A question based approach to drug development

Visser, S.J. de

Added value of bridging studies

Japanese people are considered a special target patient population by the Japanese drug registration authorities. Introduction of a western drug on the Japanese market requires proving efficacy and safety in the Japanese population, which often requires repetition of most clinical trials in Japan. A way to improve this time and cost consuming process can be to perform bridging studies between typical Caucasian and typical Japanese subjects to compare the characteristics that could potentially differ between the two populations. According to IMS health, multinational pharmaceutical companies are looking to aggressively expand their drug sales in Japan. From 1996 to 2000, the proportion of the Japanese market held by foreign companies increased from around 20% to almost 28%. Some of the biggest names in the industry, including Pfizer, AstraZeneca, Aventis and Eli Lilly, have recently made clear their intent to target the world's second-largest drug market (www.IMShealth.com). Their interest is being driven by the huge potential gains if they could match their global market shares in the Japanese market. This expansion could translate into billions of dollars in extra revenues. The task is becoming more readily achievable, as regulations overseeing drug development are harmonised between Japan, the USA and Europe, and as changes in healthcare delivery and finance foster new sales and marketing approaches.

Obviously, racial differences could occur in the pharmacological properties of investigational new drugs. Therefore, before a new drug is introduced in Japan sufficient data should be presented on the effects of the drug in a Japanese population. In some cases a comparison between the 'western' population and the Japanese population can be used to extrapolate the data from 'western' studies to the Japanese (especially when no differences are observed). Extrapolation of data could save the costs of additional studies in Japan. Therefore, it can be very rewarding to perform such a comparative (or 'bridging') study. Two examples of comparative studies are presented in this thesis.

The first example shows a study on the effects of nitrazepam, a registered drug for the treatment of anxiety. This study was first performed in Japan and afterwards repeated in matched Caucasian subjects in the Netherlands using the same protocol. The study was designed to explore the possibility and feasibility to perform

bridging studies in two study centres using one protocol. Once the infrastructure was established and both study sites' procedures were harmonised in the nitrazepam study, a bridging study for a potentially new oral contraceptive was performed as presented in chapter 10.
The Japanese registration authorities often require repetition of most clinical trials in Japanese subjects before registration. However, in some cases, a comparative trial can show that the complete repetition of all the clinical trials is not necessary. The 'population' question should nevertheless be adequately answered. Potential differences in ethnopharmacological factors would require additional trials in the Japanese population. Therefore, early comparative studies between Caucasians and Japanese have intrinsic value to the drug development program.

The comparative trial can be performed early in the development or late in the development depending on the estimated probability the study will show similar pharmacokinetics and/or drug effects and the costs associated with the study. The study presented in chapter 10 is performed early in the development and showed significant differences in pharmacokinetics. This finding requires parallel development in Japan in order to launch the product world-wide. If this study was performed at a later stage in the development, subsequent development in Japan would be delayed resulting in a loss of market value due to patent expiry and loss of revenues. It can be argued that the success probabilities for development in Japan would be higher in this case because development in the Caucasian population already produced significant knowledge about the drug.

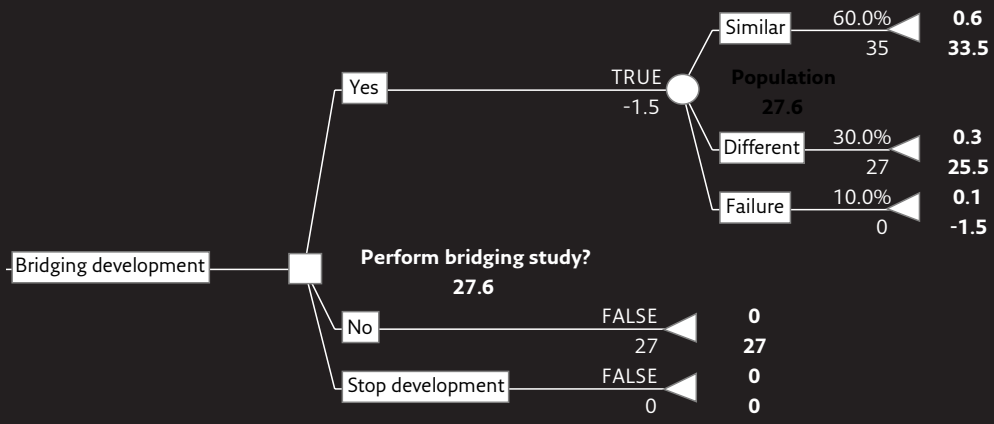
For the development of a (hypothetical) new drug a bridging scenario is considered. The drug development team has assumed that the worldwide development of the drug can be accomplished in three ways;

1. an early bridging study is performed that shows the two ethnic groups are 'similar' (this probability is estimated to be 60%)
2. an early bridging study is performed that shows the two ethnic groups are 'different' but the drug is developed in parallel in the two groups (this probability is estimated to be 30%)
3. the drug is developed in parallel in the two groups

In order to decide whether or not it is rewarding to perform the bridging study, which will introduce additional costs of M€ 1.5, a decision tree is constructed.

The risk adjusted project value after the bridging study is estimated at M€ 35 for the first option. The second option is estimated lower because the costs will be doubled (the drug will have to be developed in both groups in parallel). However, because the bridging study will enhance the success probability of the drug, the risk adjusted project value is not estimated at half the project value of the first option but at M€ 27. Similarly, if the bridging study is not performed but the drug is successfully developed according to the last option, the 'risk adjusted' project value is also set at M€ 27 but obviously, the costs of the bridging study have not been made. The constructed decision tree is represented in figure 1.

FIGURE 1 **Decision tree for a new drug, which is used to determine the feasibility of a bridging study**

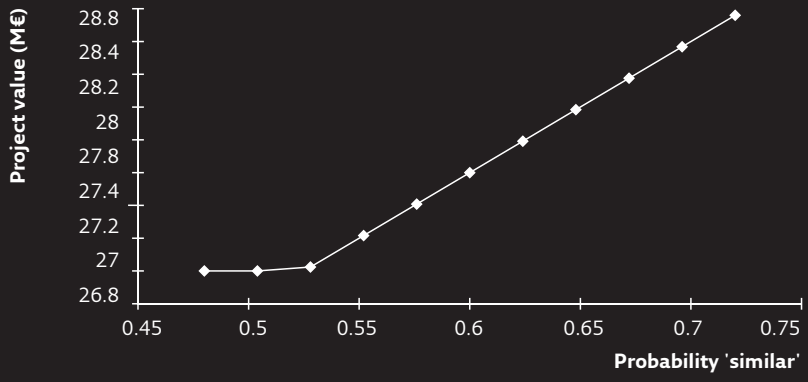


The decision tree clearly shows that the additional bridging study enhances the estimated risk adjusted project value with the current input parameters. In order to find out when the bridging scenario is no longer favourable, sensitivity analysis on the probability the two ethnic groups are 'similar' is performed. The result of this analysis is shown in Figure 2.

From this graph, it can be concluded that the probability the two ethnic groups are 'similar' may be estimated as low as 53% and still the bridging study will produce additional value despite the introduction of M€ 1.5. If the probability drops below

the 53%, it is more sensible to skip the bridging study and immediately start parallel development in both groups. The latter option produces the estimated risk adjusted project value of M€ 27.

FIGURE 2 **Sensitivity analysis on the probability that the bridging study will show the two ethnic groups are ´similar´**



However, the example of the potential oral contraceptive illustrates that it is crucial to take all questions into account when constructing the drug development decision tree. Even if one identifies the 'population' question as an important question, the other questions can have more significant impact on the optimal development strategy. In the presented case, the probability the drug would prove to have an improved side-effect profile would have to be estimated very low. The side effects associated with registered oral contraceptives are relatively rare and the exact mechanism of these effects is unknown and still subject to discussion. It would require additional evidence on the mechanism leading to these side effects to convince registration authorities that the new mechanism of action of the drug will lead to lower incidence of the side effects. Subsequent proof of improved side effect profile over existing medication would be very difficult (and expensive) due to the already relatively rare side effects.

Therefore, the probability of successfully answering the 'clinical' question would have to be estimated relatively low and the associated costs very high. Using both this low probability and high cost for the 'clinical' question in the QBD tree yields

a negative estimated risk adjusted project value instead of the M€ 27 used in the decision analysis represented in figure 1. As a consequence, the drug was discontinued after the comparative study presented in chapter 10 was completed. Adequate estimation of the costs and probabilities of success using the QBD-approach would have saved at least the presented comparative trial.
The construction of a decision tree for this drug would have revealed that the 'clinical' question far outweighs the 'population' question and abandoning the development of this drug would have been the best decision.