

The Role of Literature-Based Disease Progression Models to Support Knowledge Management and Decision-Making in Clinical Drug Development

Farkad Ezzet

Pharsight Corporation, Mountain View, California

Presented at AAPS National Biotechnology Conference

Toronto, Canada

June 24, 2008

Outline

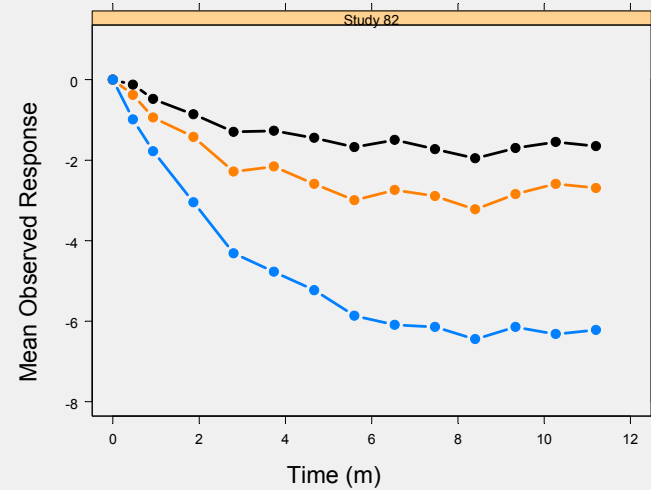
- Why utilize literature data
- A case study: Treatment of Obesity
 - Value of approach
- Issues and limitations
- Safeguards
- Conclusions

Literature Data (definition)

Data collected from publically available literature (scientific Journals + SBA's)

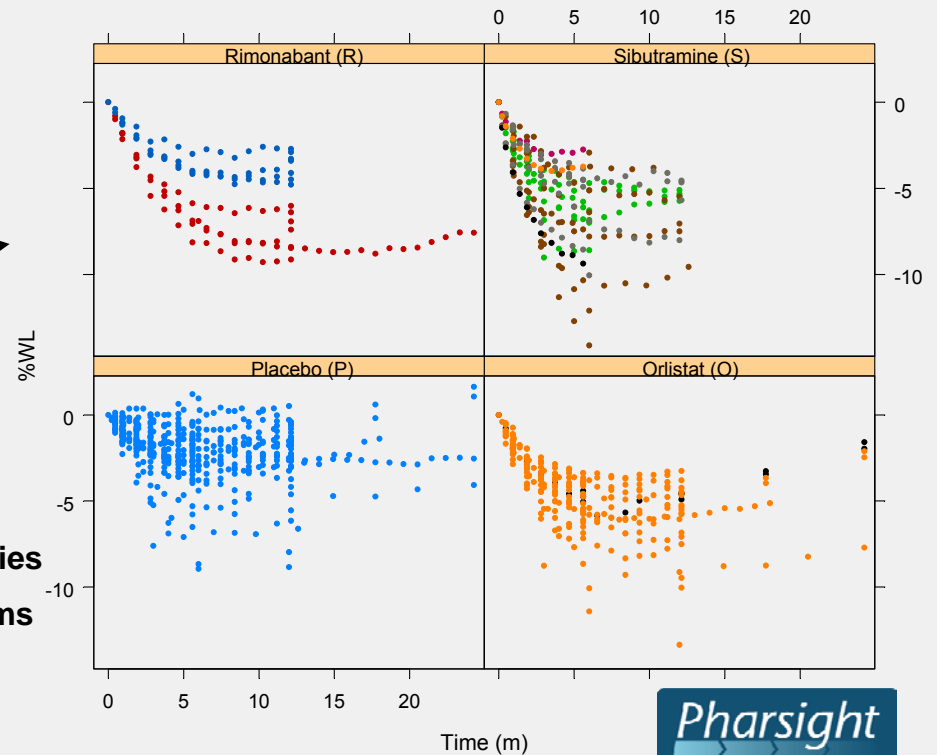
Typically a publication provides:

- Clinical response from a single study under one or more treatment arms
- Response is expressed as a summary measure (e.g. mean)
- Over time (visit)



The combined data from such publications constitute a Database.

Example: %Weight Loss vs. time for a number of treatments



Why Model Literature Data?

Informative: provides a quantitative description of

- Disease/Disease progression
- Competitive landscape: to set realistic goals
- Placebo response: a lower benchmark
- Degree of inter-trial variability



Useful for compounds currently in early development: providing a **Base model**

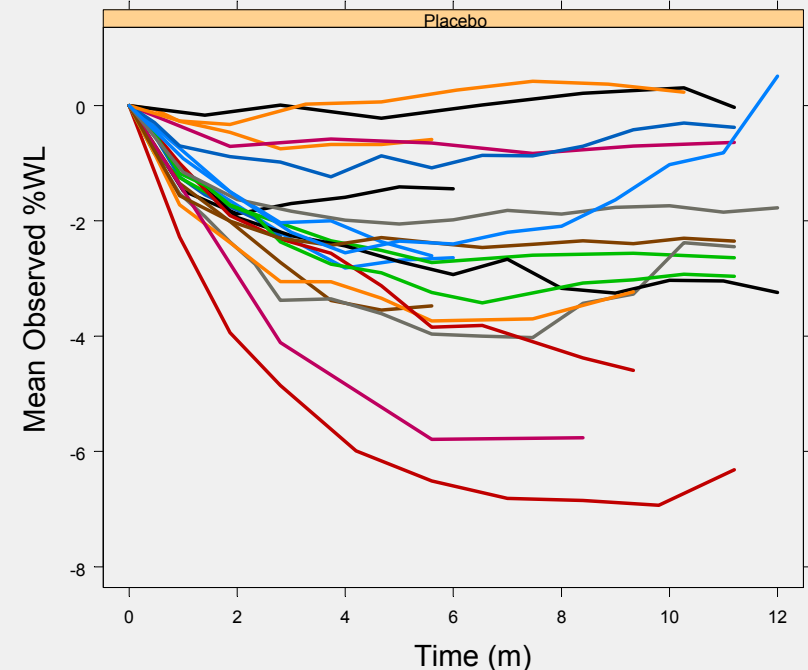
- To make use of limited data (e.g. 3 month data)
- To make projections of alternative scenarios (subpopulations, dosage strength, regimens, etc.)

Useful for compounds at pre-clinical stage

- Especially in situations with similar animal to human models (compare **projections from animal model** with literature data)

Cost effective: High return on Investment

Placebo response in obesity trials (N=21)



Steps for Literature Base modeling

Identify drugs/endpoints/population of interest

Construction of Database

- Define inclusion exclusion criteria of publications/studies
- Placebo controlled (randomized double blind)
- Size and duration of study
- Dosing strategy (fixed vs. flexible)
- Etc.

Brian Corrigan et al, ACOP 2008, Standardization of Data Collection for Literature Based Meta-Analyses: The Literature Information and Knowledge Explorer (LIKE) Initiative

Modeling

Model Validation

Simulation/Projection

Modeling Literature data

Experimental unit: Study

Observations: Response in each study arm

i.e. arm within study, thus, a hierarchical model

Requiring a mixed effect model

$$\begin{aligned} \text{Response} &= f(\text{Disease}, \text{Placebo}, \text{Drug}, \text{Patient Characteristics}, \text{Study Design}, \text{Time}) + \varepsilon \\ &= f(\Phi, \text{Time}) + \varepsilon \end{aligned}$$

If multiple time points, may consider

$$f = g(\Phi) \frac{\text{Time}}{\text{Time} + ET_{50}}$$

i. $\text{Drug} = \alpha$

ii. $\text{Drug} = \alpha + \beta \cdot \text{Dose}^\nu$

iii. $\text{Drug} = EMAXD \frac{\text{Dose}^\tau}{ED_{50}^\tau + \text{Dose}^\tau}$

A case study in treatment of Obesity

Sibutramine (S) and Orlistat (O) and rimonabant (R) are treatment options for obesity and have been studied in weight loss (WL) trials of up to 2 years duration.

ASCPT 2008: Karthik Venkatakrishnan^a, Farkad Ezzet^b, Patanjali Ravva^a, Thomas G. Tensfeldt^a, Vincent Fung-Sing Chow^a, Robert Chew^a, Todd Barbee^b, Roman V. Dvorak^a, Ann E. Taylor^a, John D. Obourn^a and Lisa J. Benincosa^a

Objective: describe the time course and dose-effect relationships for WL by these drugs using literature data

Data

- Publicly available scientific and medical literature
- Data included only summary measures e.g. means (or medians) of WL, often at monthly visits. Both types of data Observed Cases (OC) and Last Observation Carried Forward (LOCF) were used
- Only randomized placebo controlled double blind studies with fixed dosing regimens were included
- Covariate data investigated included study design factors such as intensity of diet and exercise and patient demographics (including diabetic vs. non-diabetic)

Weight Loss (W) was described as an Emax model incorporating drug effect, covariates and random study effect

$$W_{ijt} = - (W_{P,K} + DE_i + \beta X_{ij} + \eta_{1j}) \times \frac{t}{t + (ET_{50,i} + \eta_{2j})} + (\theta_{regain,i} \times Time) + \varepsilon_{ijt}$$

W_{ijt} is observed mean % weight (CFB) under ith treatment in the jth study at time t

$W_{P,K}$ is maximal % weight (CFB) under placebo (P), where $K = OC$ or $LOCF$

DE_i is drug effect under ith treatment

X_{ij} is covariate vector of the ith treatment in the jth study

β is the coefficient of X_{ij}

$ET_{50,i}$ is the time to reach 50% of combined placebo, drug and covariate effects of ith treatment

$\theta_{regain,i} = \theta_{regain,P} + \delta_i$ is regain in % weight per month for ith treatment, $i = O, R, \text{ or } S$

η_{1j} and η_{2j} are random effects of the jth study, $\eta_{kj} \sim N(0, \sigma_{\eta,k}^2), k = 1, 2$

ε_{ijt} is residual error of the ith treatment in the jth study at time t , $\varepsilon_{ijt} \sim N(0, \sigma_{\varepsilon}^2)$

* Model was fitted using nlme, Splus ® 8.0 for Windows

Drug effect (DE) was Linear for O and R and non-linear for S
 ET_{50} was different for O and S than that of placebo

$$DE_O = \phi_O \times \lambda_O^{I_{diabetes}} \times dose_O$$

$$DE_R = \phi_R \times \lambda_R^{I_{diabetes}} \times dose_R$$

$$DE_S = (\phi_S \times \lambda_S^{I_{diabetes}}) \times \frac{dose_S}{ED_{50} + dose_S}, \phi_S \text{ is thus maximal Sibutramine effect}$$

$I_{diabetes} = 0$ if non-diabetics & 1 if diabetics

$\lambda > 1$ (< 1) represents an increase (decrease) in drug effect in diabetics

$$ET_{50,O} = ET_{50,P} \times \tau_O$$

$$ET_{50,R} = ET_{50,P}$$

$$ET_{50,S} = ET_{50,P} \times \tau_S$$

$\tau > 1$ (< 1) represents an increase (decrease) in ET_{50} over that of Placebo

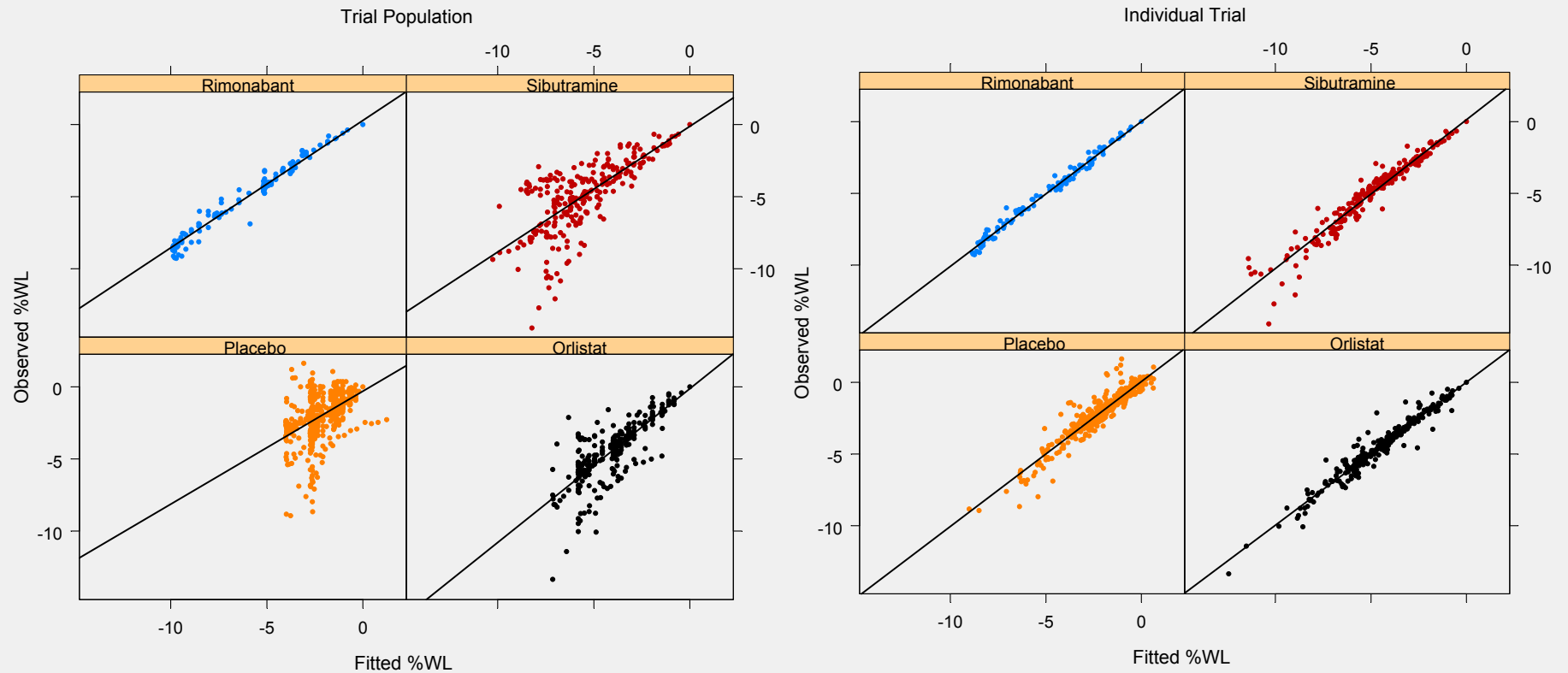
The NLME (Splus) has flexibility in defining different model for each treatment

```
f.Wt <- nlme( Wt.PCFB * sqrt(n) ~ sqrt(n)* (
(GN == "Placebo" ) * (plb( time, 0, S.emax + BLWt ... )+
(GN == "Orlistat" ) * (plb( time, 0, S.emax + BLWt ... )+
(GN == "Sibutramine" ) * (plb( time, 0, S.emax + BLWt ... )+
(GN == "Rimonabant" ) * (plb( time, 0, BLWt ... ))),
data=Wt.Gd,
random = pdDiag(list ( S.emax ~ 1, S.et50 ~ 1)),
fixed = list(emax ~ ep.obs-1, Pl.beta + beta ~ 1, Pl.et50
+ Or.et50 + Sib.et50 ~1, Or.slope + Sib.demax
+ Sib.ed50 + Rim.slope ~1, diabetes~1,BLWt~1),
start = c(4.7 ,6.5 ,.11, .18, 1.03, 1.3, 1.3, .01, 15,
2.7, .39, -2, .0001),
verbose = T, method="ML")
```

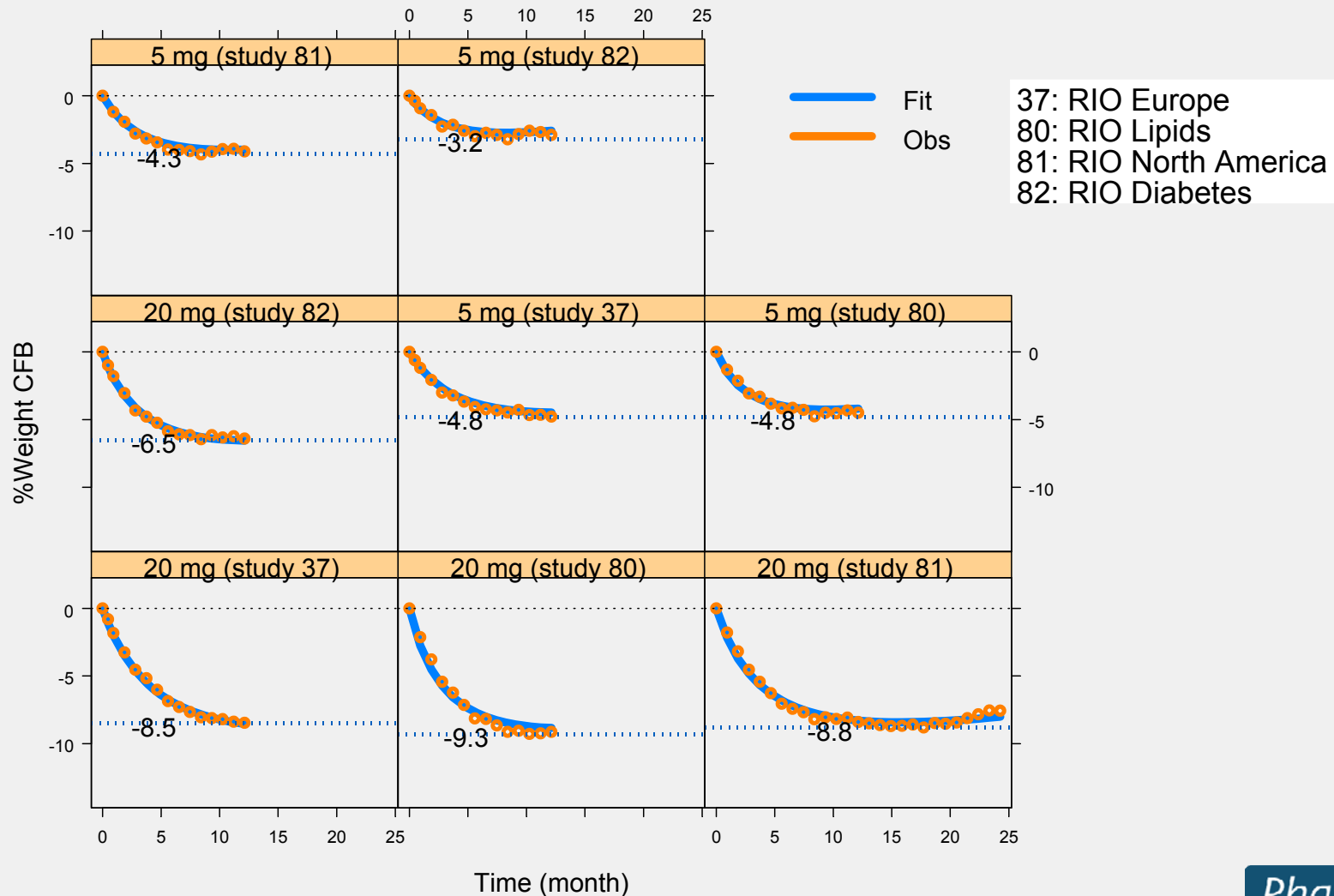
Weight Loss Model Parameter Estimates

Parameter	Estimate	%CV	ITV (σ)
$WL_{P,K}$ (%)			2.4
LOCF	5.3	8	
OC	7.0	6	
Drug effect			
Orlistat			
ϕ_O (%/mg)	0.013	3	
λ_O	0.86	4	
Rimonabant			
ϕ_R (%/mg)	0.401	2	
λ_R	0.88	5	
Sibutramine			
ϕ_S (%)	19.3	11	
λ_S	1.21	6	
ED_{50} (mg)	33	5	
β			
Diabetes (%)	-1.8	39	
$ET_{50,P}$ (month)	3.3	6	1.3
τ_O	1.07	67	
τ_S	0.78	35	
θ_{regain} (%)			
P	0.13	3	
δ (O, R, or S)	0.04	11	
σ_ε	0.46	-	

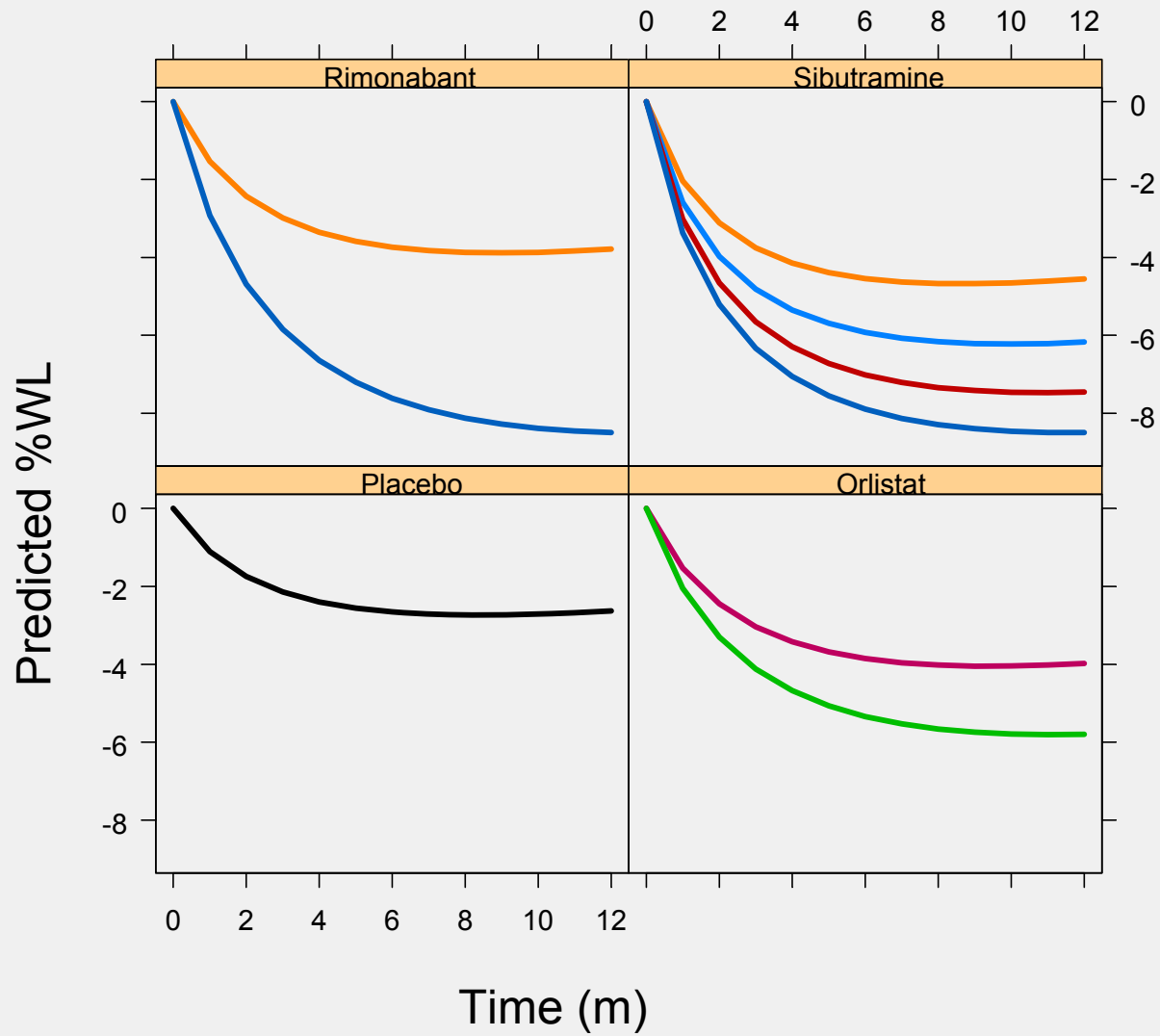
Model Diagnostics: Observed vs. Fitted (population) Observed vs. Fitted (individual trials)



Representative example of observed and fitted %WL using Rimonabant data (OC)

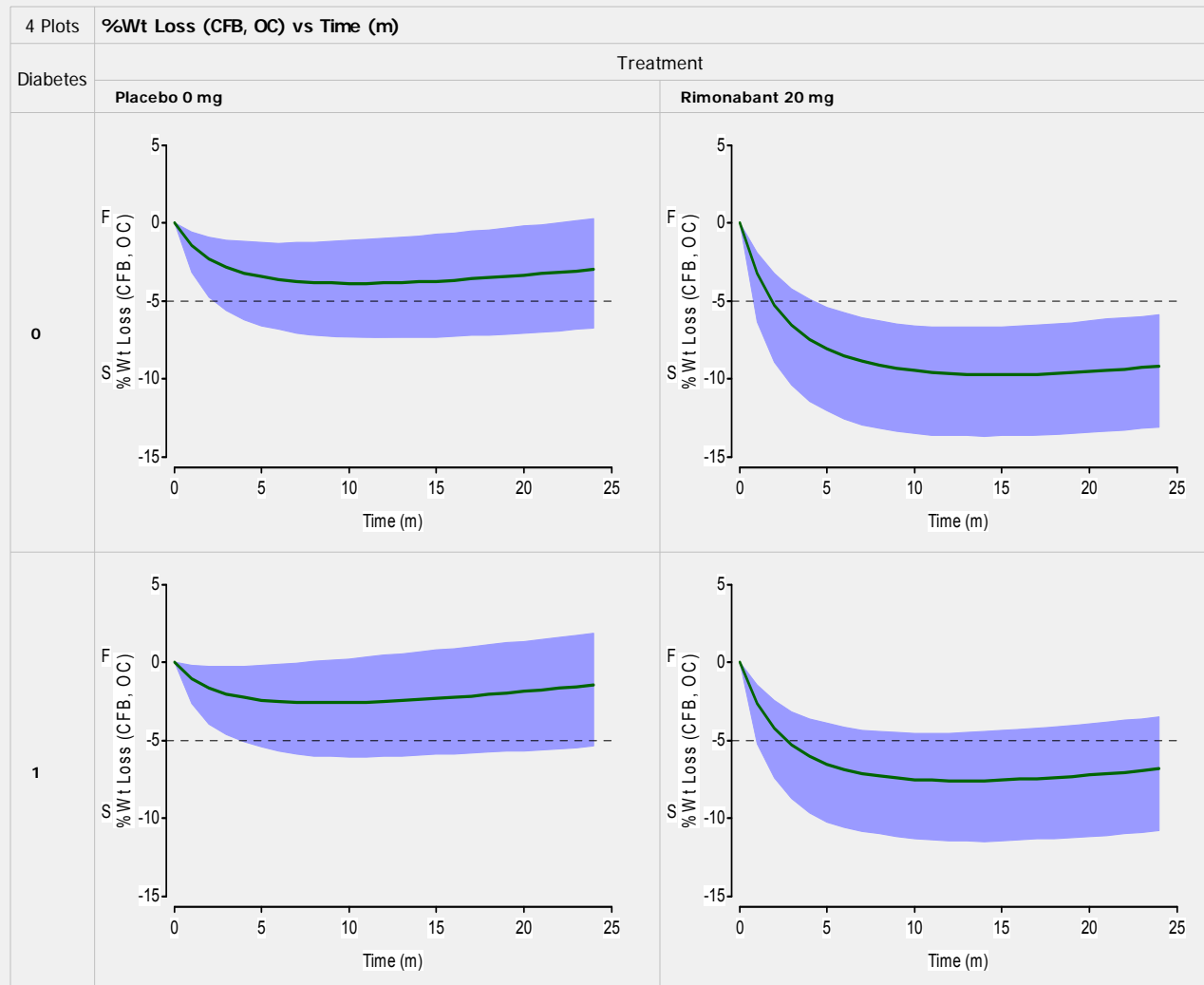


Competitive landscape: Model Predictions provide clarity as to magnitude of difference between treatments/regimens



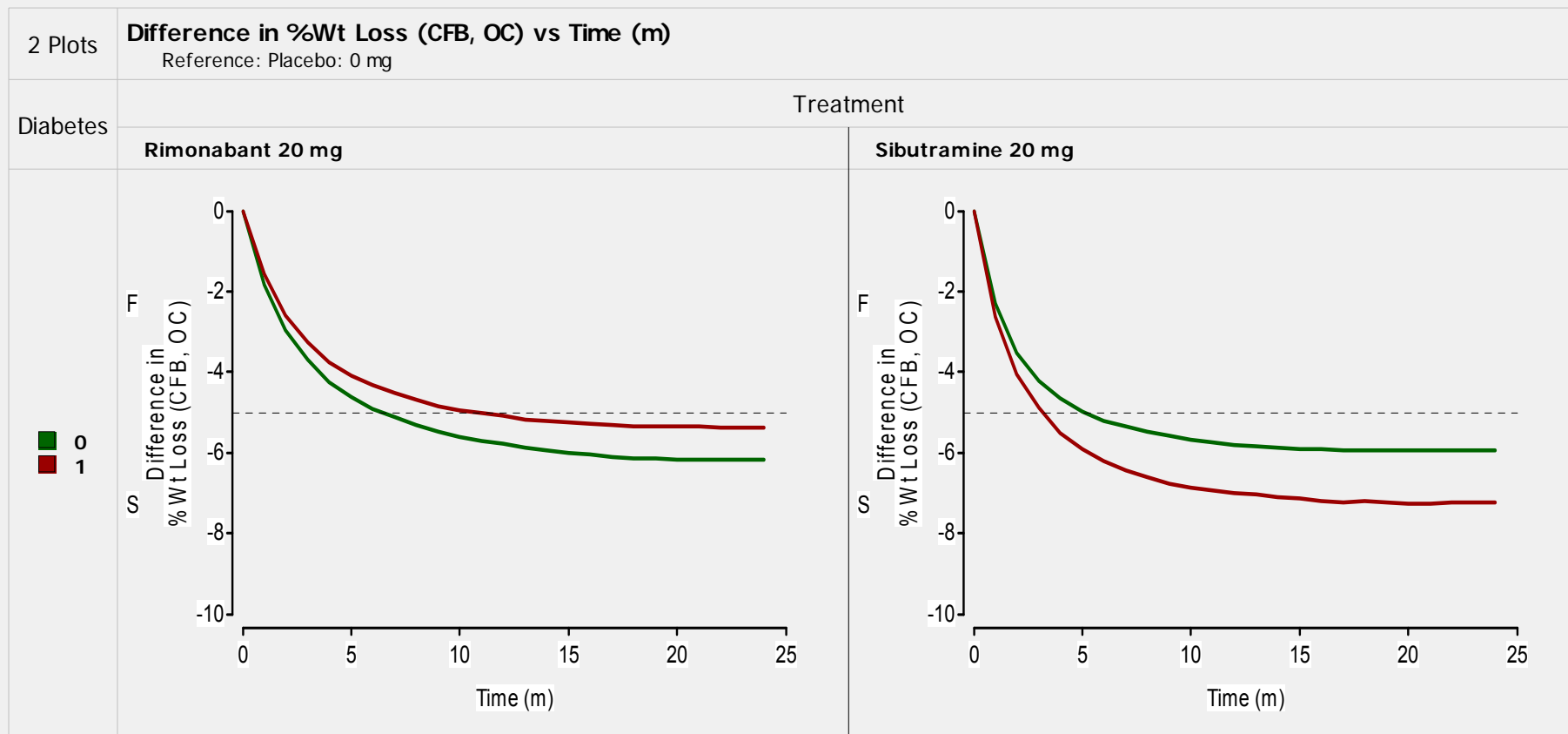
Model Predicted %CFB[†] Weight Loss against time and associated uncertainty for Placebo and Rimonabant (20 mg) in non-diabetics and diabetics

0: non-diabetic
1: diabetic



Powered by DMX®

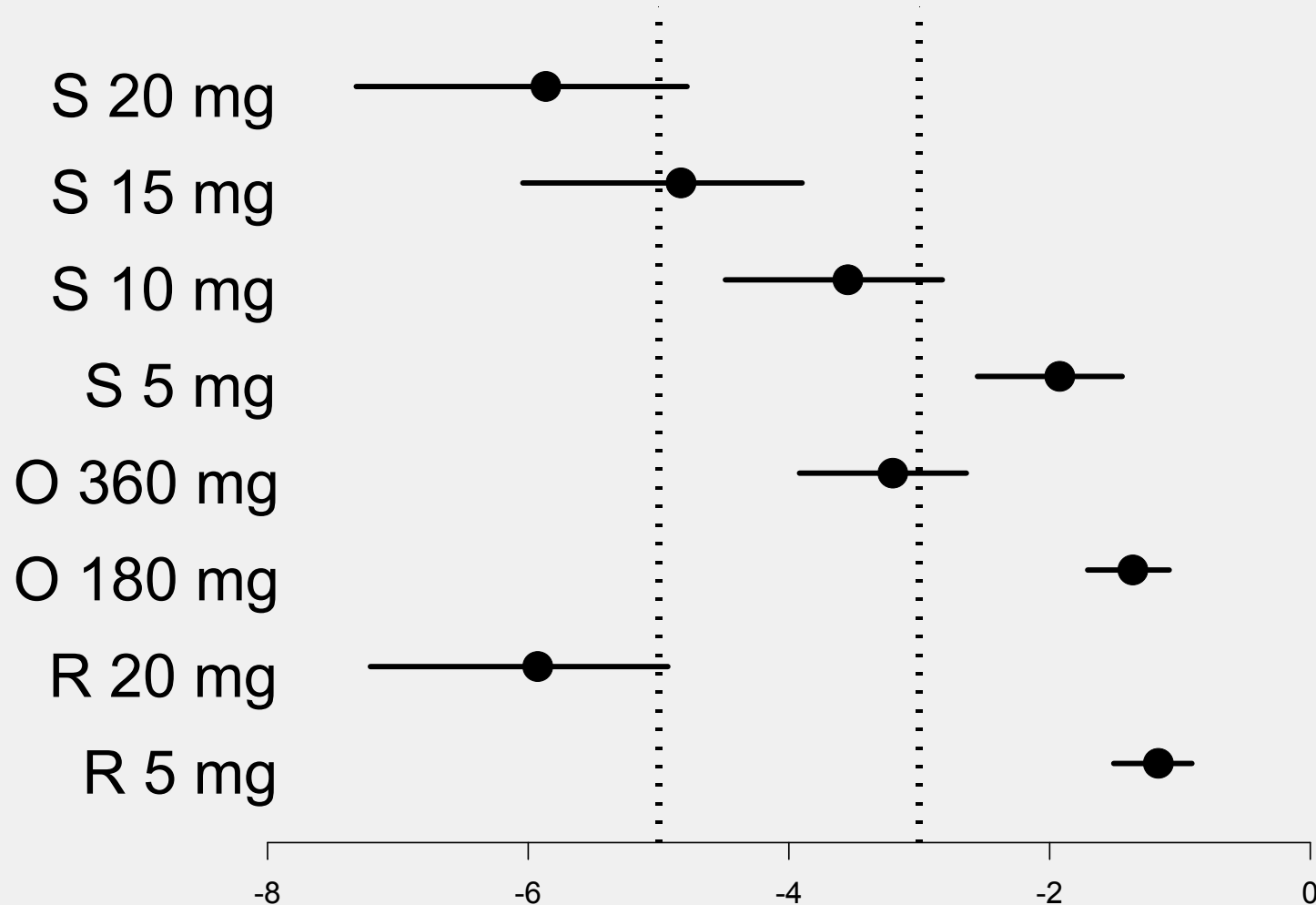
Model Predicted Placebo Subtracted % CFB[†] WL vs. Time in diabetics and non-diabetics for Rimonabant and Sibutramine (20 mg)



Powered by DMX®

0: non-diabetic
1: diabetic

Using model simulations, estimated Mean Placebo Subtracted %WL (95% prediction interval) at 12 months in non-diabetics gives a 6% WL for S and R 20 mg and only 3.2% for O 360 mg



Placebo Subtracted %Weight loss (Non-Diabetics)

© Pharsight Corporation All Rights Reserved



Utility of Literature model for compounds currently in early development

Lorcaserin (Arena Pharmaceuticals) selectively stimulates the 5-HT_{2C} serotonin receptor

Data from a 3-month POC study comparing Lorcaserin with Placebo was published

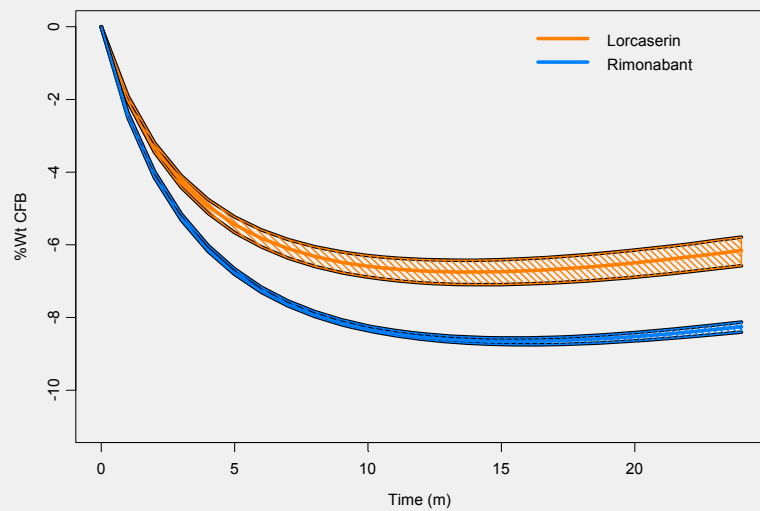
We wish to compare Lorcaserin with Rimonabant (a selective CB1 receptor blocker)

Approach:

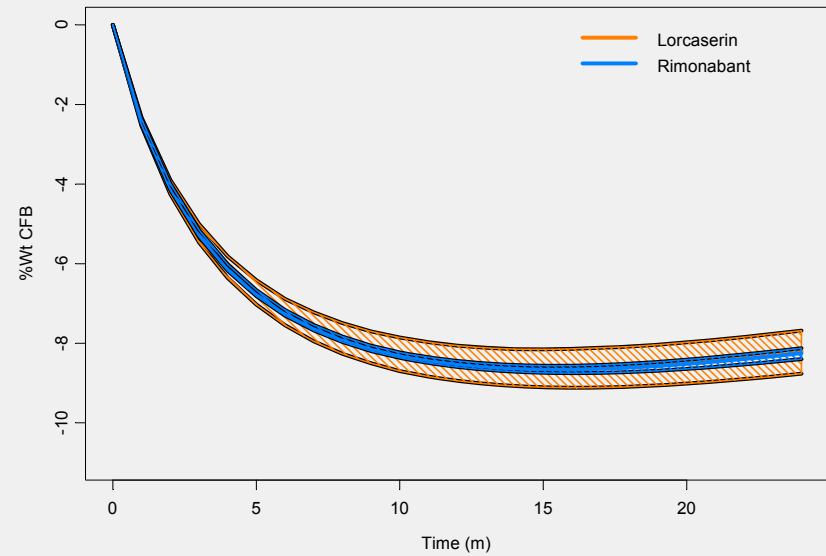
- Add Lorcaserin data to Obesity database
- Re-fit Weight Loss model by adding:
 - $(GN == "Lorcaserin") * (plb(\text{time}, 0, S.\text{emax} + \text{BLWt} \dots))$
- Assuming similar ET50 between Lorcaserin and Rimonabant

Projected response up to 24 months in comparison to 20 mg Rimonabant

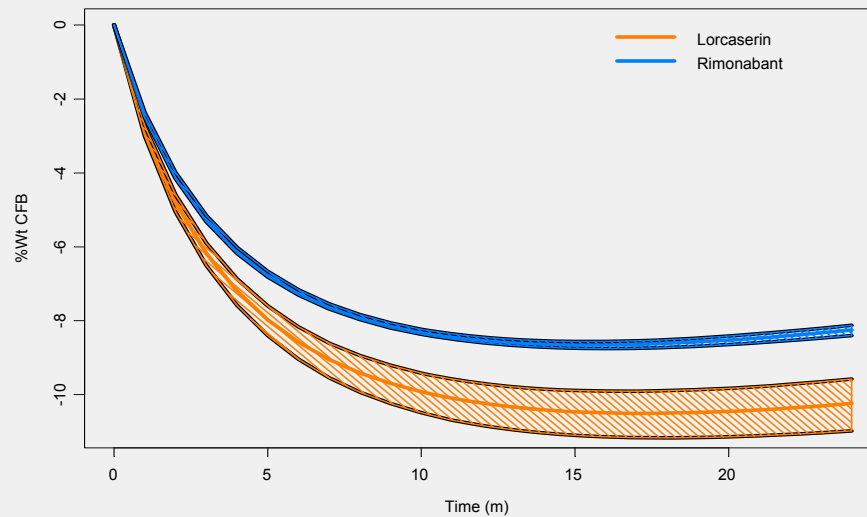
Lorcaserin 10mg vs. Rimonabant 20mg



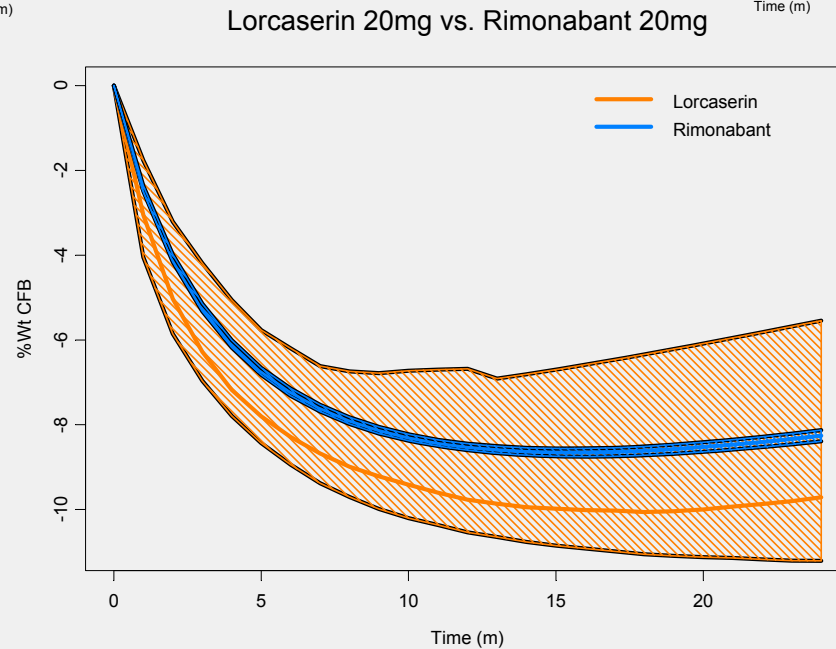
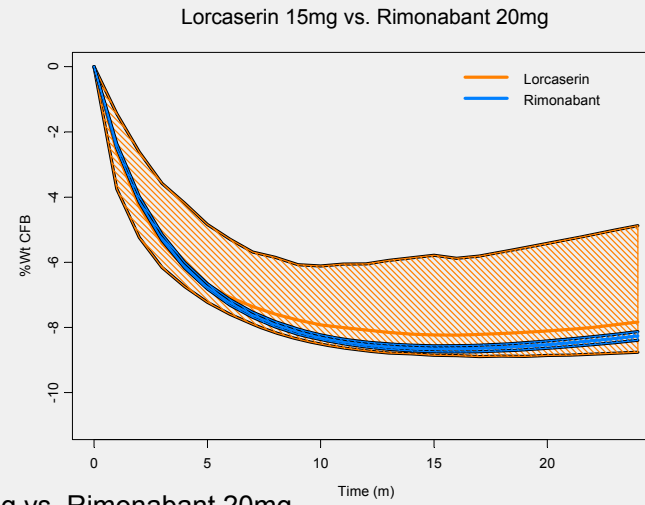
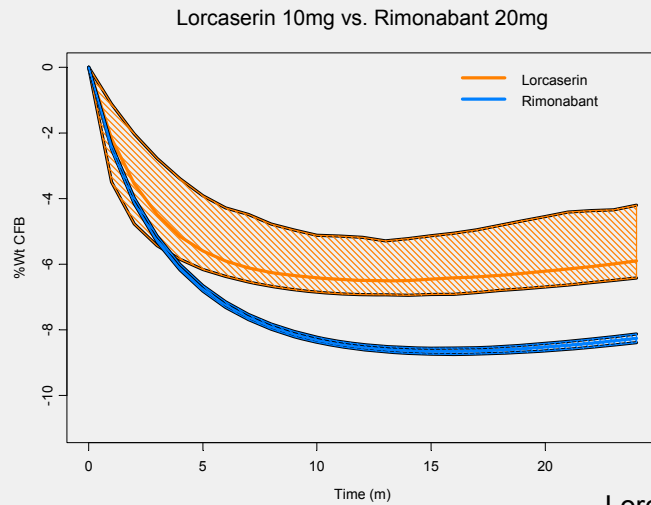
Lorcaserin 15mg vs. Rimonabant 20mg



Lorcaserin 20mg vs. Rimonabant 20mg



However, estimating ET50 from Lorcaserin data alone results in significantly wider prediction intervals



Utility of Literature models for compounds at pre-clinical Stage

Compound: CS-3030 an oral, direct Factor Xa inhibitor in development for the management of thromboembolic diseases

Model Based Development of a Direct Factor Xa Inhibitor (ACCP, 2007)

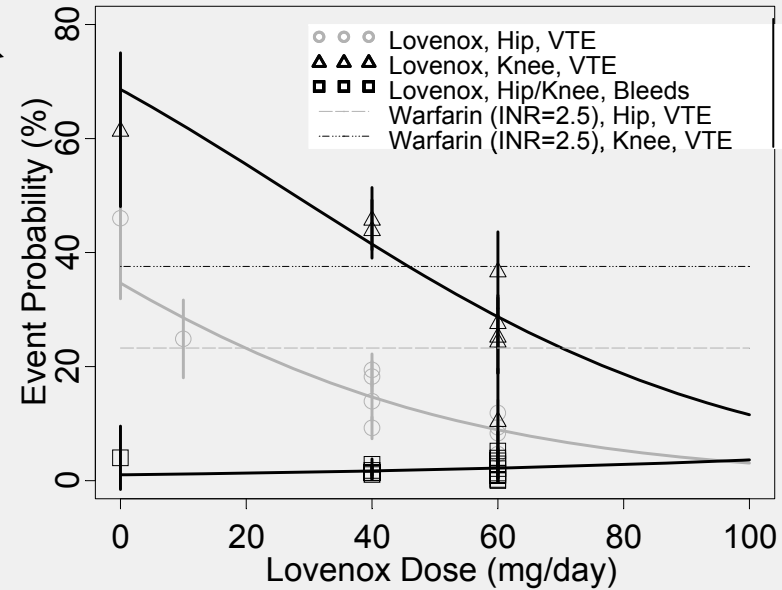
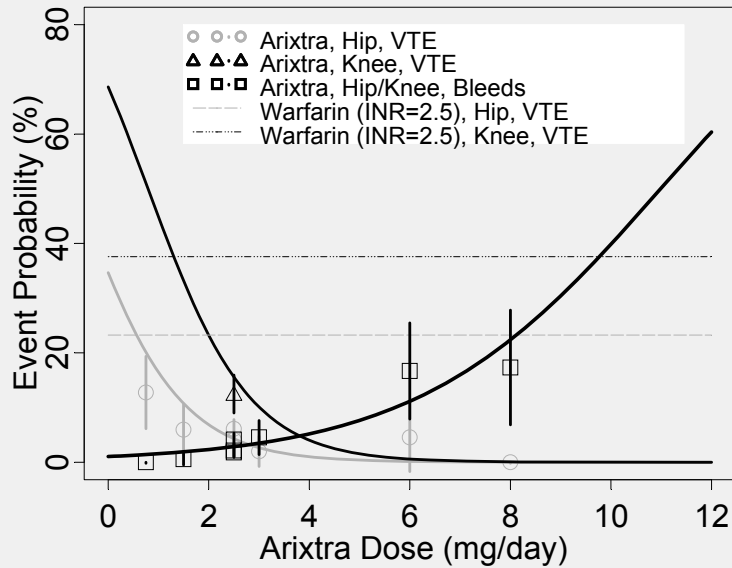
S. Rohatagi, S.J. Haworth, F. Ezzet, H. Kastrissios

Data: Animal PK and animal PD

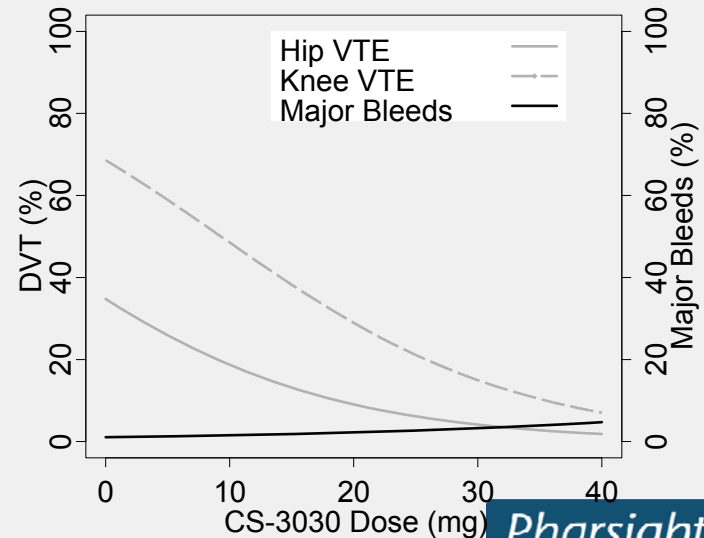
Assumptions: Relative potency of CS-3030 is 3 times that of enoxaparin (Lovenox®) for antiXa activity

Relationship Between Dose and Event Probability

Literature Models



Projected Profile



- Arixtra
 - $P(\text{Hip VTE}) = -0.63 - 0.99 \cdot \text{dose}$
 - $P(\text{Knee VTE}) = -0.78 - 0.99 \cdot \text{dose}$
 - $P(\text{Bleed}) = -0.46 + 0.42 \cdot \text{dose}$
- Lovenox
 - $P(\text{Hip VTE}) = -0.63 - 0.028 \cdot \text{dose}$
 - $P(\text{Knee VTE}) = -0.78 - 0.028 \cdot \text{dose}$
 - $P(\text{Bleed VTE}) = -0.46 + 0.013 \cdot \text{dose}$

Conclusion: doses up to 40 mg/day may provide similar efficacy and safety profiles to that of enoxaparin for doses up to 100 mg/day.

Value of modeling

Integration of animal data and public literature allowed **project human PK-PD** under plausible assumptions and scenarios

Human projections for CS-3030 **identified dosing regimens** for similar efficacy and safety profiles to that of comparators

Allowed to **optimize the Phase I program** to reduce uncertainty and test assumptions such as bioavailability and variability

Estimate the likely quality of Phase II dose-response

Quantify the **effect of covariates** (e.g. PK), magnitude and sources of uncertainty, and key assumptions.

Literature Based Modeling Can be Flexible

Can model simultaneously:

OC and LOCF data (assuming similar dropout rates across studies)

Outcome measures using different scales, e.g. HAMD 17 and HAMD 21 (depression)

Allows modeling a response variable against a variable measured with error

- Example: $HbA1c = a + b \times \%WL$
- Typically increase in variance in independent variable reduces regression slope
- Mean data thus may be useful in such case
- More research/simulations in this area is worthwhile

Allows modeling binary response. Variables as Y/N, %responders, number of AE's, etc.

Binary data retain subject level information

An example of modeling Rates (proportions)

Modeling proportions (e.g. events of AE's, percent responders, etc.) can be dealt with in a manner similar to that of **continuous** variables

However, because proportions are bound between 0 and 1, problems with model fit can arise especially **if response values are close to the boundaries** of the 0-1 range

Use of **Logit transformation** in some instances help but do not remove the problem completely

Instead, the proportions can be **converted to binary response** and then modeled as such

For example if the proportion of subjects reporting an AE is **35%** in a study arm of size 100, then the 35% is converted to a binary response with **35** 1's, representing event subjects, and **65** 0's representing non-event subjects.

Since study subjects share same design conditions, a **random study effects** is required

An example: Proportion of subjects achieving >5% weight Loss

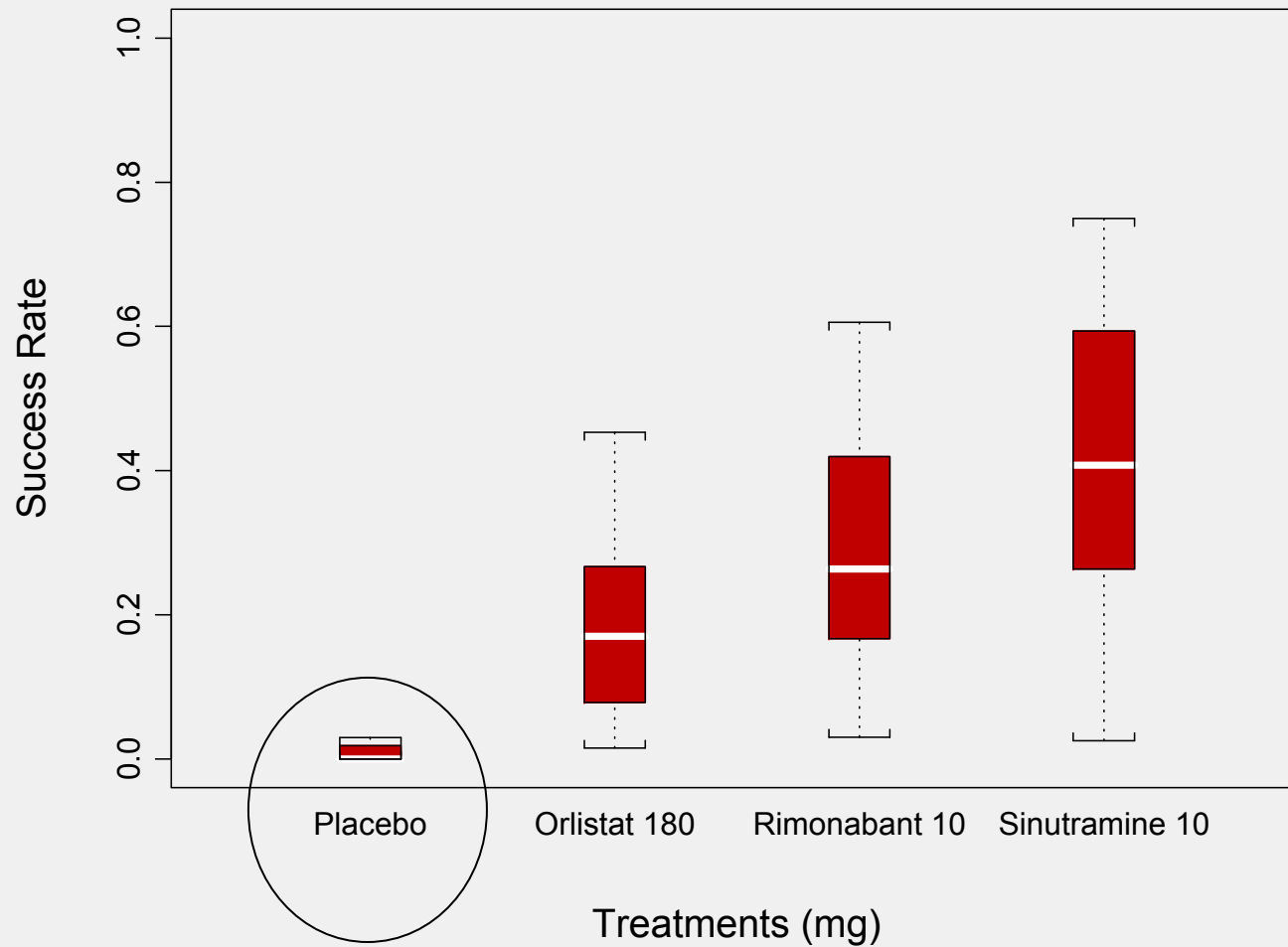
Data: Simulated from the weight model described previously

Models:

Using proportions as a continuous variable (LME)

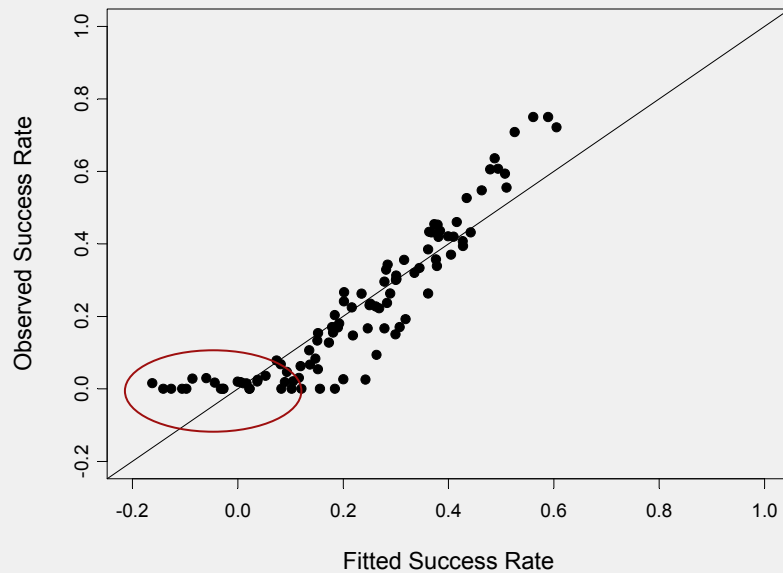
Using proportions as Binomial/binary (GLME)

Success rates for different treatments (Simulated example)

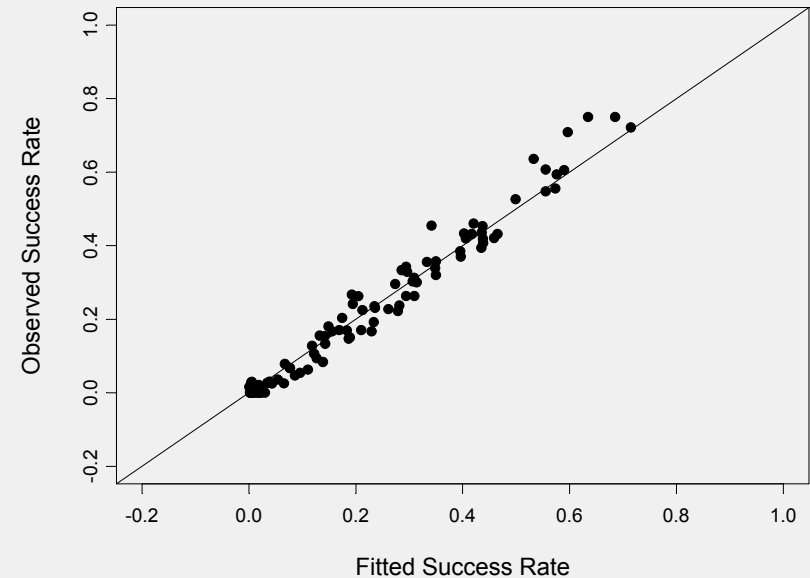


Modeling proportions as a continuous variable may lead to poor fit (left). A better fit is achieved when considered as a binomial variable (right)

Using Proportions as a continuous variable, fitted with LME



Using Proportions as a Binomial variable, fitted with GLME



Are there issues with literature modeling?

Data is a survey of a finite pool of studies, not a random sample

- Thus conceptually, classical large sample theory may not fully apply
- Imbalanced data structure. More data from mature drugs and less from newer drugs, potentially impacting robustness of model estimates
- Inconsistent definition and reporting of outcome
- Database increases sequentially, outlier studies is a moving target
- What is a sufficient database size
- Studies are of differing sample size
- Missing dropout information
- Publication bias
- ...

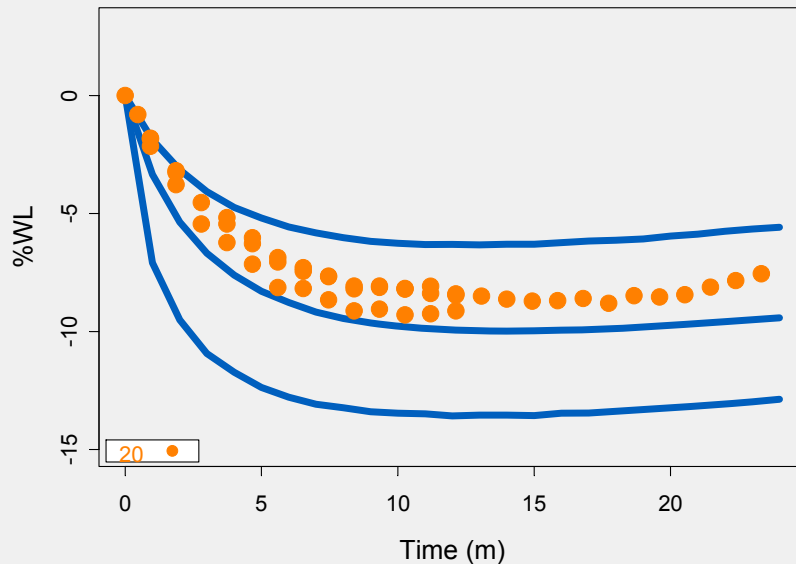
What are the limitations/difficulties of literature based modeling?

1. Covariate analysis of continuous demographic variables
 - Covariates such as age reported as mean age will have eliminated information on age distribution
 - Studies will thus have similar mean age
 - Decreasing the chance of detecting an effect
2. Covariate analysis of factor variables
 - Factor variables such as gender reported as %men or %women incur no loss of information
 - Typically studies have similar percentages
 - Also decreasing the chance of detecting an effect
3. Clinical trials in **subpopulation**, e.g. in diabetics, hypertensives, etc. will allow proper inference, if similar number of trials available for different subpopulations. Otherwise **confounding** with study random effect may bias inference
4. Study random effects are assumed $\sim N(0, \sigma^2_\eta)$, regardless of study drug. If **distribution of η** for a given drug is not centered at zero then model interpretation is difficult
5. While use of weights proportional to sample size, e.g. $\sqrt{N_{ijt}} \times R_{ijt}$ is a reasonable approach, estimate of residual SD will be **inflated** by about $\text{mean}(\sqrt{N_{ijt}})$
6. Cannot easily model fixed dosing together with **flexible** dosing regimens

Posterior Predictive Check

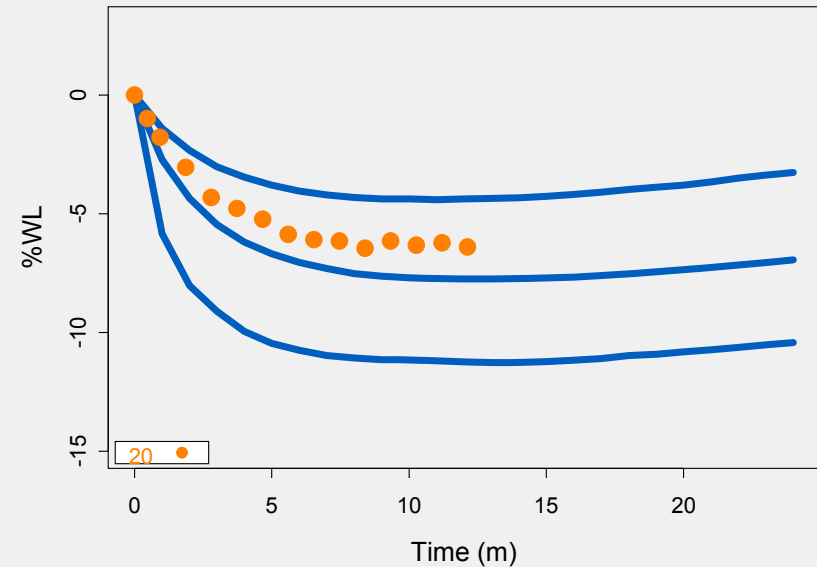
- Model diagnostics may indicate lack of fit
 - Disagreement between observed and mean prediction
- Reason: a result of smaller placebo response in Rimonabant studies
- However, Placebo subtracted observed agree with Placebo subtracted prediction (not shown)

Rimonabant OC (0)



Studies 37, 80 & 81 in non-Diabetics

Rimonabant OC (1)



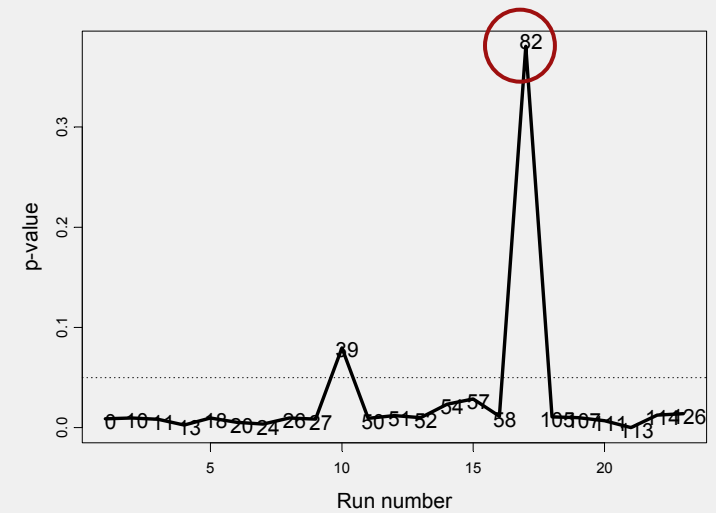
Study 82 in Diabetics

$$R_{ijt} = -(R_p + DE_i + \beta X_{ij}) \times \frac{t}{t + ET_{50,i}} + \varepsilon_{ijt}$$

Additional safeguards

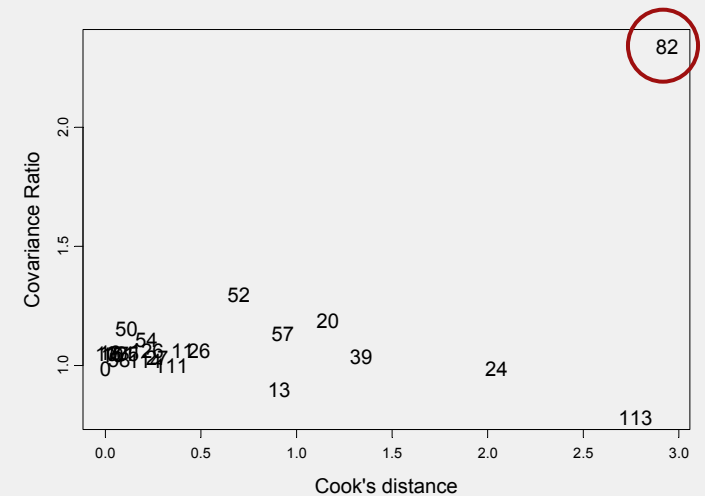
Routine use of jackknifing is recommended: elimination of 1 or more studies at a time and at random to identify influential studies

- Inspect estimates
- Changes in p-values
- Cook's distance and covariance ratio



Use model predictions to interpret model fit

- It is possible that parameters are significant because of others parameters in model



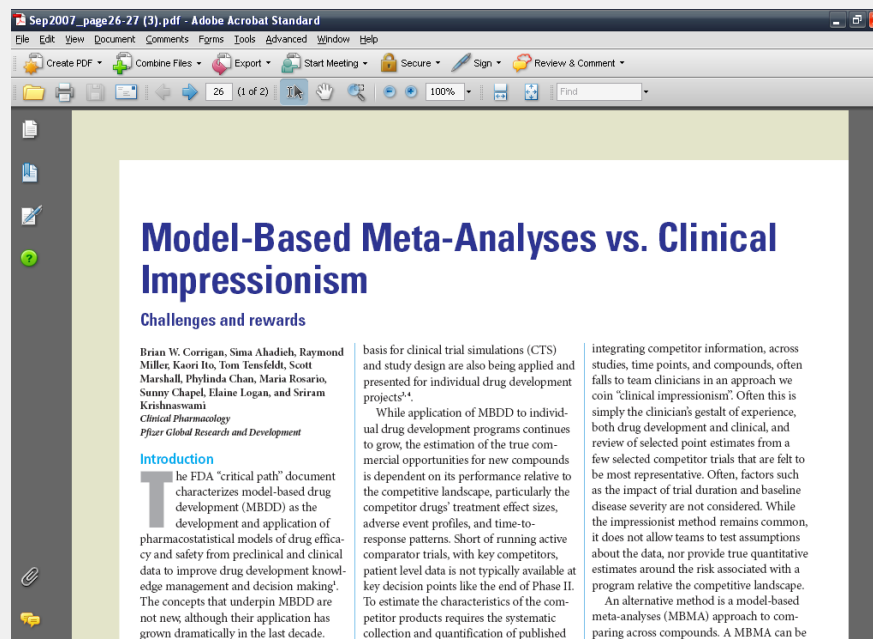
Growing Base, Interest and Body of Public Work in Literature Based modeling/Meta-Analysis

FDA

- Developing an internal library of drug-disease models (e.g., in NSCLC, diabetes, Parkinson's) based on public source data and from previous NDAs/SNDAs
- Literature estimates for comparative drug effects included as a deliverable in FDAs voluntary End of Phase IIa meeting (2-year pilot program, Guidance in progress)

Sponsors/Industry

- January 2007 DIA Forum on sharing data/models of diseases, drugs, placebo, baseline, dropouts
- Pfizer making systematic use (and reuse) of MBLMA across indications, endpoints, and drugs



Corrigan BW et al. Model-Based Meta-Analyses vs. Clinical Impressionism: Challenges and Rewards. AAPS Newsmagazine, September 2007, pages 26-27. Available at www.aapspharmaceutica.com.

Conclusion

Despite some limitations, literature based Modeling helps

- **Quantify and leverage** knowledge for development purposes
 - Providing **objective comparisons** between treatments
 - Permit **exploration of study design** alternatives to guide further development
 - Permit evaluation of likelihood of achieving clinically important target **utilizing short term data** from early efficacy studies
 - Provide a **forum** for discussion and allow **open communication** within project teams
- Literature models were successfully constructed in most therapeutic areas
- Provide a tool for evaluation of in-licensing compounds
- Helped make Go-No-Go decisions

Selected References

JW Mandema, D Hermann, W Wang, T Sheiner, M Milad, R Bakker-Arkema, D Hartman. Model-based development of gemcabene, a new lipid-altering agent. The AAPS Journal 7(3) Article 52 (www.aapsj.org).

Lesko LJ. Paving the Critical Path: How can Clinical Pharmacology Help Achieve the Vision? CPT, 81:2. February 2007.

AJ Sutton, KR Abrams, DR Jones, TA Sheldon, F Song. Methods for Meta-Analysis in Medical Research. John Wiley & Sons (2000).

DK Stangl, DA Berry. Meta-Analysis in Medicine and Health Policy. CRC (2000).