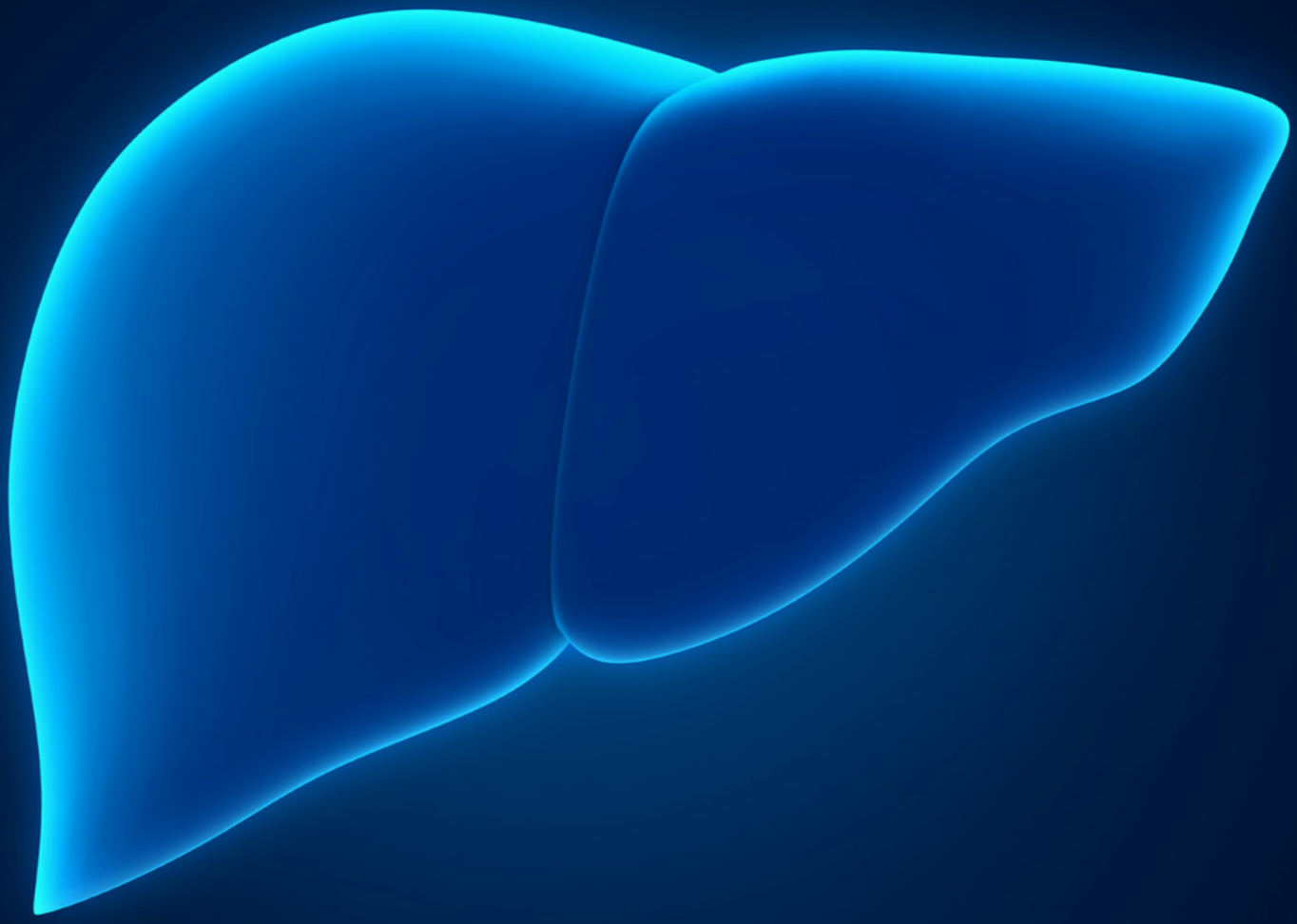
exploristics
INNOVATIVE ANALYTICS SOLUTIONS



Case Study

Creating Go/No Go Decision-making Criteria for Early Stage Studies

KerusCloud®

KerusCloud®

Creating Go/No Go Decision-Making Criteria for Early Stage Studies.

The Challenge

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

Although regulatory guidelines usually require biopsy evidence of improvement for registration of a new treatment in NASH, the short duration and small sample size meant that a liver biopsy was not likely to be informative. Therefore, the company sought alternative sources of evidence to inform decisions on the development of the novel NASH agent at this early stage.

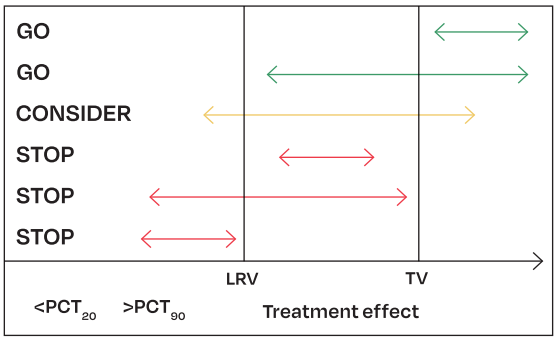
The Approach

To guide progress, Exploristics generated a formal go/no go decision-making quantitative framework based on a method from Lalonde et al., (1) and Frewer et al., (2). This method uses the upper and lower confidence intervals of a treatment effect to categorise the strength of evidence of the observed result into three decisions: Go; Consider; Stop. The boundary of these confidence intervals is compared to the lowest reference value (LRV) and a target value (TV), where LRV is the smallest clinically meaningful treatment effect and TV is the desired effect. These values are then used to construct a decision framework as shown in Figure 1.

A go decision could be made where there is ≥ 80% confidence that the true treatment effect is greater than the lower reference value (Δ>LRV). A stop decision could be made when there is ≤ 10% confidence that the true treatment effect is greater than the target value (Δ>TV). A treatment effect that does not meet the Go or Stop criteria then falls into the consider zone.

Setting up decision-making criteria using KerusCloud

To set up a decision framework for the projected study the TV and LRV needed to be defined for relevant biomarkers and the pre-specified risks set. The sample size required for the study was obtained through simulation using Exploristics' study design optimisation platform, **KerusCloud**. An extensive literature review was performed for key exploratory metabolic, inflammatory and fibrosis biomarkers to obtain information regarding the statistical distributions and variation of the endpoints in the target patient population. Once the TV, LRV, risks, sample size and variability were determined a decision framework was constructed using the Lalonde method. Performance of the framework was evaluated by obtaining the probability of being in each of the three zones (go, stop, consider) under different truths of the treatment effect.
The framework was also tested with 20% and 50% of the data missing to mitigate for trial site closures due to the ongoing global COVID-19 pandemic.



Go if (green) PCT20 > LRV and PCT90 > TV
Consider if (amber) PCT20 ≤ LRV and PCT90> TV
Stop if (red) PCT90 ≤ TV

Figure 1. Visualisation of the decision framework, where PCTx denotes the xth percentile of the distribution of the treatment effect (P(Δ)).

KerusCloud

Go/No Go Decision-making Criteria for Early Stage Studies

The Results

- Key statistical information was sourced via an extensive literature review on the metabolic, inflammatory and fibrosis biomarkers of interest.
- This information was incorporated into a decision-making framework to support 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.

The Impact

- **The client obtained a clear decision-making framework for the projected study, de-risking and accelerating the development path for their investigative agent.**
- **Key exploratory biomarkers for NASH were integrated into the framework.**
- **Mitigation for missing data gave the client an option to report on a smaller sample size in the event of clinical trial site closures resulting from the COVID-19 pandemic.**

References

(1) Lalonde, R. L., Kowalski, K. G., Hutmacher, M. M., Ewy, W., Nichols, D. J., Miligan, P. A., Corrigan, B. W., Lockwood, P. A., Marshall, S. A., Benincosa, L. J., Tensfeldt, T. G., Parivar, K., Amantea, M., Glue, P., Koide, H. and Miller, R. Model-based drug development. Clinical Pharmacology and Therapeutics 2007; 82:21-32.

(2) Frewer, P., Mictchell, P., Watkins, C. and Matcham, J. Decision-making in early clinical drug development. Pharmaceutical Statistics 2016;15: 255-263.

Why Exploristics?

Expertise In Early Development

The development of investigational drugs is a complex and expensive process with many risks. For over ten years our teams have been supporting and de-risking clinical development with their in-depth statistics and modelling expertise. Our study planning, statistical analysis and programming services add value to early stage development programmes by ensuring they deliver the robust evidence needed for incisive, informed decision-making.

With many of our development solutions built around our unique **KerusCloud** platform, we can provide exceptional, bespoke, end-to-end biometrics support from strategic decision-making and protocol development to analysis, reporting and stakeholder engagement.

Robust Evidence Packages

The unique offering of our comprehensive biostatistics services in combination with **KerusCloud** ensures that Exploristics can help to generate strong evidence packages to support regulatory engagement or investment, accelerating development timelines and increasing the value of pipelines.

Exploristics, Your Essential Biostatistics Services Partner

Exploristics Ltd.
24 Linenhall Street Belfast,
Northern Ireland BT2 8BG

find out more
T +44 (0) 28 9600 1996
info@exploristics.com