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Report on the EMEA-EFPIA Workshop on Adaptive Designs in Confirmatory Clinical Trials

The European Medicines Agency (EMEA) in collaboration with the European Federation of Pharmaceutical Industries and Associations (EFPIA) organised a first joint workshop on Adaptive Designs in Confirmatory Clinical Trials. The workshop was co-chaired by Prof. Bruno Flamion, Chair of the CHMP Scientific Advice Working Party (SAWP) and Dr Solange Rohou Chair of the EFPIA Efficacy Working Party. There was a large attendance from pharmaceutical companies as well as representatives from the regulatory authorities and some academic centres.

Introduction and Overview

Dr Armin Koch (BfArM & SAWP) held an introductory talk on minimal requirements and general principles for adaptive designs, referring to the recent CHMP adoption (18 October 2007) of the Reflection Paper on methodological issues in confirmatory clinical trials planned with an adaptive design (CHMP/EWP/2459/02). Besides controlling a prespecified type I error, it is necessary to estimate a treatment effect and a confidence interval with correct coverage and to address additional identification problems such as differences in effects due to chance and communication of interim results. Also too many design modifications may question the confirmatory nature of the trial.

Judith Quinlan (GSK) presented Industry views on the benefits of adaptive designs to clinical development. In light of high attrition rates even in Phase III, and the pressure to bring good drugs to market sooner without exposing many patients to ineffective drugs, adaptive designs were seen as a means to improve clinical development. For example to better understand the dose response, to improve dose selection and also the adverse events profile. Beyond this, it was also recognised that uncertainty can still exist in phase III, and as such, adaptive designs (with more limited adaptations) were also seen to have a potential place in confirmatory development. However it was emphasized that adaptive designs were not a remedy for poor planning, and actually require more upfront planning both statistically and in managing logistics and implementation.

Mr Robert Hemmings (MHRA & SAWP) presented real life experience from the SAWP of the CHMP, based on approximately 15-20 Scientific Advice applications with adaptive designs in confirmatory trials, mostly seamless Phase II/III combinations incorporating dose selection, sample-size re-estimation or both. Approximately 50% were single pivotal trials, and only a few were for orphan products. He presented three examples and explained why the proposals were endorsed or not. He discussed aspects of a trial which are not controversial for adaptation such as sample size reassessment and others which are more problematic such as adapting the randomisation ratio (possible shift in population recruited) or even controversial for adaptation such as the primary endpoint which should reflect patients benefit and be independent of interim data. The reasons for not endorsing several proposals for an adaptive design strategy were as follows: lack of acceptable rationale, totality of evidence likely to be inadequate, Type I error not adequately controlled, concerns over dissemination of interim information, and inadequate pre-specification of intention to adapt. Mr Hemmings emphasised that regulators are not opposed to adaptive designs; in one case the SAWP proposed to a company that for a certain development they should consider an adaptive design.

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Dr Sue-Jane Wang (FDA) presented the current FDA thinking on adaptive designs. Criteria to consider when discussing eligibility of adaptive designs in confirmatory trials include, e.g., if it is a new drug without prior/externally controlled trial knowledge, if there is a reasonable empiric safety database that can alleviate concerns, or if the new drug belongs to a class that has approved products in the market. She mentioned the importance of not mixing learning data with confirmatory data in seamless designs and of properly controlling the bias. Further she discussed firewalls to maintain the validity and integrity of trial results

In the lively discussion that followed, involving a panel of industry representatives and regulators, the latter argued that adaptive designs are mostly suitable for particular settings, e.g. small populations or otherwise difficult experimental situations. Also it is important to preplan for a very low p-value especially for a single pivotal trial. Further, the place of adaptive designs in conditional approvals was discussed, but it was mentioned that these two aspects should be kept separate.

Phase II/III Studies

Mr Robert Hemmings (MHRA & SAWP) presented the objectives of adaptive seamless trials as usually including both dose and/or population selection and confirmatory evidence of efficacy. He quoted as argument frequently rehearsed by industry that such designs may improve dose selection through encouraging larger/longer dose-finding trials but indicated that all improvements to the dose selection process are welcome, not only those related to adaptive designs in late stage drug develoment. Important issues to be addressed are: whether the confirmatory trial can be precisely planned prior to Phase II, whether adaptation is logistically possible, and whether all building blocks are in place (e.g. final drug formulation). From the regulatory perspective it is important to discuss why sufficient evidence is expected from the seamless trial compared to a program with separate trials. Safety information should be also discussed. Mr Hemmings concluded that seamless designs are in principle acceptable but increase the level of risk.

Dr Vlad Dragalin (Wyeth) discussed when it is appropriate to combine phases. A “seamless design” combines into a single trial objectives traditionally addressed in separate trials (operationally seamless), while “adaptive seamless design” describes a seamless trial in which the final analysis will use data from patients enrolled before and after adaptation (inferentially seamless). Advantages include more efficacy/dose information on clinical endpoints in the target population prior to triggering Phase III, reduced development timelines and cost, more safety information on longer-term patient exposure, and higher chance for patients within the trial to be treated with efficacious and safe doses. Challenges include: need the final formulation available at the start of seamless trials, data review at the end of the learning phase, decision process requiring additional expertise not usually represented on Data Monitoring Committees, and sponsor involvement in decision making.

Dr Andrew Stone (AstraZeneca) presented a case study of Phase II/III adaptive design with dose selection in an area of high unmet medical need. The end-of-phase II “GO” criteria are predefined and the analysis is performed by an independent DMC (two clinicians, one statistician). If the criteria are achieved, Phase II results will not be disclosed to either the company or investigators and the trial will continue as Phase III after dropping one of the two dose arms. If the criteria are not achieved, data will be unblinded and reviewed. He also mentioned that already in 1992 the company performed a similar trial with Casodex in prostate cancer.

Dr Frank Bretz (Novartis) presented a case study of a Phase II/III adaptive seamless design with treatment selection in a chronic disease. In the first stage (2 weeks) the trial has 4 test doses, 2 active control doses and one placebo; in the second stage (26 weeks) the trial continues with 2 test doses, one active control dose and a placebo. The DMC dose selection guidelines for the interim analysis decision making were described. The company plans to replicate the results with a second independent trial. The regulators were of the view that the design was adequate in the context of that particular development program.

In the discussion that followed, the regulatory experts commented that adaptive dose finding is welcome, but there is a risk of potential loss of information: the totality of the data should be as large as in a traditional late-phase development. Issues around focusing on sub-population based on pharmacogenomics were discussed, in particular the importance of quantifying whether other groups do not benefit from the treatment.

Sponsor involvement in adaptive trials

Prof Peter Bauer (University of Vienna) presented DMC experience with studies with adaptive designs. He discussed whether decisions in adaptive designs can be made by a board independent of the sponsor and whether regulatory experts should participate in decision boards of adaptive clinical trials.

Dr Michael Krams (Wyeth) presented the EFPIA view on sponsor involvement in decision making in adaptive trials. He contended that expertise present within the sponsor may be important in the adaptation. This is presently discouraged. He proposed a model for sponsor involvement: a clear rationale should be present, the individuals involved should be properly distanced from trial operations, and there should be a clear understanding of the risks by all parties involved. Moreover, restrictive firewalls and procedures should be in place. Generally the smallest number of individuals who can supply the needed perspectives only at the adaptation point should be involved and they should receive the minimally relevant information.

Mr Robert Hemmings (MHRA & SAWP) presented the regulatory perspective on sponsor involvement and the associated risks regarding the integrity of the trial. With sponsor involvement it would be more difficult to argue that importantly different results from different stages are only due to chance. He mentioned that dissemination of information happens in standard developments between Phase II and III, but in standard developments, endpoints, centres, investigators, and patient population are different between Phase II and III. He concluded that from a regulatory point of view sponsor involvement is discouraged. The challenge to the company is to justify convincingly why sponsor involvement is necessary and to establish absence of bias in the adaptive setting.

In the discussion it was mentioned that DMCs may not have the expertise for adaptation decisions since their main role is to control safety. Regulatory experts and some experts working in consultancies were of the view that sponsor involvement should remain the exception since it is very difficult to control bias. EFPIA was of the view that efforts should be made to find models ensuring trial integrity in spite of sponsor involvement.

Assessing Change / Establishing that the trial is reliable

Dr Willi Maurer (Novartis) discussed the CHMP Reflection paper requirements in relation to homogeneity when combining data from different stages of a trial with an adaptive design.. He questioned the request for at least the same careful investigation of heterogeneity as usually required for meta analyses, because differences in effect size between trials included in a post hoc meta analysis are much more likely than differences between stages within a well- planned adaptive trial. He agreed that the issue of heterogeneity should not be ignored, but stated that the problem is how to assess heterogeneity, what standards to apply and what to do if it is found, since it can exist even in non-adaptive studies and there is a risk of invalidation of a trial that overall shows a genuine effect. He asked if an initial signal of heterogeneity should not be dependent on the observed overall effect strength and presented high-level measures to be taken upfront and at final analysis to assess and control interaction between stages.

Dr Tim Friede (University of Warwick) discussed ways to explore changes in treatment effects across design stages in adaptive trials. He concluded that applying a formal heterogeneity test approach leads to great power loss that cannot practically be compensated for by larger sample size. Calendar time effects unrelated to interim analysis will make matters worse. Dr Friede suggested alternative approaches allowing for calendar effects.

Dr Keaven Anderson (Merck) presented examples of heterogeneity over time in clinical trials. He discussed whether there are cases of adaptive studies where heterogeneity related to learning may be tolerated, possibly requiring post-approval confirmation commitments. He also raised the issue that dose-selection and futility bounds introduce upward bias in naïve treatment estimates and questioned how much estimation issues due to designed-in heterogeneity in adaptive designs raises concerns. Further it was argued that heterogeneity in treatment effect can be largely due to random variation.

Dr Armin Koch (BfArM & SAWP) presented the regulatory perspective regarding heterogeneity. He argued that heterogeneity testing may be necessary. Although the current methods may not be ideal, this does not waive the requirement that grounds for heterogeneity have to be understood. If a classical heterogeneity test indicates discrepancy between stage results ($P<0.15$), this cannot be overlooked. Heterogeneity can be regarded as a secondary analysis, but it is necessary and is "the price to be paid" for having the possibility to adapt the trial.

In the discussion it was mentioned that regulators require that if there is heterogeneity in treatment effect, the case has to be made that this is not due to the adaptation and the interim analysis per se. Regulators encouraged methodological development and investigation of the validity of these methods in the context of adaptive designs.

Especially in response to Dr. Maurer's argument, that information carry over should usually smaller in a phase II / III combination trial, regulators argued that there is a difference between the two situations: in situation 1apparent knowledge from a phase II trial leads to an upfront discussion, in how far this knowledge could affect the assessment in a later trial (and which measures have to be taken to enable unbiased assessment). In situation 2 a potentially undetected information carry-over in a combination trial might lead to biased assessment without a discussion, how such biased assessment (and biased estimation of the treatment effect) could be avoided.

Harmonisation – Vision for the future

Dr Christy Chuang-Stein (Pfizer) discussed the importance of harmonization across regions. All agree that adaptive designs are not a remedy for poor planning and they require careful planning and rigorous execution. It is beneficial to crate open forums to hold scientific discussions and share experience to advance collective knowledge. She emphasized that there are differences in regulators feedback across the globe. For global development it is important that there is harmonisation regarding sample size re-estimation based on nuisance parameters and treatment effect, role of covariate adaptive randomisation in confirmatory trials, role of adaptive dose-ranging designs, role of homogeneity test in confirmatory trials, situations where phase II/III seamless designs are appropriate and situations where sponsor's involvement in a DMC is appropriate. She concluded that the goal should be an ICH guidance document on adaptive designs.

Summary of key positions from the discussion

Prof Flamion (University of Namur & SAWP) summarized the discussions as follows:

There was agreement among industry and regulators that cost of R&D is a public health issue, that there is growing patient pressure for early access to new drugs and that interim analyses can be ethical or even mandatory. However the regulators were of the view that cost of R&D and saving time per se cannot be the main rationale for using adaptive designs.

There was also agreement that adaptive designs are not a remedy for poor planning or even for unforeseen difficulties, that there is a need to control the type I error and that early stopping will reduce the totality of evidence. However regulators were not in agreement with a complete blurring of exploratory and confirmatory phases.

Open questions included whether adaptive designs improve dose selection, the role of adaptive designs in conditional approval, adaptive designs and a single pivotal trial as basis for registration, and selection of a biomarker-defined target population. The success of adaptive design studies can only be assessed after some experience has been gained.

Regarding seamless designs there was agreement that some reassuring examples exist and that there is a need for replication. However the real benefit of seamless designs and the benefit of long-term follow-up of Phase II patients remain open questions as compared to the more traditional approach, where there is extensive room for discussion after phase II has been completed. There is a clear 'risk' in committing to a specific plan for Phase III that is developed without the influence of data from Phase II.

Regarding sponsor involvement there was agreement that trial integrity is the primary interest, that there is risk of operational bias and that justification for sponsor involvement can be envisioned. However the regulators were of the view that sponsor involvement should remain an exception since it is problematic to prove the absence of information carry-over beyond reasonable firewalls being planned and incorporated.

Finally there was a lively discussion about the role of heterogeneity and methods to test heterogeneity of results in trials with adaptation.

Future Steps

This workshop was a very important and provided the opportunity for a fruitful dialogue between all stakeholders. Industry proposed the creation of a framework for ongoing discussions with the SAWP about adaptive designs and EMEA agreed to look into possibilities. For the time being any issues on adaptive designs, even if product independent, can be discussed in the context of regular Scientific Advice procedures.

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