

# 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

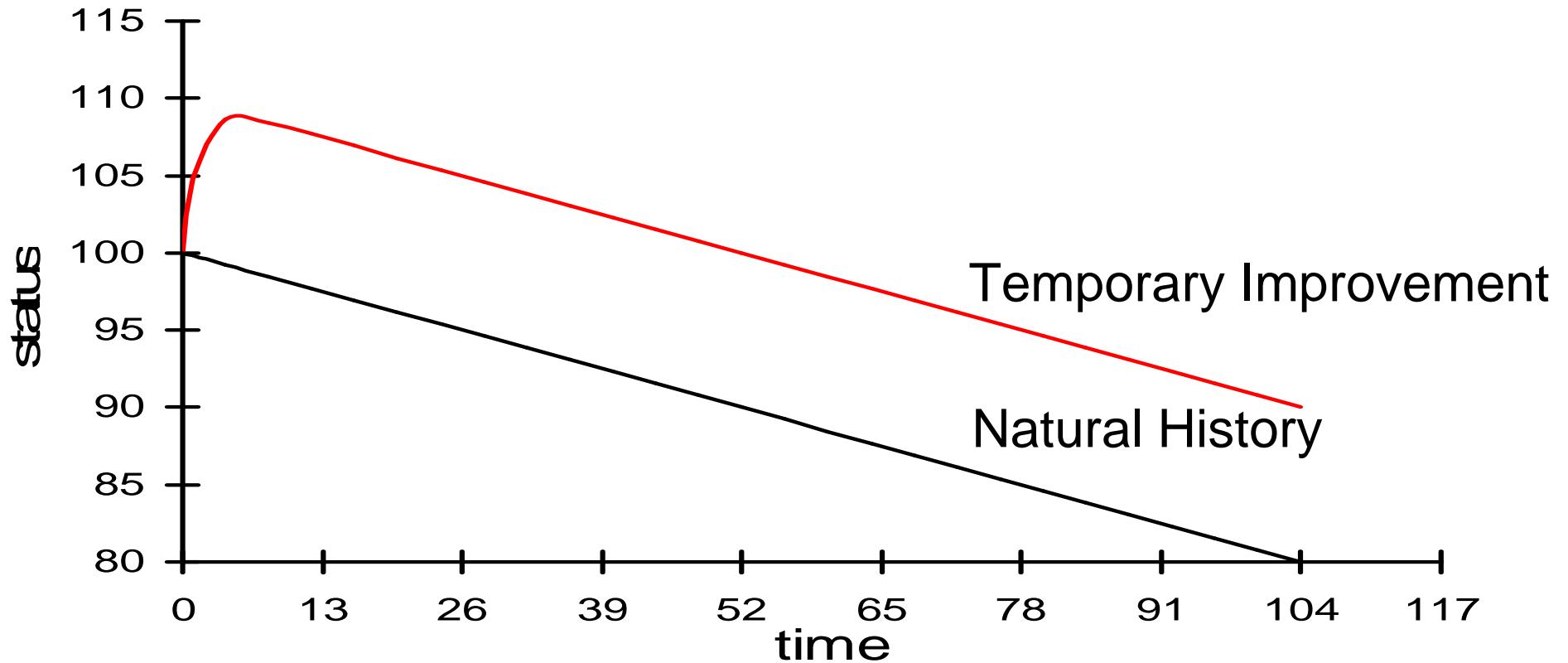
# Components of a Disease Progression Model

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

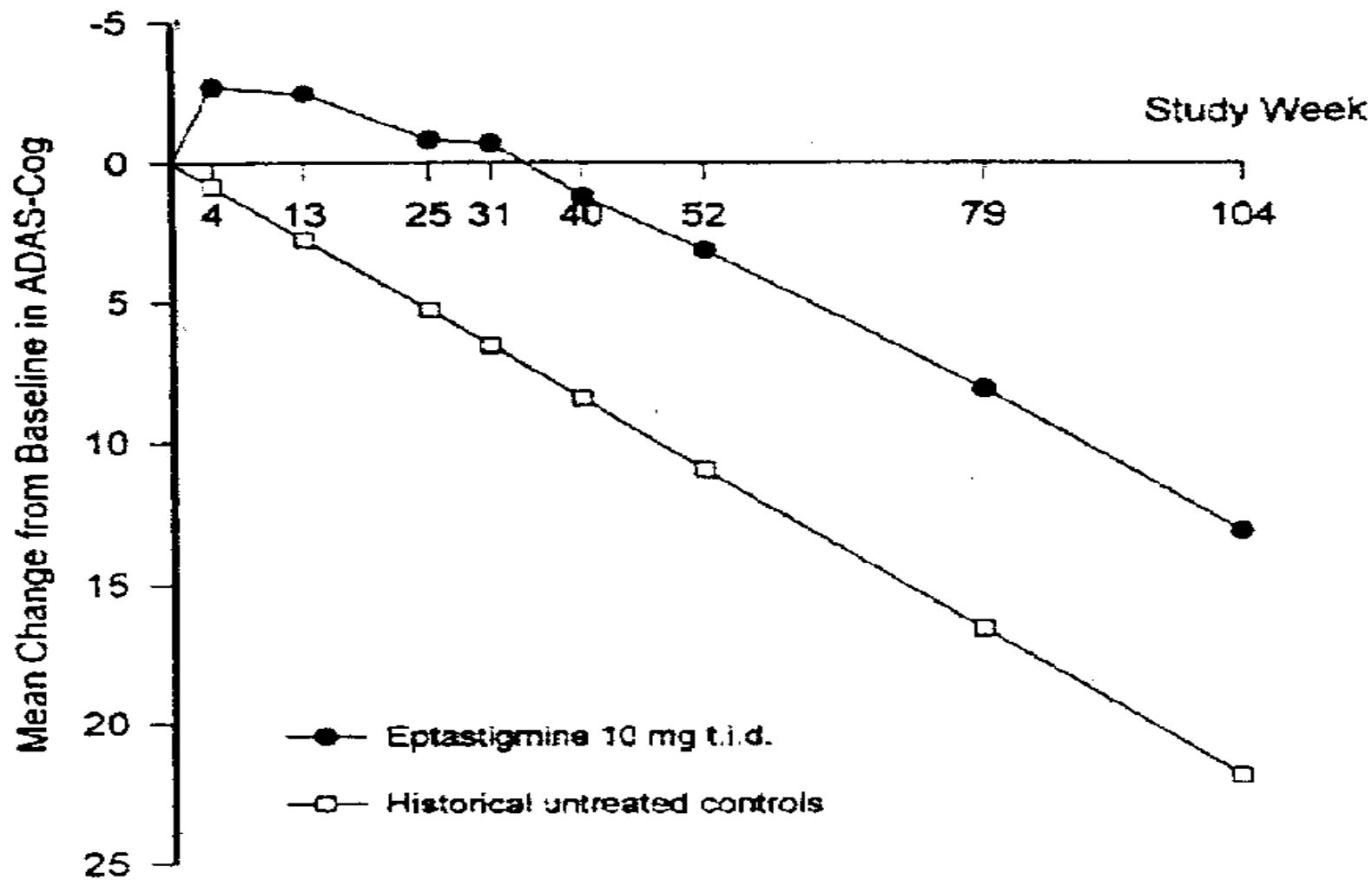
$$S(t) = S_0 + \text{Nat. Hx.} + \text{Plac} + \text{Active}$$

# Linear + Offset (Symptomatic)

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



# 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.

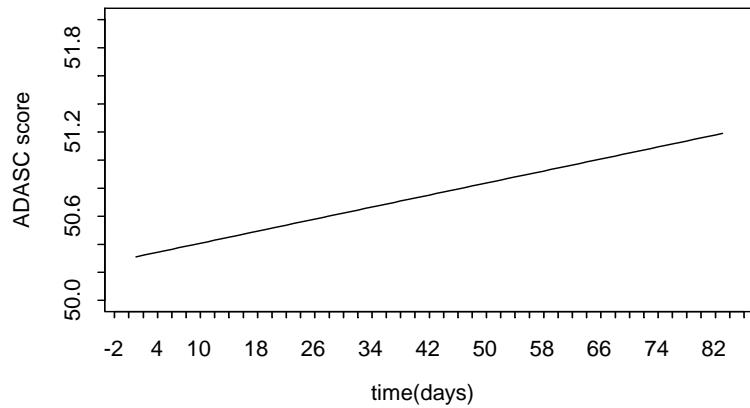
# Disease Progress Placebo Response

- 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

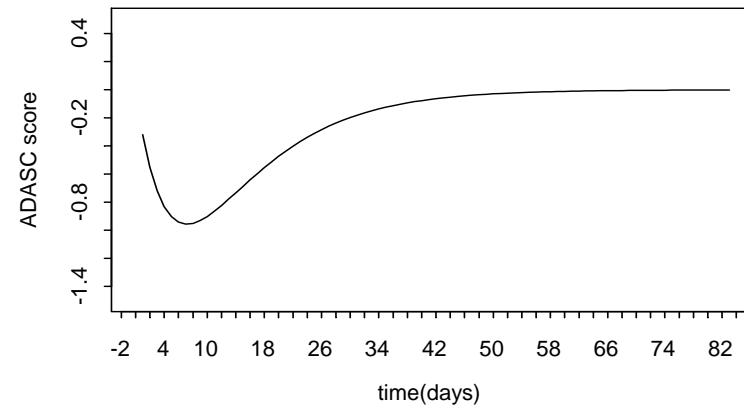
# Placebo Response

## Alzheimer's Disease

Disease Progress

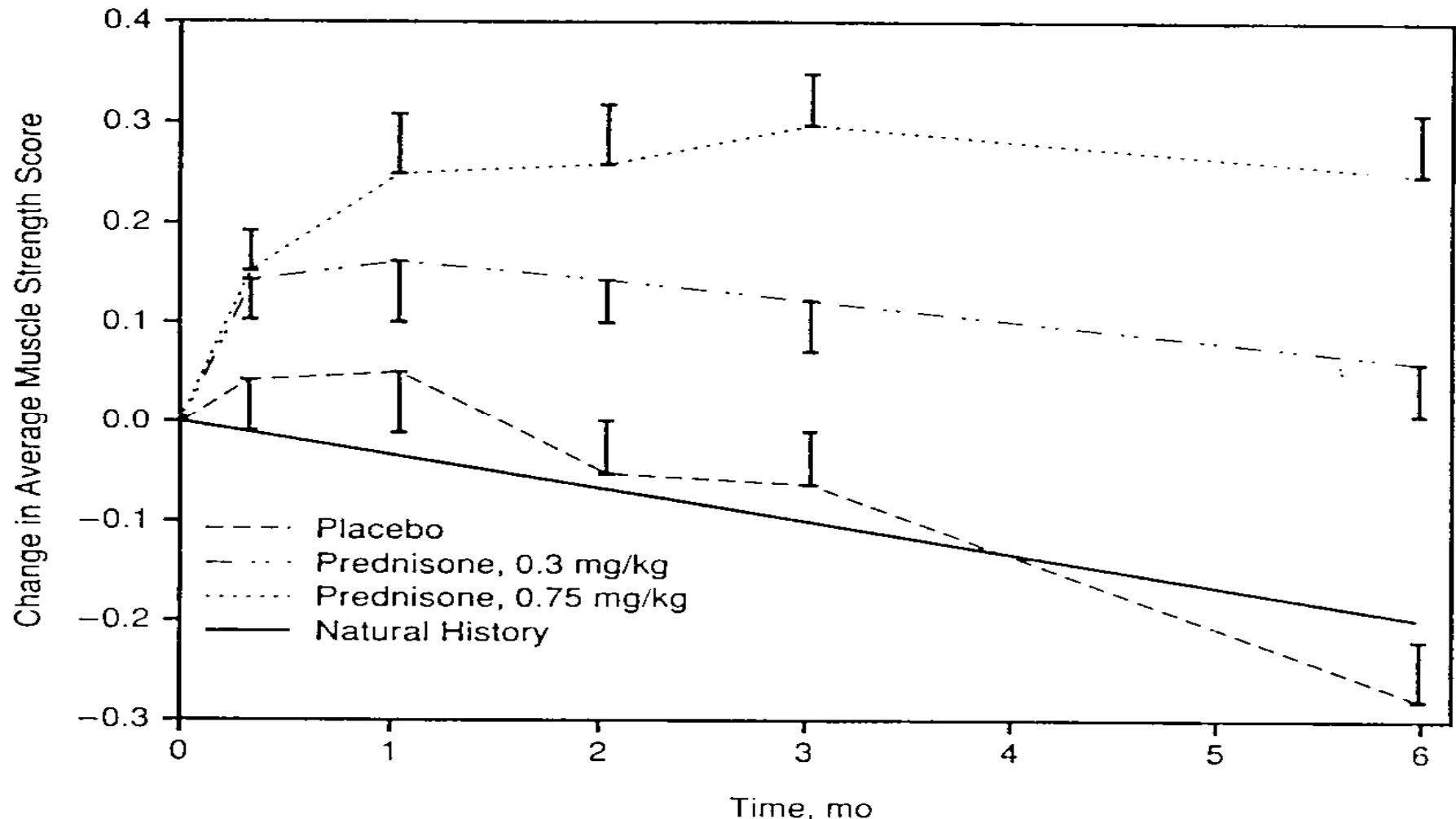


Placebo Response



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?

*It's going to work.*

Literature studies have shown placebo glycated to be consistently effective in the treatment of pain, in disorders associated with chronic muscle aches, back, muscle, muscle contractions, dysmenorrhea, dyspepsia, gout, headache, hypertension, peptic ulcers, nocturnal enuresis, temporomandibular syndrome, asthma, anxiety, and mood, and the last year, internationally there were 280,000 published trials, involving cardiac, hypertension, diabetes, dyspepsia, indigestion, functional gas, heartburn, hypertension, atrial fibrillation, stroke, headache, pain, back pain, neck pain, temporomandibular syndrome, muscle pain, facial pain, tension, tension, and myofascial pain, lower back pain, muscle cramps, spasms, vertigo, asthma, anxiety, depression, migraines, hypertension, chronic daily headache, IADP, bruxism, tension headaches, fibromyalgia, asthma, sleep disturbance, anxiety, hypertension, strengthen, insomnia, at, leg, rheumatology, elbow, knee, rheumatology, urinary continence, anxiety, joint pain, hypertension, generalized syndrome, and post-infection.

Our patients associated with the use of a placebo indicate diminished or increased blood pressure and reduced antihypertensive drugs, reduced blood glucose, diabetes, and have been experiencing reduced mental distress, anxiety, headache, physical exhaustion, vertigo, sleep disturbance, mood and personality changes; reductions in speech and movement memory impairment, confusion and decreased dimensions, increased dimensions, very small increases in pain, pain and other difficulty, reducing changes in appearance, behavior and biology of the receptor to new stimuli, but others, causing feeling such pain, skin reactions, & weight, effects on rapid emotional changes or disruption of the brain on how we think, memory and when we are told the diagnosis, physical, emotional, and social changes, change in behavior, can play an important role in helping individuals to feel well and reduce their dependence on drugs and self-medication, individuals including families from the most rural areas, which may seem unlikely to benefit from the placebo effect, however, some individuals, even those of the most rural areas, seem positively, possibly due to a placebo effect, from taking placebo or taking medications, including hypertension, depression, and changes in mood, mood and memory.

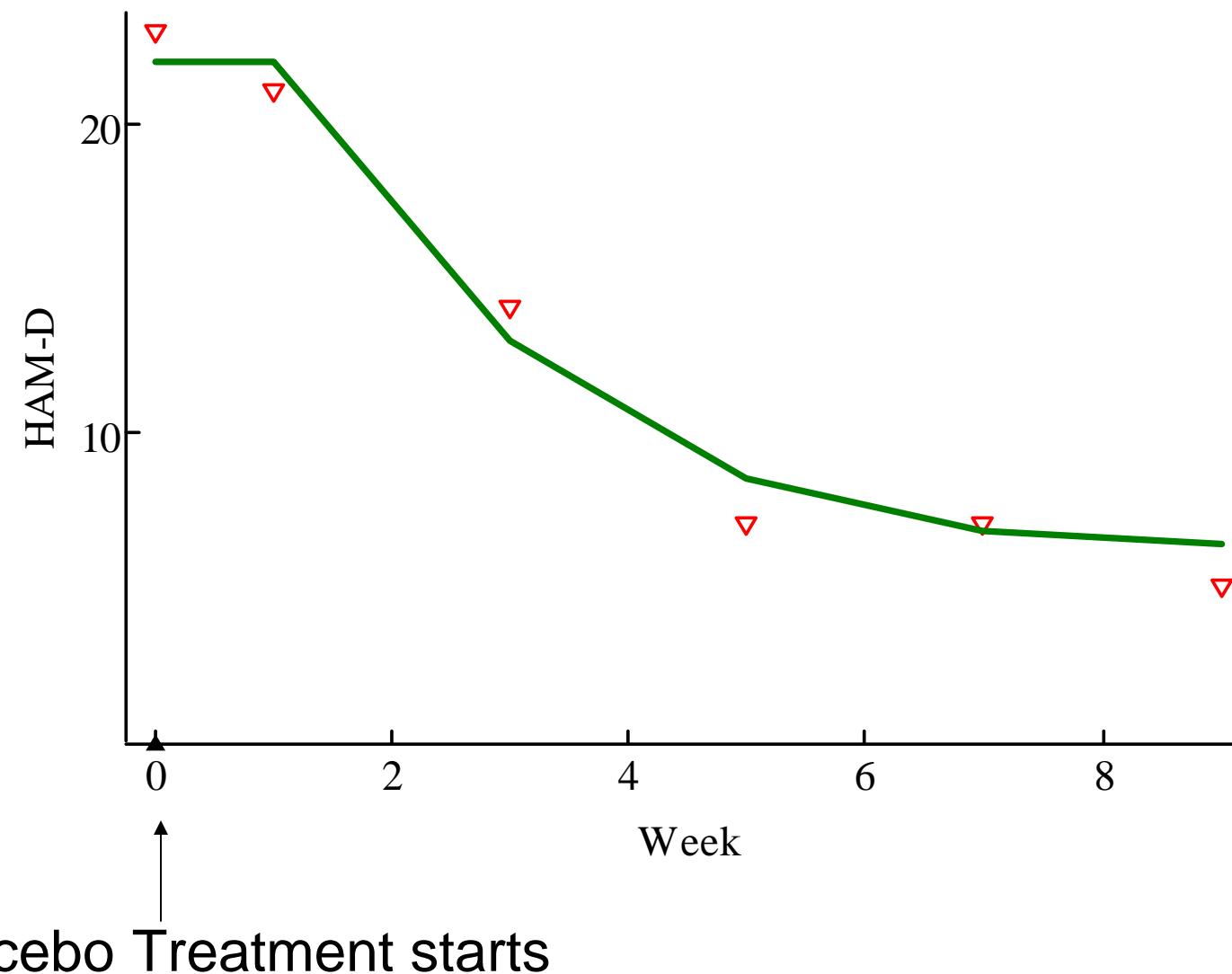
**Sucrosa**  
placebo

**AstraZeneca**

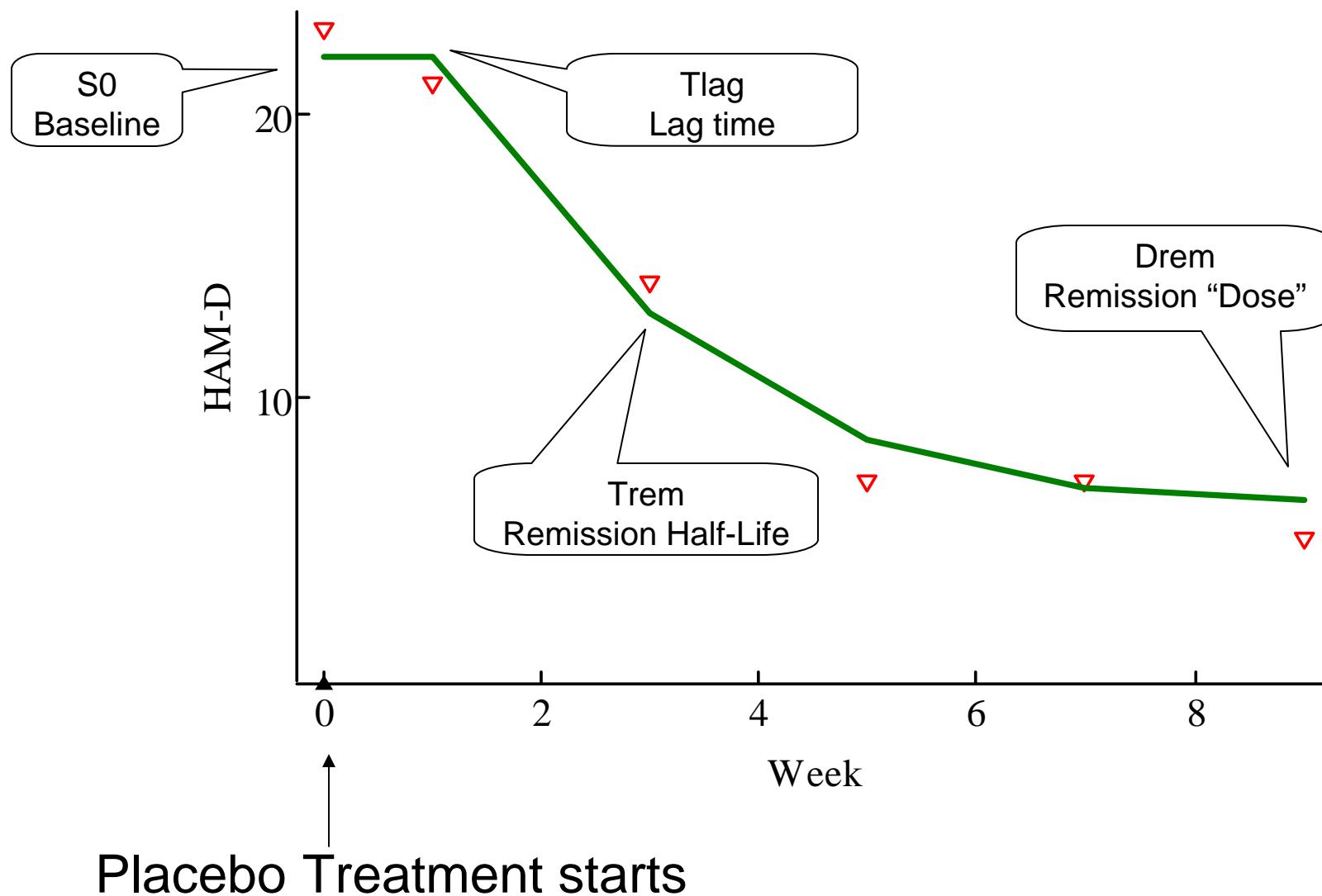
# Anti-Depressant Response

- “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
  - Known to have a rapid effect
    - “crack cocaine”
    - Serotonergic syndrome
  - Why is the anti-depressant response delayed?

# HAM-D Response

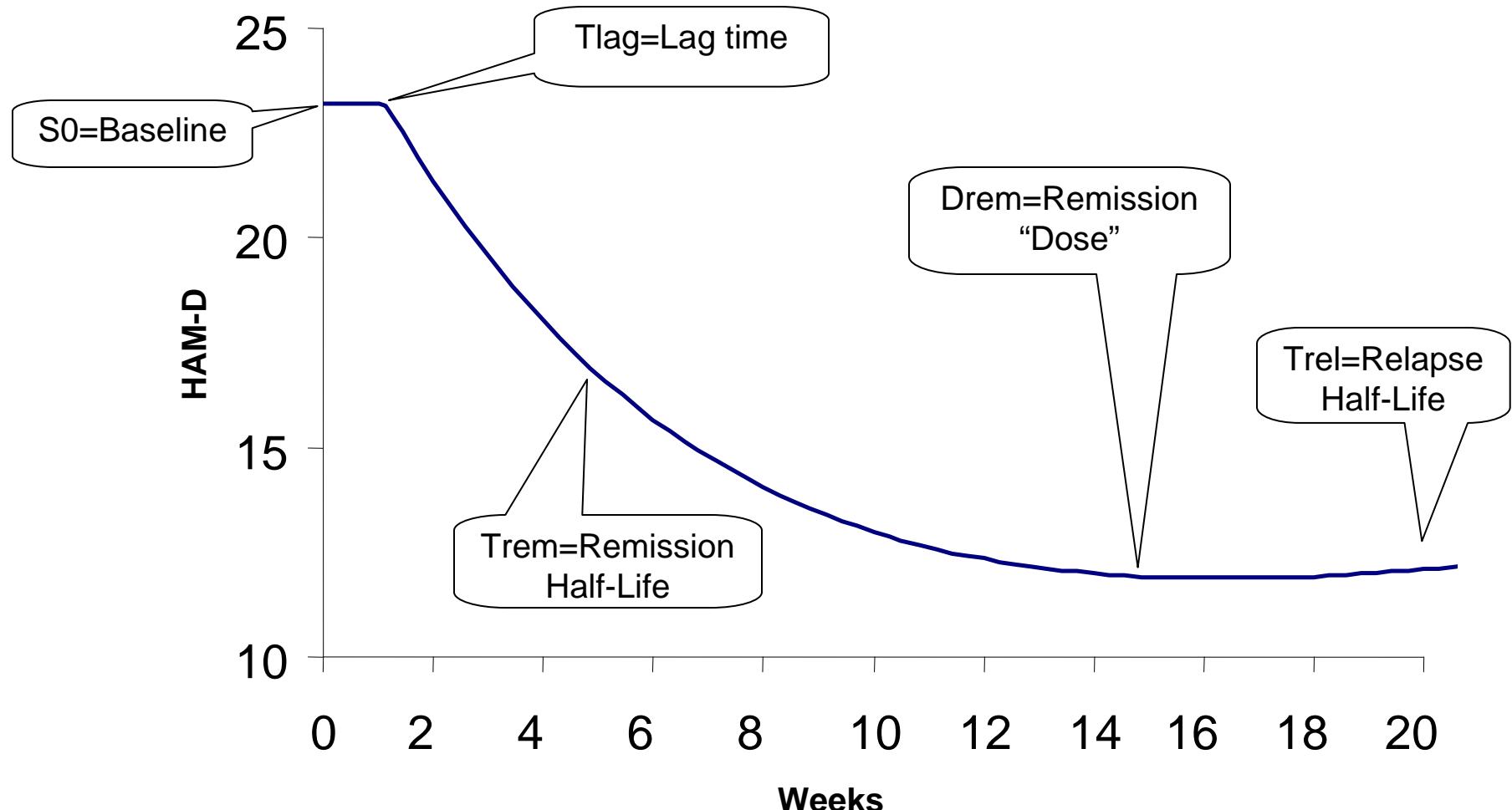


# Simple Placebo Response



# Full Placebo Response

“first order absorption and elimination”



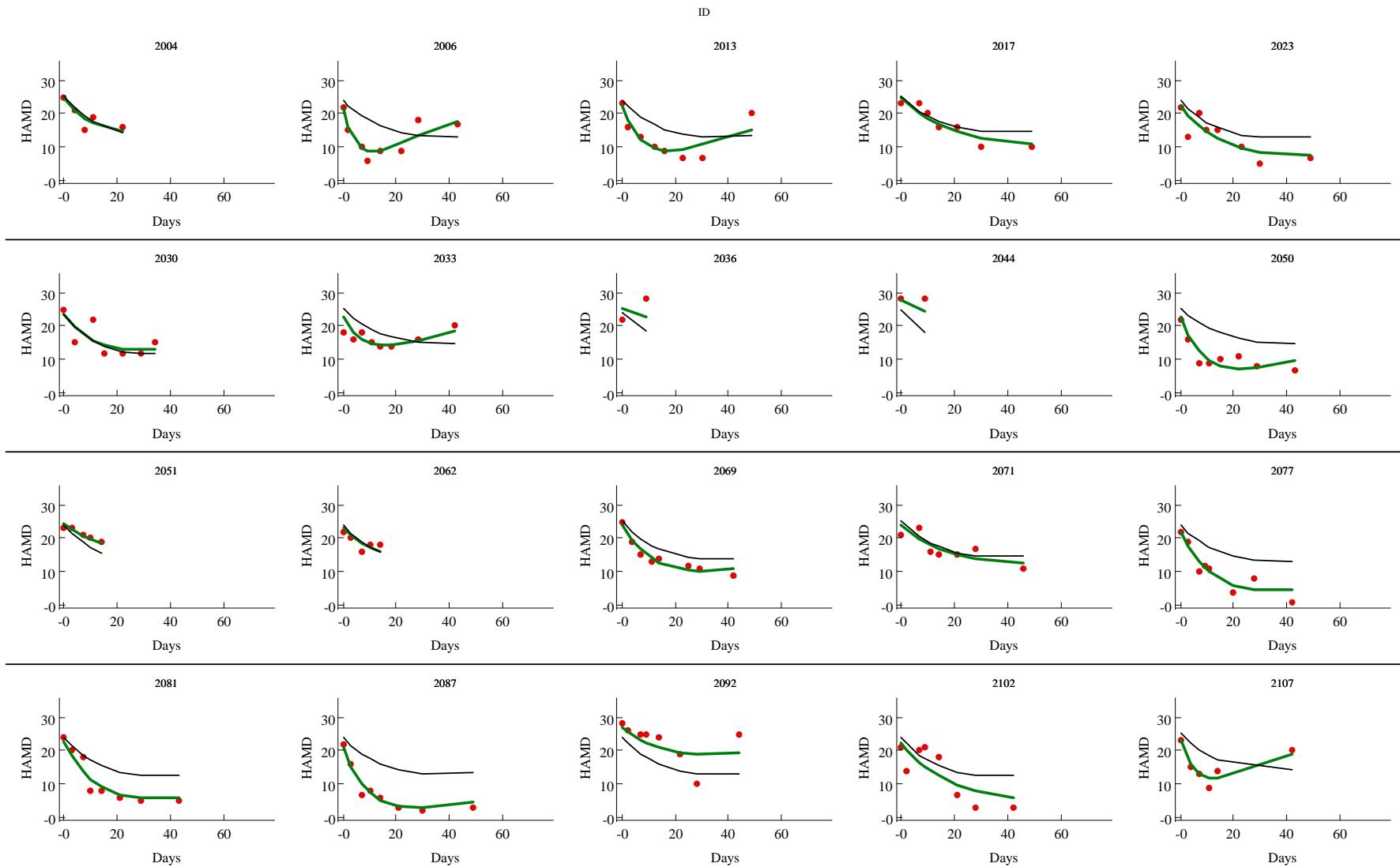
# **Investigation 1**

**Placebo treated HAM-D profiles  
from 4 clinical studies**

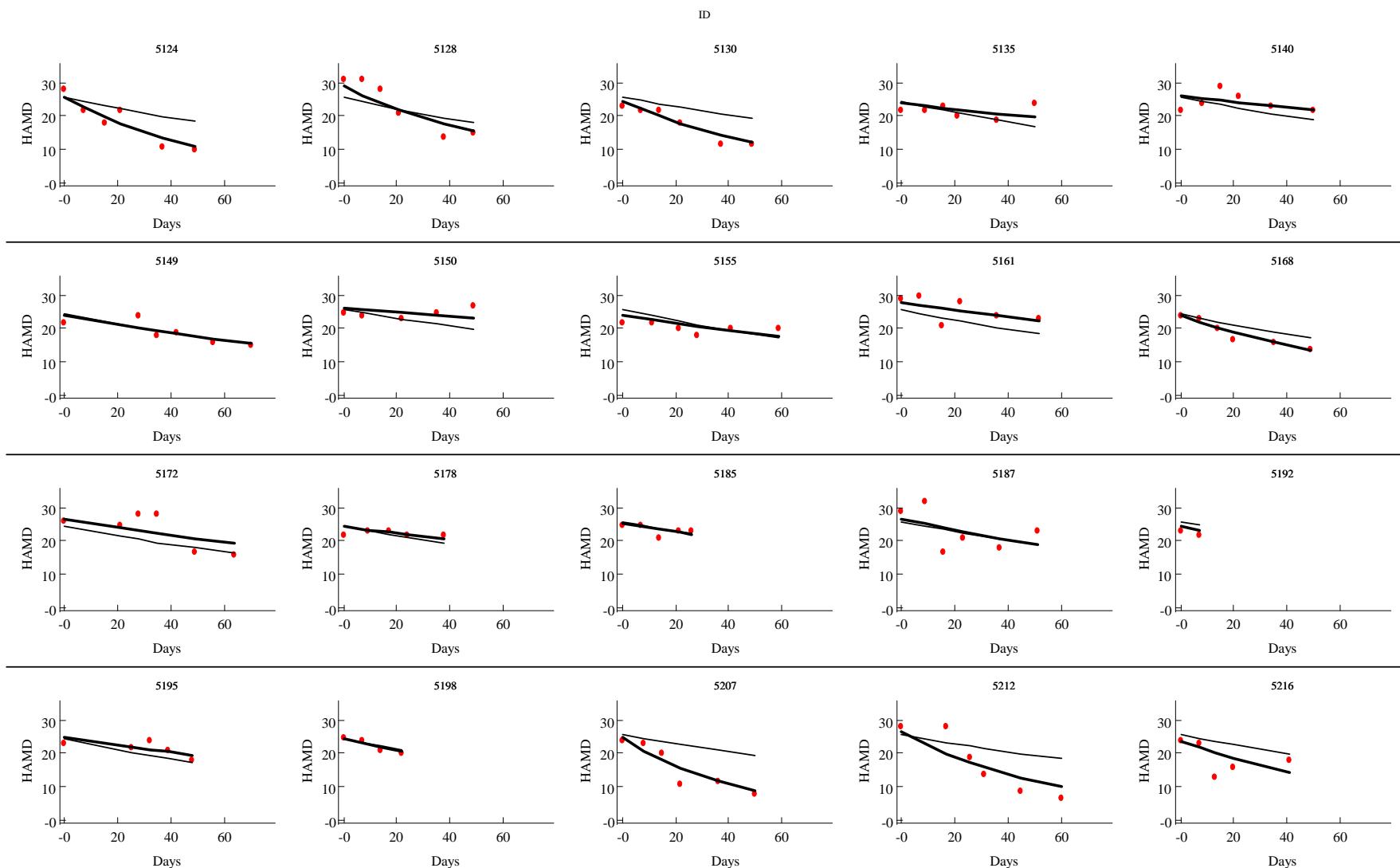
# What Determines the Time Course of Placebo Response?

- 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

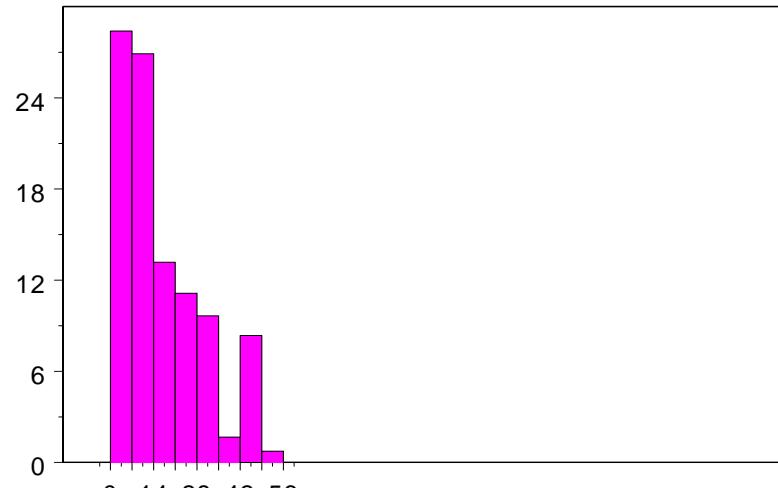
<b>Study A</b>	98%
<b>Study B</b>	45%
<b>Study C</b>	29%
<b>Study D</b>	18%

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

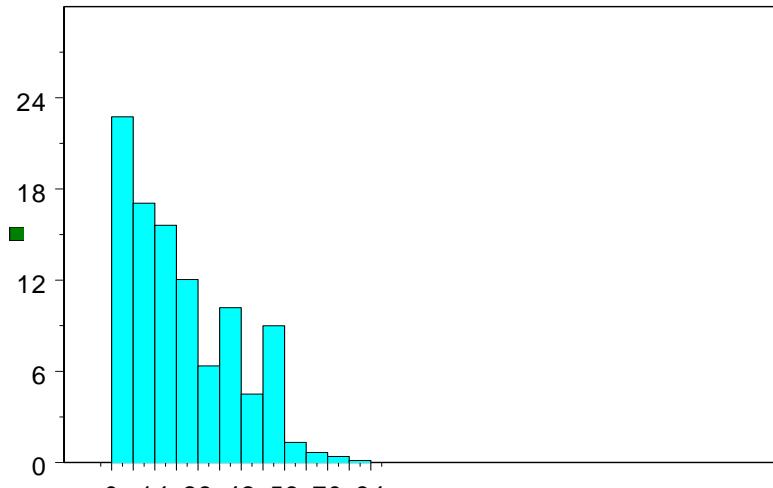
# Is It a Design Issue?

## HAM-D Observation Times

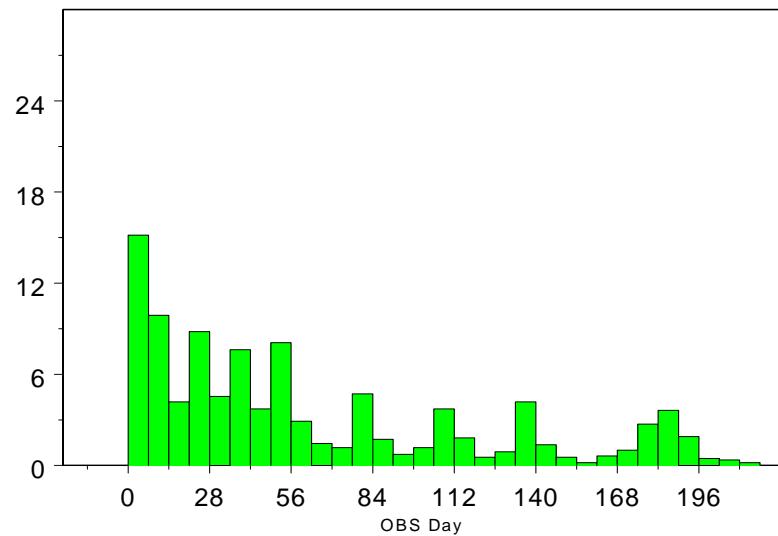
Study A



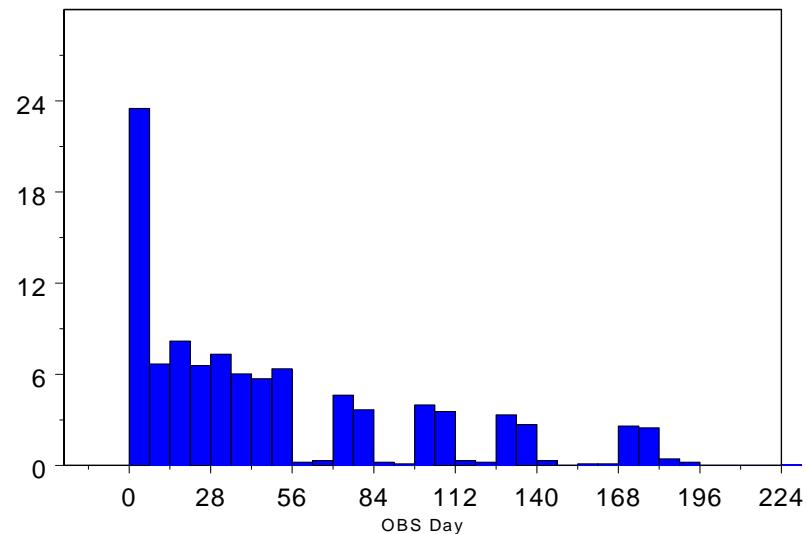
Study B



Study C



Study D



# 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

Disease Progression

Placebo Response

Effect Compartment  
Concentration

Drug Action

HAM-D Time Course

Equations

$$S(t) = S_0$$

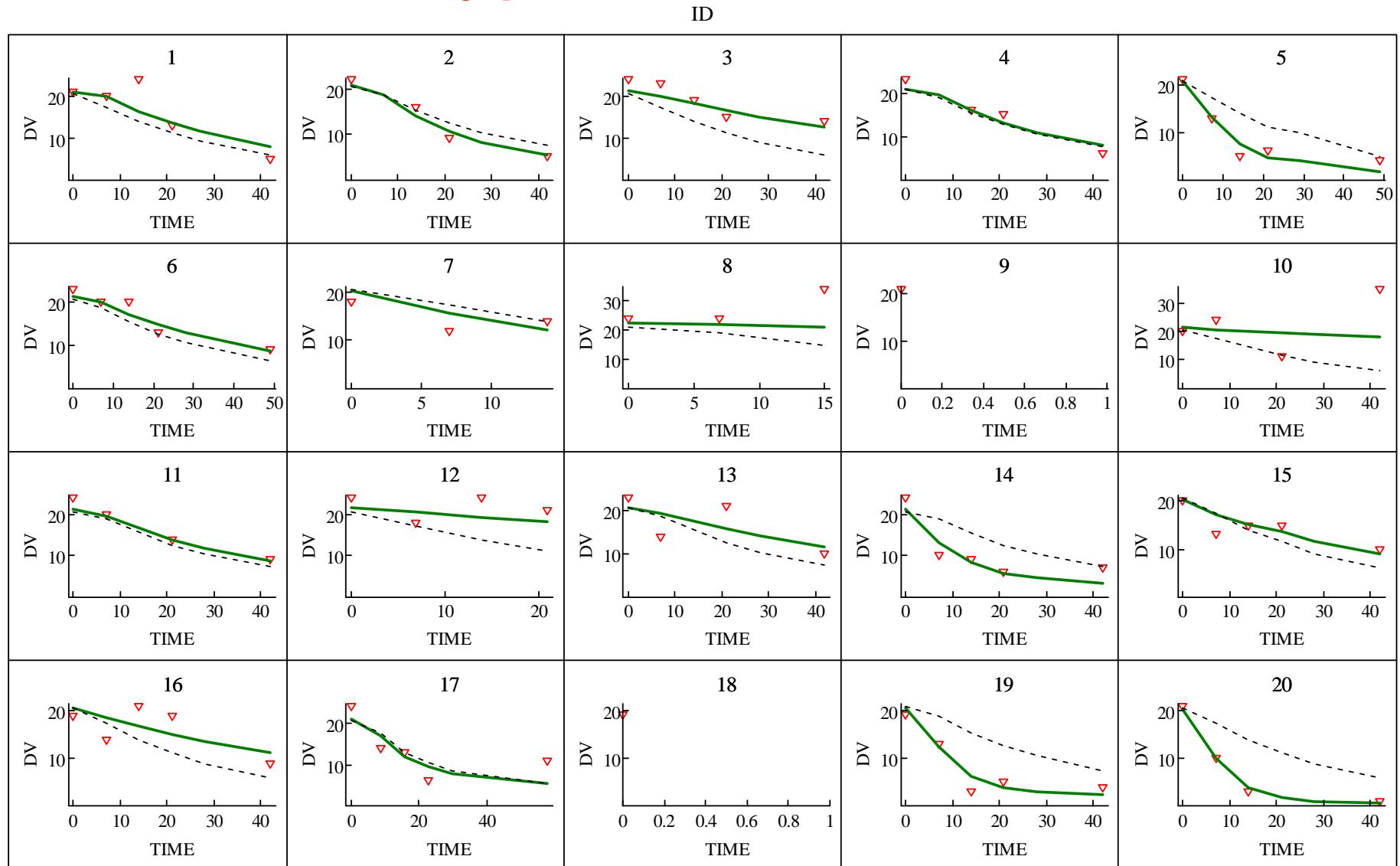
$$\text{Placebo}(t) = D_{rem} \cdot \left(1 - e^{-\ln(2)/T_{rem}(t-T_{lag})}\right)$$

$$Ce(t) = \frac{\text{DoseRate}}{\text{Clearance}} \cdot \left(1 - e^{-\ln(2)/T_{eq}t}\right)$$

$$PD(Ce) = Beta \cdot Ce$$

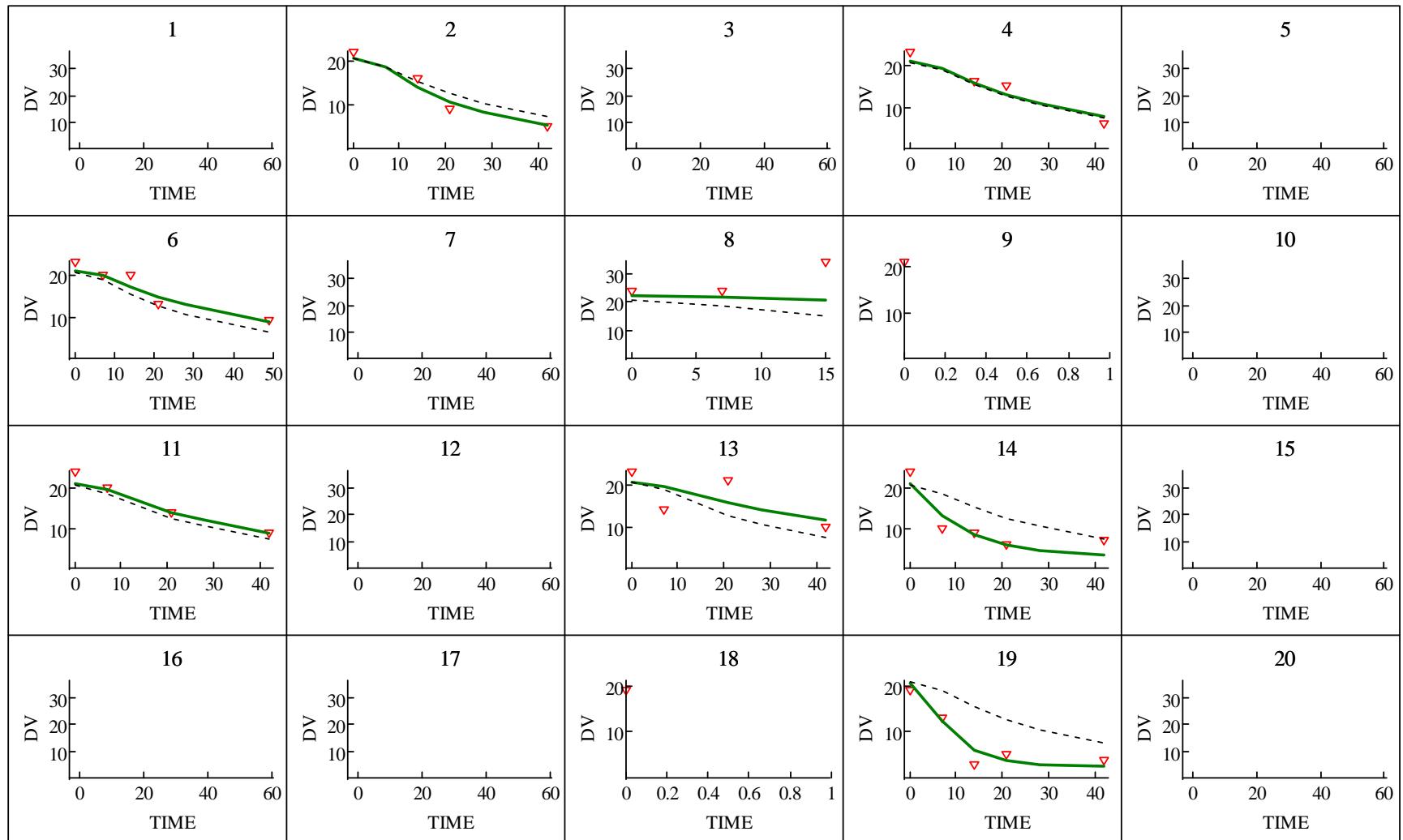
$$HAMD(t) = S(t) + \text{Placebo}(t) + PD(Ce(t))$$

# Typical Profiles

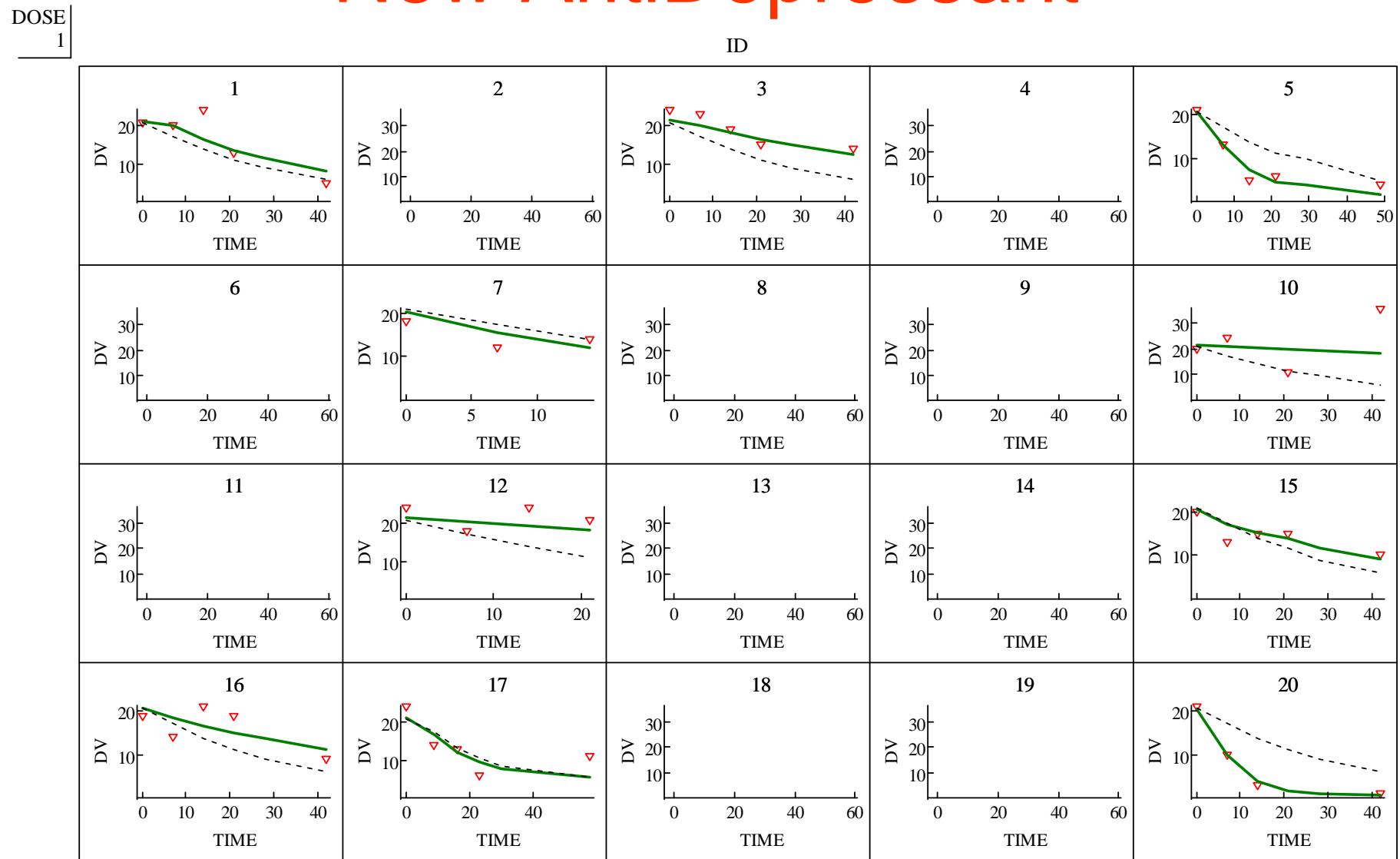


# Placebo

DOSE  
0



# New AntiDepressant



# 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	<b>-1.45*</b>	<b>-1.62</b>	<b>-0.25</b>	0.718	0.443	1.836
UV	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**

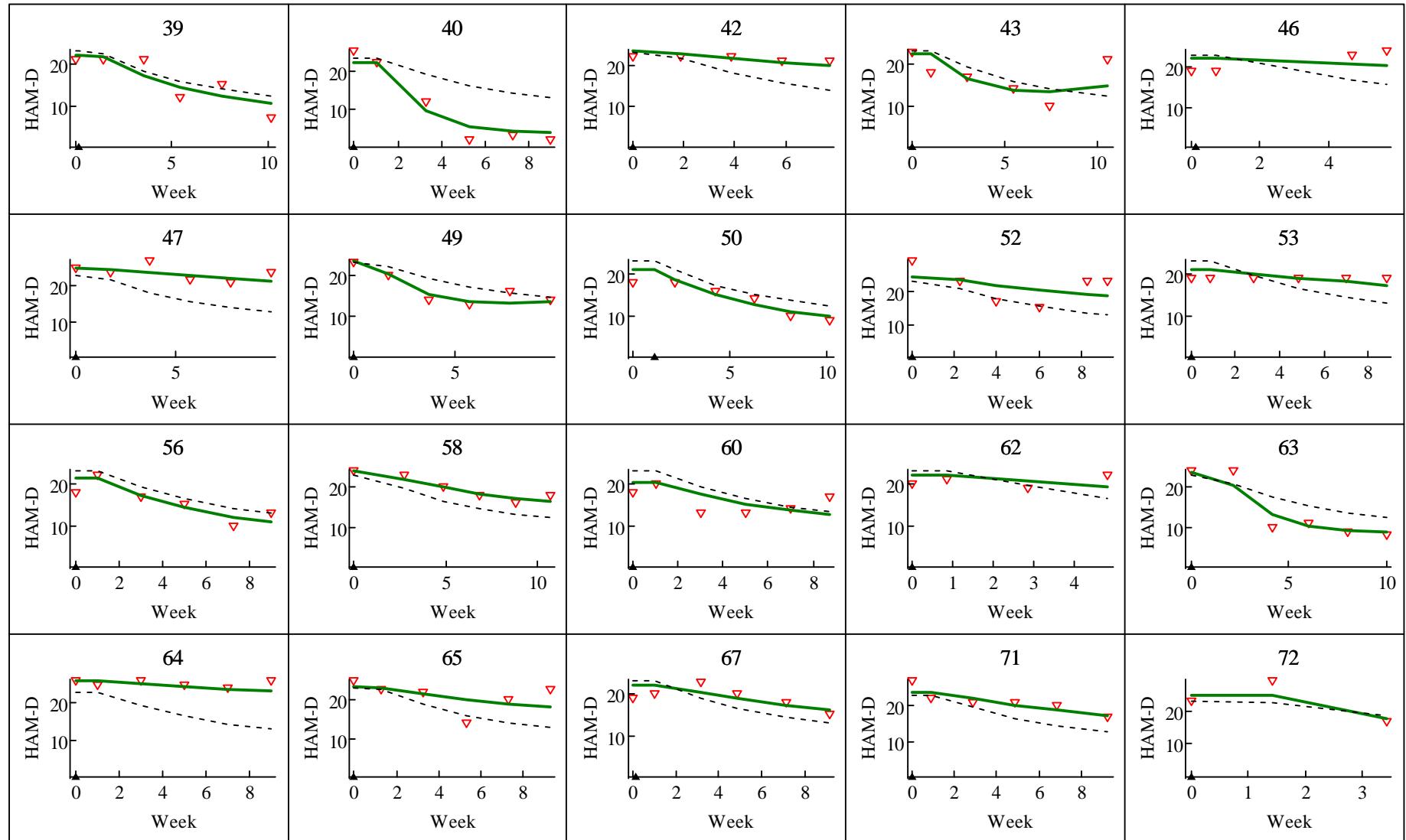
**Retrospective analysis of large  
clinical database**

**“Positive” and “Negative” trials**

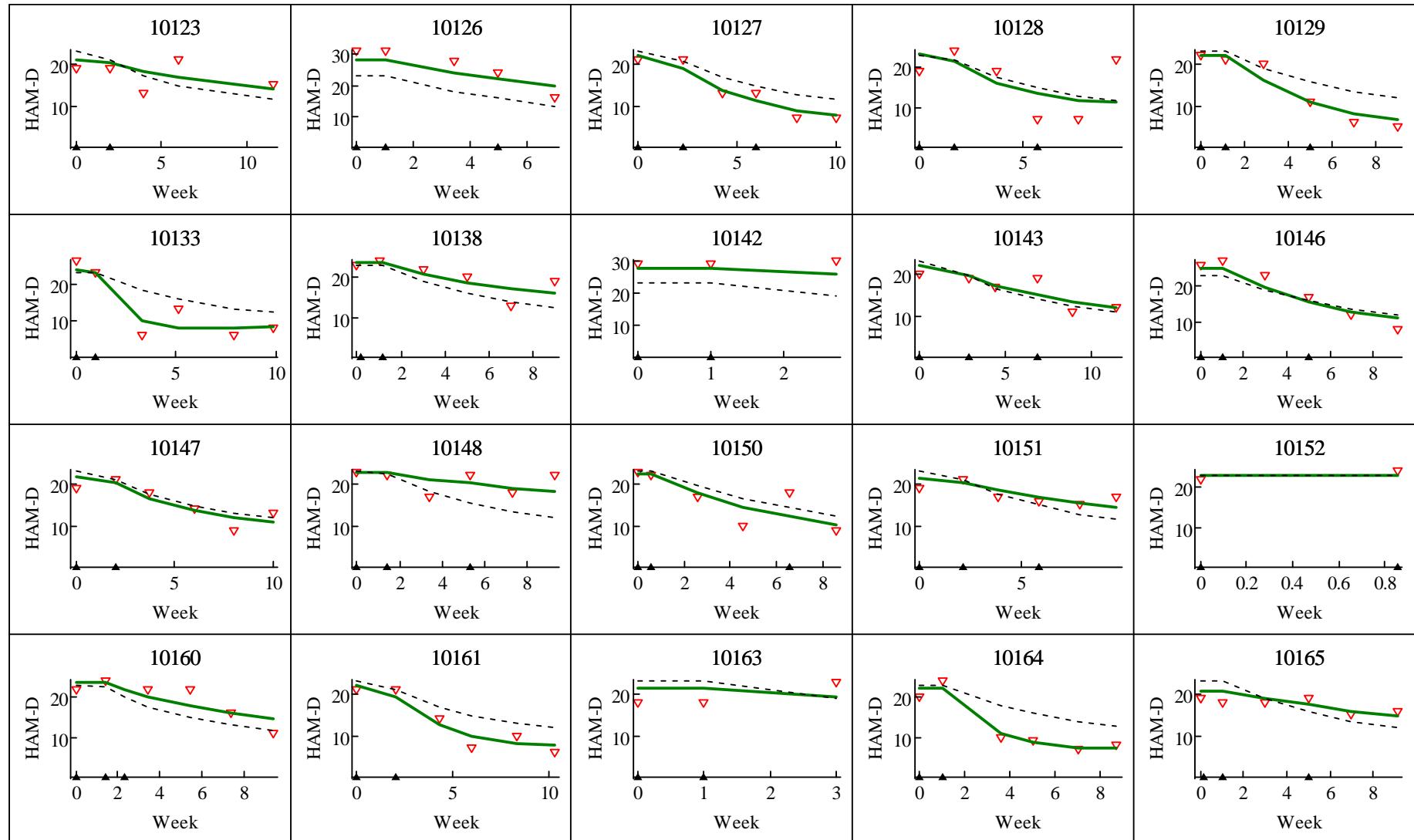
# **Patients with Major Depressive Disorder enrolled in Placebo Controlled Clinical Trials of Anti-Depressants**

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

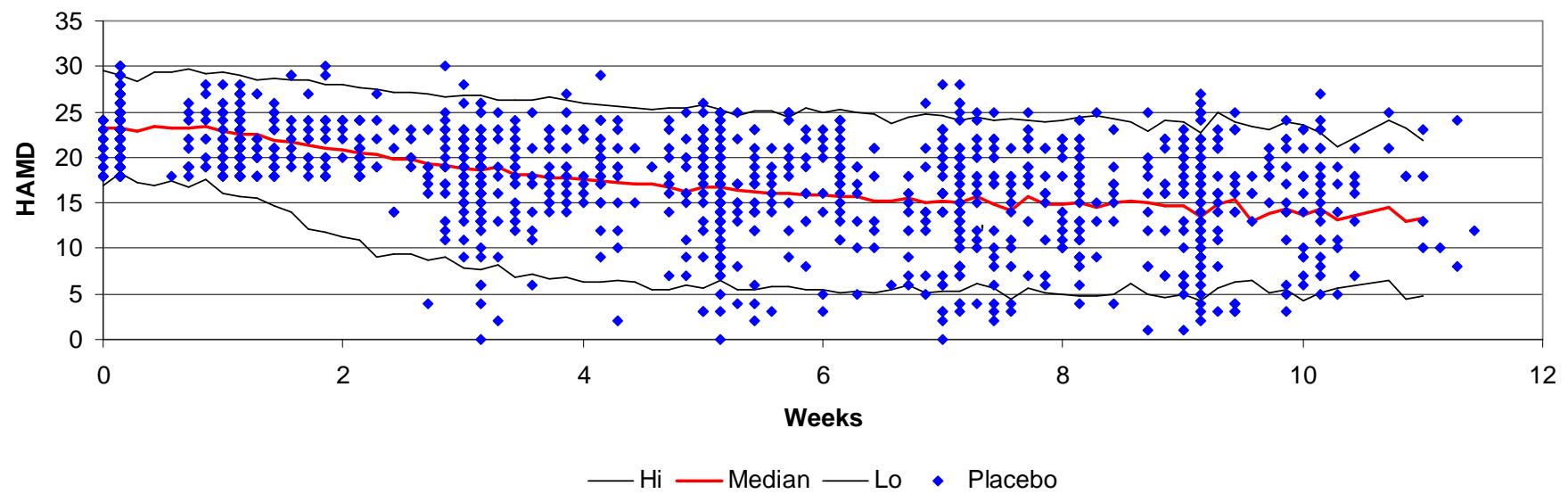
# Placebo



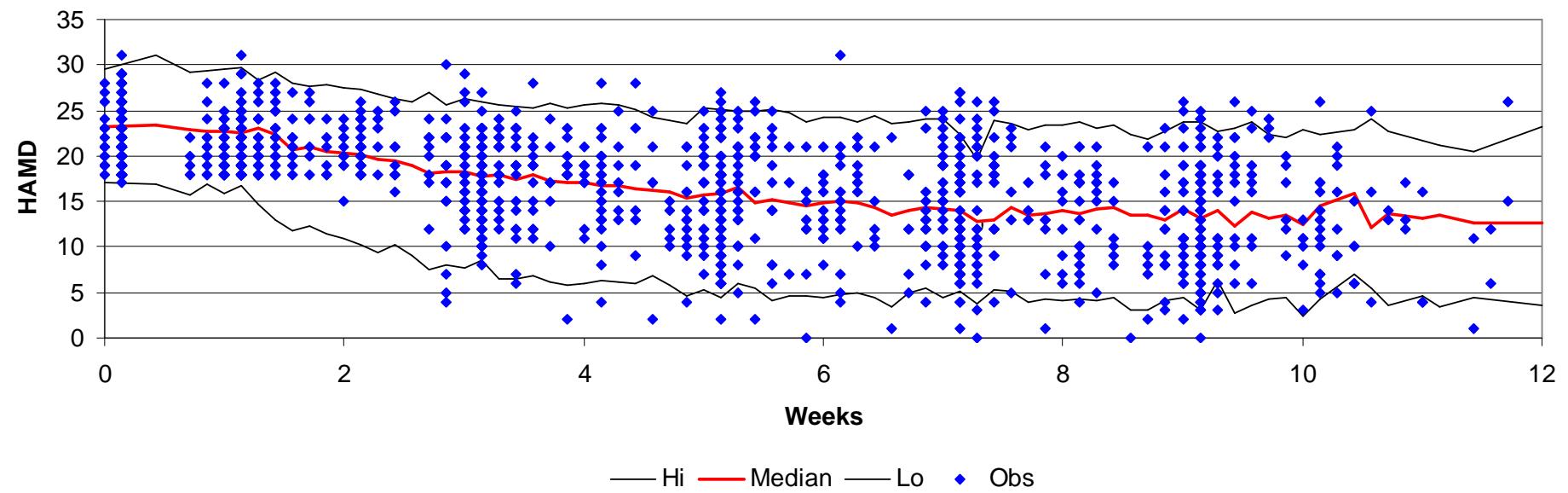
# Marketed Active Drug



# 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)

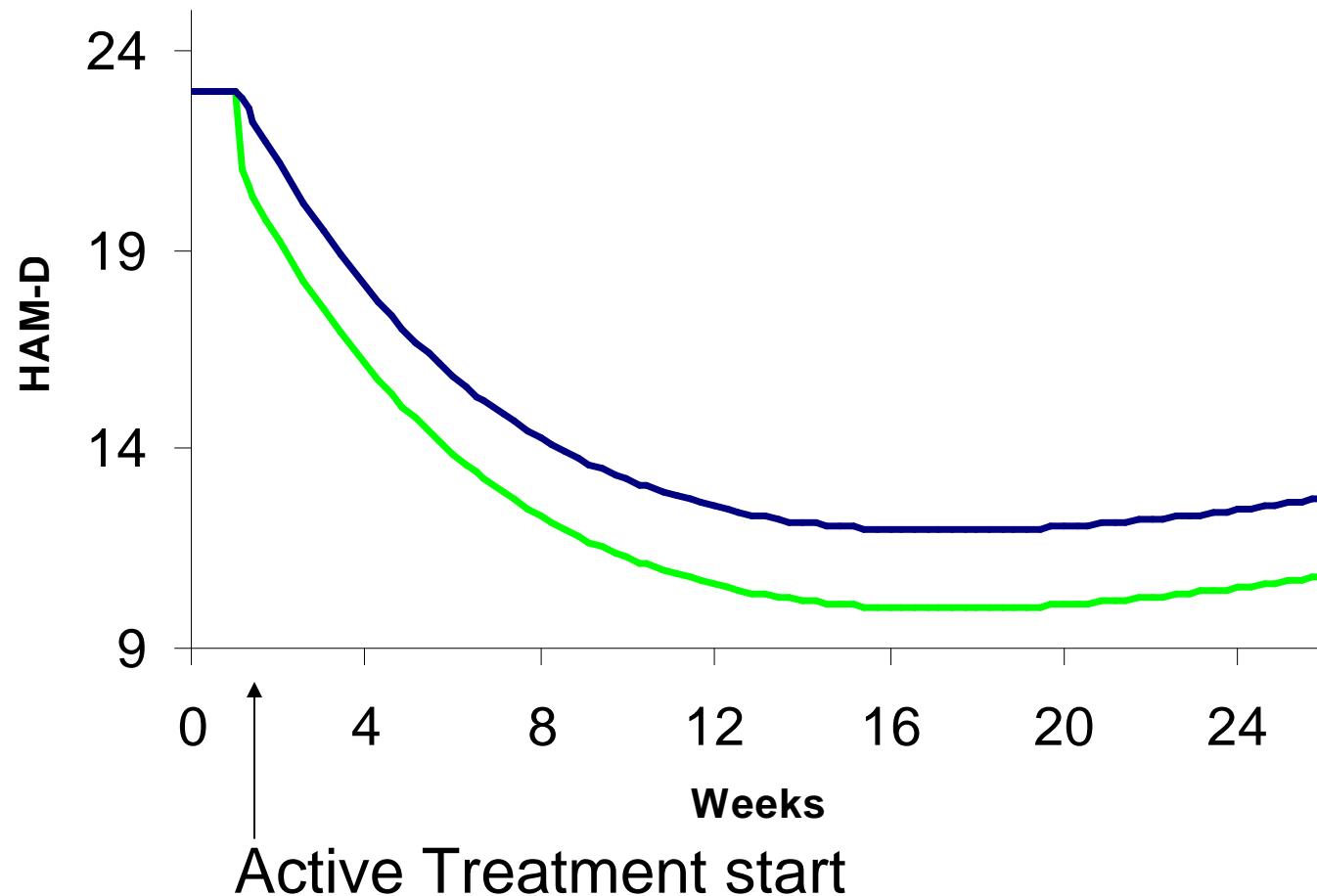
# Active Treatment Effects

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!