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EMA/EFPIA 2nd WORKSHOP
Adaptive Design in Confirmatory Trials

2nd April 2009, European Medicines Agency, Canary Wharf, London

Abstract

In April 2009 the EMA/EFPIA held their 2nd workshop on adaptive designs. The objective was to illustrate the application of "Good Adaptive Practices" through presentations and discussions of case studies. The focus was on adaptive designs in confirmatory trials, including seamless adaptive Phase II/III trials. The Workshop was co-chaired by Prof. Bruno Flamion, Chair of the CHMP Scientific Advice Working Party (SAWP) and Dr. Solange Corriol-Rohou, Chair of the EFPIA efficacy ad-hoc group. The workshop was well attended (150 attendees) and there was a good level of informal dialogue between a wide range of experts including representatives from Regulatory Authorities (Europe and the US), Academia, Industry, and external organizations.

Executive summary

On April 2, 2009, EFPIA/EMA held their 2nd workshop on Adaptive Designs in Confirmatory Clinical Trials. The 1st workshop in December 2007[1] had provided an opportunity to introduce and discuss the EMA's "Reflection Paper on Methodological Issues in Confirmatory Trials Planned with an Adaptive Design"[2].

Key outcomes and open questions were summarized by Prof. Bruno Flamion while Dr Solange Corriol-Rohou (AZ) briefly presented the expectations of the joint workshop:

- Cost of R&D is a public health issue. There is growing patient pressure for early access to new drugs: interim analyses can be ethical or even mandatory. However, the cost of R&D and time savings *per se* cannot be the main rationale for using adaptive designs (AD).
- Adaptive designs are not a remedy for poor planning.
- Regulators did not agree with a complete blurring of exploratory and confirmatory phases of drug development.

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Open questions included the following:
- Can adaptive designs improve dose selection?
- What is the role of adaptive designs in conditional approval?
- Can there be cases where a single pivotal trial with adaptive design elements can form the basis for registration?

Discussions on seamless adaptive Phase II/III designs involved the following points:
- There was agreement that there exist some reassuring examples. However the reduced time for discussion between end of Phase II and III begs the question whether there is not a substantial risk in committing to a confirmatory program in the absence of complete information from a completed Phase II program.
- Trial integrity is a primary concern to all stakeholders. The process leading to providing a Data Monitoring Committee with unblinded interim results can be associated with the risk of an undesired information leak, ultimately resulting in operational bias. To minimize operational bias, regulatory experts felt that involving a sponsor representative in the DMC – although possible, should remain an exception rather than the rule.
- Appropriate approaches to testing heterogeneity in adaptive trials with two or more stages were discussed.

There was general agreement that the value of clinical trials with adaptive designs could only be assessed after some experience has been gained. With this in mind, the 2nd workshop wanted to revisit Prof. Flamion's conclusions through closer examination of case studies. The objective was to illustrate and develop **"how to"** solutions for good adaptive design practice in confirmatory drug development.

Below a summary of key points raised during the 2nd workshop:
- There was a high level of concordance between all speakers (regulators, industry and academia) on the potential benefits of adaptive designs, properly applied, and on the potential problems and methodological issues that need to be further addressed.

- Concern was expressed that removing the time between completion of exploratory trials and the initiation of confirmatory trials (which has been referred to as "white space" or "thinking time") as required when planning seamless Phase II/III designs may lead to confirmatory evidence that is less well planned as important data gained from exploratory trials is not fully taken into account for the design of the confirmatory phase. Some contributors' representatives argued that thinking time was being redistributed to the front end of the drug development process, rather than being cut or reduced, which itself could be a positive thing. It is likely that there will be some situations for which early planning of an entire development programme is feasible (though might still represent an additional risk), and other experimental situations where it is not.

- Regulators argued that there is a need to distinguish between exploratory and confirmatory drug development, if only to ensure that the confirmatory evidence base is clearly identifiable for sponsor and regulator decision making. It seems sensible to define the scope for adaptive approaches for either as the importance put on methodological difficulties will differ in both scenarios. Industry representatives argued that seamless adaptive Phase II/III trials effectively were confirmatory trials, with an opportunity for further improvement on answering the research question, e.g. selection of the optimal dose to be tested in Phase III. If properly applied, there is no regulatory objection in principle to a seamless Phase II /III design forming one part of a confirmatory evidence base. It is acknowledged that situations exist, where the conduct of an additional phase 2 trial may be less informative than initiating a phase II/III trial, where then e.g. one treatment arm is dropped once better information about efficacy *and* tolerability is available.

- There is unanimous agreement that strict control of the experiment wise Type 1 error is an important requirement for trials in the confirmatory package.

- Sponsor involvement in interim decision-making is not recommended: although important decisions have to be made at an adaptive interim analysis that would be best handled by statisticians that have been well educated about the trial at hand, it would be difficult to guarantee, that no information leakage has occurred once results before and after the interim analysis are substantially differing.

- Sharing of experience among all interested parties was strongly encouraged to foster the development of "Good Adaptive Practices" and establish the appropriate scope of applying adaptive designs.

- Dr Sue-Jane Wang (Associate Director for Adaptive Designs, FDA) provided a preview on FDA draft guidance on adaptive designs, expected to be released before 2010. FDA's document aims at a wide audience and is not limited to statistical issues. FDA distinguishes the use of adaptive design for exploratory studies versus confirmatory studies. FDA feels that the term "seamless" is confusing the boundaries between exploratory and confirmatory drug development and would prefer to classify adaptive designs as clearly belonging to either one of these phases or stages of drug development.

- EMA's Scientific Advice requests' survey (2007-2008) indicates that, increasingly, adaptive designs that are being proposed to the agency adhere to the framework set out in CHMP reflection paper[2].

- The process of interaction between sponsor and regulatory agencies, in the EU currently limited to the Scientific Advice procedure, may benefit from a less formal and more ongoing approach, to be discussed further at future meetings.

- EMA and EFPIA both were supportive of wide public dissemination of the material used at the workshop and proceedings that would be derived from it.

- One benefit described for an adaptive approach is that the basis for decision making (e.g. dose selection) would be better than from a standard development programme as the seamless Phase II / III design permitted more patients to be recruited and evaluated before the decision point. It seems that some sponsors would only be prepared to improve the evidence base for this sort of decision making if the patients recruited were also contributing to the confirmatory tests for efficacy. The regulators pointed out that recruiting more patients than an otherwise standard (i.e. stand-alone) Phase II study remained a viable, and often a preferable, option. In particular, it is not understood why sponsors are satisfied in making decisions to initiate large and expensive Phase III programmes when so many questions about dose and predicted efficacy and safety remain imprecisely answered. The consequence seems likely to be an unnecessarily high Phase III failure rate. The regulators reassured sponsors that conducting a large Phase II programme was viewed positively when considering the totality of data available for regulatory decision making.

- A 3rd workshop may be considered in the future and should allow for ample time for discussion.

WORKSHOP DETAILS

Case Study 1: Implementing "Good Adaptive Practices" in a seamless adaptive Phase II/III

An objective of this session was to illustrate the application of "Good Adaptive Practices" through a Phase II/III case study with novel design features. . Also of interest was to understand the rationale for using this particular design instead of 2 separate designs, the impact on cost and development time, and whether or not this approach could be replicated in the future. This session also provided the opportunity for a discussion of the novel features of the design by academia experts and EU and US regulators.

Dr Brenda Gaydos (Lilly) provided an overview of an ongoing adaptive seamless 2/3 study developed in type 2 diabetes. This study was developed in collaboration with Berry Consultants and as a Critical Path Initiative pilot project with the FDA. The adaptive study is part of a robust clinical package including 2 exploratory studies (one single dose study in healthy volunteers and one Bayesian adaptive multiple dose/Proof of Concept Study in patients) developed prior to this adaptive study and a minimum of 4 fixed design pivotal studies. The seamless adaptive design was chosen to more effectively learn about dose response early, reduce uncertainty, and increase probability of technical success in identifying viable doses over that of a two separate trial paradigm from 0.18 to 0.89. This randomized, placebo-controlled, double-blind inferentially seamless Phase II/III trial consists of two stages based on two randomization schemes: an adaptive scheme (Stage 1) and a fixed scheme (Stage 2). The adaptive scheme is a novel feature for a 2 stage confirmatory adaptive design and currently requires more extensive use of trial simulation to substantiate control of the type 1 error rate. The goal of Stage 1 is to select two active doses for further study in Stage 2. Patients are assigned to placebo, active control, or 1 of 7 study drug doses in Stage 1. After five patients are assigned to each arm, a Bayesian adaptive randomization scheme (monitored by the independent Data Monitoring Committee [DMC]) assigns patients to the study drug doses and adapts every 2 weeks based on accumulating data of pre-specified efficacy and safety endpoints. These measures are transformed into a single metric, a clinical utility index (CUI) which is another novel feature, to assess relative benefit/risk for each dose over the dose range of study drug. An important benefit of the adaptive randomization scheme implemented with the CUI is that new patients have a higher probability of being allocated to study drug doses predicted to provide therapeutic benefit (greater CUI) while minimizing exposure to less effective doses (lesser CUI). Based on a mathematical algorithm, when sufficient data have been gathered, study drug dose selection will occur or the trial will terminate based on pre-specified decision rules. If dose selection occurs, Stage 2 begins. However, for the trial to continue, the dose selection must be endorsed by the DMC and a small firewalled sponsor internal review committee (IRC). If the doses are not endorsed, the study will be stopped. Alternative doses cannot be selected by either the DMC or the IRC. If the study continues, patients assigned to the selected study drug doses and comparator arms in Stage 1 will continue on their therapies and patients assigned to doses not selected will be discontinued. New patients will be randomized to the selected doses of the investigational drug and comparator arms using a fixed randomization scheme. Patient data on the selected doses of investigational drug and comparator arms will be pooled across both stages in the final analysis. Due to the novel features of this design, additional robust features were incorporated to insure the quality and interpretability of the data, thus providing a great opportunity for the scientific community to gain experience needed to expand the status quo and improve drug development. These features include ensuring that no more than 30% of patients are randomized in Stage 1, and that the sample size in Stage 2 is sufficiently large to independently demonstrate the study objectives with reasonable power. Dr Gaydos described the extensive simulation work conducted to establish the robustness of the design, the setup of the company's IRC and the independent DMC, the approach to mitigate heterogeneity along the 2 stages, the management of missing data and the interaction with regulatory authorities in both Europe and the US. She mentioned that in this situation, the adaptive design maximizes the use of available

information to make decisions while reducing the probability of exposing patients to an ineffective drug or the wrong dose in Phase III. The experimental situation that leads to the vast improvements seen in the seamless design was the need to balance safety and efficacy in dose selection, and the large variability typical in the safety measures under assessment. In the view of the product development team, by comparison with separate classical trials, the totality of evidence at the decision point, at the start of the Phase III trials and at submission is preferable to the separate trial scenario as data from longer exposure to doses are available, enabling better dose decision and data from longer exposure in Stage 1 available at submission contribute to superior data package while maintaining data integrity.

Prof Peter Bauer (Medical University of Vienna) was a discussant of the Lilly case study. Given the complexity of the logistics of this trial, he queried to which extent it is indeed possible to maintain the integrity and persuasiveness of the results. Modeling the time course of key biomarkers or the dose response using some informative priors, modeling clinical utility, evaluating the impact on the multiple Type I error rate prospectively via simulations are important and fascinating issues which were in his view, extensively performed when this study was developed. However, he raised important questions like if the impact on the type I error rate could ever be sufficiently explored by simulations in such a complicated trial process (relying on an abundance of parameters and assumptions)? How can simulation programs and results be convincingly checked and communicated? In the regulatory setting it would not matter whether he believed in simulation results of a specific design or not. Especially for the regulatory setting, but also for medical publications, rules and standards are required how to perform and communicate simulations in a convincing way.

While discussing selection and bias[3], he noticed that bias might not be the crucial issue in the present scenario with early treatment selection, at least as compared to a conventional multi-armed fixed sample size trial with post trial treatment selection. He acknowledged the challenges when performing flexible Phase II/III designs under the existing regulatory rules, and welcomed Lilly's approach to sharing this case study with a wider audience.

Prof Andy Grieve (King's College, London) was the 2nd discussant of the Lilly study. He focused on the Bayesian aspect of the seamless Phase II/III study and reviewed three topics: (i) clinical utility index, (ii) early stopping, futility, prediction and curtailment and (iii) mixed strategies including estimation and testing. He illustrated that the proposed clinical utility index was based on desirability functions, which are widely used in industry to optimize multiple response processes. He asked if a specific form of utility could be "acceptable" for all stakeholders involved in these processes, e.g., for patients or physicians. Reasons for early stopping in clinical trials are mainly due to proven efficacy, proven safety issues or lack of benefit. Curtailment is applied in experiments to stop as soon as the ultimate result becomes inevitable. The two main approaches to calculate appropriate probabilities for curtailment are the conditional (frequentist) and predictive power (Bayesian). Although the notion "stopping of futility" was quite frequently used when stopping trials early, Prof Grieve pointed out that this notion was not the same as stopping due to a lack of benefit, i.e. strong evidence was available that a drug was not working.

Bayesian methodology is used in the "Learning" phase because it might be more efficient and provide a better use of information. So he queried why methodologies acceptable for the "Learning" phase should not also be applied in the "Confirming" phase. The more general question was how should regulators combine efficacy/safety data in making their decision to approve a drug? Would it not be more appropriate to do it more formally? Then that could become part of the mechanism of seamless phase II/III designs, as illustrated in the Lily case. But this would require more academic research in the future.

Mr. Robert Hemmings (MHRA, CHMP member) stressed that the value of any one trial should be made in the context of the totality of the evidence. This is a package with multiple confirmatory trials and that, whilst this design had clearly been carefully considered, the

importance of any methodological issues with this type of approach were lessened given the multiple other sources of confirmatory evidence that would be available at the time of the regulatory decision. He commented that submission package with only one pivotal study of this type of design would not be sufficient. He discouraged, in principle, the involvement of Sponsor representatives on the Data Monitoring Committee but welcomed the efforts that had been made by Lilly in the context of this trial. The obvious diligence and forethought given to potential problems around interactions with the Data Monitoring Committee (DMC) mitigated some of the risks inherent in this strategy and gave credibility to the approach taken by the company and their reassurances that the data integrity would be preserved, though this would be subject to close scrutiny at the time of assessment. He stressed that to achieve acceptance from Health Authorities for the strategy developed by Lilly, extensive interactions between the Sponsor and regulators had been necessary. He highlighted the challenge of not having "thinking time" at the juncture between Phase II and III and the possible consequences for dose selection. He also highlighted that it was arguable in principle whether a simulation-based control of the Type 1 error could ever be comprehensive.

Dr Armin Koch (BfArM, Hannover Medical School) mentioned that the EMA's reflection paper[2] does not cover the type of design Lilly had implemented. However, he reminded the audience that the ICH-E4 guidance stated that a well-controlled dose-response study could also serve as primary evidence of effectiveness. In this aspect investment into the phase II part is a reasonable strategy to improve the confirmatory package. In his view, agencies should be open to the use of Bayesian statistics and PK/PD modeling for identifying the promising dose-range. Thereafter Phase II studies should provide evidence that the lowest dose providing the desired efficacy has been identified. He questioned whether in general optimality of the dose taken into Phase III could be determined in the absence of time for a thorough review of Phase II data (i.e. whether it is possible to combine early and late phase II-dose finding into one Phase II/III trial, but also felt that the overall programme is sufficient to assess efficacy of the experimental drug. He concluded by thanking Lilly for sharing this experience and re-iterated, that the proposed development plan is an experiment in experimental design, pushing adaptation to an extreme. This trial, when finalized, will be extremely helpful for all parties to understand, in how far such an approach improves the efficiency of drug development and in how far a carefully developed plan can ultimately be assessed by regulators. He emphasized again that under these circumstances regulators (and probably nobody else) can have enough evidence to assure that this can be successful. Under these terms, although the responsibility and thus, the risk of successfully conducting this study remains with the Sponsor, assessors will welcome to see the results of this trial.

Dr Sue-Jane Wang (FDA) asked whether the setup of the DMC achieved independence and objectivity and whether in the perception of reviewers validity and integrity of the study results could be maintained. Pointing out the various models used and the assumptions made and the complex simulations, she wondered whether Stage 1 can be considered adequate and well controlled. In light of these concerns, she applauded Lilly for providing regulators and the scientific community with an opportunity to learn and assess whether an inferential seamless adaptive design has indeed identified optimal dose(s) that result in favorable benefit/risk balance. In this case, confirmatory evidence was to be gathered from four additional Phase III trials with fixed parallel group designs using the doses identified in this adaptive seamlessly designed trial.

Q&A session

In the lively discussion that followed, the challenges of controlling the Type I error through a simulation based approach and the lack of white space to review the data emerging from Stage 1 of the seamless design were revisited. The key question was whether the study results and inferences drawn from it would ultimately be convincing and considered reliable by regulators and the scientific community. For this specific case it was concluded that whilst some of the design aspects might be criticized in general terms, in the context of this

development programme (including several other pivotal trials) this was widely agreed to be an acceptable trial.

Case Study 2: How to implement "Good Adaptive Practices" in a seamless adaptive Phase II/III trial with dose-selection at an interim timepoint?

Prof Frank Bretz (Novartis) revisited a study that is now completed and currently under regulatory review. The design was presented during the 1st EMEA/EFPIA workshop. This is a seamless adaptive Phase II/III design with treatment selection in a chronic disease. In the first stage the trial had four test doses, two active control doses and one placebo. A selection on the dose(s) to be taken forward was made based on a two-week endpoint. In the second stage the trial continued with two test doses, one active control dose and a placebo, using a 26-week primary efficacy endpoint. Once the main body of evidence was available at the end of stage 1 of the seamless adaptive design, a second pivotal study of 'standard' design was triggered, using the dose(s) emerging from stage 1 of the seamless adaptive design, to establish confirmation of efficacy, safety, and tolerability of the selected doses and support registration and label claims. Prof Bretz discussed the process for decision making as it was laid out in the DMC charter under different scenarios, and in particular reviewed a scenario with unforeseen complexities, circumstances under which the DMC was allowed to consult properly distanced senior management representatives of the sponsor. In this case study, the independent DMC comprised of experts external to the sponsor. Abdicating the decision on which dose(s) to take into Phase III to an external DMC represented a fundamental change for a clinical team, which traditionally would own this decision. Prof Bretz reviewed how Sponsor involvement in the DMC was structured, limiting it to individuals properly '*distanced*' from trial operations. The seamless adaptive approach allowed the Sponsor to reduce development time and cost by approximately 15%. However, this came at a price of more upfront planning and negotiation efforts within the company and with regulatory agencies, focusing on issues such as the DMC charter, pre-planned analysis, investigator training.

Mr. Robert Hemmings (MHRA, CHMP member) focused on the difficulties of pre-specifying the way in which doses of interest for continued study would be identified and highlighted the challenge for sponsors to write "guidelines" for dose decision in the absence of a gap (thinking time) between Phase II and III where all important data could be qualitatively and quantitatively considered and relevant expertise consulted. He reiterated that this resulted in additional technical and regulatory risk for the Sponsor. In his judgment in this trial the type 1 error was adequately controlled. He emphasized that regulators would look at the totality of the available evidence, and that he did not anticipate major issues related to the design of the study in the context of this particular development programme.

Dr Sue-Jane Wang (FDA) highlighted the design was based on the large amount of early exploratory data mostly efficacy and the perceived saving and benefit of the Novartis design which need confirmation. The adaptive algorithm placed the emphasis on the effect size, in particular, the effect size from the active comparator. She noted that as designed, the study maintains the strong control of the Type 1 error while identifying some logistics challenges and practical caveats specifically when multiple indications are of interest.

Considerations of US FDA Draft Guidance on Adaptive Design Clinical Trials

Dr Sue-Jane Wang (FDA) also provided a high level overview of FDA's draft guidance, due to be released before the end of 2009. This will be a comprehensive document which drafting has involved all relevant FDA functions. It will discuss not only statistical issues, but will also review challenges related to the complex logistics, in particular with regard to the information flow and decision making based on interim analyses. Blinded sample size re-estimation (SSR) appeared acceptable, whereas unblinded SSR reviewing not only the variability of the data, but interim results on the effect size of the different treatment arms, appeared more challenging. Dr Wang noted that FDA ask for justification of the prospectively

planned adaptation. Sponsor's involvement in interim analysis and decision still remains controversial.

The value of Adaptive Dose Ranging through two different case studies: lessons learnt

Case study 3: the value of a dose finding trial in "Learn"

Dr Michael Krams (Wyeth) presented a "Learn" study with early decision-making based on a clinical utility captured in real time in a two-stage approach, at first establishing proof-of-concept and then opening up the trial to a larger number of doses to learn about the viable dose-range. He described the Bayesian design which was jointly developed with Berry Consultants, and reviewed the setup of an internal Data Monitoring Committee distanced from the project team, reviewing emerging data on a weekly basis. He highlighted the need for appropriate infrastructure to support real time learning whilst maintaining integrity and validity of the trial. He discussed how the operating characteristics of the design were established through large-scale simulations, and encouraged the audience to review the value of the design in the context of the overall drug development strategy. He stressed that the planning and implementation of the adaptive design led to strong cross-functional cooperation enabling early decision-making with the objective to "fail efficiently" or "succeed efficiently". In this case study the adaptive design enabled a conclusive futility decision at an early time point, enabling the company to redirect resources to other projects.

Case Study 4: An adaptive dose finding trial for MK-0974 in acute migraine

Dr Franck Fan (Merck&Co) presented a randomized, double blind, placebo- and active-controlled, parallel group, outpatient study to evaluate the efficacy and tolerability of MK-0974 in patients with an acute migraine attack[4]. A two-stage adaptive design was employed to facilitate optimal dose selection for further studies and to minimize patient exposure to non-efficacious doses. During stage 1, patients were allocated to one of the following treatment groups: 7 different doses of MK-0974, an active control or placebo. Approximately one-third of all patients were randomized to placebo. Once 192 patients were randomized, an interim efficacy analysis was conducted to select the doses to be taken forward into Stage 2. Clinical trial simulations were used to determine the optimal number of patients (300-400) and the adaptive design strategy to maximize the power to detect a treatment effect and a dose response and to adequately control the type I error. This study provided helpful information to guide dose selection for future clinical trials while maximizing patient exposure to effective doses of experimental treatment. After the interim efficacy analysis, the four lowest MK-0974 groups were discontinued due to insufficient efficacy and, per the pre-specified algorithm; the three highest dose groups were carried forward into the second stage.

Dr Armin Koch (BfArM) discussed the Wyeth and Merck studies. He noted that both examples were outside the scope of the EMA's reflection paper, as they were clinical trials in the exploratory phase of drug development. Both provided valuable material for learning about decision-making based on adaptive designs.

Dr Koch found the design by Merck very interesting, in particular, there was no concern about information leakage and heterogeneity moving from stage 1 to stage 2, given that this was totally pre-specified and programmed into an IVRS-system. On the other hand, as always, also in this example, adaptation comes at a price: because recruitment was stopped in some of the treatment arms, less information was available at lower doses (precisely speaking: precision of estimates was lower) and thus additional information is probably necessary for identifying the appropriate dose for the confirmatory trial.

Dr Koch was impressed by the logistic challenges and savings enabled by the Wyeth case study. He used the example to reiterate his preference for an approach to drug development, where “Learn” and “Confirm” are properly delineated from each other, where the emphasis is that confirmatory clinical trials should be planned in a way to identify that a certain dose (or treatment schedule) is effective in a concept with control of the type 1 error. In “Learn” he accepted that the DMC can include company’s representative if properly “distanced” from the project team, but this would not be recommended in the confirmatory setting for reasons mentioned above.

Dr Sue-Jane Wang (FDA) encouraged the application of adaptive designs in “Learn” phase, provided that good adaptive principles were followed. Adaptive designs can help evaluate the dose-response and selecting the promising dose(s) to take into confirmatory trials. She was open to both Bayesian and frequentist approaches as good design tools which can be used at various stages of the drug development. She highlighted the importance of basing statistical inferences on objective evidence and encouraged clinical trialists to set up the logistics of the information flow and decision making to enable acceptability of the approach to third party reviewers, including regulatory agencies.

Q&A session

In a lively panel discussion the pro and cons of the presented dose ranging studies were discussed. A crucial question raised was whether the promoted use of innovative methodology, e.g., like adaptive designs or biomarkers, would include the risk of a decline in clinical pharmacology. It was concluded that it was always the triad of clinical pharmacology, medical research experience and statistical methodology to make drug development programs successful. New methodologies should not replace basic studies in clinical pharmacology, e.g., sometimes an n-of-1 experiment might be sufficient to answer certain questions with a minimum costs.

The advantage of adaptive dose-ranging studies would be that if the observed data did not provide a precise answer to the question, there would be the option to go on and recruit more patients to get more precise information. However, budgeting might be more difficult for adaptive dose ranging studies compared to fixed-sample designs. The whole range of costs has to be considered including expected and worst case costs.

It was discussed how important the role of DMC is in AD. The decision to stop a trial at an adaptive interim analysis should not be made on the primary endpoint solely. There should be clear stopping rules for DMC. How to get the right decision at an interim analysis if all important data are not available? The rules for the DMC should be compatible with the regulatory decision i.e. considering secondary endpoint, subgroups and safety and not only the primary endpoint. What is the amount of generated safety data at interim? Are there a sufficient number of patients? Is there enough information already available at interim to support the safety assessment?

These issues are of extreme importance: while obviously a trial after completion will be scrutinized with regard to consistency of findings in relevant subgroups (where then sometimes not sufficient evidence can be provided), at least at the interim there is the formal possibility to continue until such evidence is available.

Which strategic approach should be taken to Phase II? It is often confusing since sample sizes in phase II varies from 20 to 600 patients, sometimes even up to 2000 patients. The question is what are we trying to accomplish in phase II? How to establish a dose-response relationship? How to pick the right dose(s) for phase III? If one was mainly interested in establishing dose-response relationships, it was shown by simulations that different adaptive approaches were more efficient compared to fixed sample designs[5]. Even if the drug was not effective, these methods would allow to “fail efficiently”, i.e., as soon as possible. When using adaptive studies there is a loss of time before initiating the trials for planning and

simulations, but the overall time for drug development might be shorter higher with a higher level of success. Another argument to apply adaptive methods especially in exploratory phases is the benefit/risk to the patient. Adaptive designs might help to minimize exposure of patients to ineffective and/or toxic doses.

Adaptive Designs: A users' guide to implementation

In this session, all interested parties interacted to give their view on some "how to" solutions when considering AD in a clinical programme, which could help implementing "Good Adaptive Practices"

Dr Keaven Anderson (Merck&Co) reviewed how to identify opportunities for Adaptive designs in confirmatory trials. He used examples in cardiology and oncology, focusing on the implementation of the design and the decision-making enabled by it. He highlighted that:

- Adaptive designs should be selected only when they are the most appropriate way to address critical development questions.
- Adaptive designs are not the default choice for a confirmatory clinical trial.
- Adaptive design options in confirmatory trials are more restricted than in exploratory trials.

He reviewed a checklist used at Merck to review whether an Adaptive Design might be appropriate. Adaptive design elements include early discontinuation for futility, blinded sample size re-estimation (SSR), and dose-selection, taking selected doses forward to later stages of a design. The use of unblinded SSR might be more contentious and may require detailed discussion with regulatory agencies. Whilst optimizing the trial design on the primary efficacy endpoint, he highlighted that it was equally important to establish an adequate safety database for submission to regulators. Dr Anderson stressed the need to apply good adaptive practices, including appropriate control of the Type I error. Prerequisites for the use of adaptive designs in confirmatory trials are the availability of validated endpoints, availability of study drug with a well-characterized manufacturing process. The intention is to minimize the number of patients treated with unsafe or non-efficacious therapies and maximize the number treated with effective therapy, to stop the trial when there is adequate data to produce the desired substantial evidence for purposes of drug approval. There was also some discussion that strict adherence to guidelines for adaptive programs may be relaxed somewhat on a case-by-case basis in development of treatment for rare diseases with serious, irreversible outcomes.

Dr Sue-Jane Wang (FDA) presented FDA's experience with adaptive designs, based on U.S. regulatory applications involving clinical trials with some kind of adaptive design elements. Overall there was growing exposure to adaptive design proposals. All 15 medical divisions have received "adaptive design" proposals. A large number of proposals did not prospectively define the adaptation, which is a concern in particular for confirmatory trials. In principle, FDA is open to adaptive design proposals. FDA's Critical Path Initiative was quoted as an opportunity to rethink existing paradigms, such as the idea of independent replication implicit in the two-trial paradigm. Dr Wang recommended to control both type I and type II error rates, to pre-specify adaptive decision rules, to address the impact of operationalizing Adaptive Designs in multi-regional trials (potential for regional differences), to ensure appropriate informed consent and to build appropriate firewalls to maintain validity and integrity of the clinical trial. She emphasized the need to build an adequate safety database per regulation. She recommended a firm distinction between "Learn" and "Confirm" and mentioned that the term "seamless adaptive design" bridging Phase II and III will not be used in FDA's draft guidance.

Dr Michael Krams (Wyeth) highlighted the differences between a classical staged and a Learn & Confirm based drug development. The concept of Learn and Confirm was developed by Lewis B. Sheiner[6]. He identified two distinct activities in the clinical development: *Learn*

and Confirm, each with different goals, study designs, and analysis modes. In the Learn stage, the goal is to understand a new drug candidate, to maximize its medical value and determine whether it justifies continued investment. During "Learn", the drug candidate will be used in a representative patient population to identify the relationship between the dose, dose regimen, and its "likely" efficacy and safety. "Learn" trials are more flexible than traditional Phase I and II trial designs: the ambition is to adapt to the emerging clinical safety and efficacy data, ideally in real time. The real benefit of the adaptive approach in "Learn" lies in improving the information value, increasing the probability of down stream success. A ***seamless design*** combines into a single trial objectives traditionally addressed in separate trials. This type of design eliminates the time ("white space") that would have occurred between the trials had they been conducted separately, and may provide additional efficiencies in terms of the total number of patients or long-term follow up. An ***adaptive seamless design*** is a seamless trial in which the final analysis will use data from patients enrolled before and after the adaptation (*inferentially* seamless). The speaker discussed benefits and challenges of implementing seamless adaptive Phase II/III designs. He argued that there is an opportunity to further refine the selection of the correct dose to be taken into confirmatory trials by using seamless adaptive Phase II/III designs, where appropriate.[6,7] Such an approach is already being applied in several programs and is also discussed in the EMA's 2007 reflection paper [2].

Ms. Judith Quinlan (Cytel Inc.) provided a preview of a paper authored by PhRMA's adaptive design working group on "Good Adaptive Practices"[7]. This paper provides recommendations relating to the planning, designing, implementation, execution and reporting of adaptive designs, compiling experience gained across the pharmaceutical industry.

Clinical development needs to become more efficient; "Good Adaptive Practices" will enable better efficiency. The objective within each trial is to aim for the highest information value per resource unit invested. It is crucial to review adaptive trials in the context of the overall clinical development plan.

Dr Franz Koenig (EMA) and Mr. Robert Hemmings (MHRA, CHMP member) reviewed recent experience (2007 and 2008) of the CHMP/SAWP reviewing Adaptive Design proposals. A survey of the SAWP database since the finalization of the Reflection Paper identified a noticeable increase in the use of confirmatory AD in a broad range of therapeutic indications including anti-fungal, HIV, uveitis, anti-biotic, Type 2 diabetes, colorectal cancer, glioblastoma, multiple sclerosis, NSCLC. About one-third of adaptive design proposals were applications for orphan drug development programs. Here the question was whether a single adaptive design could be sufficient to support approval. It was stressed that not endorsing adaptive design without strict type I error control is not due to a **negative position** towards adaptive designs ***per se*** but rather due to a **positive position** towards the importance of the type I error control in clinical trials. Despite some obvious controversies, it appears that sample size re-estimation and use of Phase II/III combinations for treatment (dose) selection can be accepted providing proper implementation. Such adaptations have only been refuted if adaptation was an indicator of insufficient research in phase II. There is still limited experience with the use of Phase II/III combinations for patient selection. In general there is the tendency to keep the number of interim analysis in adaptive designs as small as possible, whereby in the vast majority (~65%) of submitted designs one adaptive interim analysis was proposed by the applicant. The SAWP always required a clear rationale for the number and timing of all pre-planned interim analyses.

In conclusion while the need to promote the use of AD where appropriate was stressed, e.g., for difficult experimental situations or confirmatory studies where efficiency gains do not compromise basis for regulatory decision, there still remain controversial areas such as Adaptive Designs as single pivotal study, sponsor involvement or trial heterogeneity. However, as more experience is gained, decision being made on the totality of the data, it is

likely that the position on sponsor's involvement could change in 10 years time. The EMA is planning to create a Biostatistics ad-hoc group to deal with AD issues and missing data.

Workshop Summary by Co-Chairs

Prof. Bruno Flamion in his conclusive remarks asked whether in light of the expected FDA draft guidance document, the EMA should consider revising its own reflection paper[2]. He also asked for a less formal and timelier approach for interactions between Sponsor and Health authorities, than the one which is currently based on the formal procedure of requesting scientific advice.

Dr. Solange Corriol-Rohou welcomed the opportunity for an exchange of experience on adaptive designs between regulators and representatives from industry and academia. She underlined the need to properly understand each other's expectations and concerns. She welcomed the willingness of the participants to share case studies in some detail. Applying "Good Adaptive Practices" will be key to establish credibility and respect for the adaptive approach to clinical research, and although there still are a number of open issues (e.g. sponsor involvement in DMC), there clearly is an important momentum across the industry. Once the FDA draft guidance will be published, a 3rd workshop may be considered in the future and it was noted that, if this occurs, more time should be allowed for discussion.

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[1] Report on the EMEA-EFPIA Workshop on Adaptive Designs in Confirmatory Clinical Trials (Doc Ref: EMEA/106659/2008) http://www.emea.europa.eu/meetings/conferences/14dec07.htm

[2] Committee for Medicinal Products for Human Use (CHMP). CHMP reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design 2007. Available from URL: www.emea.europa.eu/pdfs/human/ewp/245902enadopted.pdf

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