

Case Study

Go/No Go Decision-Making

Creating Go/No Go Decision-Making Criteria For Early Stage Studies

KerusCloud®

KerusCloud® is a revolutionary simulation-guided study design tool that ensures clinical trials are designed effectively to collect the right data, from the right patients, in the right way. Its use supports evidence-based design decisions to extensively de-risk real clinical studies, reducing development time, costs and patient burden.

The Challenge

A privately held biotechnology company was developing a novel therapeutic targeting fibrosis and inflammation. Following a successful first-in-human Phase I study of the investigational agent in healthy adult volunteers and patients with suspected non-alcoholic steatohepatitis (NASH) and liver fibrosis, the company wanted to evaluate safety and efficacy over 12 weeks of continued administration, observing changes from baseline in metabolic, inflammatory and fibrosis biomarkers.

Regulatory guidelines usually require biopsy evidence of improvement to register a new treatment in NASH. Here, the short duration and small sample size meant a liver biopsy was unlikely to be informative. The company therefore needed an alternative source of evidence robust enough to inform development decisions for the agent at this early stage.

The Approach

1. A formal quantitative Go/No Go framework

MMS built a formal Go/No Go decision framework based on the method described by Lalonde et al. and Frewer et al. The method uses the upper and lower confidence intervals of the treatment effect to categorise the strength of evidence into three decisions – **Go, Consider, Stop** – by comparing those interval boundaries to a lowest reference value (LRV, the smallest clinically meaningful treatment effect) and a target value (TV, the desired effect).

The Approach

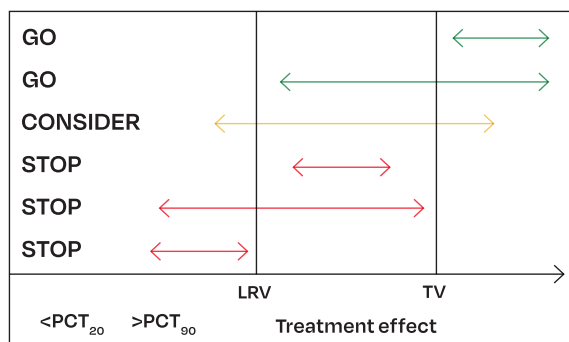
The framework supported three possible study outcomes:

- **Go** – $\geq 80\%$ confidence that the true treatment effect exceeds the lower reference value ($\Delta > \text{LRV}$)
- **Stop** – $\leq 10\%$ confidence that the true treatment effect exceeds the target value ($\Delta > \text{TV}$)
- **Consider** – a treatment effect meeting neither the Go nor the Stop criteria, where more data may be required

2. Setting the criteria using KerusCloud®

To apply the framework to the projected study, the TV and LRV had to be defined for the relevant biomarkers and the pre-specified risks set. The required sample size was obtained by simulation in KerusCloud®. This involved:

- Sourcing key statistical information – the statistical distributions and variation of the endpoints in the target patient population – through an extensive literature review covering the metabolic, inflammatory and fibrosis biomarkers of interest.
- Constructing the decision framework using the Lalonde method once TV, LRV, risks, sample size and variability had been determined.
- Evaluating the framework's performance by obtaining the probability of falling in each of the three zones (Go, Stop, Consider) under different truths of the treatment effect, using KerusCloud's interactive heatmap.
- Stress-testing the framework with 20% and 50% of the data missing, to mitigate for trial site closures during the COVID-19 pandemic.



Go if (green)

$\text{PCT}_{20} > \text{LRV}$ and $\text{PCT}_{90} >$

Consider if (amber) $\text{PCT}_{20} \leq \text{LRV}$ and $\text{PCT}_{90} > \text{TV}$

Stop if (red)

$\text{PCT}_{90} \leq$

Figure 1. Visualization of the decision framework, where PCT_x denotes the x th percentile of the distribution of the treatment

The Results

- The collated information was successfully incorporated into a decision-making framework supporting decisions for the projected safety and efficacy study of the candidate NASH treatment.
- The framework was shown to be robust in the event of a large proportion of missing data.

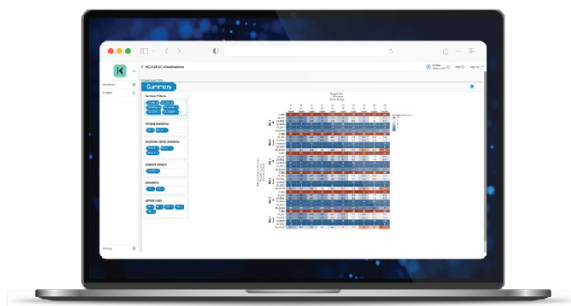


Figure 2. A typical results heatmap in KerusCloud®

The Impact

The client obtained a clear, quantitative decision-making framework for the projected study, de-risking and accelerating the development path for the investigational agent. Key exploratory NASH biomarkers were integrated directly into that framework.

Because the framework was tested against missing data, the client also had the option to report on a smaller sample size in the event of clinical trial site closures resulting from the COVID-19 pandemic.

Let's talk!

If you'd like to discuss this case study further or learn more on how our technology enabled services can support your development project, please visit mmsholdings.com or get in touch info@mmsholdings.com