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Role of PK/PD, Biomarker Analysis in the Expansion of Phase 1 Trials

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ABSTRACT

Traditional phase I drug development involves single ascending dose studies followed by multiple ascending dose studies in healthy volunteers with safety, tolerability and PK as endpoints. However, this conventional approach presents several challenges, including limited generalizability to patient populations, inefficiencies in dose selection, and prolonged development timelines. The reliance on healthy volunteers may not fully capture the pharmacodynamic (PD) and biomarker responses relevant to the target disease, potentially leading to suboptimal dose predictions for later phases. To address these challenges, drug development is shifting toward more adaptive and biomarker-driven Phase I designs to enhance the success of the trials through better identification of responders, improved dose optimization, and earlier efficacy signals leading to better success in later phases of the trials.

So, what is the role of PK/PD/biomarkers and what is their analysis telling us? How are biomarkers correlated to drug exposure and biological effect? How did they contribute to the development of late phase clinical trials?

Is it hard to recruit and retain study teams to work on Phase 1 studies as they are assumed to be simple and straightforward?

INTRODUCTION

Phase I trials play a critical role in development of new drug/treatments typically conducted in First-in-Human and/or First-in-Kind (new molecule – never tested in Humans) or patients (with advanced diseases). Traditionally, the primary objective of these trials is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics. Conducted with small, diverse populations, typically 20 to 100 participants, these trials use dose-escalation designs to determine the maximum tolerable dose (MTD) by balancing rapid escalation to effective doses while minimizing toxicity risks. Starting doses are often based on preclinical animal studies, such as the mouse dose causing 10% lethality (MELD10). While efficacy is not the primary focus, patient selection excludes those with impaired organ function to reduce the likelihood of serious adverse effects.

Traditional Phase 1 Trial designs

- Single Ascending Dose (SAD) Studies: Participants receive a single dose of the drug, with dose levels gradually increased in subsequent groups to assess safety and identify the maximum tolerated dose (MTD).
- Multiple Ascending Dose (MAD) Studies: Participants receive repeated doses over a period to study drug accumulation, tolerability, and pharmacokinetics at steady state.
- Food-Effect Studies: Conducted to assess how food intake impacts the absorption, distribution, metabolism, and excretion of the drug.
- Cohort-Based Dose Escalation: Groups of participants (cohorts) receive increasing doses, with safety data from one cohort guiding dose levels for the next.
- New drug development is expensive, and the failure rate remains high. By identifying patient populations expected to respond to the study agent and tailoring the treatment with a novel drug, investigators will be one step closer to personalizing treatment. The ‘fail early and fast’ approach is acceptable if the appropriate patient population is evaluated in the phase 1 trial leading to the need for evolution of phase 1 trials by:
- Incorporating adaptive designs that adjust dosing and schedules in real time based on safety and efficacy data.
- Combine Phase I and Phase II
- Use biomarkers to monitor drug activity, predict efficacy, and refine dosing.
- Focus on precision medicine and targeted therapies, leveraging molecular profiling to select patients likely to benefit.

The FDA-NIH Biomarker Working Group describes a biomarker to be “a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention”. They are playing increasingly more critical roles in the development of new drugs and are therefore being incorporated earlier in the drug development pipeline – such as in early-phase trials.
A study at MIT evaluated 406038 clinical trials between 2000 and 2015 to estimate clinical trial success rates and durations. They concluded that using biomarkers to stratify patients doubled the probability of success (having the most significant effect in phase 1 and 2)[(1).] From a different point of view, another study conducted at the university of Toronto, that screened 8630 clinical trials across 4 oncology indications concluded that the use of biomarkers increases the length of time gap between the phases and one of the reasons for that is that there is more data to process and understand the implications of pharmacodynamic data.

Pharmacokinetics paints a clear picture of what is happening to the drug once it is in the body. Immunogenicity experiments only give information on the body’s response to the drug. Biomarkers, however, can provide insight into the overall effect of the drug on the patient’s body. These effects include if the drug mechanism of action is functioning as expected what the body’s response to the drug is, what the drug is interacting with, where the drug is having an effect, and others. Furthermore, biomarkers are commonly used now for diagnosis, prognosis, and disease progression. During trials, screening criteria may be put in place using biomarkers to assess disease progression which, as stated above, has shown a tremendous increase in the probability of success of the trial. On the other hand, biomarkers that are unrelated to the disease state might be monitored for continued safety during the trial. For example, proinflammatory cytokines might be added as an exploratory endpoint to assess the possibility of cytokine release syndrome. Thanks to an increase in technologies available, these markers are typically multiplexed together in one panel now allowing for the analysis of several analytes from just one sample.

The benefit of biomarkers goes well beyond just oncology studies. **Table *1*** shows a brief list of common disease types along with affiliated biomarkers that have been monitored in a clinical setting. An example is a new method developed and qualified in-house at Syneos Health which was submitted for publication. The paper chronicles the qualification of an electrochemiluminescent method to detect a biomarker for ALS called the extracellular domain of the p75 neurotrophin receptor (p75ECD) using entirely commercially available materials. Typical biomarkers for neurodegenerative diseases like ALS require analyzing cerebrospinal fluid obtained from a spinal tap. Such procedures are very uncomfortable for patients and create barriers to entry for healthy volunteers in Phase 1 trials. p75ECD is detectable in urine and proven to be indicative of not only disease diagnosis but progression as well. This data be used for screening and for creating a pharmacodynamic profile of the drugs effect. Our hope is that this new, robust method can be cheaply applied to future neurodegenerative trials to gain further insight into which disease indications might benefit from such analysis.

Indication	Example Indications	Common Biomarkers
Neurodegenerative	ALS, MS, Alzheimer's	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

Table 1: List of common disease types along with biomarkers that have been measured within a clinical trial setting

The use of biomarkers in clinical trials is quite unique. While the governing bodies have strict criteria documenting what is considered a validated method for both PK and Immunogenicity assays, ICH M10 has no defining criteria for what would be considered validated in terms of pharmacodynamic endpoints. While PK and ADA assays are overwhelmingly conducted on mass spectrometry and ligand binding assay platforms, biomarkers can be accessed via numerous technologies including the following: mass spectrometry, ligand binding assays, flow cytometry, qPCR, next gen sequencing, immunohistochemistry, and many other methods. This list continues to grow and grow as the understanding of both disease and drug mechanisms grows. Currently, there is a large initiative among industry peers to standardize the way that these methodologies are conducted, regulated and analyzed.

Currently biomarker endpoints use qualified methods, instead of validated methods. A tiered approach is a more promising solution. These tiers allow the trial to use a qualification that is fit-for-purpose depending on the context-of-use of the biomarker within the overall protocol. If there is an exploratory endpoint that will be just used for observational data, a low-cost qualification is sufficient in this case which saves the trial sponsor both time and money. However, if a biomarker is to be used as a primary or secondary endpoint, the rigor of the qualification would be much higher to assure that the assay is performing at a high level.

PD/BIOMARKER ANALYSES

As mentioned in the introduction, a biomarker is a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention. Some examples of biomarkers that most of us worked on at some point (even if not in the context of PD/biomarker analysis) could be changes in weight, BMI, waist and hip circumference, fasting glucose, fasting insulin, lymphocyte counts, FSH. There are also some others less known as for example HOMA-IR inhibin, C-peptide, glucagon, fasting lipid profile, fasting free fatty acids, ketone bodies, adiponectin, PRO-C3, CK18, or FIB-4.

In general, for these PD/Biomarker analyses we will use the PD population, which we usually define it as all participants:

- who received at least one dose of active or placebo.
- for whom at least one post-dose exploratory PD endpoint can be adequately estimated. (Note: “adequately characterized” is understood as having a non-missing baseline and at least one post-baseline value)
- satisfy all inclusion/exclusion criteria
- have acceptable times for visit dates and measurements
- they have been compliant with treatment
- they didn’t have major protocol violations
- they did not discontinue too early

Depending on the type of PD parameter or biomarker proposed different analyses could/should be planned, and we are including some of most common here, but not all would be applicable for your type of PD parameter or biomarker.

The most common type of analysis is related to the actual results, the absolute change from baseline and percent change from baseline. These will be usually summarized in the PD population by treatment groups (or dose levels) and by time point, using descriptive statistics (arithmetic mean, standard deviation [SD], minimum [Min], maximum [Max], and median, and, if it makes sense or needed, geometric means and coefficient of variation [CV%]). Most times, these changes and percent changes from baseline will also be analyzed using statistical methods to compare amongst the different dose level groups (see below)

In addition, for these concentration-type parameters individual and mean serum concentration versus time curves could be presented on both linear and semi-log scales (***Figure 1***)

```
proc sgplot data=stat1 ;
     by paramn param ;
     series x=TIME y=MEAN / name='srs' group=TREAT lineattrs=(pattern=solid)
grouporder=data clusterwidth=1 markers;
     scatter x=TIME y=MEAN / name='sct' group=TREAT yerrorlower=MEAN-SD
yerrorupper=MEAN+SD;
     xaxis label = "Nominal Time" fitpolicy=stagger minor minorcount=1 min=0
max=1700 values=(0 to 1700 by 100) ;
     yaxis label = "Concentration (unit)" minor minorcount=3 LOGBASE=10
logstyle=LOGEXPAND type=log minor values=(0 0.01
 0.1 1 10 100 100 10000);
run;
```

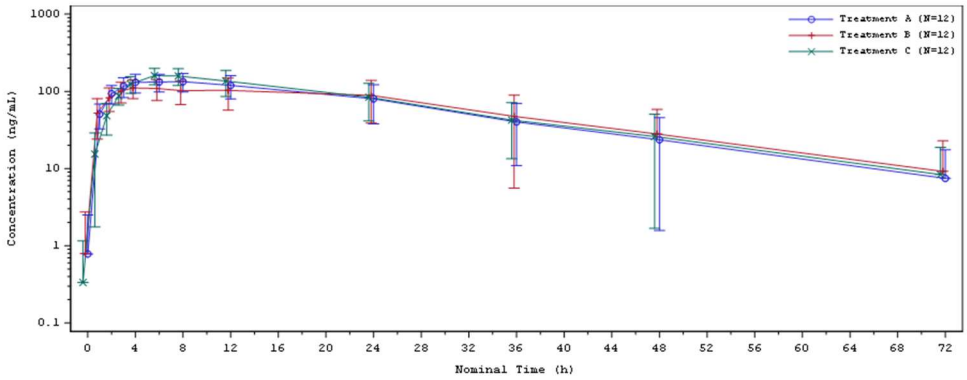

Figure 1 :Mean Serum Concentrations versus Time

The change from baseline and percent change from baseline over time could also be presented graphically in linear scale.

As mentioned, the PD parameters/biomarkers are also often compared between the treatment groups.

For the cases where the assessment is repeated over several visits, the model used for the analyses will usually include treatment group, visit, treatment-by-visit interaction, and baseline values. Subjects will be considered as repeated measure units over visits. Linear contrast from the model will be used to test the treatment difference between each dose group and placebo at each time point. In the models we would generally initially fit an unstructured covariance matrix, and if this fails to converge, other covariance matrix such as AR(1) or compound symmetry will be considered (everything including the order in which these will be tested being specified in the SAP). The Kenward and Roger adjustment for standard errors is usually implemented.

The SAS code that we usually use in this situation below and the results are displayed in ***Table 2***

```
proc sort data= dataset;
      by trtn subject visitn;
run;

proc mixed data=dataset;
    class SUBJECT TRTN VISITN;
    model RESP=TRTN VISITN TRTN*VISITN BL/ ddfm=kr;
    repeated VISITN/subject=SUBJECT type=UN;
    lsmeans TRTN*VISITN /cl diff=control ("1");
run;
```

Notes:

- RESP= change from baseline or percent change from baseline
- BL = baseline values for each parameter
- VISITN indicates all scheduled visit timepoints of PD assessments

- TRTN includes the treatments

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	

Table 2: Results of the full mixed model (repeated option)

In case we have PD parameters calculated once during study for example in a cross-over design, or we are analyzing the max change, instead of using the repeated option the below code would be more appropriate (results are displayed in **Table *3***)

```
proc mixed data=dataset;
    class treatment (ref='xyz') subject;
    model resp = treatment bl/ ddfm = kr;
    random subject;
    estimate 'abc Vs. xyz' treatment -1 1 / cl alpha = 0.1;
    ods output estimates=estimates;
run;
```

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	

Table 3: Results of mixed model at a specific visit

ASSESSMENT OF DOSE AND EXPOSURE EFFECTS

Another important aspect of PD/Biomarker analyses is the relationship dose-effect on selected PD biomarkers

which is assessed by the analysis of changes from baseline in biomarker level across dose levels.
To explore the relationship exposure-effect, the PK parameters can be considered as exposures and the change from baseline in selected PD biomarkers as the effects. The relationship exposure-effect is then assessed using:

- linear regression analyses. The linear regression models will include all data from the PK population (all dose levels) and will consider the change from baseline of a PD biomarker as the dependent variable and the associated baseline value and a PK parameter as the independent variables. There will be one model per PK parameter and PD biomarker (see **Figure 2**)
- Spearman correlation coefficient will be estimated between each PK parameter and the change from baseline in a specific PD parameter/ biomarker. PD/biomarker. There will be one correlation coefficient for each PK parameter/PD biomarker.

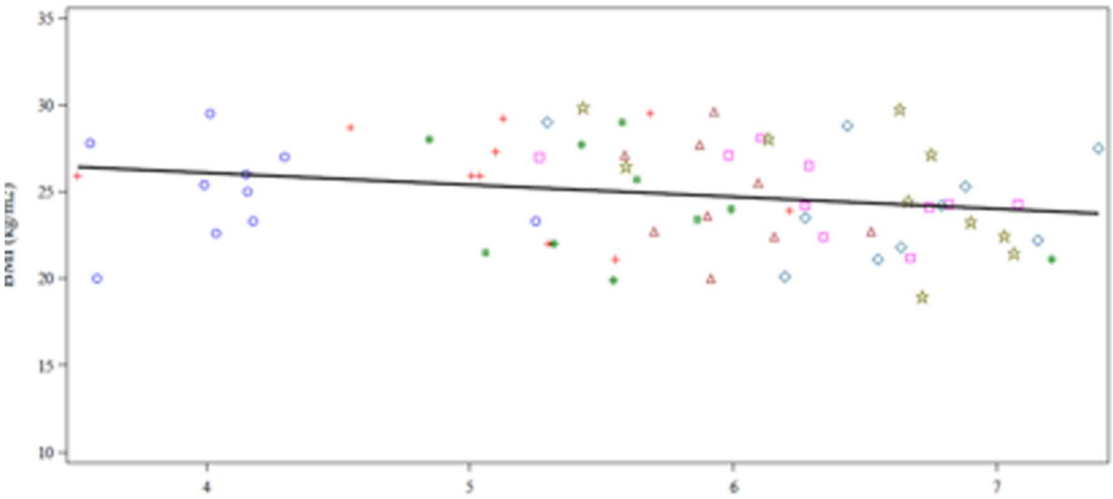

Figure 2: Scatterplot of the results with regression line

To further explore the dose-response relationship of some parameters, the maximum change from baseline (Δmax) expressed also as % (relative to baseline) could be calculated for each study drug dose and the pooled placebo.

Lastly, this relationship can be visually analyzed. The time-matched mean values and mean change from baseline the PD parameters (y-axis) will be plotted against the mean PK concentrations (x-axis) (***Figure 3***). Each dose level would be plotted on separate figures. Each pair of (x,y) points will display a timepoint marker (e.g. xx hrs), and the points will be connected in a chronological manner, thus, also depicting the time-order aspect of the relationship.

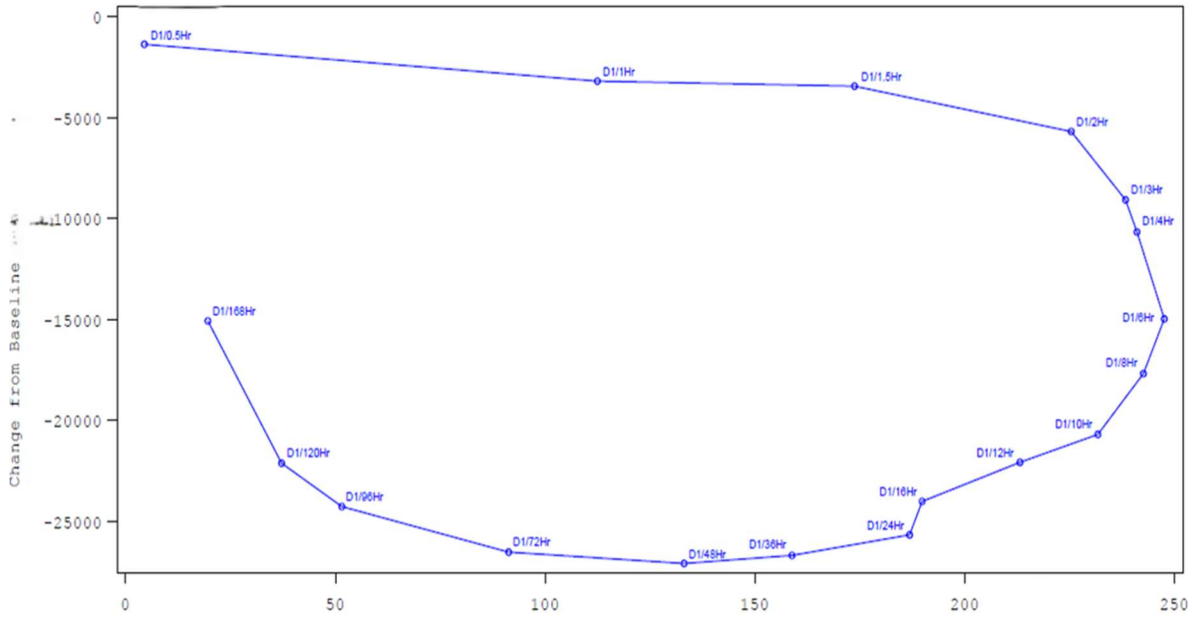

Figure 3:Time-matched mean change from baseline in the PD parameters against the mean PK concentrations

CONCLUSION

Biomarkers have significantly transformed Phase 1 clinical trials, shifting them from traditional dose-escalation studies in healthy volunteers to more precise, patient-centric approaches. By enabling early assessment of drug effects, dose optimization, and patient selection, biomarkers enhance the efficiency and success of early-phase trials, reducing trial failures in later phases through improved safety prediction, PD responses and potential efficacy.

The statistical analysis of PD/biomarker parameters varies based on the type of biomarker, often requiring specialized expertise to determine the most appropriate analytical approach.

REFERENCES

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