ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE (ACPS)
Clinical Pharmacology Subcommittee (CPSC)
November 14-15, 2005

Case study: A quantitative approach to assess the benefits of incorporating pharmacogenomic testing in a phase III clinical Study

EXECUTIVE SUMMARY

This case study demonstrates the utility of clinical trial simulation (CTS) in regulatory review of efficacy study design, specifically for those studies incorporating pharmacogenomic information.

Drug X was developed by a sponsor as an oral treatment for a chronic disease. The sponsor and FDA discussed how to design a phase 3 trial for this drug. The challenging issues in designing the phase 3 trials include (1) difference in PK between populations with different genotypes will lead to clinically significant difference in drug response, (2) the response of a biomarker to the treatment is slow and the traditional titration based on biomarker level requires long time of treatment, and (3) there is a need to get the dose right as quickly as possible in the early treatment to ensure the maximum effect on surrogate endpoint can be observed at the end of the trial (26 weeks).

Phase 1 and phase 2 studies suggested that the apparent clearance of drug X (CL/F) is different in subjects with different genotypes on an allele. Subjects with homozygous wild-type (a/a) or heterozygous mutation (a/b) genotypes typically showed higher clearance than those with homozygous mutation (b/b) genotype. Population pharmacokinetic (PPK) analysis showed that the CL/F in subjects with a/b and b/b genotypes was about 85% and 35%, respectively, of CL/F in subjects with a/a genotype. Therefore, subjects with a/a and a/b genotypes are considered as extensive metabolizer (EM) and subjects with b/b genotype are considered as poor metabolizer (PM). Phase 2 efficacy studies suggested that the difference in exposures due to different genotypes resulted in different efficacy outcome.

The mechanism of action for this class of drug suggests that the drug exposure influences the level of a biomarker (B), which will further affect the level of a surrogate endpoint (S) that is used for effectiveness evaluation in pivotal trials. Under a regular dosing regimen, it takes approximately 12-14 weeks for the drug's effect on biomarker level to reach steady state and 26-28 weeks for the drug's effect on surrogate endpoint level to reach steady state. Phase 2 efficacy studies for drug X lasted for 12 weeks.

A mechanistic disease model was developed for another drug (Y), which is in the same class as drug X. Extensive phase 3 data (900 subjects monitored for 36 weeks) exist for drug Y. Since both drug X and drug Y are for the same patient population, the disease specific information is believed to be similar and could be shared to strengthen the outcome prediction of drug X. While the disease specific information is borrowed from

drug Y, parameters related to drug X, such as E_{max} and $EC_{50,}$ were obtained from the two phase 2 studies for drug X.

To optimize the benefit risk ratio, two dosing strategies have been considered: (1) genotyping based enrichment trial and (2) biomarker based enrichment trial. In genotyping enrichment trial, to reach comparable exposure among the population, the dose for EM is three times that for PM. In biomarker based enrichment trial, the same dose of drug X was initiated for all patients and dose will be tripled at week 12 for non-responders according to the biomarker level change. The non-responders are defined as subjects with less than 2 unit biomarker level reduction from baseline at week 12. The two strategies are evaluated using modeling and simulation approaches.

The clinical trial simulation considers the following components which may influence the study outcomes and design power: (1) disease model, (2) pharmacokinetics in different genotypes, (3) PK-PD relationship, (4) treatment regimen, (5) sensitivity and specificity of genotype assay. The objective of the trial simulation is to (1) Evaluate two alternative phase 3 trial designs and (2) Select the appropriate doses and dosing frequency

The trial simulation results indicated that in genotype based enrichment trial, 20 mg and 40 mg daily dose for PM are informative (naïve and experienced). BID regimens perform better than QD regimens, especially in EM population. In response based enrichment trial, similar findings were observed. Overall, higher response rate (surrogate endpoint reduction >5 units at week 26) was observed for genotype based enrichment design than for biomarker based enrichment design. The limitation of this simulation is that no safety information was quantitatively evaluated.

STUDY DESIGN

Two dosing strategies have been considered: (1) genotyping based enrichment trial and (2) biomarker based enrichment trial. In genotyping enrichment trial, to reach comparable exposure among the population, the dose for EM is three times that for PM (reference dose). In biomarker based enrichment trial, the same dose of drug X (reference dose) was initiated for all patients and dose will be tripled at week 12 for non-responders according to the biomarker level change. The non-responders are defined as subjects with less than 2 unit biomarker level reduction from baseline at week 12. The two strategies are evaluated using modeling and simulation approaches. Three reference daily doses were evaluated (10, 20 and 40 mg). BID and QD regimens were compared. Each treatment group includes 100 subjects. Treatment group was defined based on reference doses, e.g. 1 0mg QD group includes both PM patients taking 10mg QD regimen and EM patients taking 30mg QD regimen in a genotyping based enrichment trial.

CTS METHOD

Clinical trial stimulation was conducted with Pharsight Trial Simulator® V2.1.2. A population PK/PD model was used in the simulation. Pharmacokinetics of drug X can be described by a two compartment model with genotype being the covariate for CL/F and body weight being the covariate for the central compartment volume. A mechanistic

disease model (Figure 1) was applied to describe the relationship among drug exposure, biomarker level (B) and surrogate endpoint level (S).

Two simulation scenarios were examined, genotyping based enrichment and biomarker based enrichment. The response rate at week 26 was evaluated to compare different regiments. The responder is defined as subjects whose surrogate endpoint reduction relative to baseline level is greater than 5 units. One hundred trials were simulated for each design. Longer trial (38 weeks) was simulated for biomarker based enrichment trial because non-responders did not receive the appropriate doses until week 12.

RESULTS

The responder analysis showed that at week 26, genotyping based enrichment design achieved a consistent higher response rate compared to biomarker based enrichment design across different regimens (Figure 2). The results also showed a clear dose-response relationship and the superiority of BID regimen over QD regimen (Figure 2). When stratified by genotype, the advantage of BID over QD was more evident in EM patients (Figure 3). Comparable PK exposure (3 times dose in EM patients compared to PM patients) led to similar response in EM and PM patients. For the biomarker enrichment design, 45% of PM patients (13% of the overall patient population) will get 3X doses (potential over-dose) because they will be non-responders at week 12 based on biomarker level.

DISCUSSIONS

The trial simulation results indicated that in genotype based enrichment trial, 20 mg and 40 mg daily dose for PM are informative. Higher response rate was observed for genotype based enrichment design than for biomarker based enrichment design. BID regimens perform better than QD regimens, especially in EM population. The limitation of this simulation is that no safety information was quantitatively evaluated. However, a potential safety concern is 45% of PM patients will get 3X doses for the biomarker enrichment design.

Figure 1. Disease Model for A Chronic Disease and Drug effect

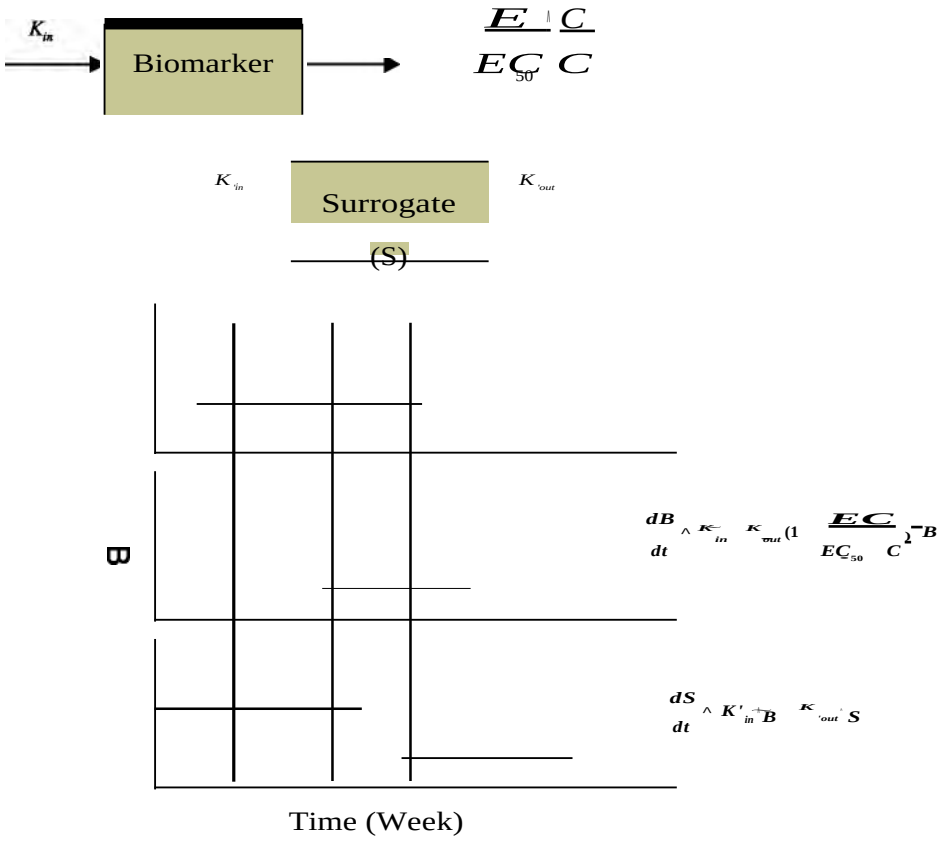


Figure 2. Response Rate under Different Dose Regiments

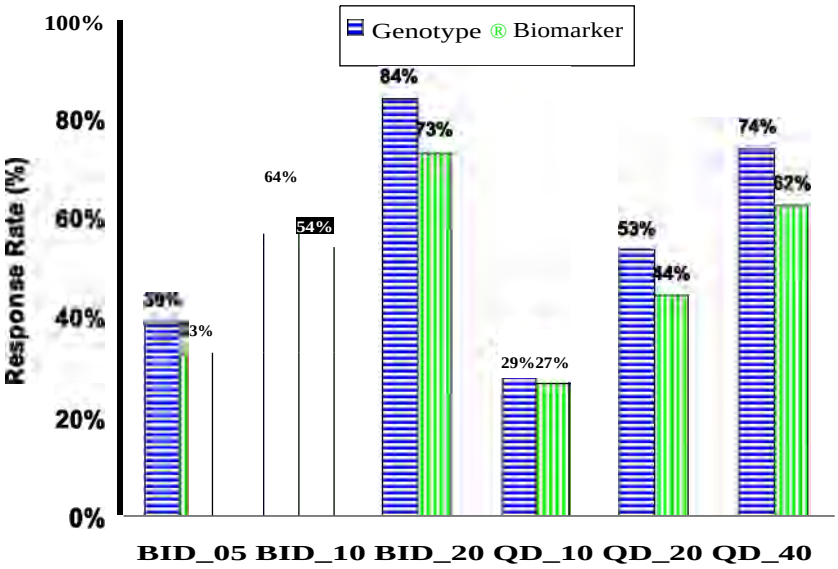
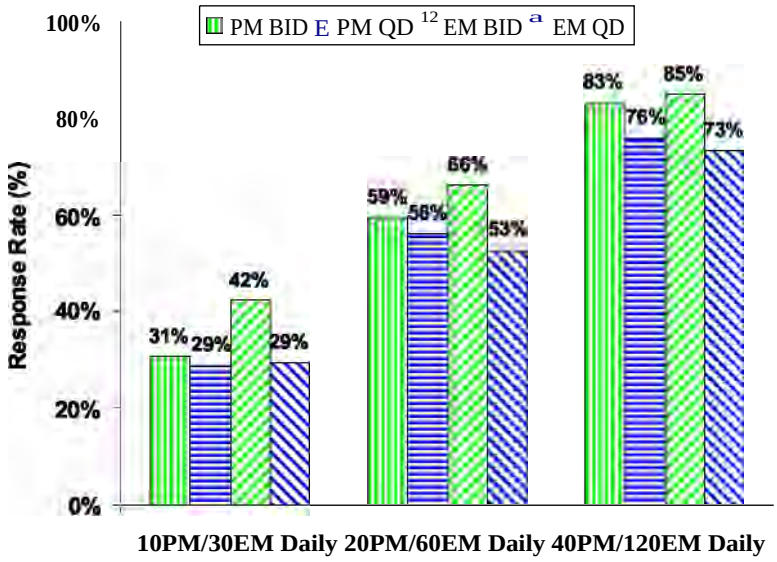


Figure 3. Response Rate under Different Dose Regiments Stratified by Genotype



QUESTIONS TO THE COMMITTEE

1. Comment on the quantitative approach used in this case study

2. Comment on how we would incorporate & evaluate genotype clinical trial design recommendations in different scenarios
   - metabolism genotype
   - pharmacodynamic genotype
   - disease genotype
   - narrow vs wide therapeutic index