

AS12: Roles of Biomarkers in the evolution of Phase 1 studies

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AGENDA

- Introduction to Phase 1 clinical trials
- Study designs
- Objectives of Phase 1 clinical trial
- PK/PD definitions and purpose in Phase 1 trail
- Biomarkers explained
- Analysis of PD Parameters and Biomarkers
- Conclusion

Phases of Clinical trials pre-marketing

Pre-Clinical

- Laboratory studies
- Cell studies – often on new treatments
- Animal studies – promising in cell studies

Phase 0

- Not widely used
- <15 subjects
- Small doses for shorter time
- NOT required as part of new drug

Phase 1

- Usually, FIH
- HV or Patients
- +/-10 to 100 subjects
- MTD without SAEs
- Dose escalation starting with low dose
- PK

Phase 2

- Usually same dose
- Balance of Safety and Response
- +/-25 to 100 subjects

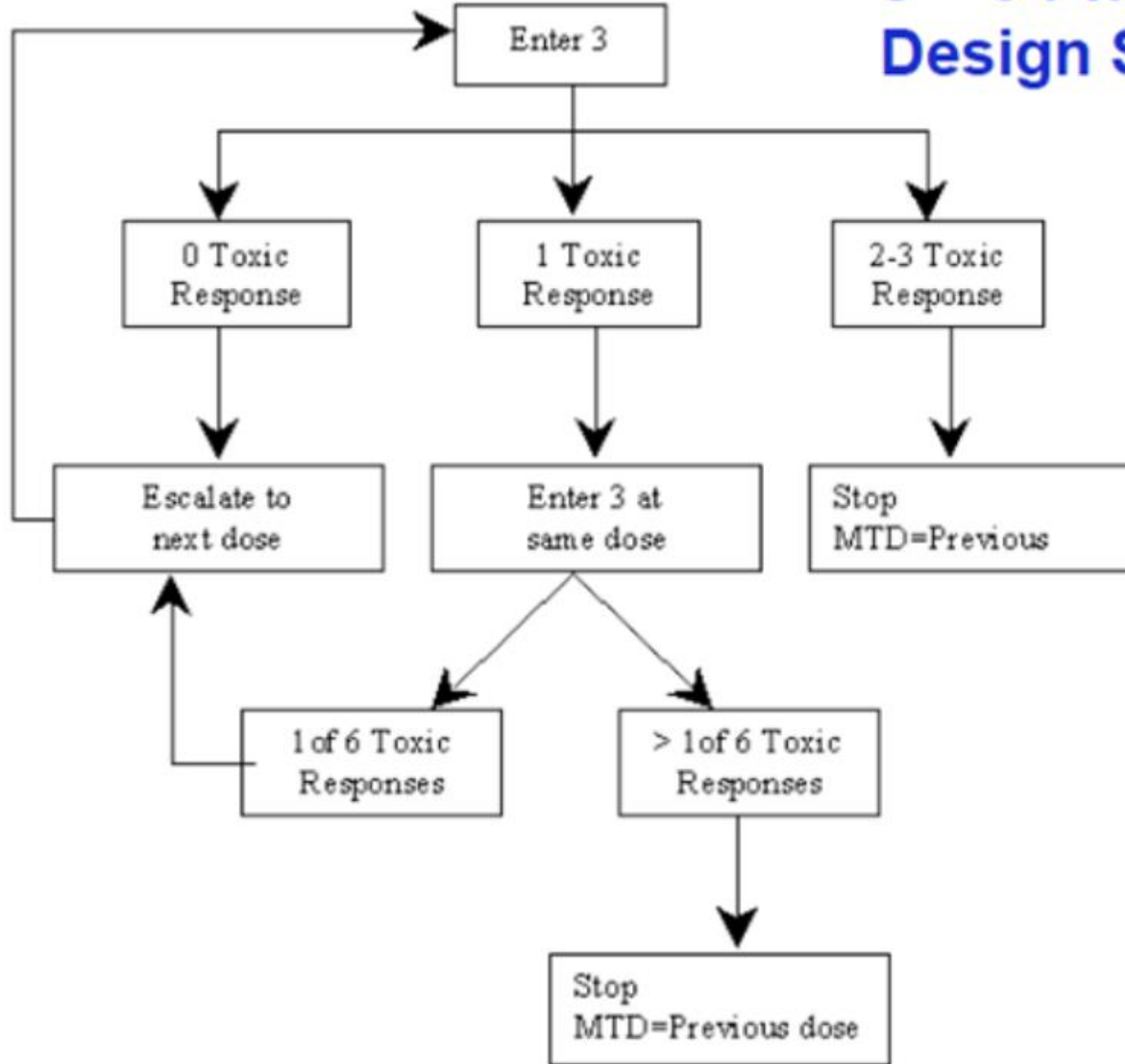
Phase 3

- Large population size – at least 100
- Safety and Efficacy
- Longer duration studies
- Various geographic locations

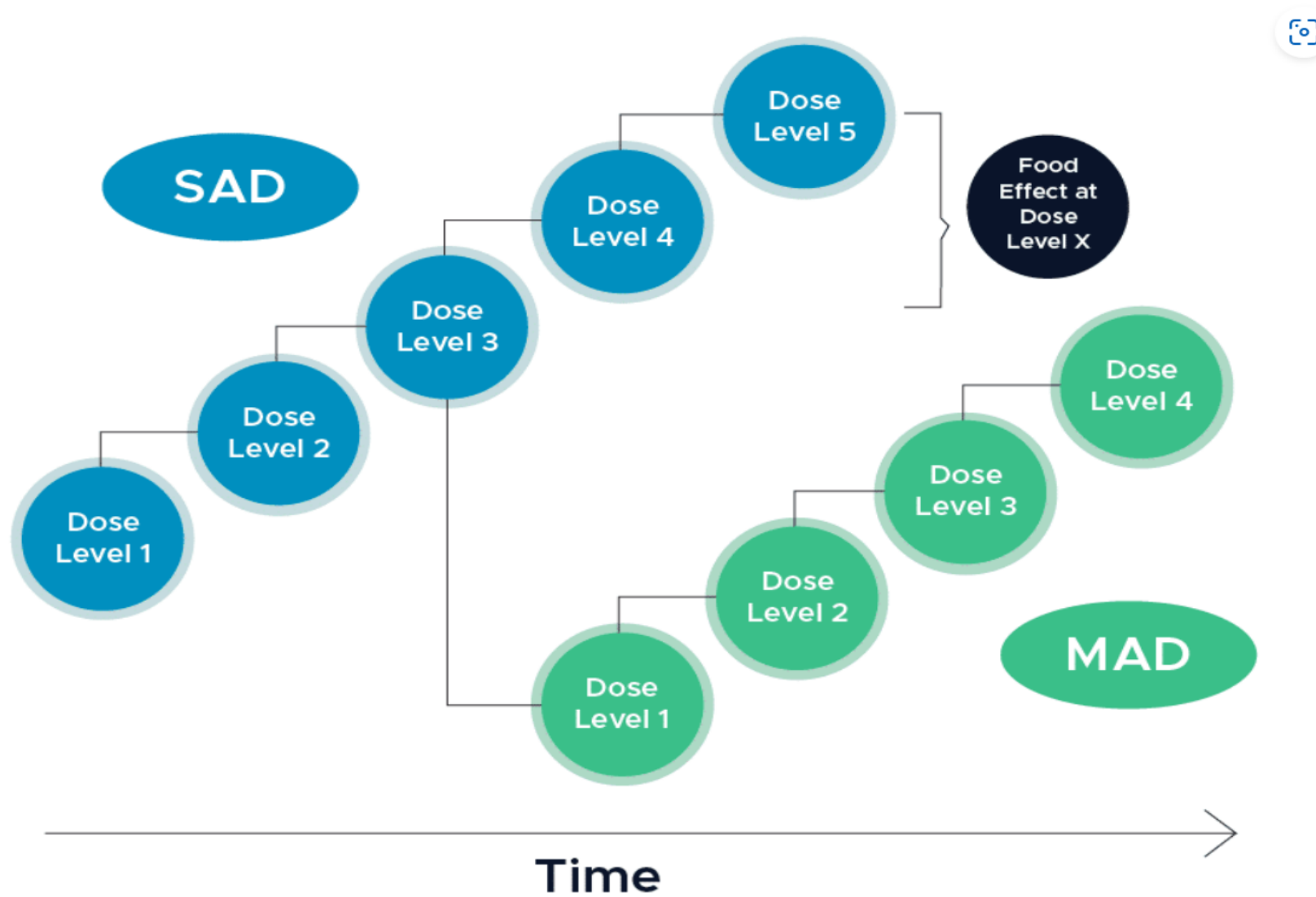
Introduction to Phase 1 trials

Primary endpoints:	Evaluation of pharmacology and toxicity of an investigational drug in humans Pharmacokinetics: Absorption, distribution, metabolism and excretion of the drug in the human body Pharmacodynamics: Effect of the drug on the human body Safety & Tolerability: Safe dose range of the drug for future trials
Subjects	Healthy volunteers (sometimes seriously ill patients with no other options or when drug is toxic to healthy volunteers, such as cytotoxic chemotherapy agents)
Study Designs	SAD, MAD, FE, DDI, BE/BA
Sample size	6-20, typically healthy volunteers
Duration	9-18 months

3 + 3 Phase 1 Study Design Schematic



SAD, MAD, FE Phase 1 Study design



Criticisms of standard design



Bruce A. Chabner

- The dose escalation is unnecessarily slow, leading to treatment of excessive numbers of patients at dose levels less likely to be efficacious
- The MTD definition is unnecessarily imprecise in that it does not make adequate use of all the available first course toxicity data - 25% of oncology agents registered with the FDA are labeled at a dose different from that identified in phase I (Letourneau, JCO 2010;28:1401.).
- Too few patients treated at the MTD

PHARMACOLOGY

"THE STUDY OF THE EFFECT OF CHEMICALS"
ON LIVING TISSUES.

PHARMACODYNAMICS

- WHAT THE DRUG DOES TO
THE BODY



- PHYSIOLOGICAL & BIOCHEMICAL
PROCESS OF MECHANISM OF ACTION
OF DRUGS.
- INVOLVES:
 - ① DOSE-RESPONSE RELATIONSHIP
 - ② RECEPTOR BINDING/AFFINITY
 - ③ POTENCY + EFFICACY

PHARMACOKINETICS

- WHAT THE BODY DOES TO
THE DRUG.



- CHANGES IN CONCENTRATION
OF DRUG THROUGH PHYSIOLOGIC
PROCESSES.
- INVOLVES:
 - ① ABSORPTION
 - ② DISTRIBUTION
 - ③ METABOLISM
 - ④ EXCRETION

Biomarkers explained

- A biomarker is a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention.

Indication	Example Indications	Common Biomarkers
Neurodegenerative	ALS, MS, Alzheimers	Neurofilament Light Chain, Total Tau, Amyloid β
Metabolic Disorders	Diabetes, Obesity	Insulin, Glucagon, Leptin
Renal	AKI, CKD	Cystatin C, Kidney Injury Molecule-1, NGAL
Cardiovascular	CVD, HF	C-Reactive Protein, N-terminal proBNP, Thrombin
Autoimmune Diseases	RA, LN, SLE	Matrix Metalloproteases, C-propeptide type collagens
Safety	CRS	Interleukins, Tumor Necrosis Factor, Interferons

- Pharmacokinetics - Immunogenicity – Biomarkers
- Can be used for diagnosis, prognosis, and disease progression.
- The benefit of biomarkers goes well beyond just oncology studies.
- Qualified methods vs validated methods; tiered approach (fit-for-purpose depending on the context-of-use of the biomarker within the overall protocol).

PD/Biomarker Analyses

- For the PD/Biomarker analyses we usually use the PD population
- Descriptive statistics for actual results, the change from baseline and percent change from baseline (arithmetic mean, standard deviation [SD], minimum [Min], maximum [Max], median, and, if applicable geometric means and coefficient of variation [CV%]).
- Comparison of changes (and percent changes from baseline) using statistical methods amongst the different dose level groups or treatments

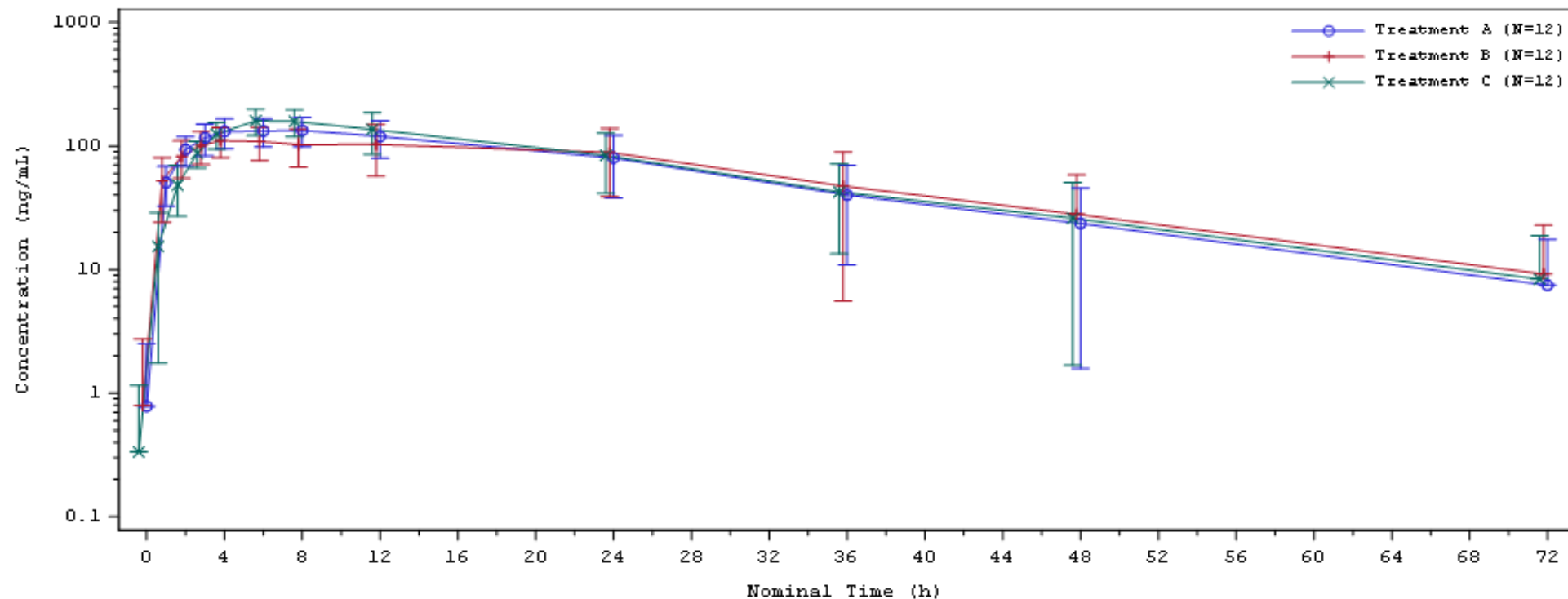
PD/Biomarker Analyses

Visit	Statistics	Active	Placebo
Day 8	LS Mean (SE)	-2.976 (0.611)	-0.015 (0.789)
Day 8	LS Mean 95% CI	(-4.190, -1.763)	(-1.583, 1.554)
Day 8	LS Mean Difference (SE)	-2.961 (1.004)	
Day 8	LS Mean Difference 95% CI	(-4.957, -0.966)	
Day 8	p-value	0.0041	
Day 15	LS Mean (SE)	-3.743 (0.611)	0.152 (0.789)
Day 15	LS Mean 95% CI	(-4.956, -2.529)	(-1.416, 1.720)
Day 15	LS Mean Difference (SE)	-3.895 (1.004)	
Day 15	LS Mean Difference 95% CI	(-5.890, -1.899)	
Day 15	p-value	0.0002	

Statistics	Active	Placebo
LS Mean (SE)	-30.009 (7.784)	-5.960 (6.860)
LS Mean 95% CI	(-46.825, -13.193)	(-20.780, 8.861)
LS Mean Difference (SE)	-24.049 (10.403)	
LS Mean Difference 95% CI	(-46.524, -1.574)	
p-value	0.0378	

PK/Biomarkers analyses- continued

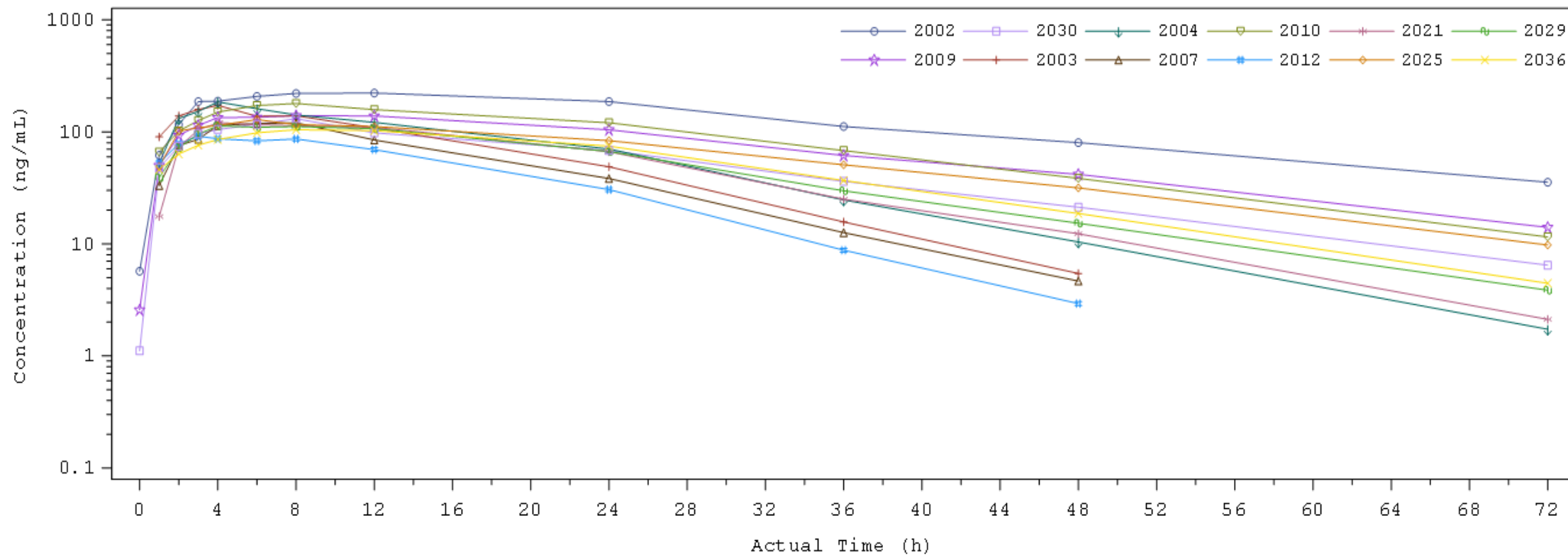
- If appropriate (i.e. concentration type PD parameters/biomarkers) individual and mean serum concentration versus time curves could be presented on both linear and semi-log scales.



PK/Biomarkers analyses- continued

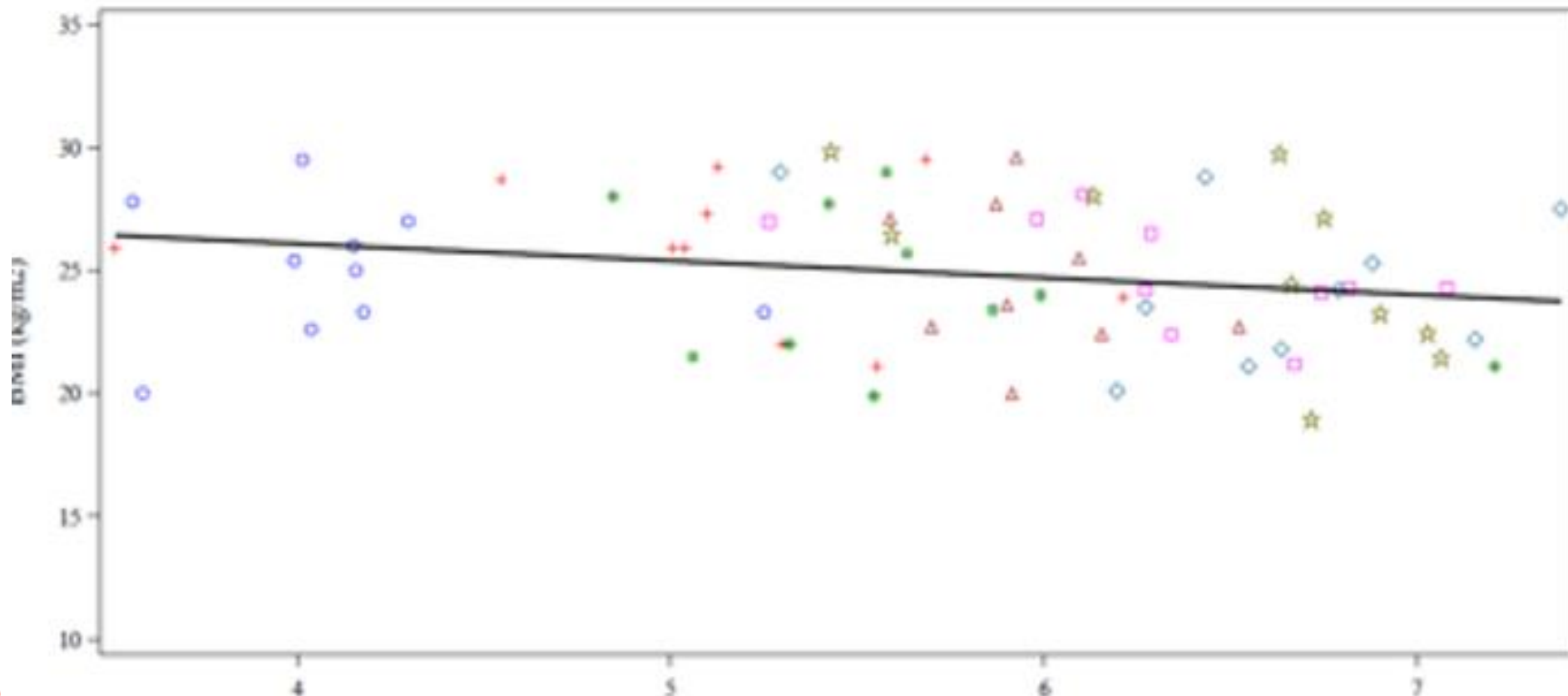
Treatment Group: Treatment A (N=12)

Visit: Day 1



PK/Biomarkers analyses- PK PD relationship

- The PK parameters are considered as exposures and the change from baseline in selected PD biomarkers as the effects.
 - linear regression analyses.
 - a Spearman correlation coefficient

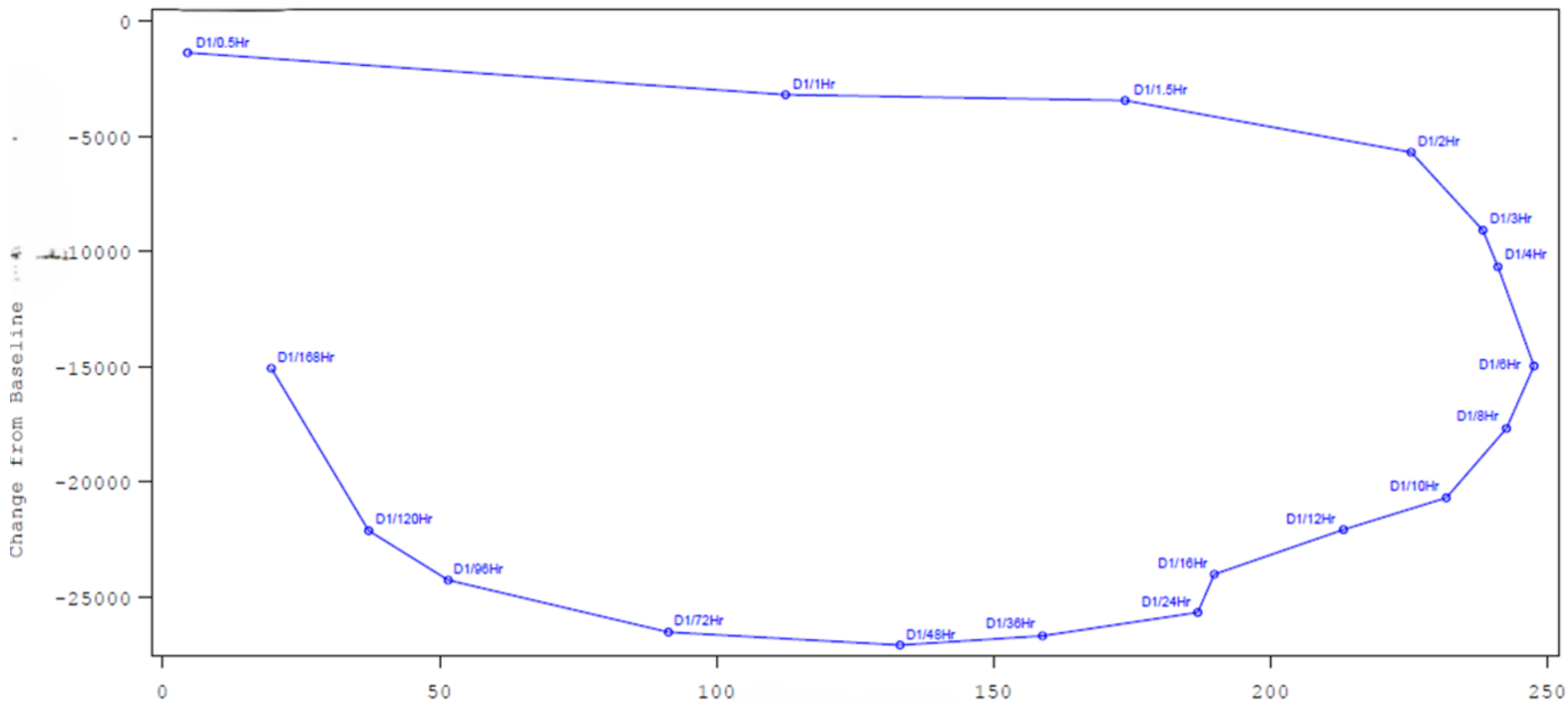


PK/Biomarkers analyses- PK PD relationship- continued

- the maximum change from baseline ($\Delta_{\max}$) could be calculated for each study drug dose and the pooled placebo.

Statistics	Active	Placebo
LS Mean (SE)	-47.524 (8.866)	-1.545 (7.597)
LS Mean 95% CI	(-67.039, -28.009)	(-18.266, 15.176)
LS Mean Difference (SE)	-45.979 (12.095)	
LS Mean Difference 95% CI	(-72.601, -19.358)	
p-value	0.0029	

PK/Biomarkers analyses- PK PD relationship- continued



Conclusion

- In Phase 1 studies, Biomarkers can provide insight into the overall effect of the drug on the patient's body.
- Biomarkers are commonly used now for diagnosis, prognosis, and disease progression.
- The statistical analysis of the PD/Biomarker parameters varies depending on the type of the parameter, and you would generally need a specialist to determine the appropriate statistical analysis for your parameter.