

Proof-of-Concept Studies and the End of Phase IIa Meeting with the FDA

DR. JIM WEI: Today my topic is going to be Proof-of-Concept Studies and FDA End of Phase 2a Meetings and why the FDA has such guidance requests of End of Phase 2a Meetings. There are a number of reasons. There are many failures in the late phase clinical trials. So during my talk I will outline the demand of the Phase 2a Meetings and the dose-response and concentration exposures and their exposure-response and the latest FDA draft guidance for End of Phase 2a Meetings to discuss the purpose of the meetings, the goal of the meetings, and the general discussion points for the meetings.

Reasons of Late Phase Trial Failure with Sponsor

So why would the people like to have FDA to conduct, to have such End of Phase 2a meetings? Because there are a number of reasons for the late phase clinical trial failures which include the poor dose selection. This is the most popular one in the FDA's experience. And also inadequate design for clinical trials and anticipated placebo response. The drug works very good in the model but when it goes to the clinical trials, particularly in naive patient populations, the placebo response may kill the drug. Also inefficient data analysis. That includes hard-to-handle missing data and the drop-outs. And also unanticipated toxicities occurred in the human populations.

Past FDA Experience of Exposure Response Analyses During NDA Review Process

In the past FDA had already experienced, during the NDA Review Processing, that many sponsors already had informal exposure-response analysis

for their drug products and that FDA staff had conducted re-analysis of such exposure-response data. And the impact includes: approved lower doses and dosage regimens different from those proposed by sponsors; avoided the need to request additional clinical efficacy trials from the sponsor; and also includes identified desired missing doses and special population studies not studied by sponsor that would delay for the approval of the applications.

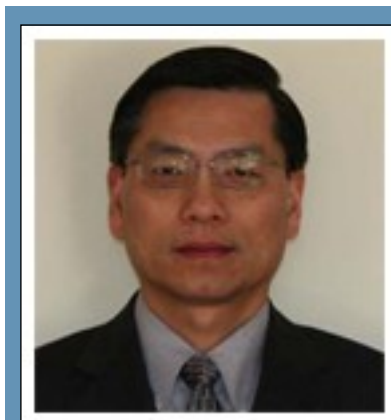
Proof-of-Concept (POC) Studies

So for proof-of-concept studies usually is a phase 2a study under another name is mainly to demonstrate clinical efficacy. And the dose-response – in such clinical studies – we would like to say the dose is high enough to reach the plateau in the response in the drug efficacy. So that in another term is to reach the Emax level in the modeling work. And also in the proof-of-concept study we would have some observations for adverse reactions and the foundation for proof-of-concept study actually came from single-dose, multiple-dose escalating studies. In such studies, usually the MTD is determined. So that is a very important concept in the proof-of-concept

study because we know what dose the human subject can tolerate and that's the dose we would like to reach particularly to observe the efficacy.

Dose-Response

And this is a typical figure that we often see in the FDA review processing. And you have placebo. In the right panel you see a placebo – low, medium, high doses. From that pattern you can see, from the left panel figures, the response it continued to



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go up but you don't know where they reach the plateau. So in such a dose response, such a steady design, it's very difficult to see if the design is adequate to reach the maximum effect or not.

So what we would like to see is such – like the left panel – in the S shape which is typical for the receptor or enzyme mediating drug action that will reach the plateau at the certain dose. Then in that type of the exposure response pattern and in certain drug dose levels or concentration levels you would expect increase in dose. You won't increase efficacy. The only thing is more adverse reactions. So this is very important – where you stop the dose for the further increasing.

In the right panel you can see the dots. This is a real drug concentration which is, you can see, they are approaching the plateau levels. So that type of design actually is what we would like to see cover that range.

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Time Course of Inhibition of Plasma DPP-IV Activity

This is actually a study conducted by Merck in the sitagliptin program, which is DPP 4 inhibitors and you can see in the panel A we have four doses. Either 1.5, 12.5, 50, and 200 milligram dose. And we can see that this is a response. Actually it is deep before activity inhibited a percentage. And in panel B we can see another dose response they conducted – the 5 milligram and then the 25 milligram and the 100 milligram. We can see that 50 milligram and 200 milligram are very close in the drug response. And also 100 milligram we can see also is very close to the panel A. The top two doses similarly responded.

Individual Values for Plasma Sitagliptin

For the simulation done by Merck Group, we can see that we have reached a very nice exposure response which is for sure a very nice S curve in the Emax plot. We can see that after the drug concentrations at the 400 Nm, the response won't increase significantly. So therefore it's very important after a certain dose level you don't want to continue to increase the dose because it won't help the efficacy at all. So this is a kind of exam-

ple of how important for those selections and how to design the dose regimen.

Pharmacometrics

So this is a model actually of how the FDA works. We have the drug concentration, the regular PK information, and also we have the dose and drug concentration information. And also in a lot of experience, FDA built up a model – the drug concentration versus a clinical endpoint like hemoglobin A1c levels. And also the hemoglobin A1c level versus the time of the treatment. And also at FDA, based on the data we developed with the disease models in the type 2 diabetes, we have developed the relative risk versus hemoglobin A1c level in terms of different type 2 diabetes complications.

So all of this is actually integrated work managed by different software. And the software tools we use are by the WinNonlin which is the most popular PK software. They also can be used in some PK/PD simulation work. And also the NONMEM, which is a population PK software. We also have S Plus that do a lot of the figure work, and SAS, and also the Clinical Trial Simulation. All these are tools used for these types of simulation works in the pharmacometrics research.

And pharmacometrics actually is the relatively young subject of science in the pharmaceutical science. It is a quantitative pharmaco-statistical analysis to answer clinical drug development and regulatory questions and pharmacometrics analysis which have a way to influence the regulatory decisions. And pharmacometrics staff usually have training in clinical pharmacology, biostatistics, and work very closely with medical experts such as medical reviewers and the FDA physicians who have good judgment in therapeutics, drug development, and the regulatory decisions. Pharmacometrics at the FDA now is centralized as a division of pharmacometrics located in the office of Clinical Pharmacology since 2005 at the CDER/FDA.

Evolution of EOP2a Meeting

So the End of Phase 2a Meetings actually have quite a long history and many people try to promote such activities at the regulatory authority. This first concept was actually introduced in the late 1990s when the Population PK Guidance was issued and also in the early 2000. And End of Phase 2a Meetings, the idea was first emerged in the scientific meetings. And in 2002 at a FDA subcommittee for clinical pharmacology studies and the End of Phase 2a meeting was discussed and emphasized pharmacometrics solutions in the drug regulatory processing.

In 2004, the FDA started a pilot program to start End of Phase 2a Meeting and we actually stopped in 2006 due to lack of resources and a staff to conduct the work.

In 2008 – late last year – in September 2008, the FDA issued draft guidance for End of Phase 2a Meeting. Is it ready to resume End of Phase 2a Meetings? But as far as of today, the FDA still has not formally accepted the request. But it should start any time from now.

Resume End of Phase 2A Meetings after Draft Guidance Issued in Late 2008

So this is the guidance issued late September last year. So End of Phase 2a Meeting mainly is you already have finished phase one and you have Phase 2a study which is a pro-concept study in general. And you are ready for a dose selection for the Phase 2b study or Phase 3 studies. It usually takes the FDA about four to six weeks to work on such a re-analysis and make comments back to the sponsors. And this actually is negotiating the PDUFA 4 to such activity in the guidance.

When the End of Phase 2a Meeting Occurs

So as I mention that, usually, after you have a completion of early phase collected from Phase 1 and Phase 2a, and you have very good data sets to explore, what is potential dose selection for future studies? In Phase 2a meetings, the dose estimation and dose selection is the main topic to discuss.

Purpose of EOP2a Meetings

So the purpose of End of Phase 2a Meeting actually is to try to reduce unnecessary failure of late phase clinical trials, mainly the data collected in Phase 2b and Phase 3, by facilitating interactions between FDA and a sponsor who seeks guidance related to a clinical trial design employing clinical trial simulation and the quantitative modeling of prior knowledge such a drug, disease, placebo effects, etcetera. Designing trials for better dose response estimation and the dose selection and other appropriate issues. And the format for the EOP2a Meeting is the same as other meetings. It is non-binding. It is a scientific interchange between the FDA and the sponsors. And this type of meeting package usually they are performing modeling work which is relevant to Phase 1 and Phase 2a data and a simulation of next trial design employing the mechanistic or empirical drug disease model or the rates for the dropout and the compliance based on the prior FDA experience.

General discussion points at FDA meetings include dose selection strategy; exposure-response to support efficacy safety trials; dose adjustment in special populations; design efficacy and safety trials; population PK/PD study design; exposure-QT response study design; and the clinical pharmacology development general plan.

Goals for EOP2a

So goals of the End of Phase 2a Meeting is decision making about the design and analysis of exposure-response studies earlier in the IND phase; strategy development in dose choices and special population studies while there is time to do something. Other goals for this stage are implementation of FDA exposure-response guidance; applying quantitative analysis such as clinical trial simulation tools to integrate relevant pre-clinical and clinical exposure response data; and closing the gap between what is known at the End of Phase 2a stage and what is applied in Phase 2b and Phase 3.

EOP2a Meeting

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Topics for Discussion at an EOP2a Meeting

The topics for discussion at End of Phase 2a meetings include use of quantitative information for dose selection; use of quantitative knowledge

of drug effects in animals and human subjects to aid in both dose-ranging trial design and safety assessment. Examples include placebo effect, disease severity effect, disease endpoint variability and time course.

We are continuing with the topics for the discussions at the End of Phase 2a meeting. Use of available preclinical and clinical exposure-response data and a discussion of implications for dose-response trial design; contrasting alternative trial design strategies such as parallel, adaptive, randomized, withdrawal; use of pharmacogenetic information from preclinical studies and the clinical trials; a quantitative evaluation of genetic effects on dose selection and the use of genetics to inform assessments of drug safety and effectiveness in future trials.

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Considerations Used to Evaluate an EOP2a Meeting Request

When the FDA considers how to accept an End of Phase 2a Meeting request, the following are usually appropriate conditions for the FDA to do the assessment.

Are the appropriate FDA resources available for the project? That is why the FDA, during the two-year pilot program, always had very rigid requirements. You know how much we can do for the FDA to offer. So this is very important. You know if we have enough staff to handle the work.

Would the product fill an unmet therapeutic need? This is also very important. Some certain test drug is very urgent for medical need because there is no satisfactory medical treatment available. So this type of project will make the FDA consider the priority to accept such a request.

Also does past experience suggest there could be a high clinical trial failure rate in the therapeutic area? Because that is the FDA trying to help based on the FDA's experience how to help with the better design to succeed in the trials.

Does FDA have experience that would be of value to the project? Because it depends on the therapeutic area and it depends on the data the FDA has. If it is an anti-diabetic compound, for them as I mentioned earlier, in type 2 diabetic patient trials, the FDA has gained a lot of experience and has developed a very good model if you have similar mechanics of drug action, the FDA basically can use the past experience and use the model already established to help the sponsor to determine if that trial is a good design and also does the dose selection fit the efficacy models.

And would the project benefit from modeling and simulations? Because the sponsors may have a variety of reasons to ask the FDA to consider End of Phase 2a trials but meanwhile it is very important you have to have FDA make judgment if such modeling work will benefit the project.

Background Information for EOP2a Meeting Package

If the sponsor tried to bring the request to the FDA for the End of Phase 2a Meeting, what is the background information you have to provide to the FDA? That includes proposed trial designs or analysis methods if the sponsor wants them to be discussed; the appropriate nonclinical data, Phase 1 data, and Phase 2a trial data; specific questions about the dose response and PK/PD relationship; strategies for selecting doses; and an overview of the clinical development plan.

And also that should include preliminary exposure response analysis and its interpretation that support the proposed designs and analysis methods. Relevant tables and figures should all be included. Because the sponsor does the preliminary work for the modeling work, those exposure response analysis. So this information is critical for the FDA to evaluate how appropriate your modeling work is and how much it needs to be improved.

Now also the background information includes conditions and methods used for the modeling and simulation so that the FDA can provide comments on it. Alternatively, the sponsor should indicate if they wish the FDA to do such modeling work. While this is feasible, the FDA resources are limited therefore the decision to do this work is made on a case-by-case basis. So as I mentioned, if there's an unmet medical need in that particular area, the FDA would be willing to put a lot of resources to help the sponsor do such modeling work. Analysis and interpretation of available exposure-response data supporting the proposed trial design which ideally would include a list of completed studies describing the key design features, trial data used for drug modeling, details and results of modeling and simulation methods, and copies of relevant literature. This is all the information that would be needed for the FDA to conduct a reanalysis and also to comment on the sponsor's analysis work for the modeling.

Summary of all Meetings Between FDA and Various Sponsors

This is actually the publication published last year by the FDA pharmacometrics group where they summarize 11 End of Phase 2a Meetings and they conducted these all in different therapeutic areas. And mainly you can see that the key question proposed by sponsors is dose selection. Okay? So it's very important – dose selection. So all of these 11 applications all focus on the dose selections. And some of them also try to have the design of the later phase trials. And this is covered from neuropharm, endocrine, also infections area.

Average Score for the Overall Value of EOP2a Meetings

This was actually surveyed after the project was completed. It was surveyed by both the FDA staff and the sponsors. You can see the overall response from every application: usually, the sponsor's side is more satisfactory than the FDA's side because I think the sponsor is very eager to explore such activities and particularly how to select the dose. And the FDA has relatively high standards when they evaluate such processing. But

overall, the responses from the FDA's side and the sponsor's side are very positive for such an approach.

Summary

So this is a summary. And what the FDA has proposed for End of Phase 2a Meeting is to try to help the pooled quantitative analysis of dose response; to reach optimal dose selection and in the future trial designs. And End of Phase 2a Meeting also is a new approach for the FDA to commit to reduce the cost of new drug development and the sponsors are encouraged to interact with the FDA at early stages of drug development.

So I will conclude my presentation here. Thanks.

About the Presenter

Dr. Wei worked with the FDA where he served as a Senior Reviewer in the Office of Clinical Pharmacology for almost 10 years. He was heavily involved in reviewing NDAs and INDs for the Division of Metabolism and Endocrinology Products. He is certified by the American Board of Clinical Pharmacology and is a member of the American Society of Clinical Pharmacology and Therapeutics. Dr.

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The overall response from every application: usually, the sponsor's side is more satisfactory than the FDA's side because I think the sponsor is very eager to explore such activities and particularly how to select the dose. And the FDA has relatively high standards when they evaluate such processing. But overall, the responses from the FDA's side and the sponsor's side are very positive for such an approach.

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