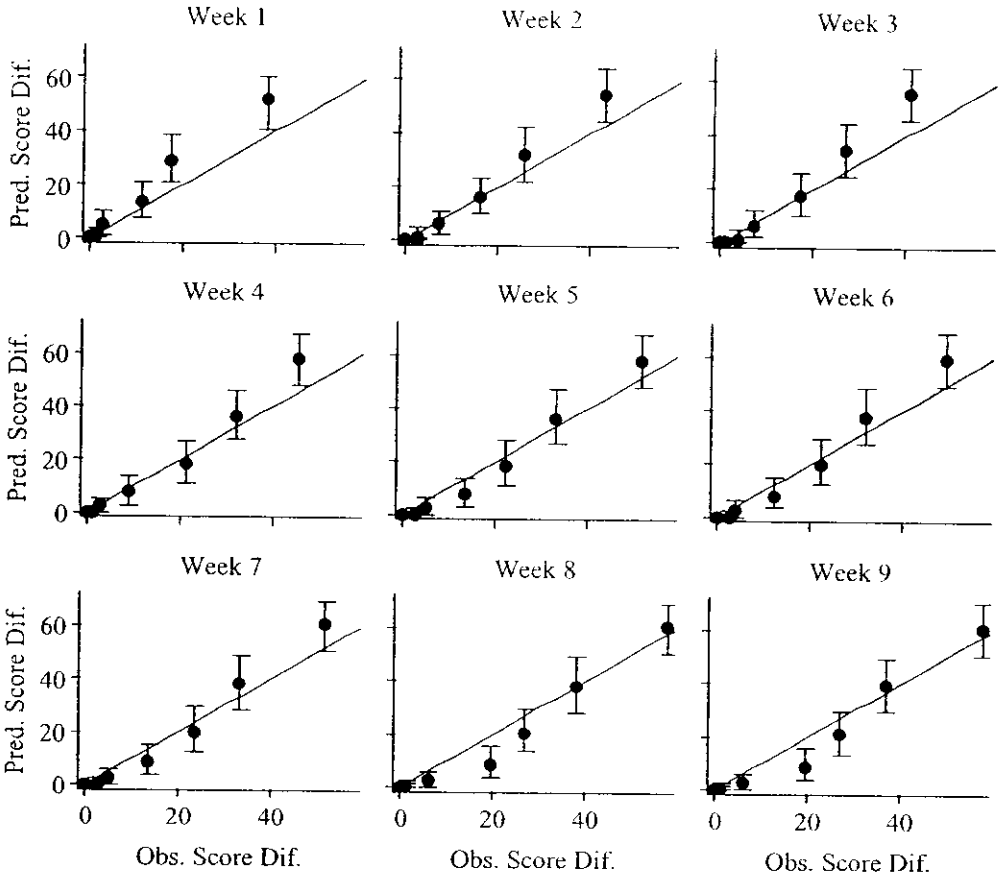
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30

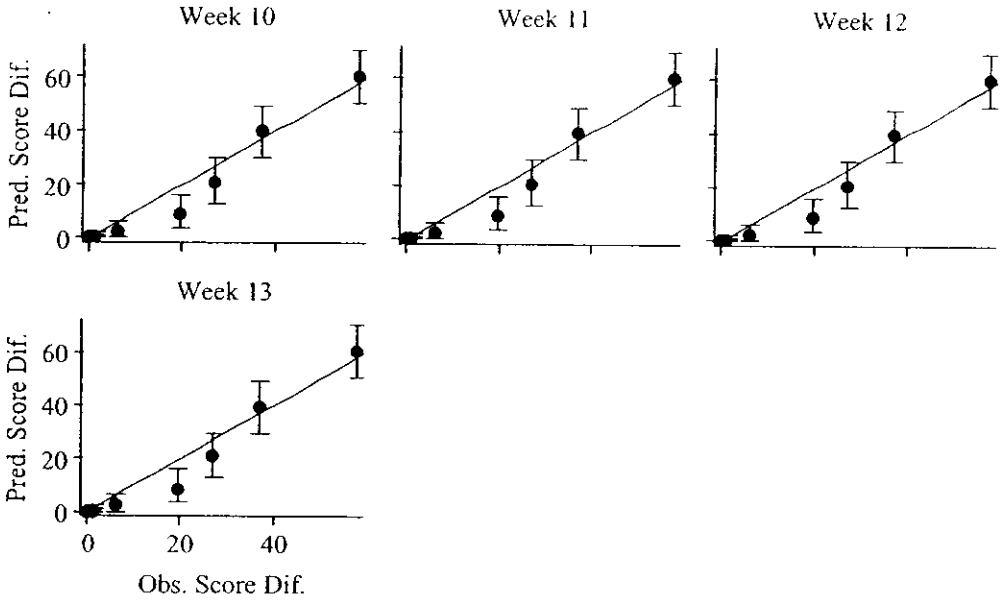
Placebo


Week 10
Week 11
Week 12
Week 13
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30

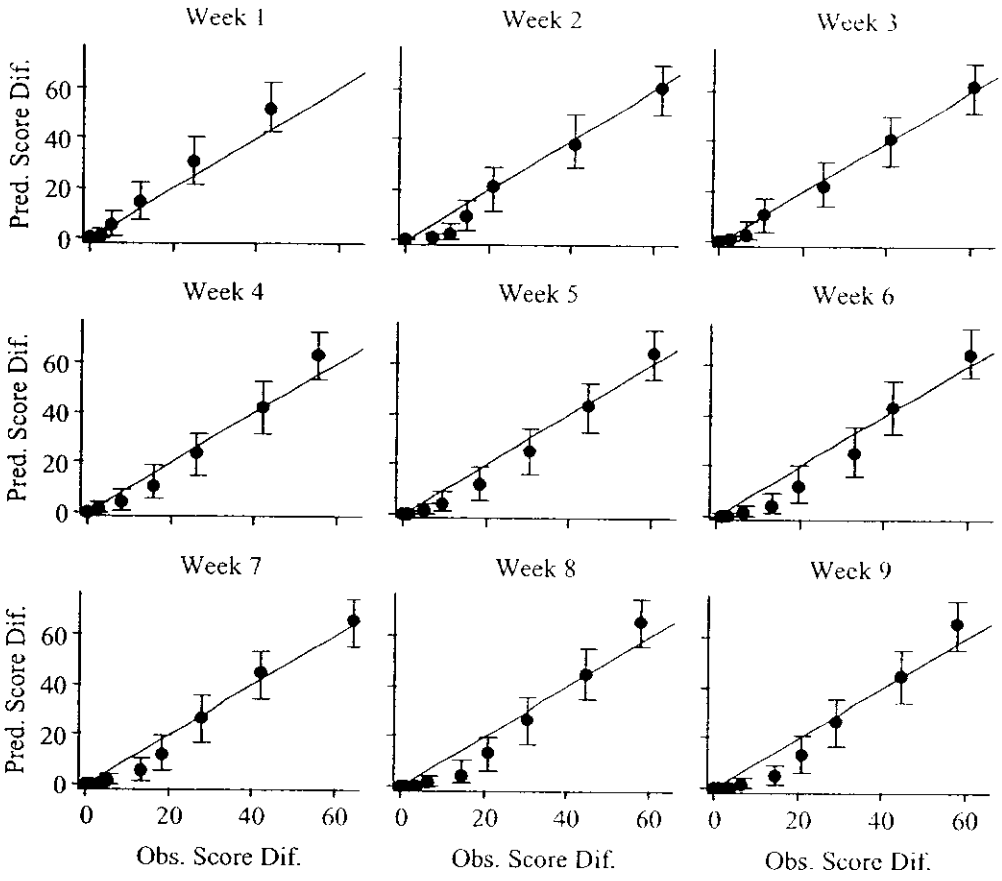
150 mg/Day TID



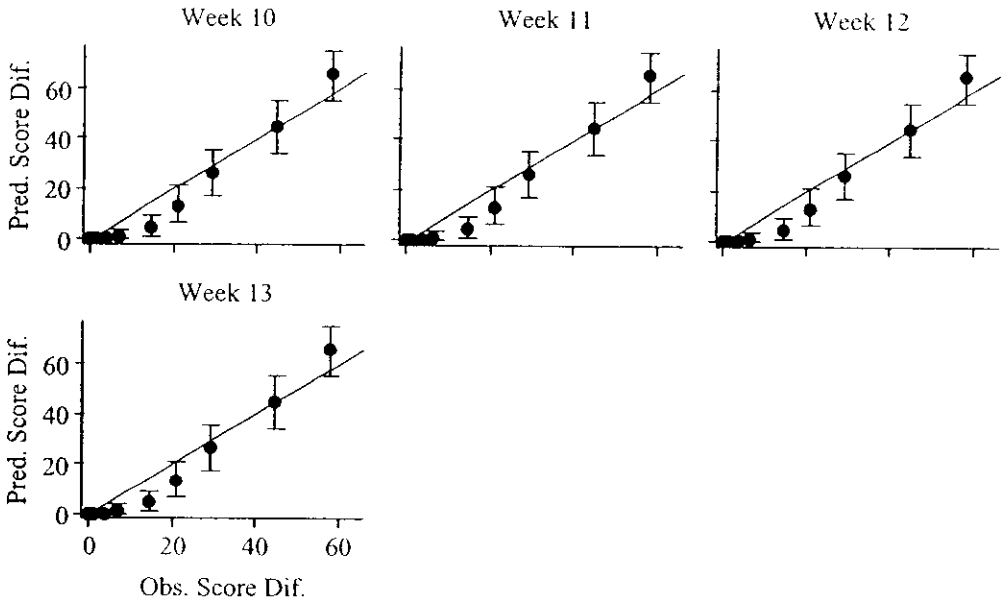
150 mg/Day TID



300 mg/Day TID



300 mg/Day TID

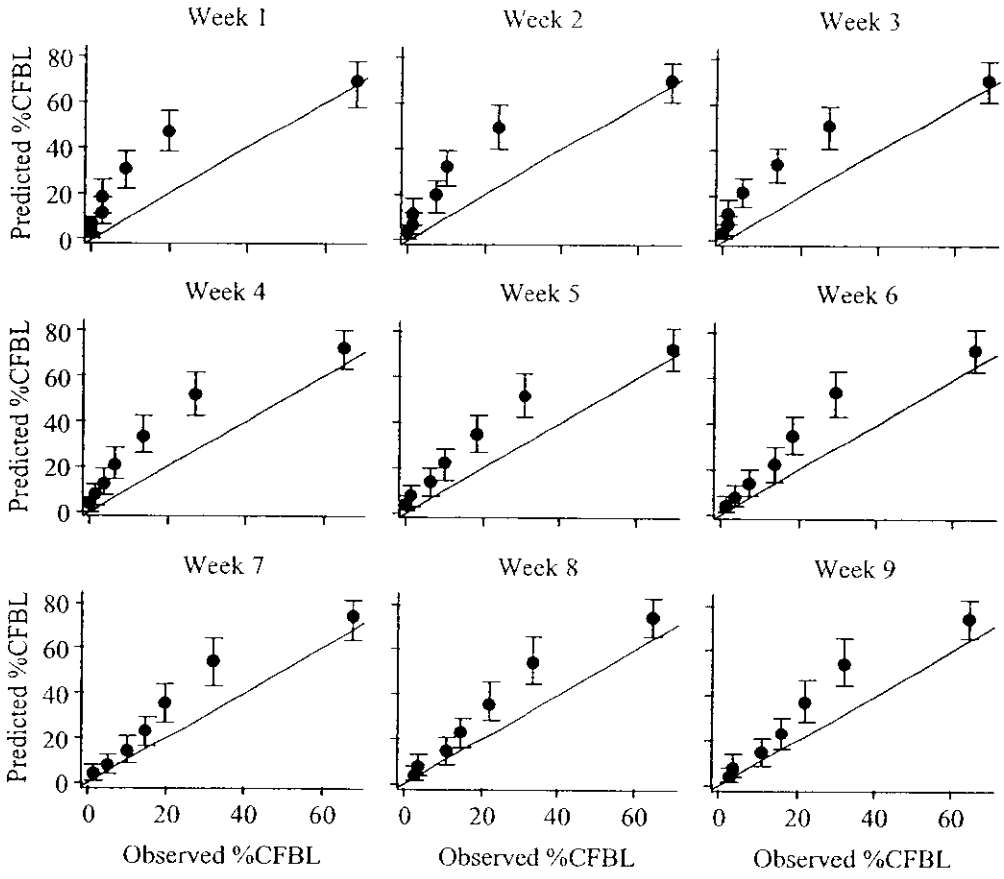


Attachment A.3

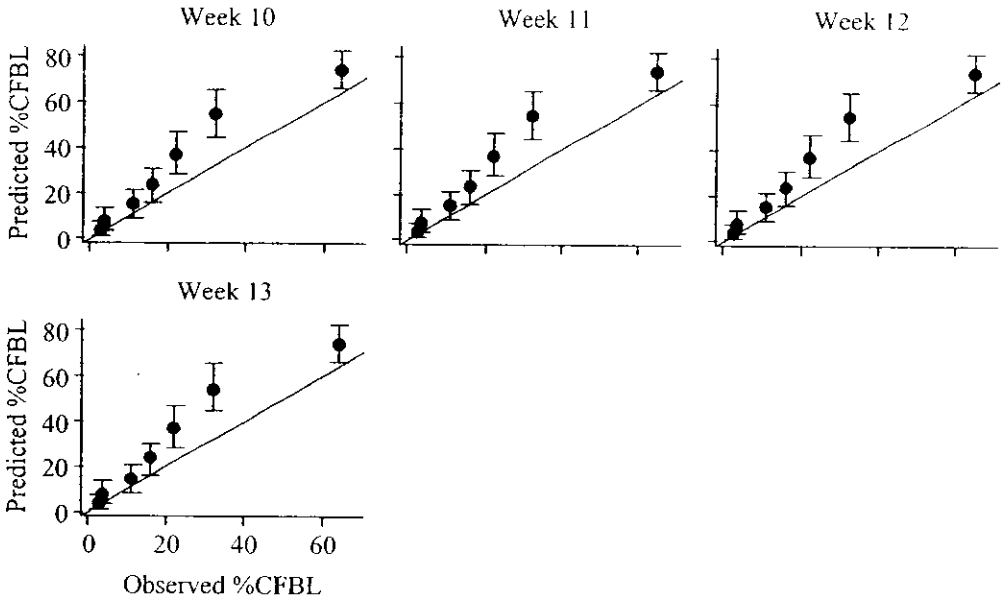
BID Model (Study 196) Prediction of TID Data (Study 045) – External PPC

Type 2B: Concordance Plot of Predicted Versus Observed Percentage of Patients (%Change in Pain Score) by Week and Treatment Group

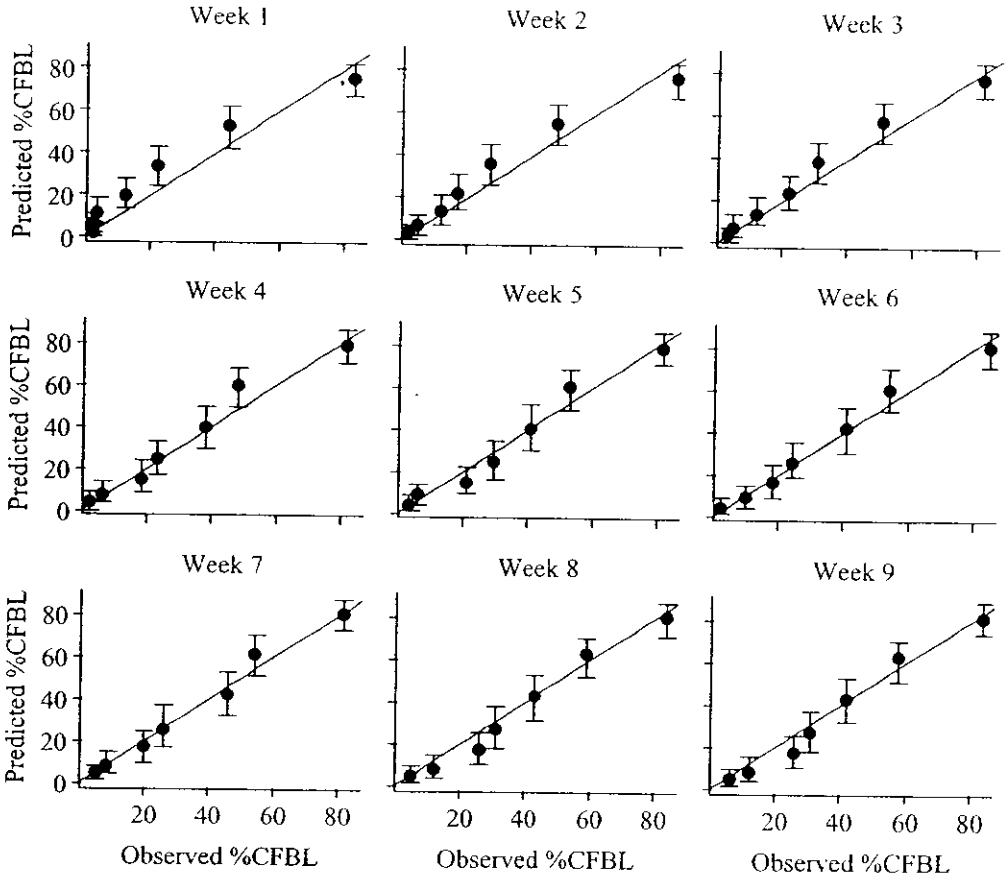
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

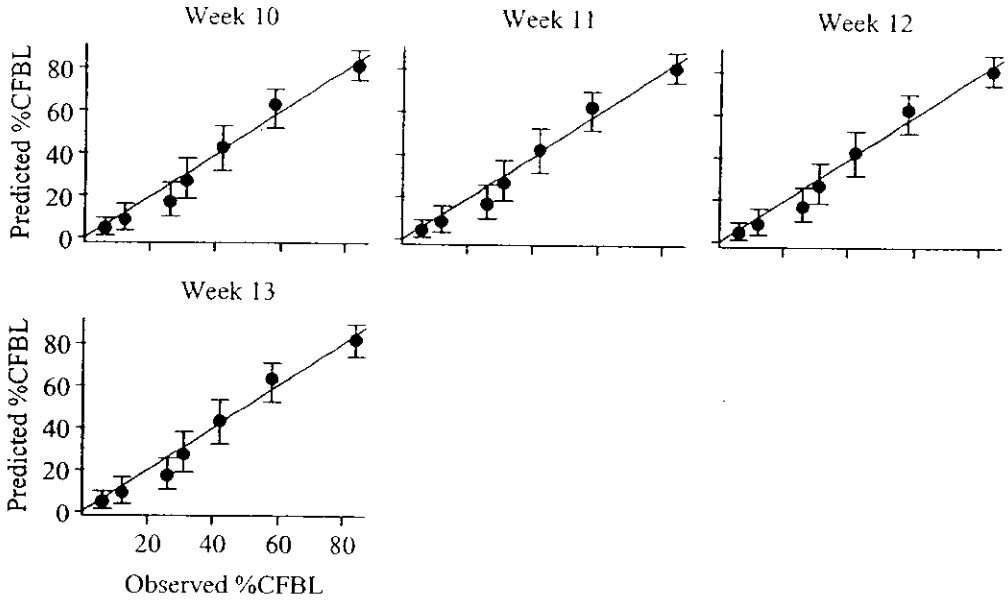
Placebo


Week 10
Week 11
Week 12
Week 13
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

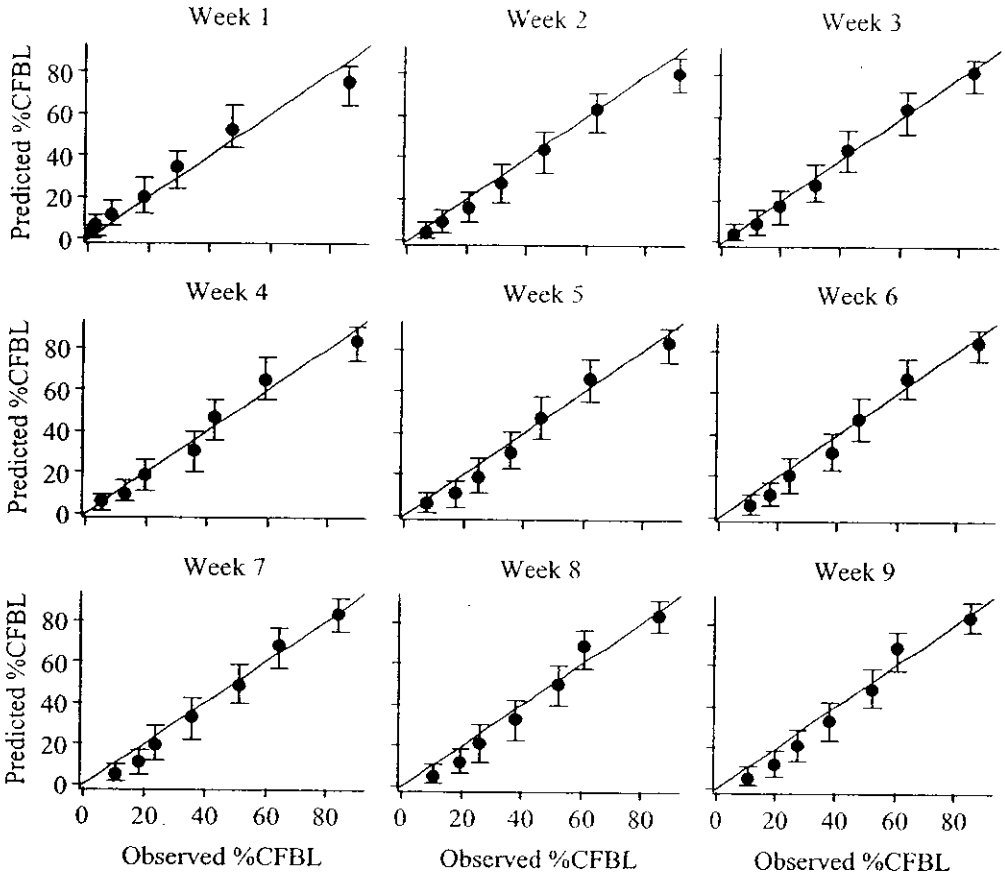
150 mg/Day TID



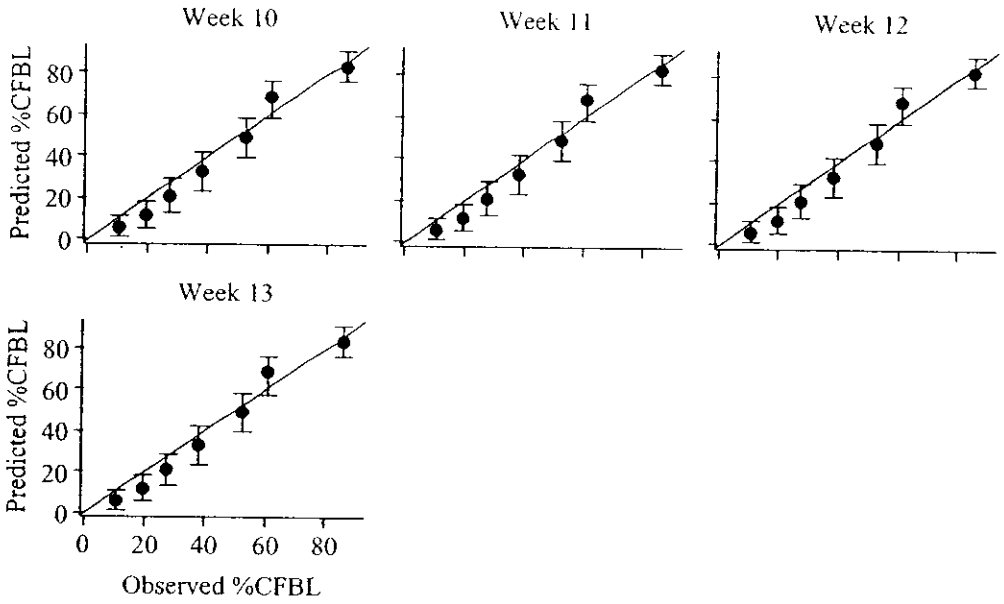
150 mg/Day TID



300 mg/Day TID



300 mg/Day TID

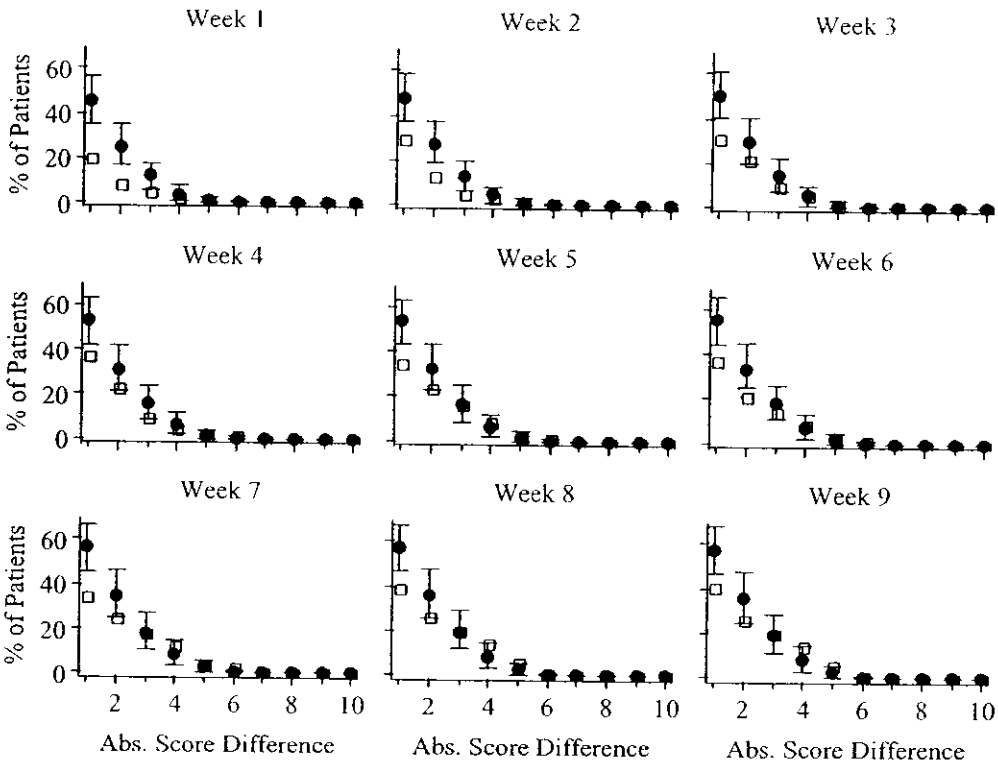


Attachment A.3

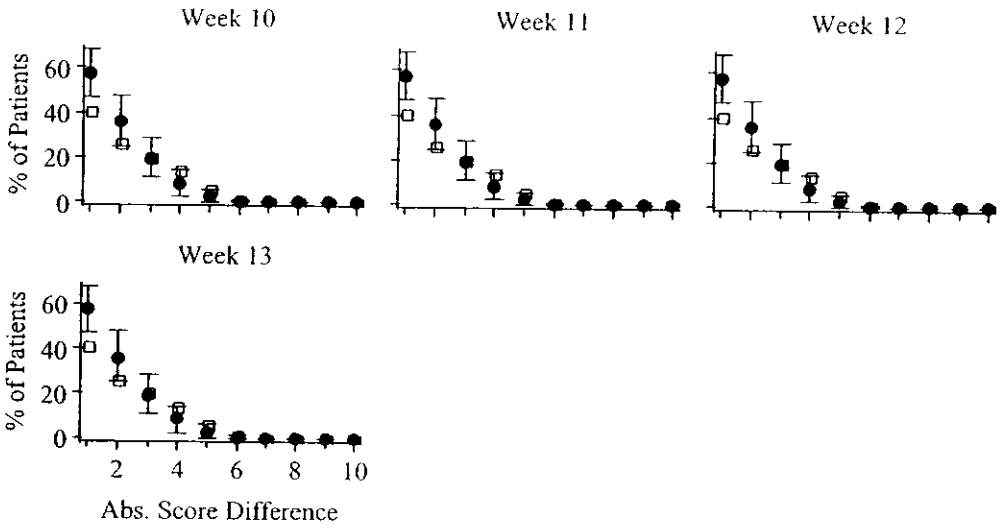
BID Model (Study 196) Prediction of TID Data (Study 127) – External PPC

Type 1A: Percentage of Patients Versus ΔScore by Week and Treatment Group

Placebo

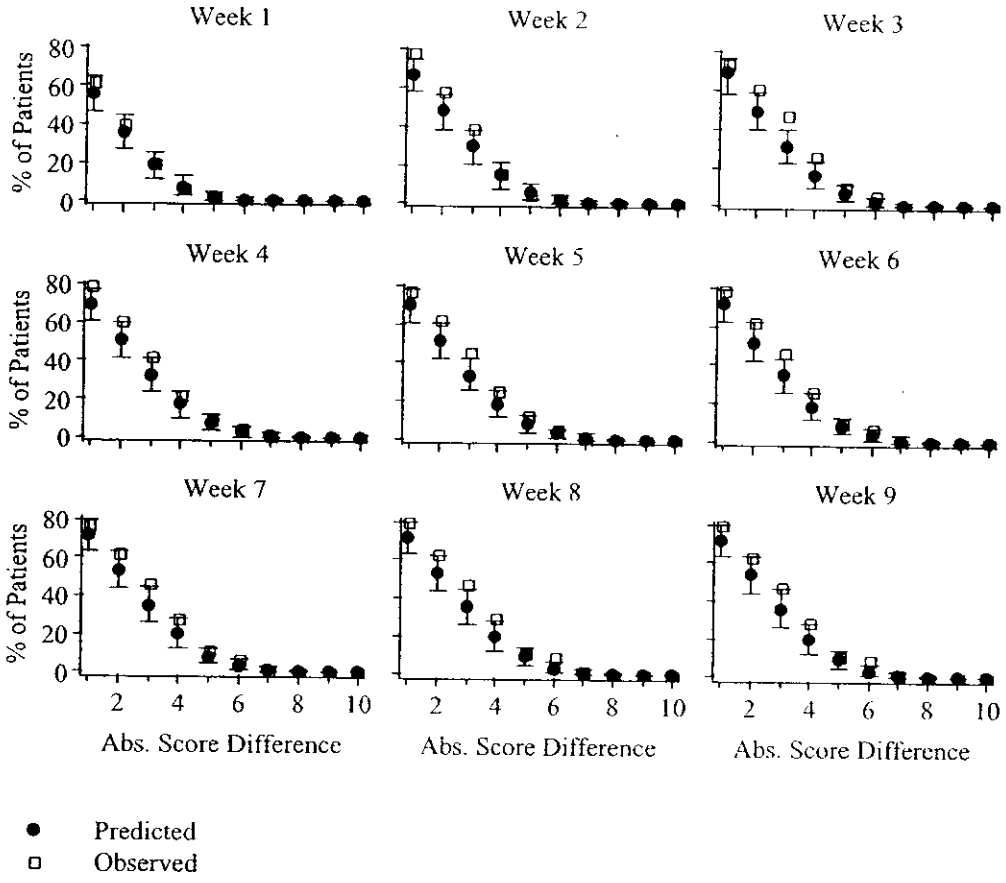

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
2
4
6
8
10
Abs. Score Difference
Predicted
Observed

Placebo

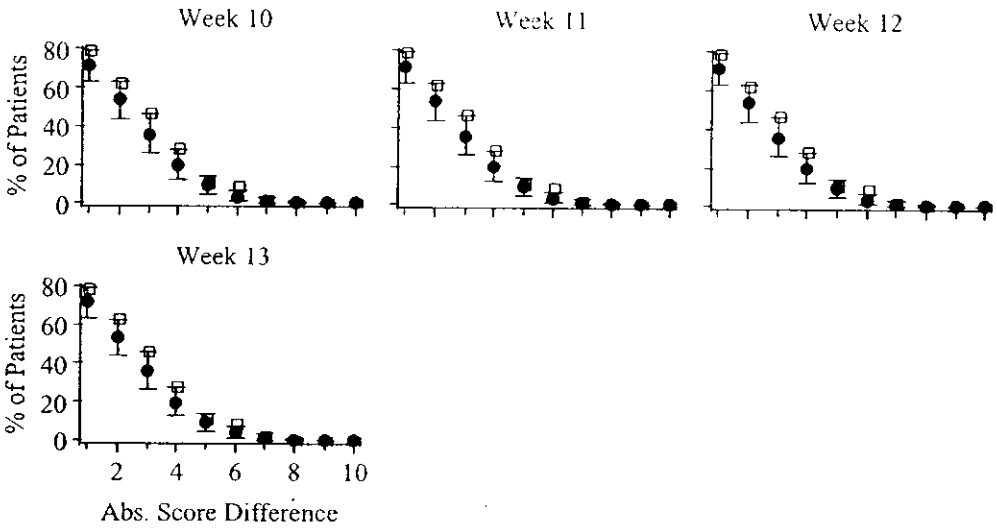


● Predicted
□ Observed

300/600 mg/Day TID



300/600 mg/Day TID



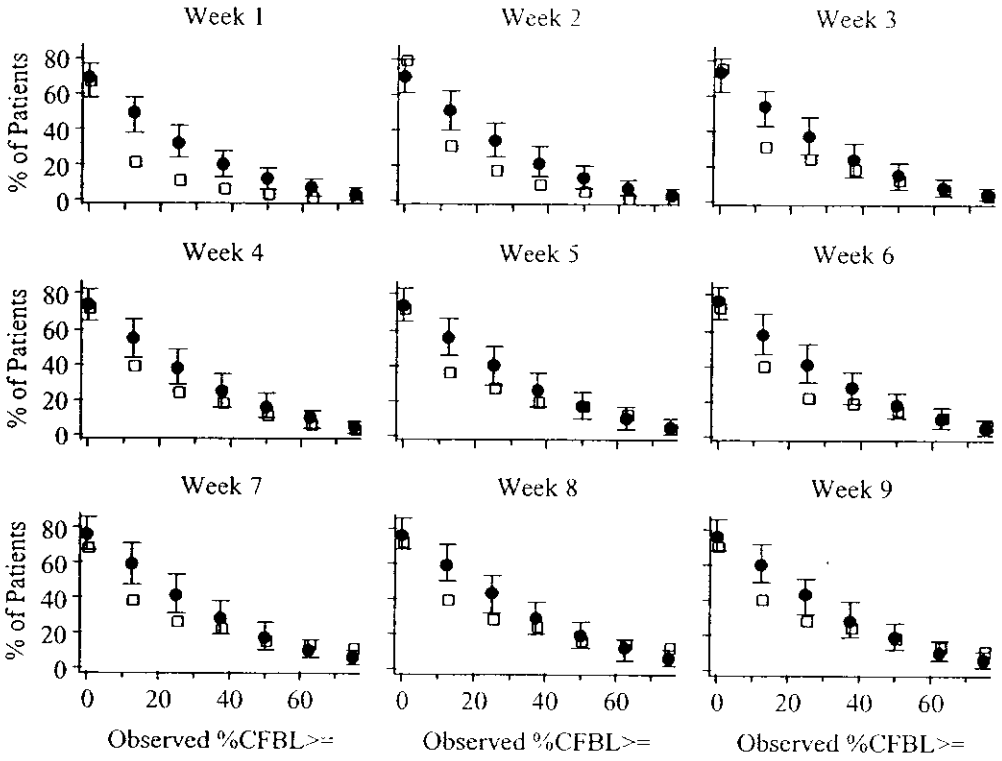
● Predicted
□ Observed

Attachment A.3

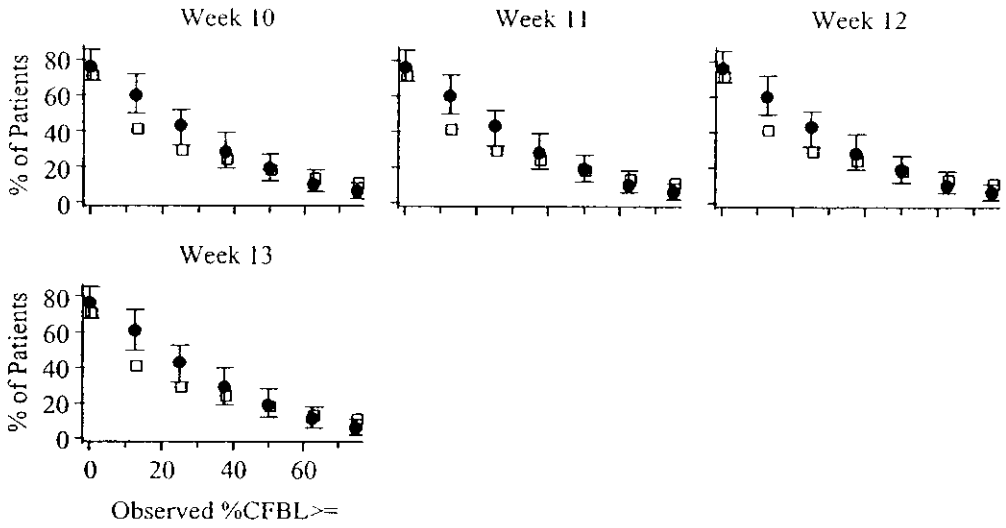
BID Model (Study 196) Prediction of TID Data (Study 127) – External PPC

Type 2A: Percentage of Patients Versus %Change in Pain Score by Week and Treatment Group

Placebo

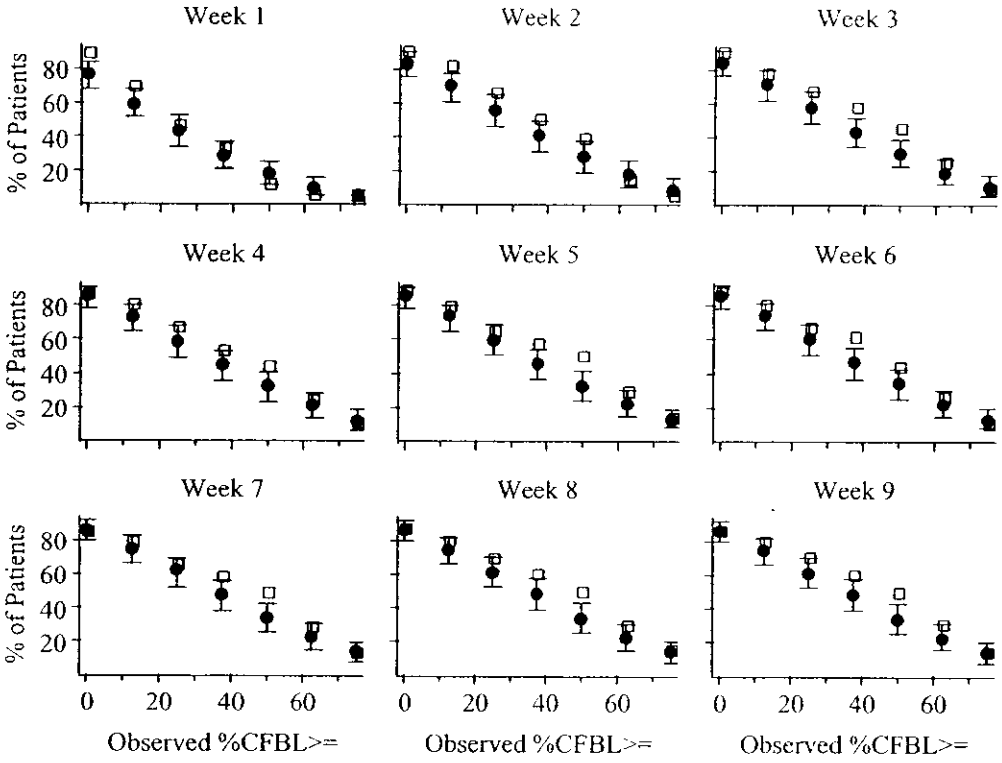

Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
% of Patients
0
20
40
60
80
Observed %CFBL>=
Predicted
Observed

Placebo

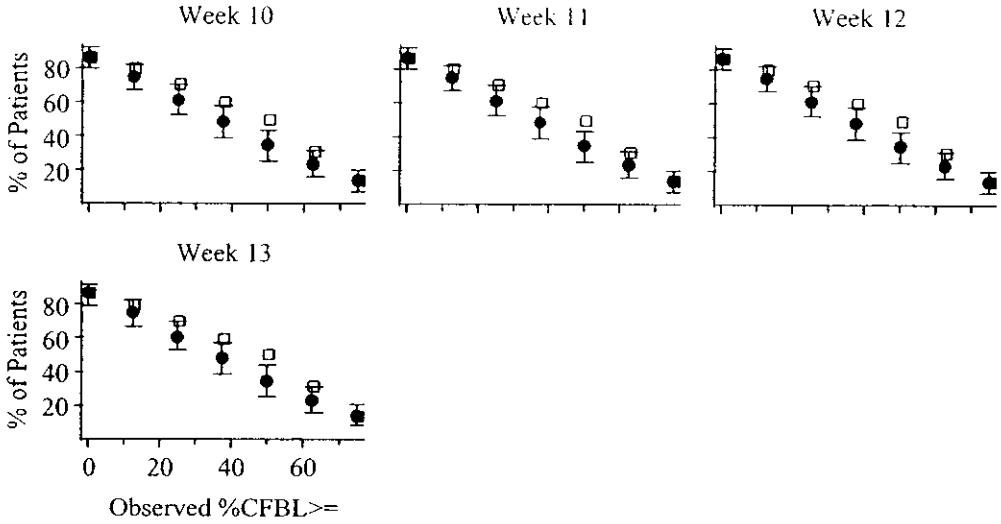


● Predicted
□ Observed

300/600 mg/Day TID



300/600 mg/Day TID



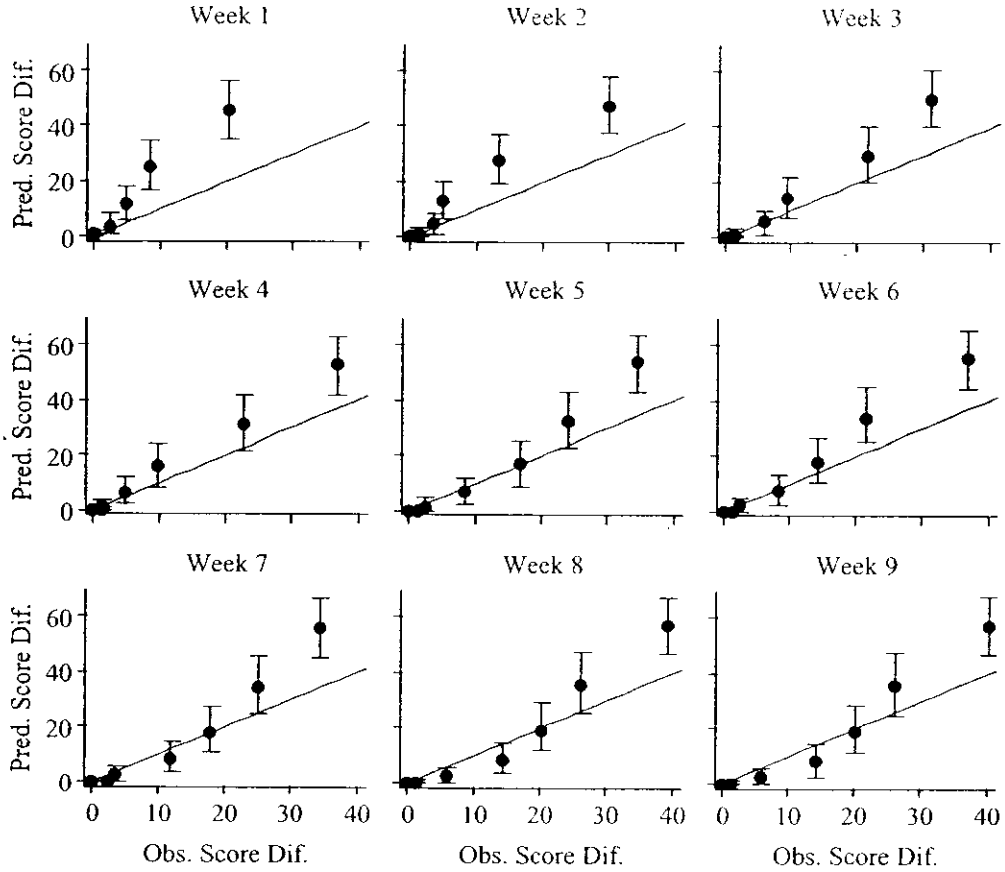
● Predicted
□ Observed

Attachment A.3

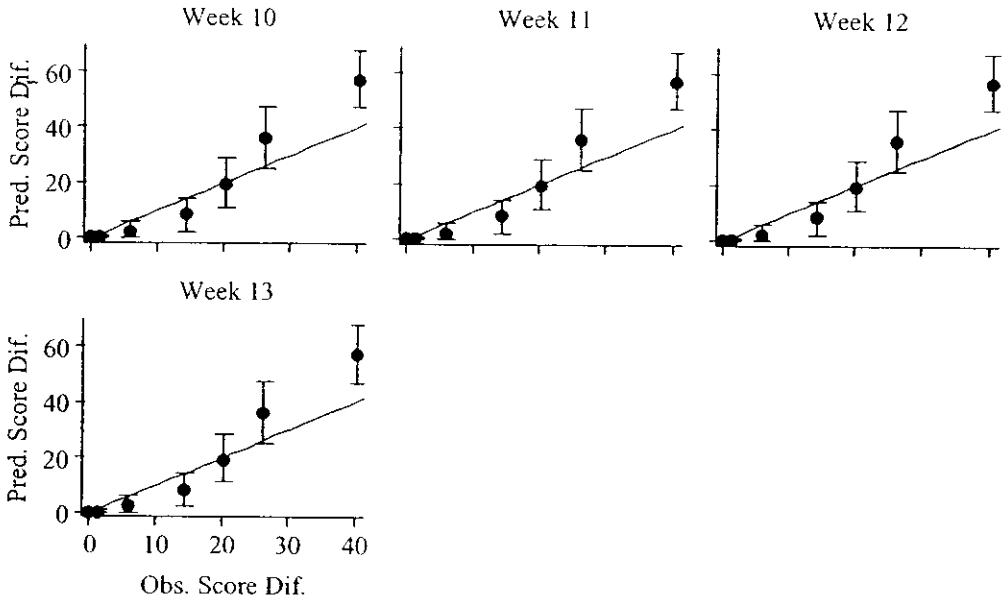
BID Model (Study 196) Prediction of TID Data (Study 127) – External PPC

Type 1B: Concordance Plots of Predicted Versus Observed Percentage of Patients (ΔScore) by Week and Treatment Group

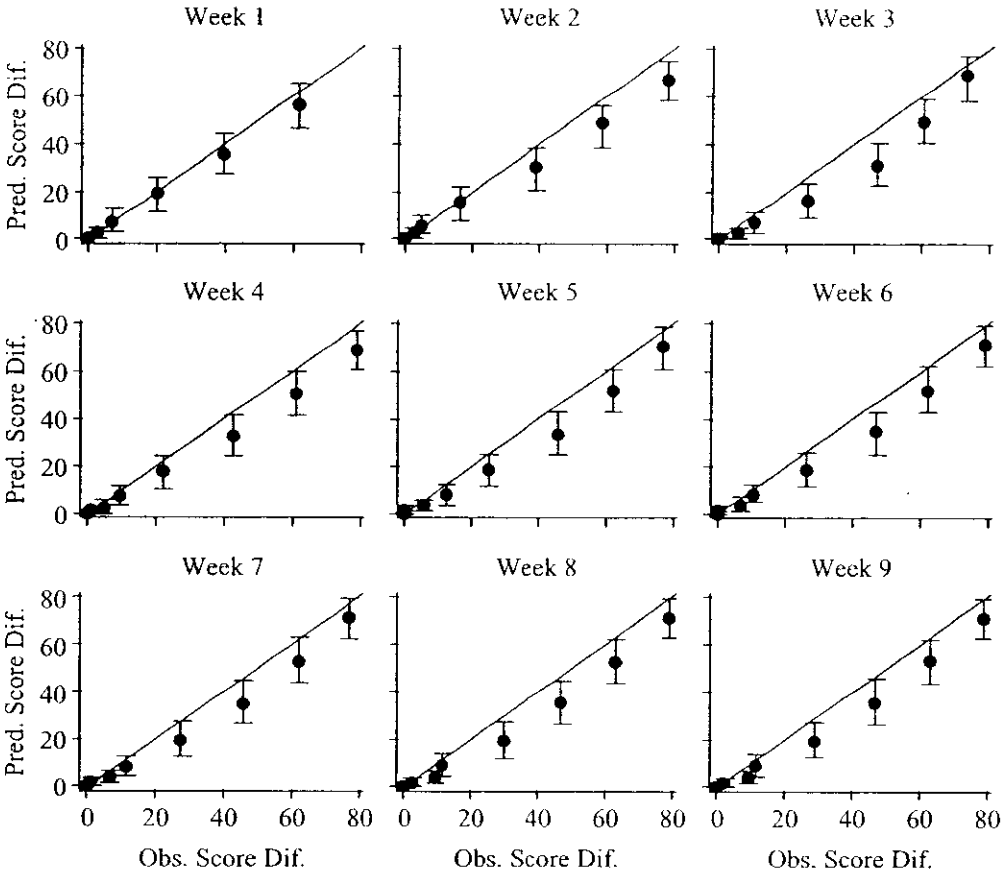
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30
40

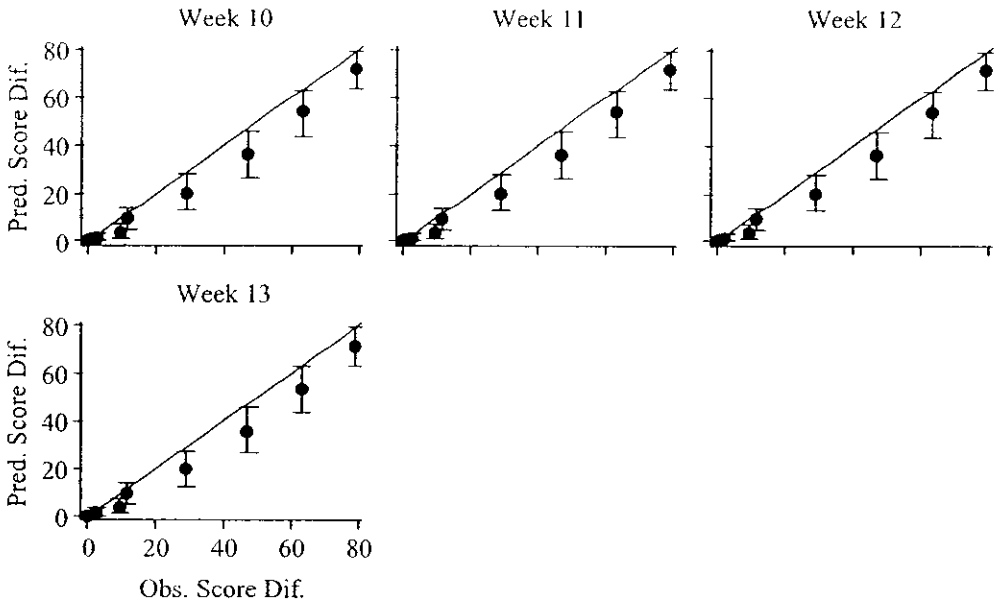
Placebo


Week 10
Week 11
Week 12
Week 13
Pred. Score Dif.
Obs. Score Dif.
0
20
40
60
0
10
20
30
40

300/600 mg/Day TID



300/600 mg/Day TID

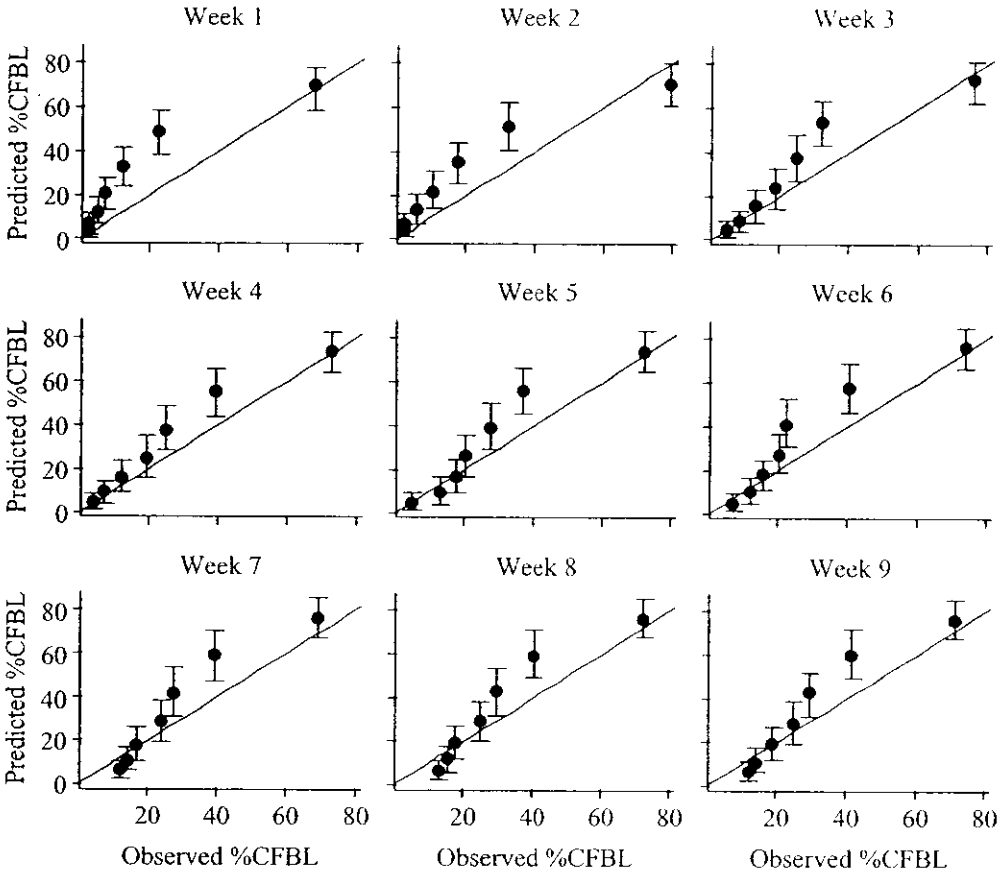


Attachment A.3

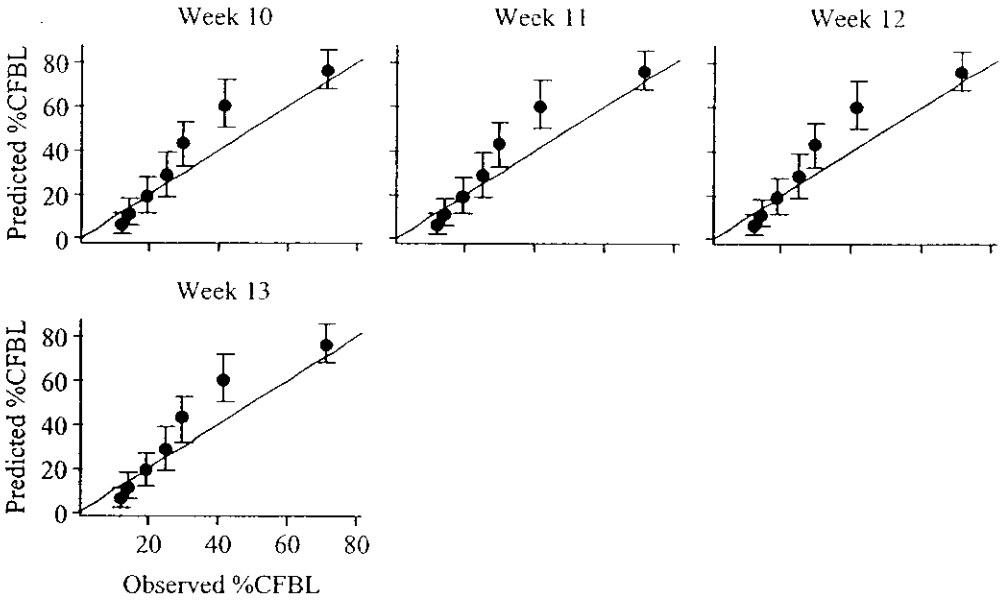
BID Model (Study 196) Prediction of TID Data (Study 127) – External PPC

Type 2B: Concordance Plots of Predicted Versus Observed Percentage of Patients (%Change in Pain Score) by Week and Treatment Group

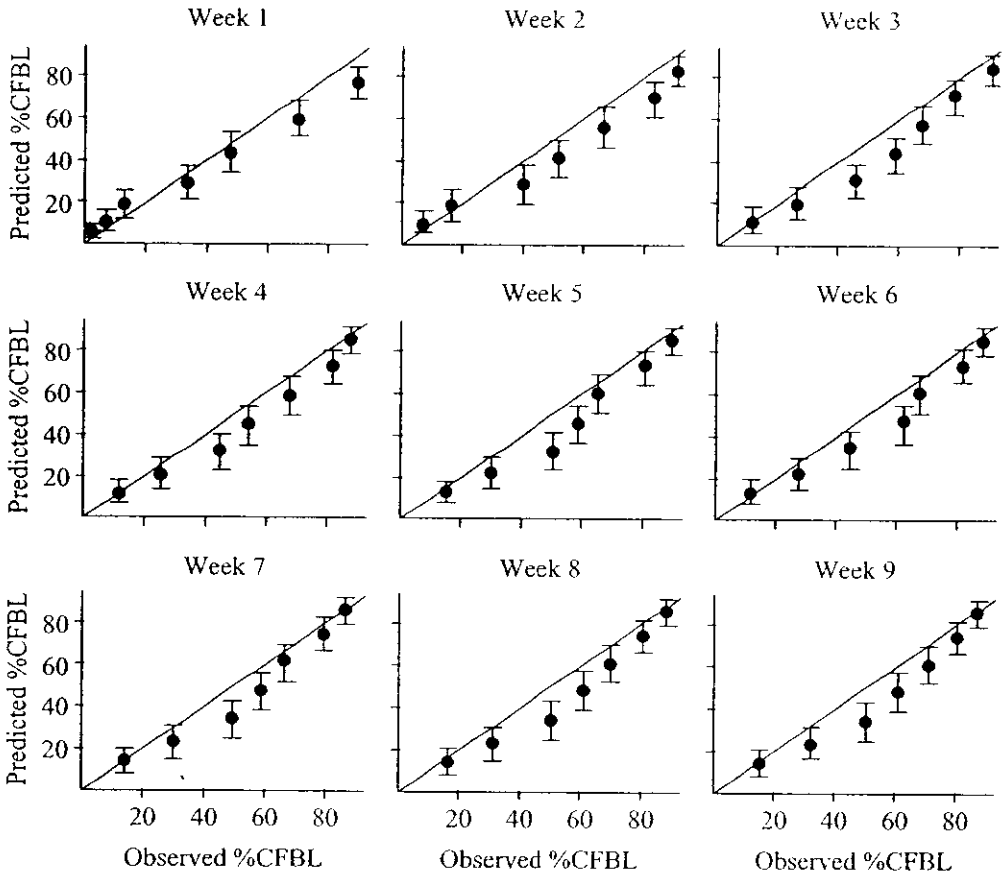
Placebo


Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

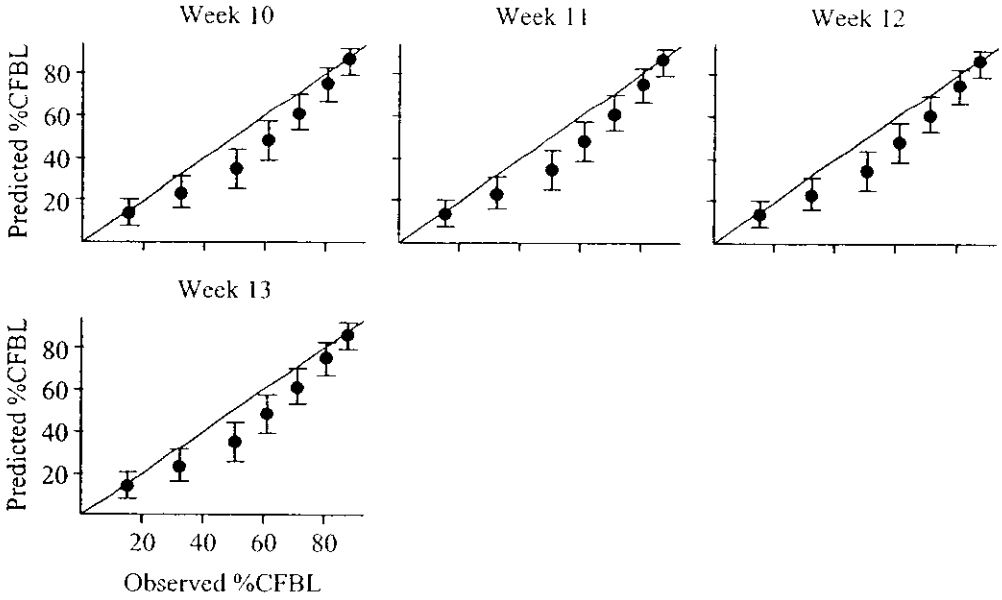
Placebo


Week 10
Week 11
Week 12
Week 13
Predicted %CFBL
Observed %CFBL
0
20
40
60
80

300/600 mg/Day TID



300/600 mg/Day TID



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suresh Doddapaneni
8/31/04 10:21:30 AM
BIOPHARMACEUTICS

Conclusion from Modeling and Simulation Analyses submitted by Pfizer on August 12 is that TID and BID regimens are adequately linked. He Sun has technical problems signing off the review in DFS.