A question based approach to drug development

Visser, S.J. de

The value of determining critical questions early

This section presents a study in the development of a potential new drug for the treatment of generalised anxiety disorder (GAD). The development of a partially selective GABA-a agonist could have a therapeutic advantage over existing anxiolytics (existing benzodiazepines in particular). The main issue for these kinds of new drugs is that, after reaching the site of action (*i.e.* it must pass the blood-brain-barrier), the proposed mechanism of action points to a differentiation of the effects. The presented study indeed showed differentiation of effects.

The input parameters for the question-based development tree of this compound are presented in table 1. These input parameters are based on a classic drug development program of this type of compound (*i.e.* the parameters are estimated without the impact of the presented study).

TABLE 1 **Input parameters for the question based development plan of mr1a023 without the presented study**

Parameter	Value
Success action site	75%
Success pharmacological effect	65%
Success clinical efficacy	80%
Success therapeutic window	85%
Success population	90%
Costs action site	M€ 25
Costs Pharmacological effect	M€ 25
Costs Clinical effect	M€ 60
Costs Clinical window	M€ 30
Costs Population	M€ 35
Estimated market value	M€ 400

Similar to the value estimation of section 1, an optimal question sequence is determined by decision analysis. This priority list is represented in table 2. The estimated risk adjusted project value of this optimal sequence is M€ 27.

TABLE 2 **Optimal path in the question based development tree of MRLA023**

Priority ranking	Question
1	Pharmacology
2	Site
3	Window
4	Clinical
5	Population

According to the priority list presented in table 2, the two most important questions for this novel drug are 'pharmacology' and 'site'. In the classic NPV approach, performance of an additional cross-over study to determine the pharmacodynamic effects on sedation, body stability and memory compared to the existing market leader introduces extra development costs and maybe extra time. However, because of the early evaluation, a less sedative dose can be selected to examine the efficacy in patients. This maximum dose with a differential effect profile is crucial because it is the core of the market advantage over the existing benzodiazepines. Furthermore, the study prevents late failure created by an unwitting selection of a dose set too high. With this study, a maximum dose can be selected that is less sedating without any effects on memory, therewith providing important information regarding the 'window' question. Furthermore, the pharmacokinetic parameters of the drug, as estimated in the presented study, provide a first indication of what the optimal dosing regimen could be. The 'site' question is not fully answered, but the effects observed in the presented study are indicative of CNS penetration.

In order to estimate the impact of the additional study presented in this section, a new set of input parameters can be estimated that incorporate the knowledge and costs obtained in the presented study. Since an important part of the 'window' question is resolved, the probability of success on 'window' is now at least 86%. The probability of successfully answering the 'pharmacology' question is raised to at least 66% because of the demonstrated differential profile on the pharmacodynamic measures in the presented study. It remains uncertain if the differential profile is observed in patients. The indications for central activity observed in this study enhance the probability of success on 'site' to at least 76%. The costs of the study are added by elevating both 'window' and 'pharmacology' costs with M€ 1 (this includes the introduction of preparatory expenses, sponsor resources/time etc.). These updated input parameters are listed in table 3.

TABLE 3 **Input parameters for the question based development plan of MRLA023 after the presented study**

Parameter	Value
Success action site	76%
Success pharmacological effect	66%
Success clinical efficacy	80%
Success therapeutic window	86%
Success population	90%
Costs action site	M€ 25
Costs Pharmacological effect	M€ 26
Costs Clinical effect	M€ 60
Costs Clinical window	M€ 31
Costs Population	M€ 35
Estimated market value	M€ 400

With this new set of parameters the estimated risk-adjusted project value is estimated at M€ 28.2. With the NPV approach, the inclusion of this additional early pharmacology study would decrease the project value because it increases the costs of development without increasing the value of the drug. In other words, the knowledge obtained in this relatively inexpensive study is less likely to be adequately valued using NPV analysis. Question-based development shows that the introduction of extra costs can increase the project value by increasing the probabilities of success at a later stage in the development of this drug.

The negative impact of the additional study presented in this section could have led to a more classical approach to the development of this drug. This 'classical approach' could consist of a single ascending dose study in healthy volunteers to investigate safety and tolerability, followed by a multiple dose study and a food interaction study. Thereafter, the drug would enter phase II where in small groups of patients the efficacy would have to be established and the less sedating dose selected. This approach introduces substantially more costs.

The investigation of new centrally active drugs in patients is severely hampered by several factors. The heterogeneity of the clinical population, the differences in drug responses, and the methodology available to investigate sedative effects in patients

would require a substantial increase in the number of patients needed to show a statistically significant effect. Furthermore, the costs of investigating patients instead of healthy volunteers would further increase the costs of the development. Combined, a study in more patients than the twelve healthy volunteers used in this study would have a considerable impact on the project value.