The Time Course of Placebo Response in Clinical Trials

Do Antidepressants Really Take 2 Weeks To Work?

Nick Holford

Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

Clinical Pharmacology

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Disease Progress + Drug Action

Old Model - New Meaning

$$E = E0 + \frac{E\max \cdot Conc}{EC50 + Conc}$$

Disease Progress Drug Action

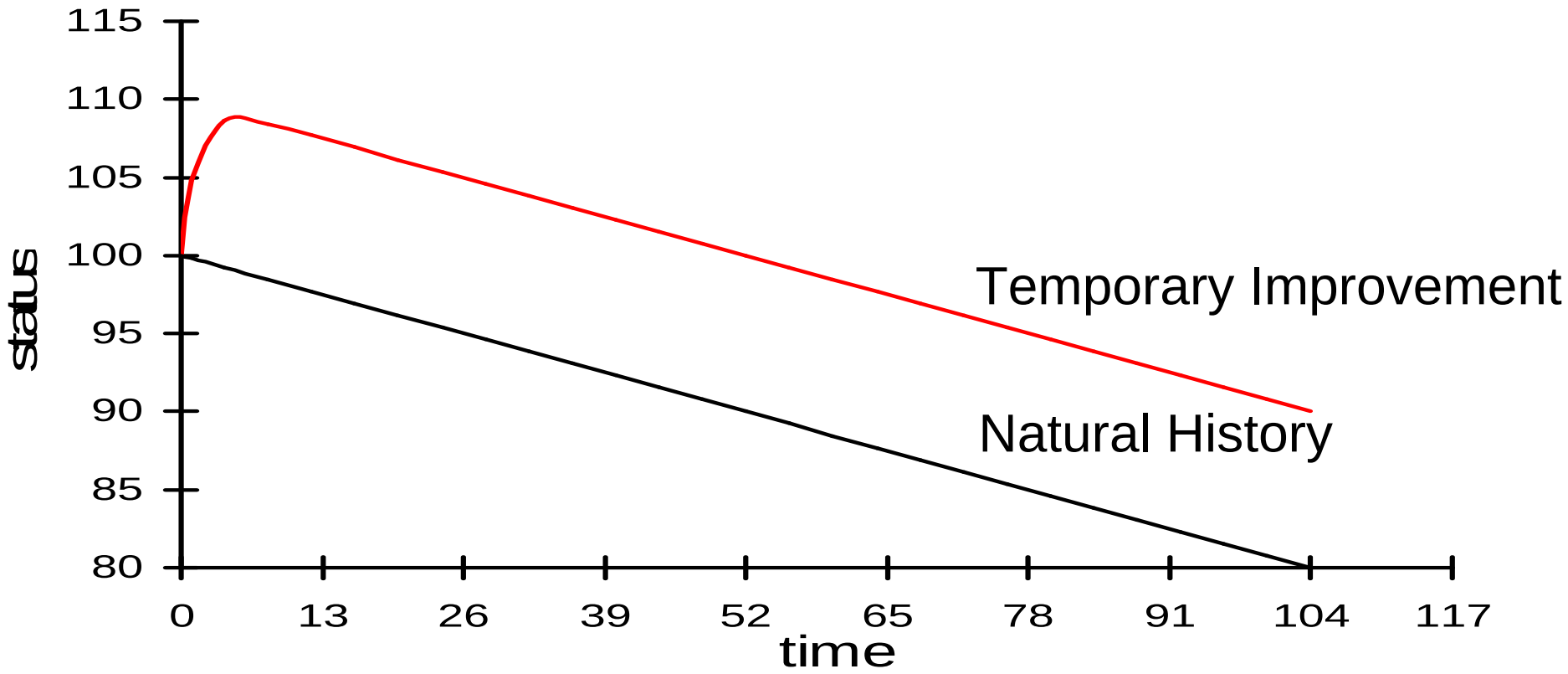
Components of a Disease Progression Model

- Baseline Disease State
- Natural History
- Placebo Response
- Active Treatment Response

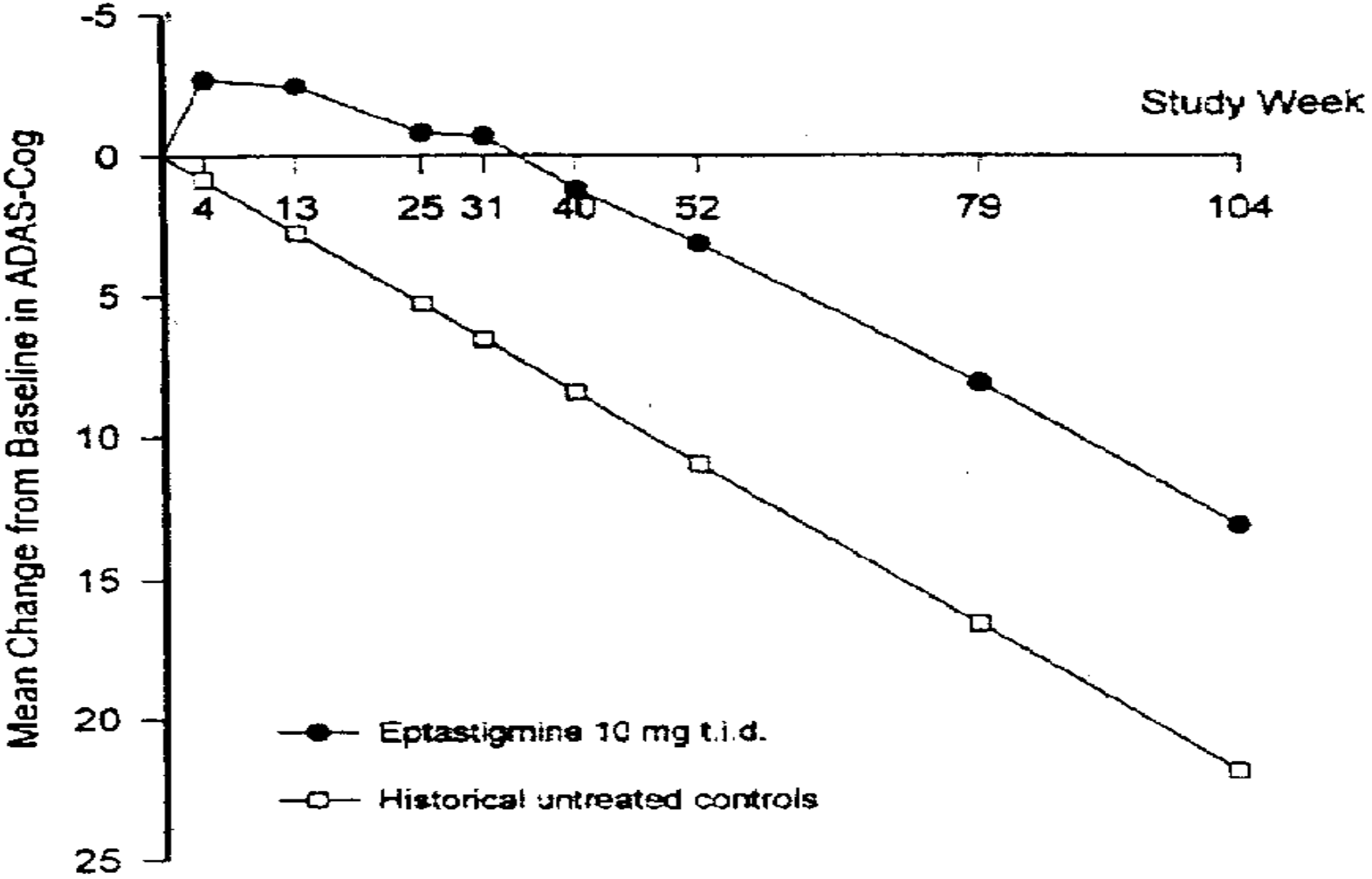
$$S(t) = S0 + Nat.\ Hx. + Plac + Active$$

Linear + Offset (Symptomatic)

$$S(t) = \left(S_0 + E(t)\right) + \alpha \cdot t$$



Eptastigmine



Imbimbo et al. Two-year treatment of Alzheimer's disease with eptastigmine. The Eptastigmine Study Group. Dementia and Geriatric Cognitive Disorders 1999;10(2):139-47.

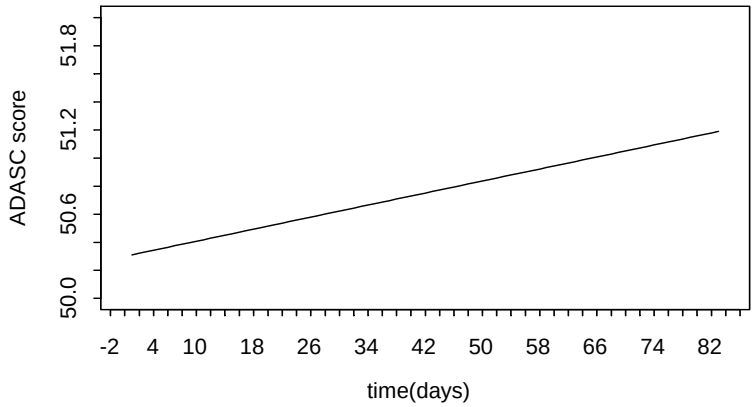
Disease Progress Placebo Response

- Q: How can disease progress and placebo response be separated?
- A: Model based assumptions e.g.
  - disease progress is linear
  - placebo increases, reaches peak, decreases

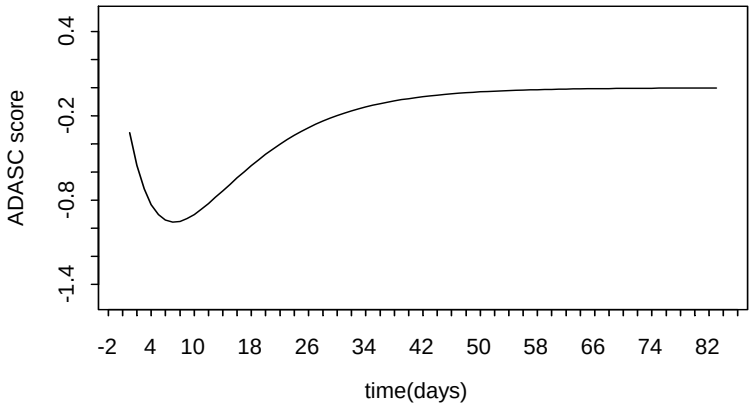
Placebo Response

Alzheimer's Disease

Disease Progress

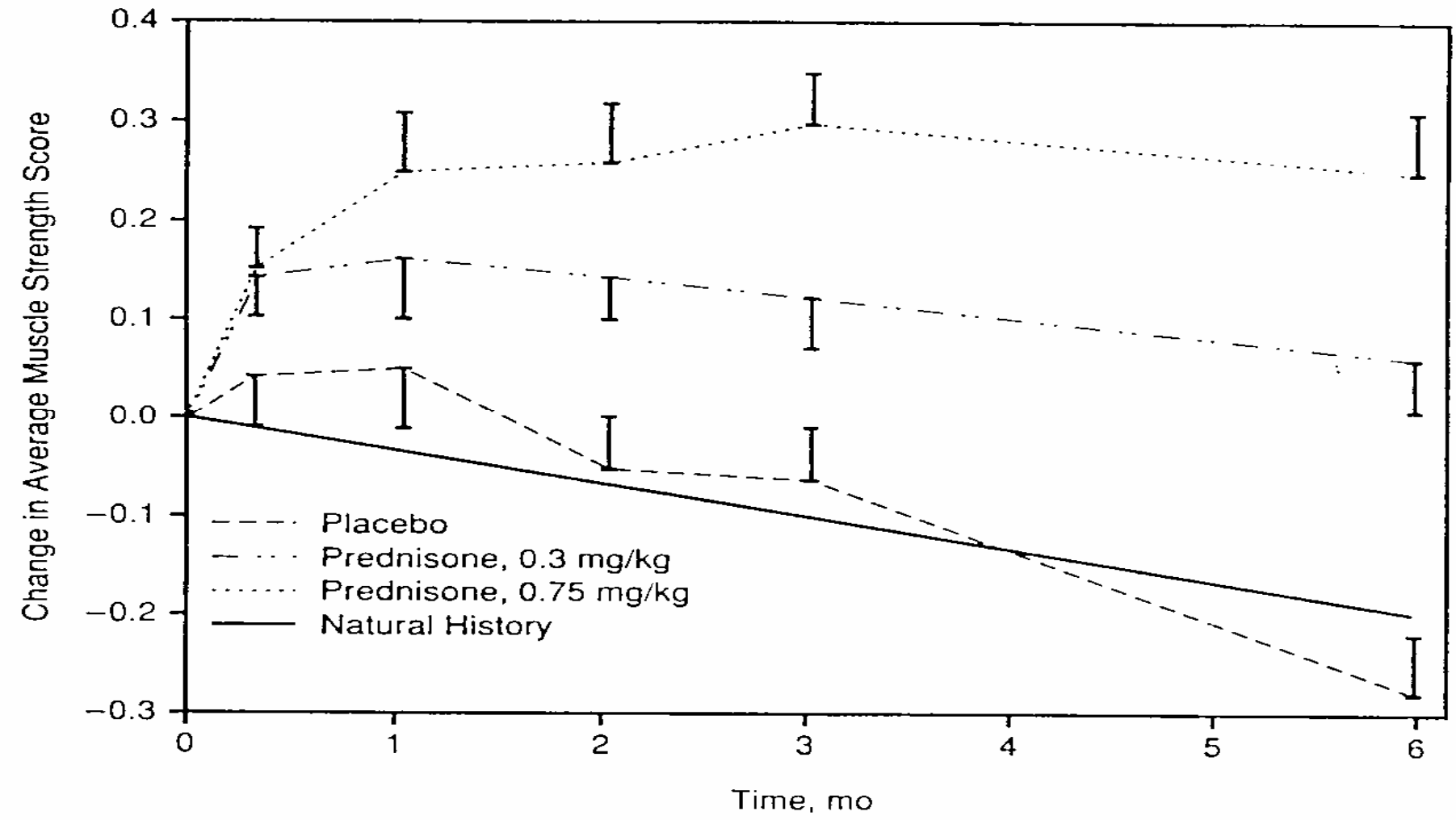


Placebo Response



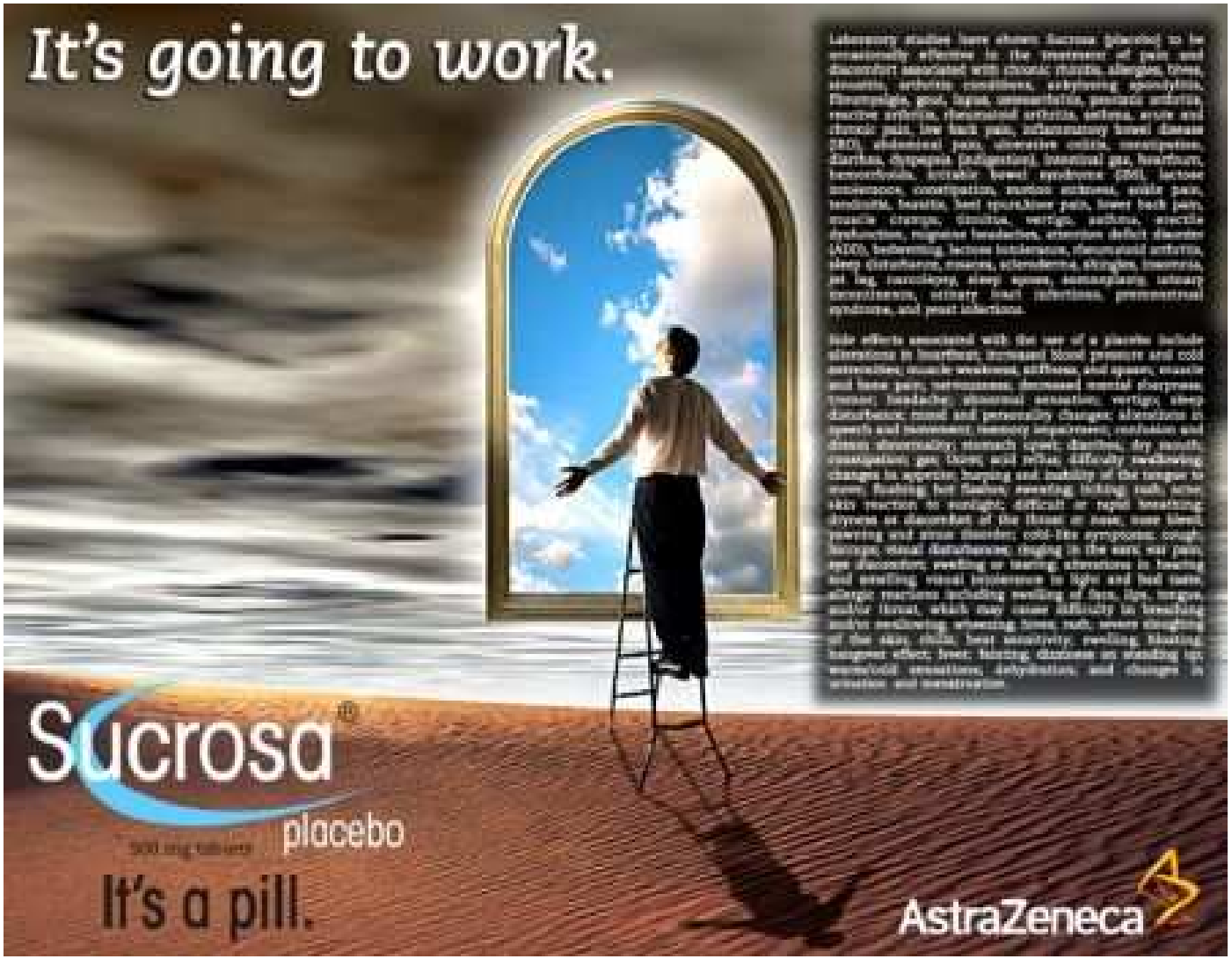
Holford & Peace, Methodologic aspects of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. Proc Natl Acad Sci 89 (1992):11466-11470

Linear + Offset + Placebo



Griggs RC, Moxley RT, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, et al. Prednisone in Duchenne Dystrophy: A randomized, controlled trial defining the time course and dose response. Archives of Neurology 1991;48:383-88

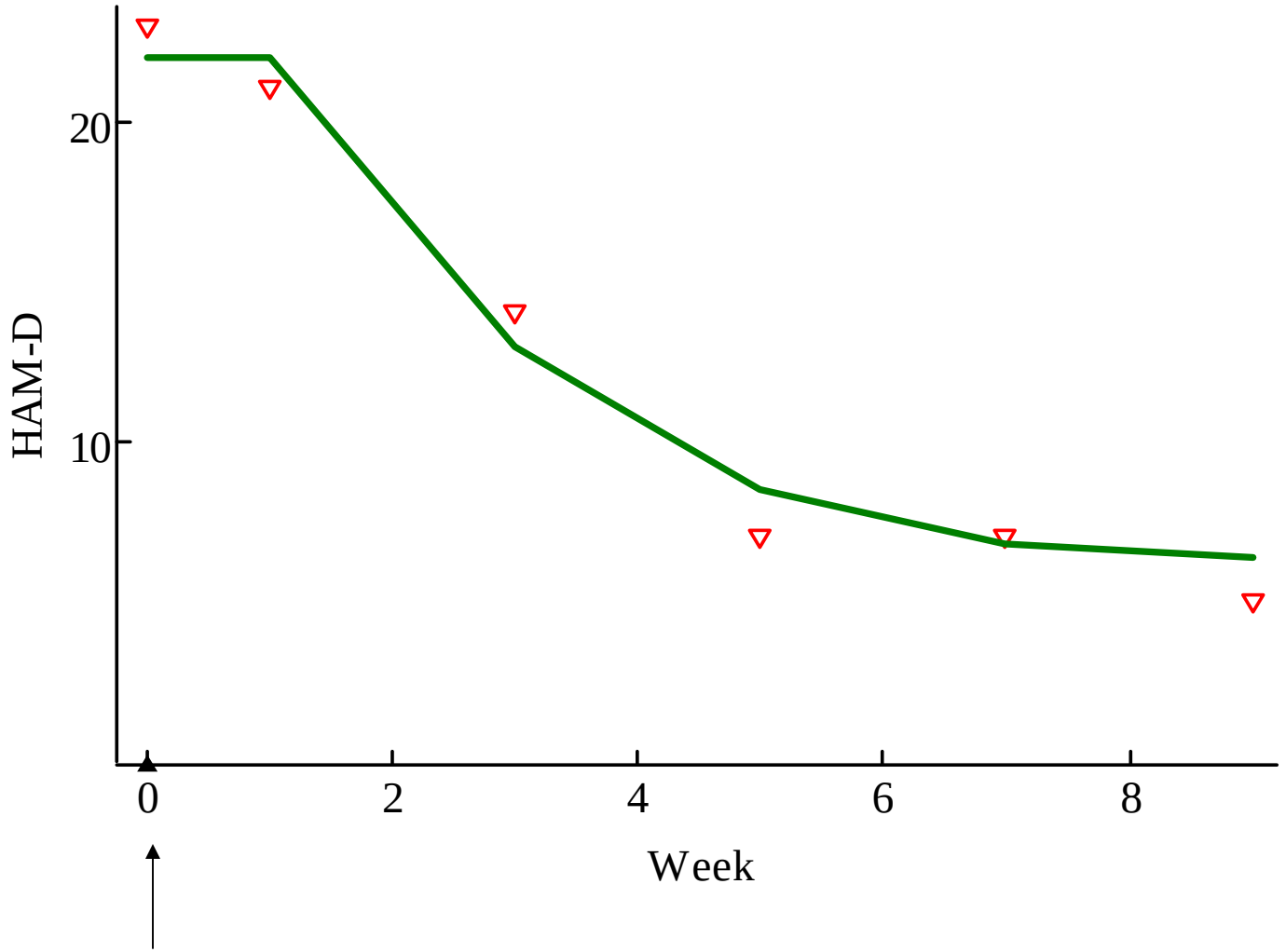
The Placebo Effect – True or False?



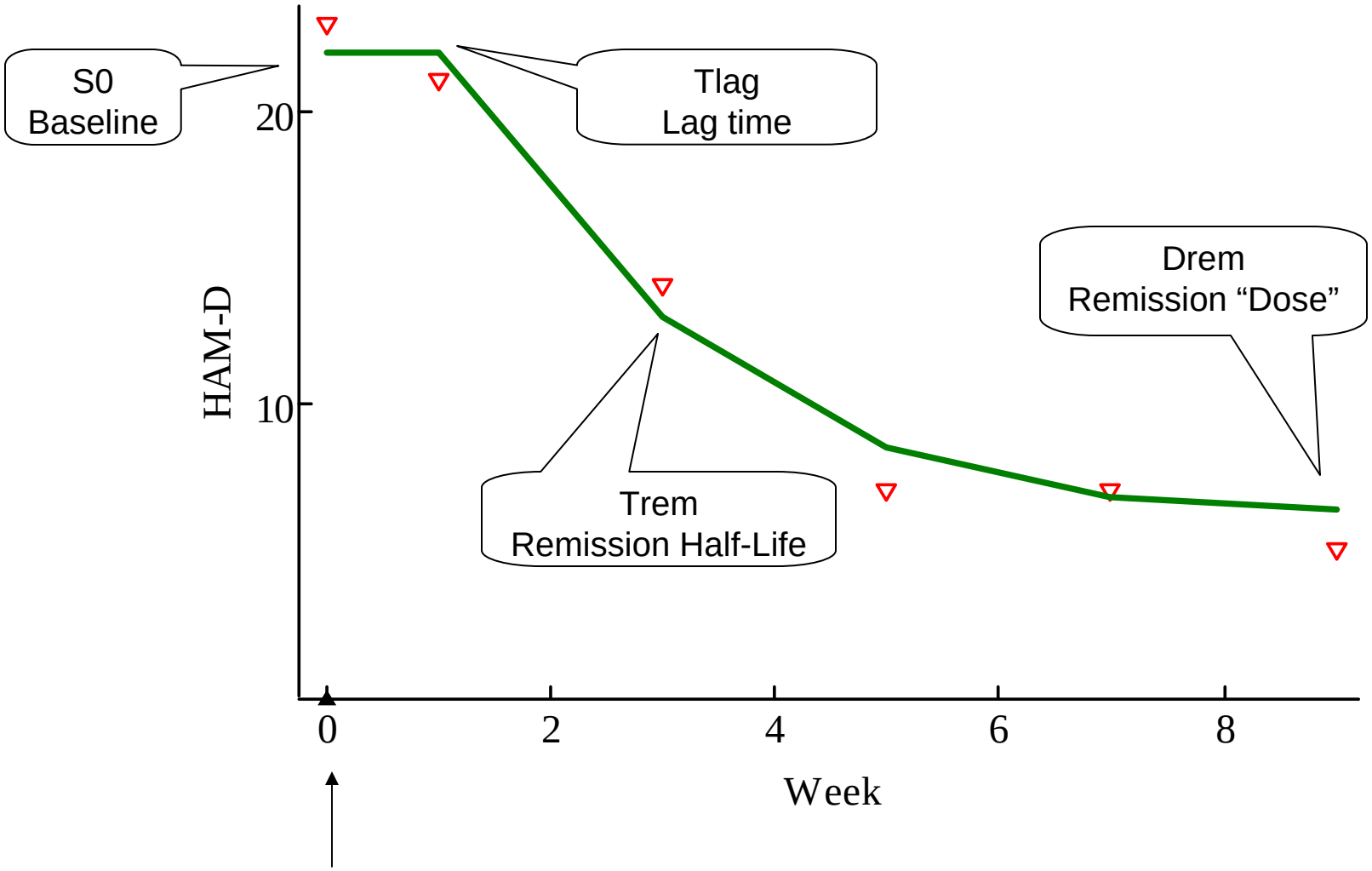
Anti-Depressant Response

- “Everybody knows anti-depressants take 2 to 4 weeks to work”
- Almost all anti-depressant drugs block amine transporter re-uptake
  - 5-HT, dopamine, noradrenaline
  - Know to have a rapid effect
    - “crack cocaine”
    - Serotonergic syndrome
  - Why is the anti-depressant response delayed?

HAM-D Response

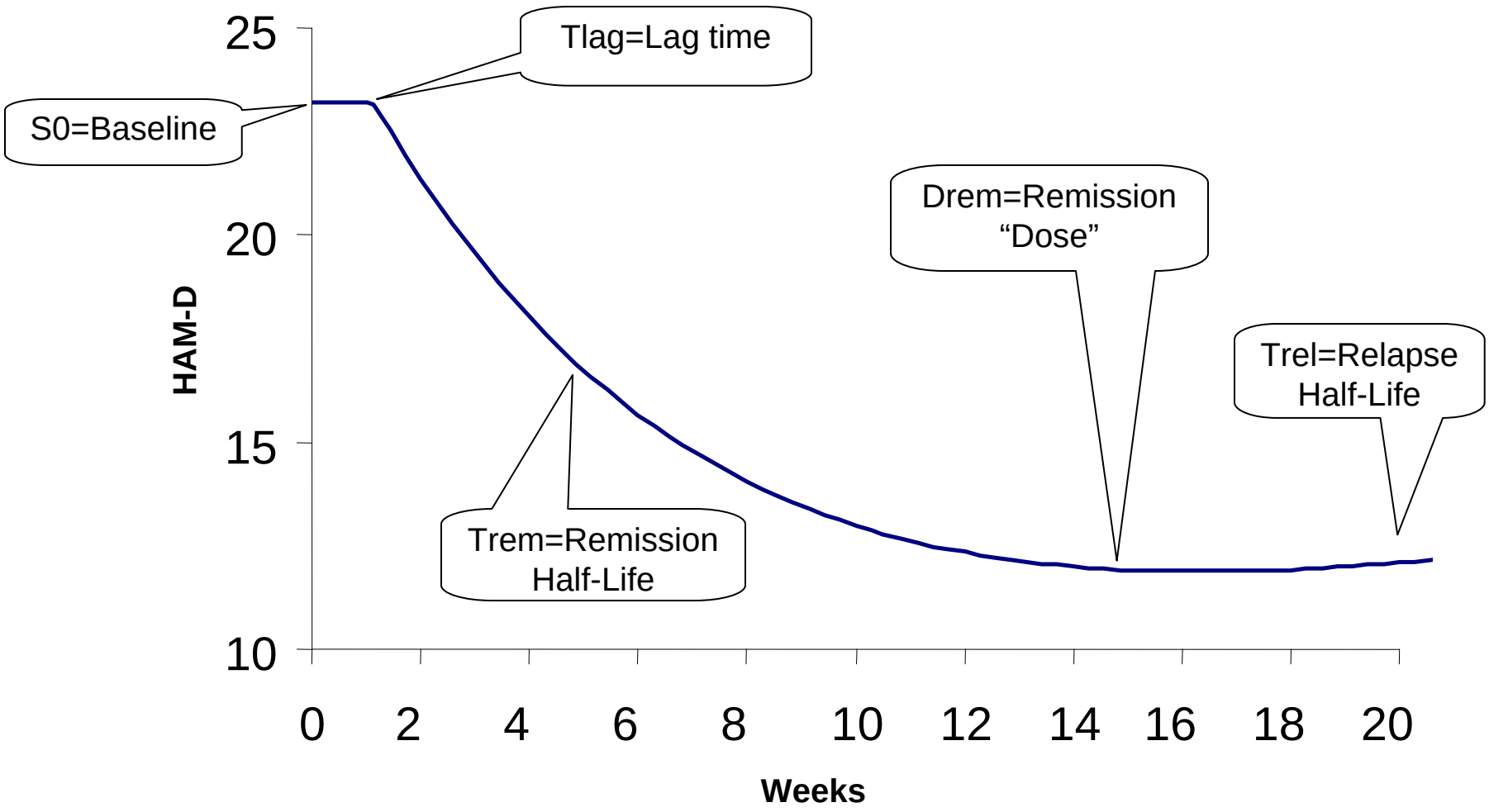


Simple Placebo Response



Full Placebo Response

“first order absorption and elimination”



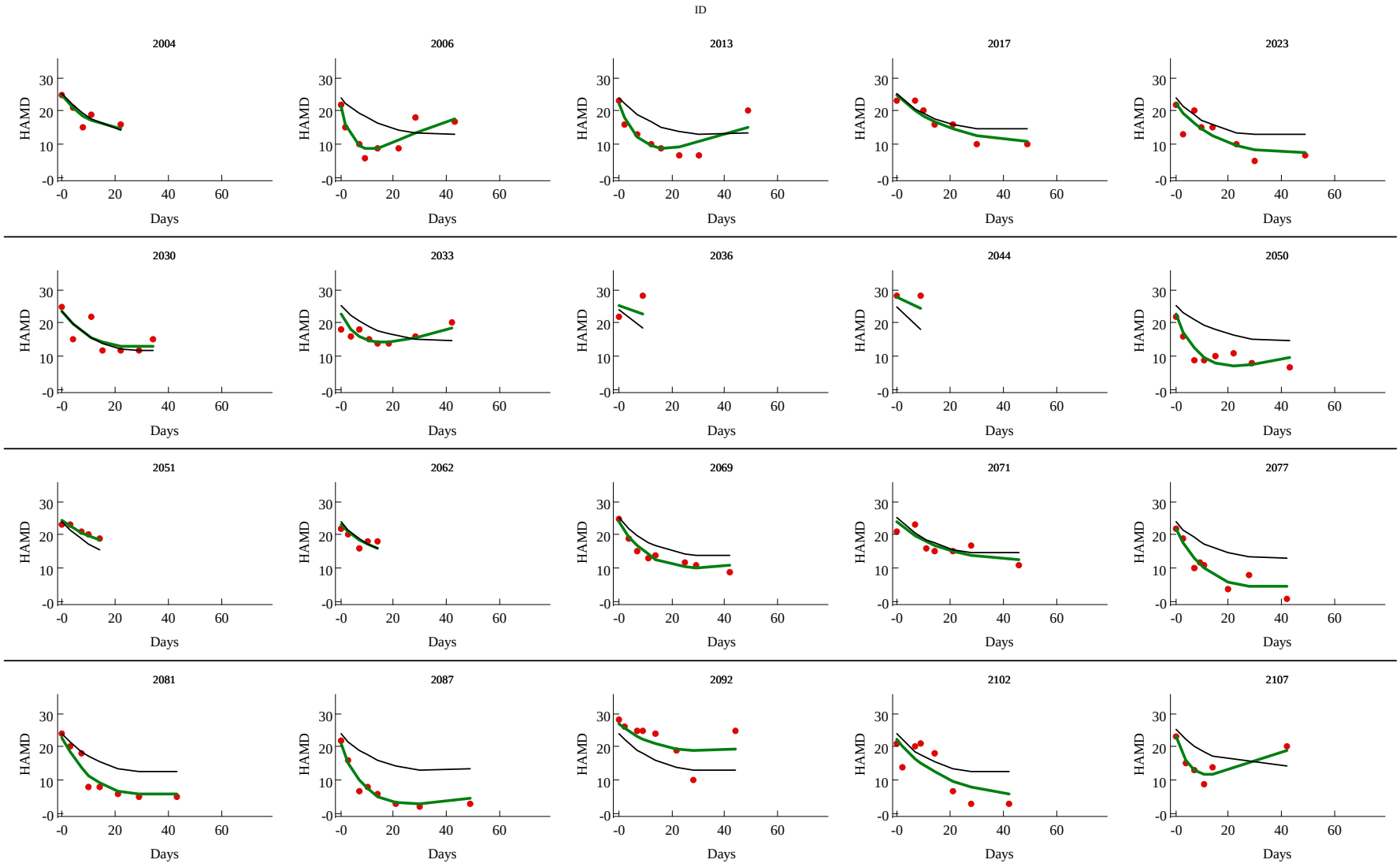
Investigation 1

Placebo treated HAM-D profiles
from 4 clinical studies

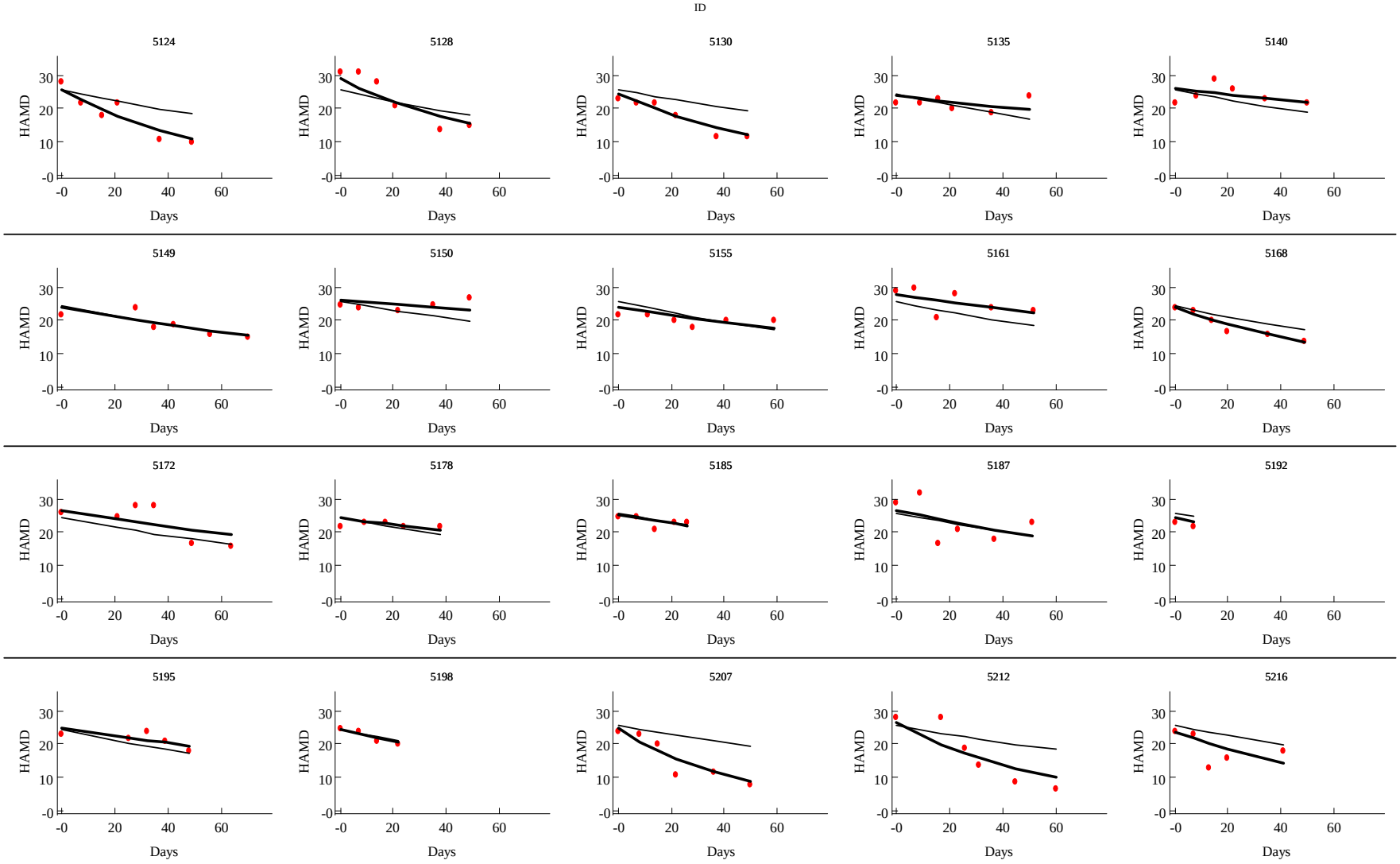
What Determines the Time Course of Placebo Response?

- Placebo Arm of Double Blind Randomized Phase II Study of Four New Potential Anti-Depressants
  - Total 582 patients, 3864 observations
    - Developer 1, Study A (154 patients)
    - Developer 1, Study B (141 patients)
    - Developer 2, Study C (149 patients)
    - Developer 2, Study D (138 patients)

Study A Placebo



Study B Placebo



Study Placebo Model

4 Placebo Data Sets

Parameter	Description	Estimate	Units
S0	Baseline	24	HAMD
Tlag	Lag time	4.7	days
Drem	Remission ‘dose’	20.6	HAMD
Trem	Remission half-life	60	days
Trel	Relapse half-life	280	days

Relapse Mixture Model

- Assume some patients have relapse
- Patients who do not relapse have infinite relapse half-life
- Probability of patient having a relapse is estimated

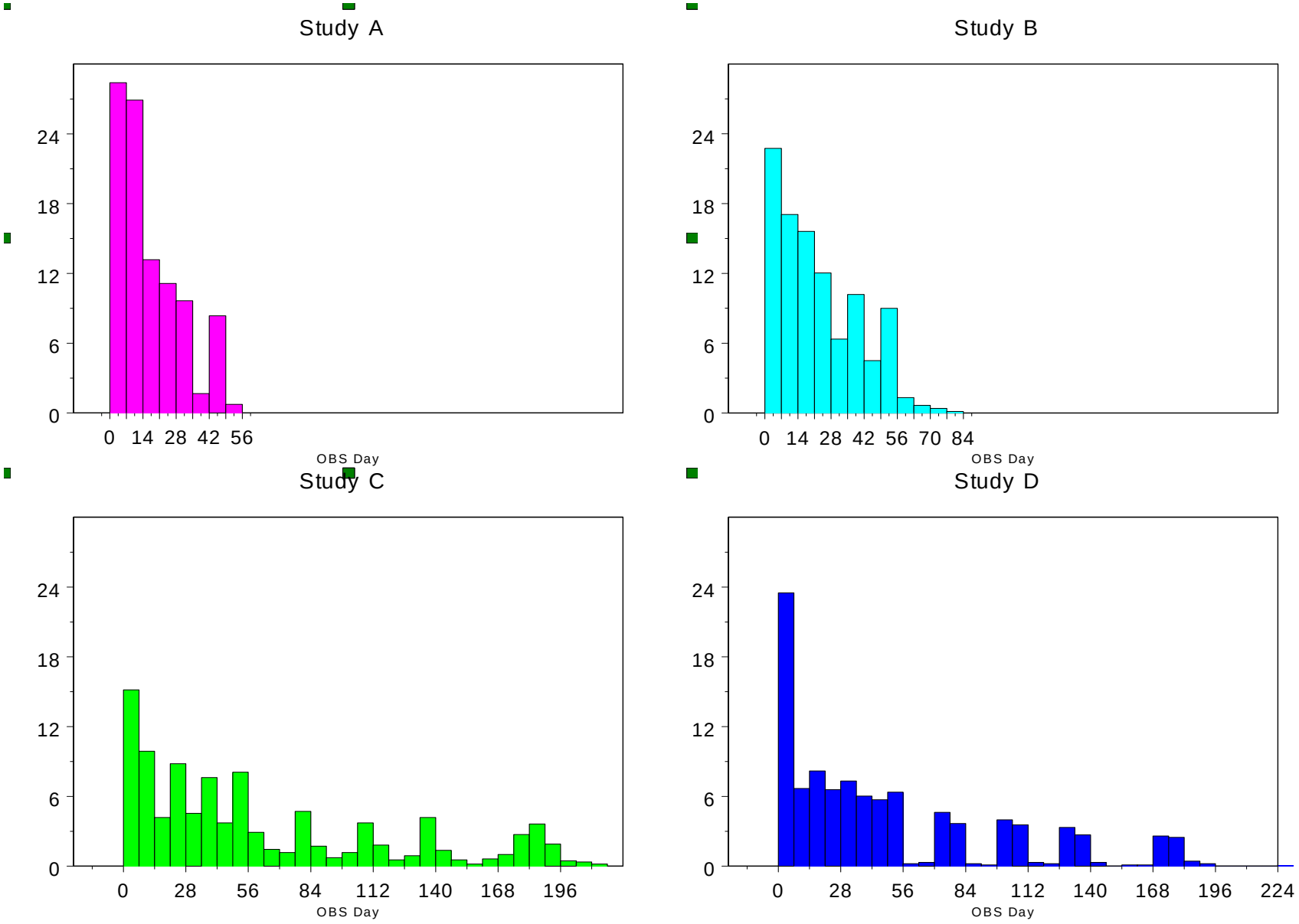
Relapse Probability

Study A	98%
Study B	45%
Study C	29%
Study D	18%

There are clearly study specific influences on the probability of relapse during the clinical trial

Is It a Design Issue?

HAM-D Observation Times



A Second Kind of Placebo Effect
The Observation Placebo

- Each HAM-D observation acts as a “dose” of observation placebo
- Observation placebo “conc” rises and falls like oral drug absorption model
- Observation placebo “conc” can shorten remission and relapse half-lives of the study placebo model

Observation Placebo Effect

Obs Placebo onset half-life	0.12 days
Obs Placebo disappearance half-life	31 days
Obs Placebo effect on remission	-40%
Obs Placebo effect on relapse	-64%

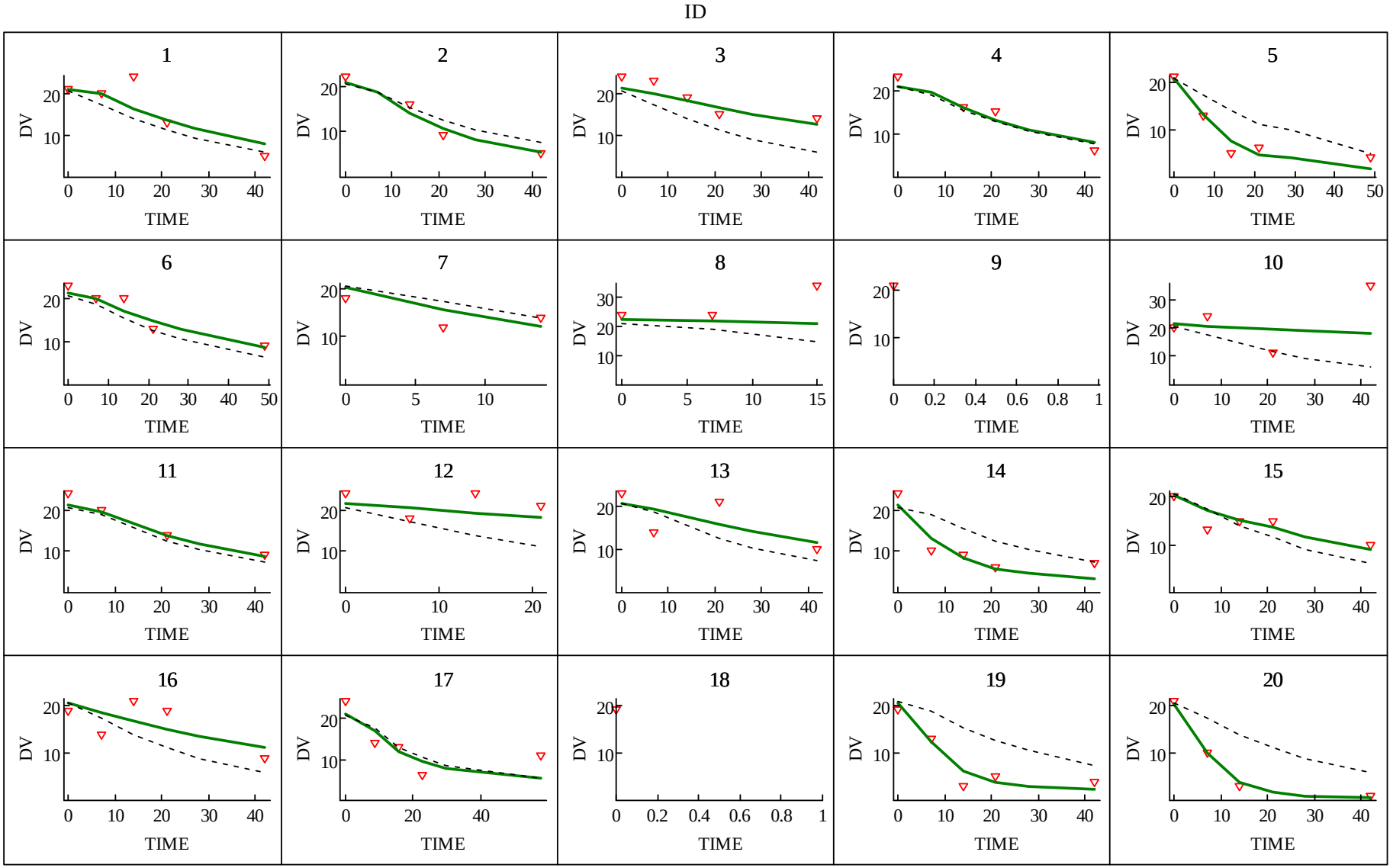
Investigation 2

A traditional placebo controlled study of a potential new antidepressant

HAM-D Model

Models	Equations
Disease Progression	$S(t) = S0$
Placebo Response	$Placebo(t) = Drem \cdot \left(1 - e^{-\ln(2)/Trem \cdot (t - Tlag)}\right)$
Effect Compartment Concentration	$Ce(t) = \frac{DoseRate}{Clearance} \cdot \left(1 - e^{-\ln(2)/Teq \cdot t}\right)$
Drug Action	$PD(Ce) = Beta \cdot Ce$
HAM-D Time Course	$HAMD(t) = S(t) + Placebo(t) + PD(Ce(t))$

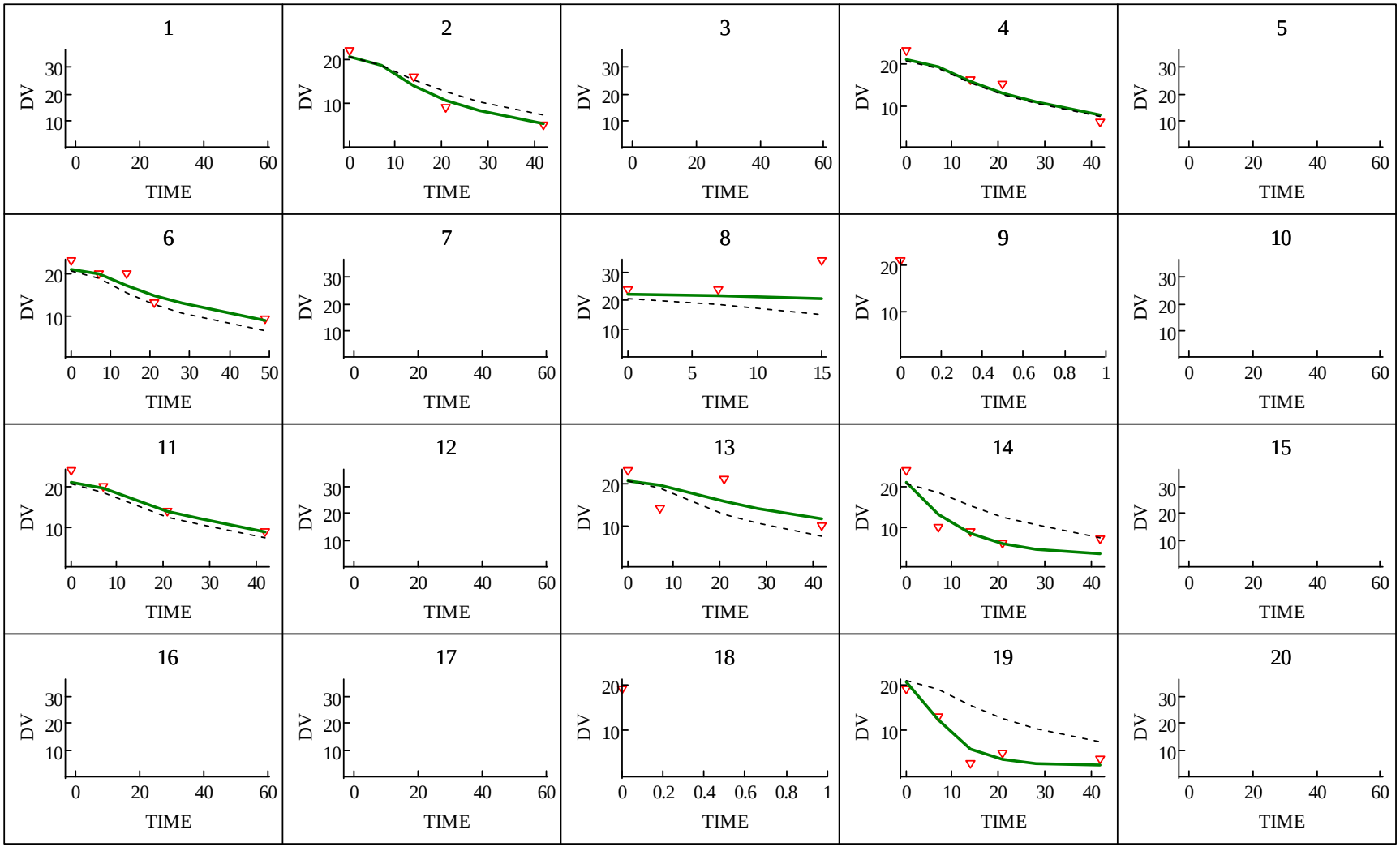
Typical Profiles



Placebo

DOSE
0

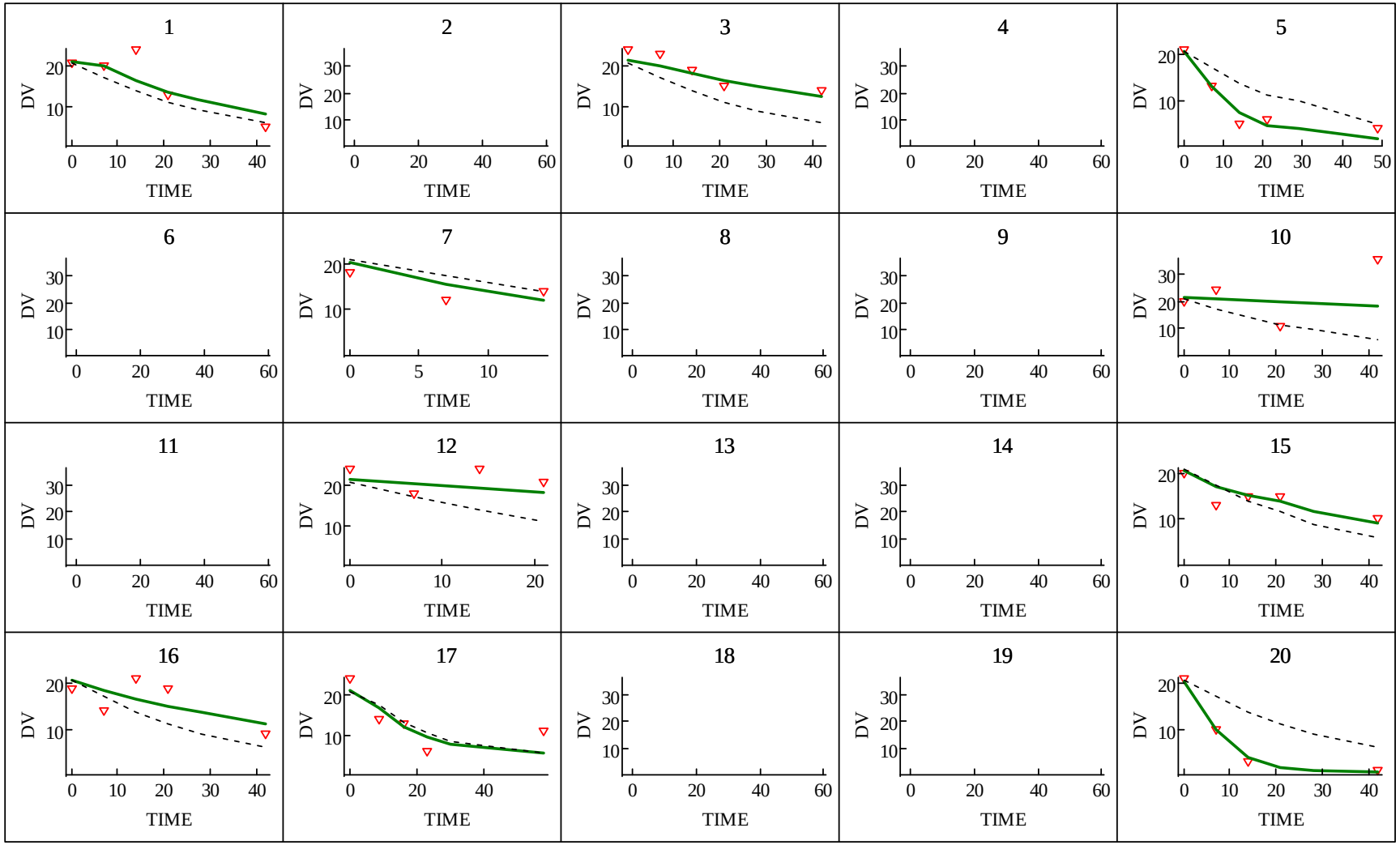
ID



New AntiDepressant

DOSE
1

ID



Parameter Estimates

Parameter	Description	Units	Estimate	PPV
S0	Baseline HAM-D	HAM-D units	20.7	0.045
Tlag	Lag time	days	3.76	0.845
Drem	Remission decrease	HAM-D units	-18.1	0 FIX
Trem	Remission half-life	days	20.2	0.929
Beta	Effect “potency”	HAM-D units	-1.46	0.718
Teq	Equilibration half-life	days	0.5 FIX*	0 FIX
RUV	Residual Error	HAM-D units	2.69	0.134

PPV=Population Parameter Variability (coefficient of variation of a log normal distribution)
RUV=Residual Unidentified Variability (standard deviation of a normal distribution)

*=Longer Teq worsened objective function. Design of trial did not allow estimation of shorter Teq. 0.5 days is PK half-life.

Bootstrap Statistics

Table 3 Bootstrap Statistics (1000 replicates) of Parameter Estimates for the HAM-D Model

Parameter	Population Estimate			Population Parameter Variability		
	Median	Lower 2.5% ile	Upper 97.5%ile	Median	Lower 2.5% ile	Upper 97.5%ile
S0	20.70	20.30	21.10	0.0448	0.0105	0.0519
Tlag	3.75	2.61	4.22	0.849	0.760	0.980
Drem	-17.90	-19.10	-16.80	0 FIX	-	-
Trem	20.10	15.80	21.40	0.930	0.764	0.984
Beta	**-1.45***	**-1.62**	**-0.25**	0.718	0.443	1.836
RUV	2.70	2.48	2.95	0.134	0.123	0.188

* = Significantly different from zero based on 95% bootstrap confidence interval

Investigation 2 Conclusion

Big placebo response

Small antidepressant effect

Rapid onset of active drug?

Investigation 3

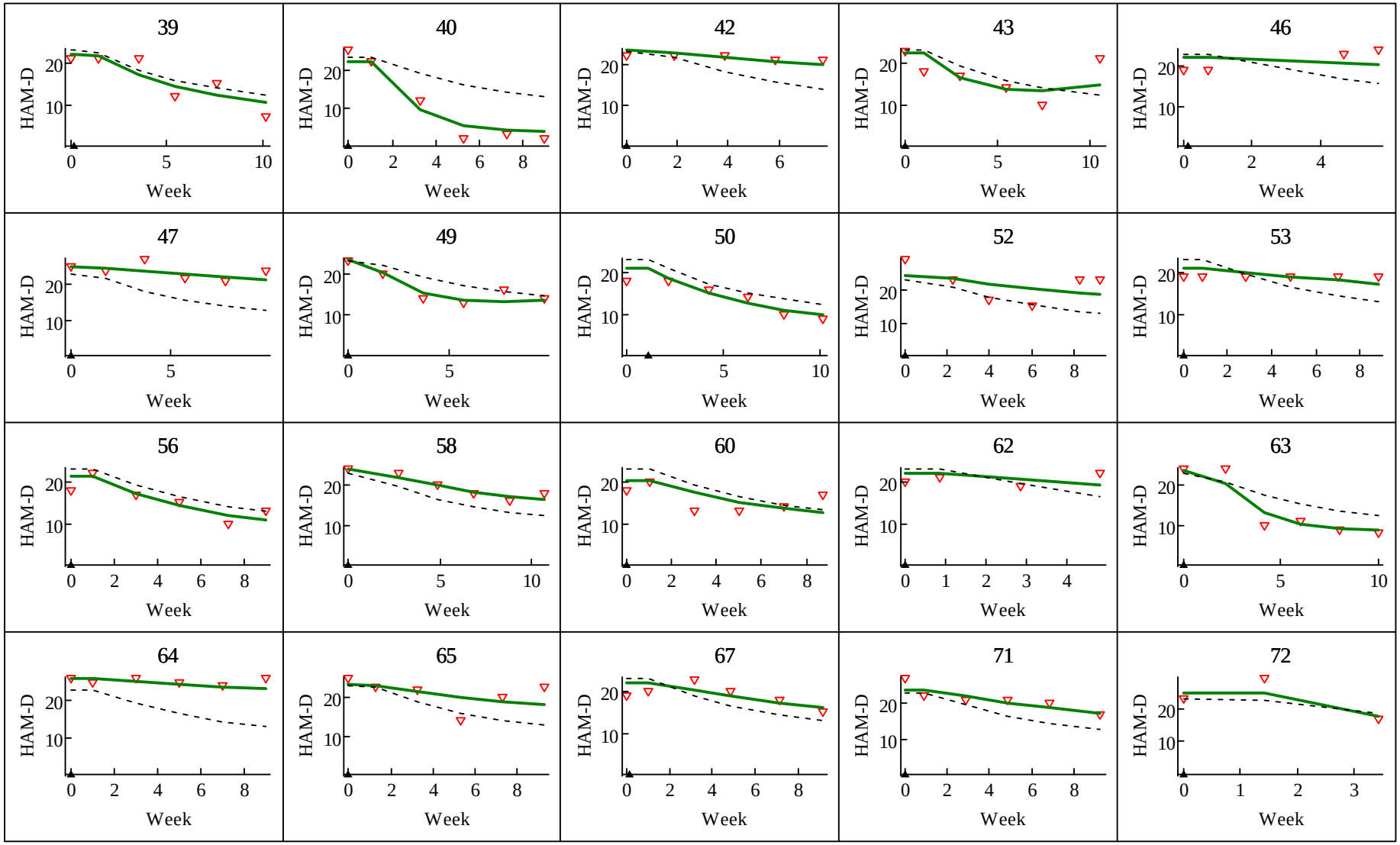
Retrospective analysis of large clinical database

“Positive” and “Negative” trials

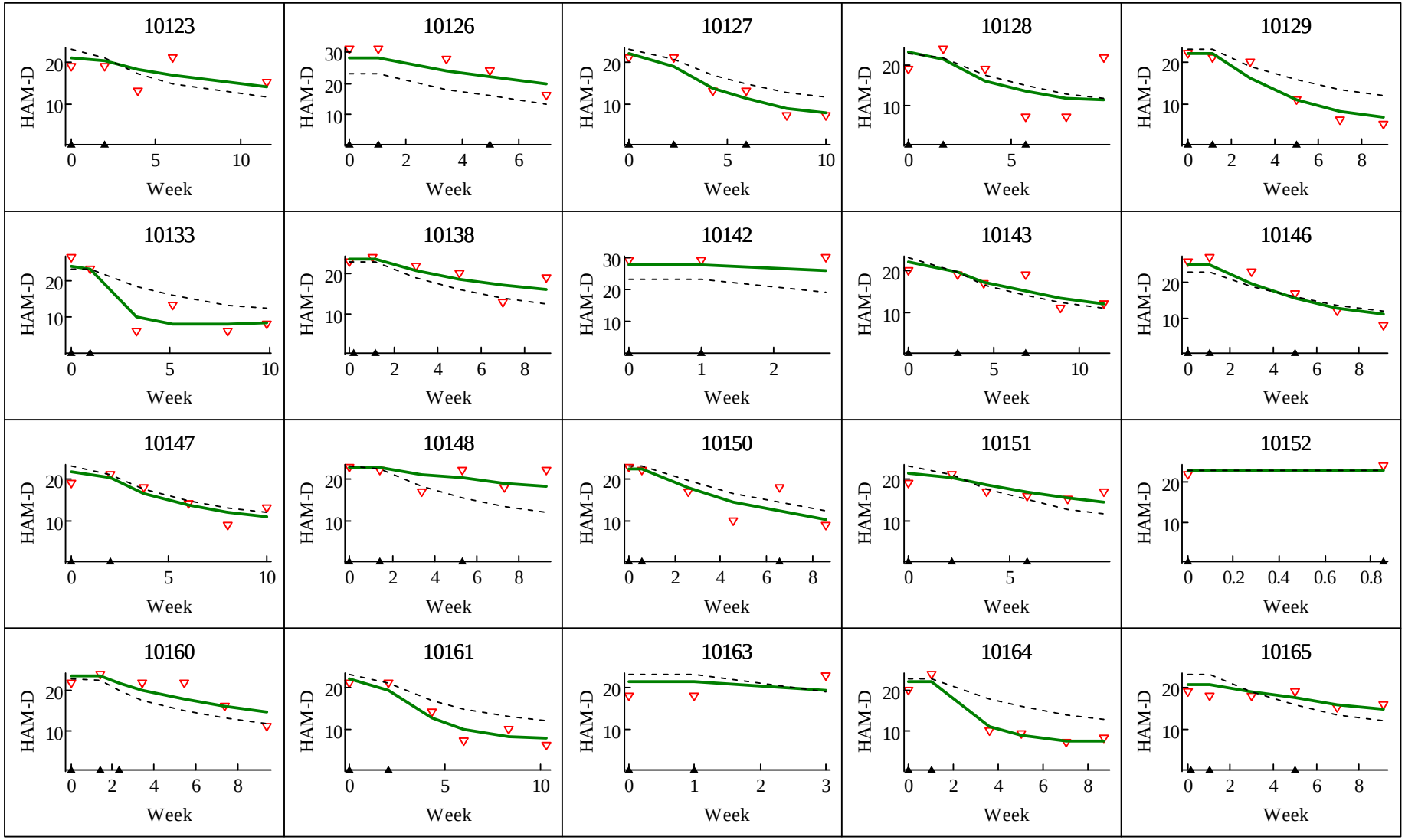
Patients with Major Depressive Disorder enrolled in Placebo Controlled Clinical Trials of Anti-Depressants

Data Set	Patients	HAM-D
4 Marketed Antidepressants + 2 IND (Active) Drugs + Placebo	2,794	15,968

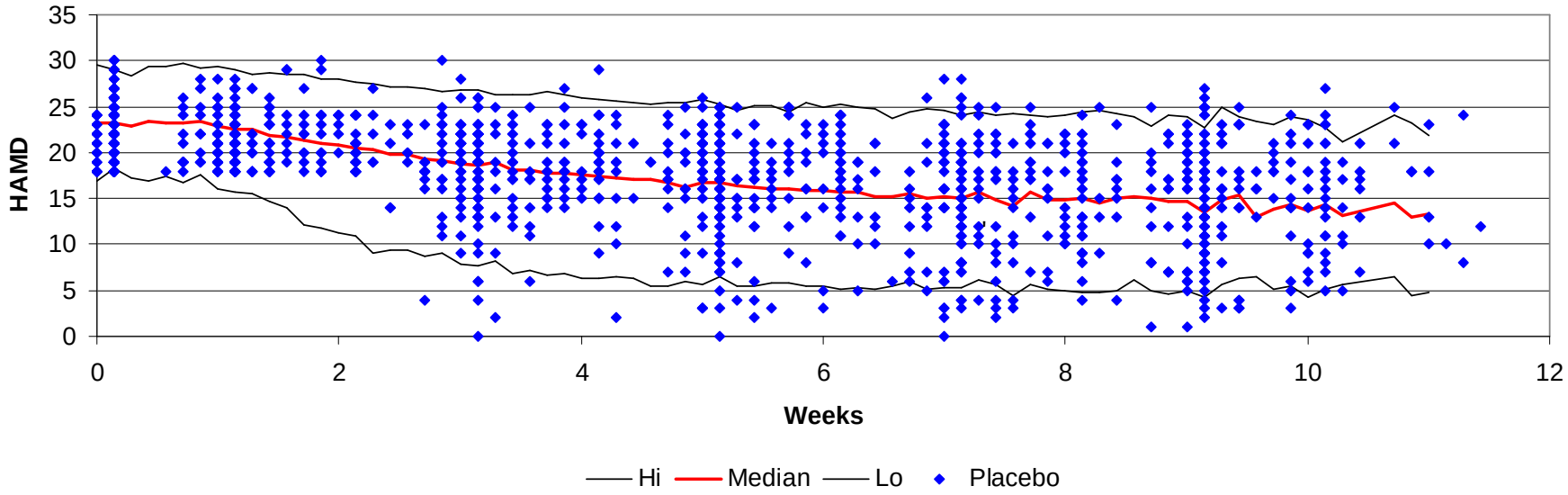
Placebo



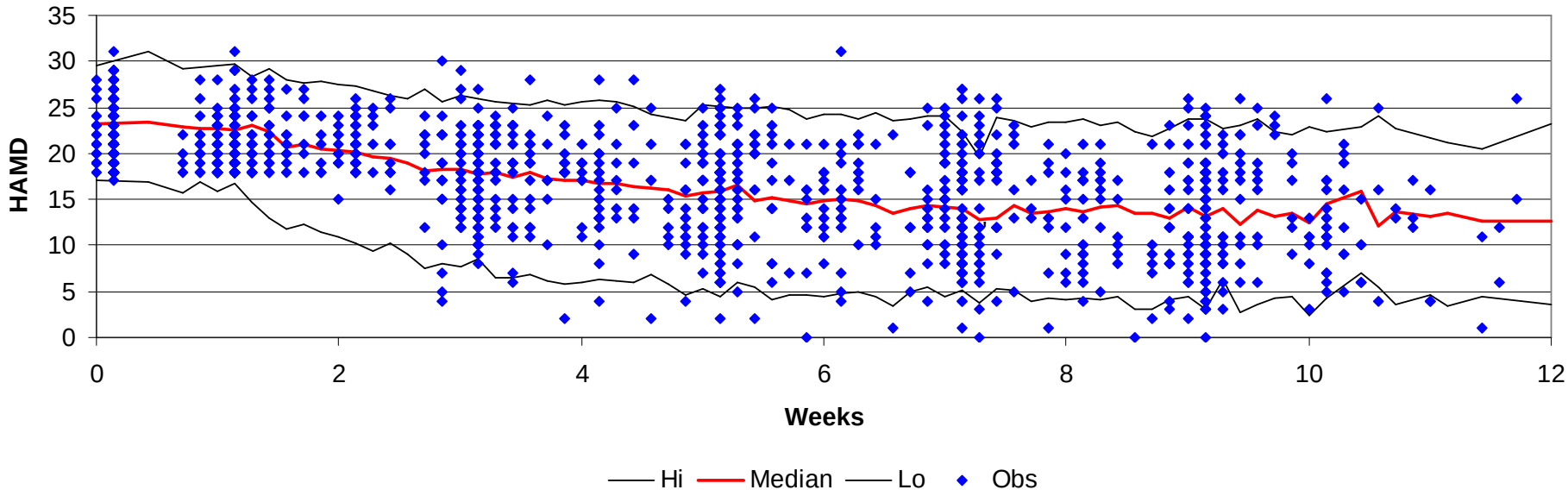
Marketed Active Drug



Placebo



Marketed Active Drug



Placebo Response Parameters

Parameter	Units	Population Estimate	Variability (PPV x 100)
S0	HAM-D	23.0	11
Tlag	Day	7.3	65
Remission Dose	HAM-D	-15.9	7
Thalf Remission	Day	36.9	139
Thalf Relapse	Day	217	108
RUV	HAM-D	2.96	13

PPV=Population Parameter Variability (coefficient of variation of a log normal distribution)
RUV=Residual Unidentified Variability (standard deviation of a normal distribution)

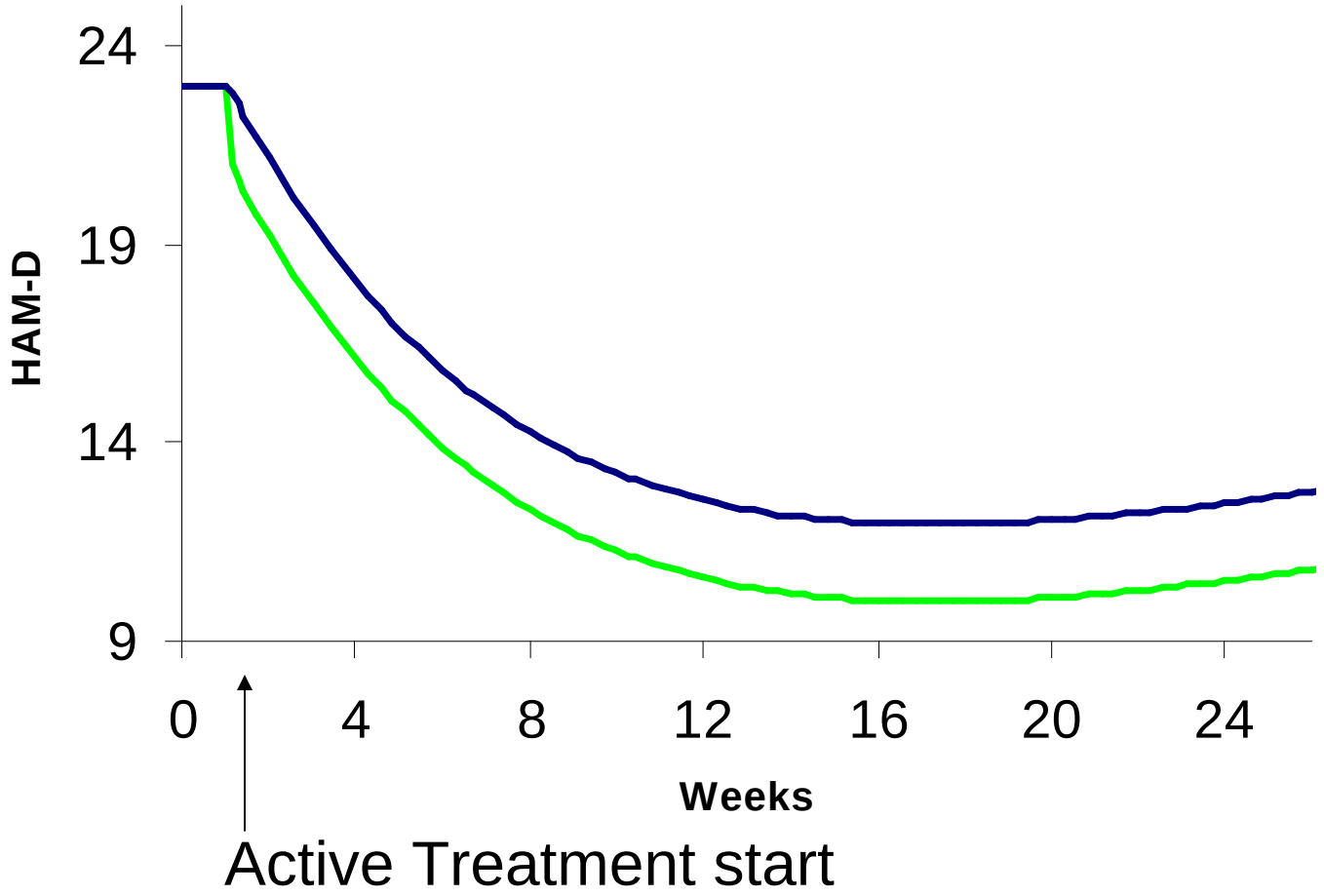
Active Treatment Effects

Parameter	Units	Population Estimate	Variability (PPV x 100)
Emax	HAM-D	-3.4	74
ED50	dose/day *	0.73	51
Teq	days	0.44	85

Teq=Effect compartment equilibration half-life

*=Dose rate for each drug normalized to the median dose

Placebo and Active Drug HAM-D Response



Investigation 3
Conclusion

Big placebo response

Small antidepressant effect

Rapid onset of (marketed) active drugs

Application of Placebo Models to Depression

- Clearer description of depression
- Separation of Magnitude and Time Course of Drug Action
- Dispel unsubstantiated mythology!