exploristics
INNOVATIVE ANALYTICS SOLUTIONS

Case Study

Establishing Biomarkers of Treatment Efficacy

Establishing biomarkers of treatment efficacy in liver disease.

KerusCloud®

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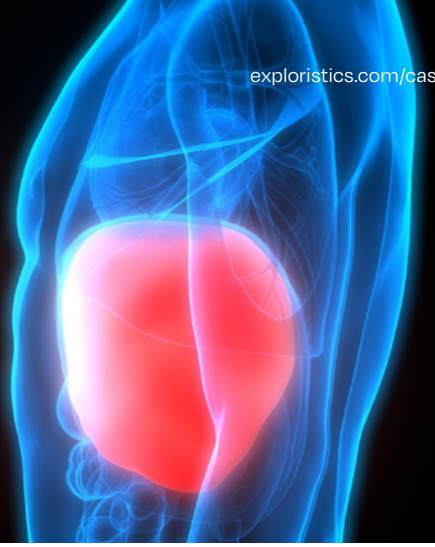


The Challenge

A privately held biotechnology company at an early stage of clinical development was interested in designing a study using biomarkers to indicate treatment efficacy in subjects with stage 2/3 fibrosis with non–alcoholic steatohepatitis (NASH). NASH is a liver condition characterised by inflammation and fat accumulation and is usually accompanied by fibrosis (Figure 1). Five biomarkers are believed to be involved in the disease process - ELF, PRO-C3, GAL-3, aPAI and YKL-40. The Sponsor wanted an early assessment of the potential efficacy of their treatment within a Phase I/IIa safety and pharmacokinetic (PK) study. As part of this process, they wished to consider the following questions:

- Which of these biomarkers will give the best chance of success in clinical trials?
- Are some biomarkers more variable than others and what impact will that have?
- What if the chosen biomarker/s are more variable than anticipated?
- What is the advantage of using a change from baseline approach in the analysis?
- What sample size should we plan for?
- What effect will different treatment allocation ratios have?

The Approach

To support the assessment, Exploristics carried out literature searches to collate information on each biomarker e.g. expected response of ELF in the untreated target population and expected level of variability.

KerusCloud was then used to develop and implement a study simulation framework. Distributions were defined using parameters determined from the literature review e.g. mean change from baseline response in placebo distribution vs treatment distribution. 'What if' scenarios were used to anticipate issues such as variability that was larger than expected or treatment effect that was smaller than expected.

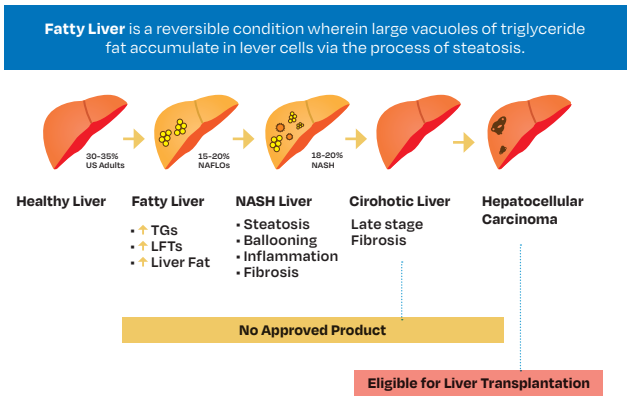
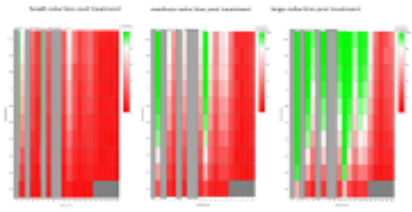


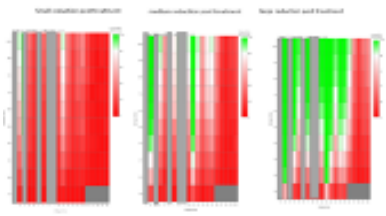
Figure 1. Liver disease progression. Fibrosis is categorised by severity of liver scarring.

Simulations were carried out using **KerusCloud** to evaluate multiple scenarios. An example set of heatmaps indicating the effect of different treatment allocation ratios across the five different biomarkers is shown in Figure 2. This simulation included two dose levels and placebo with analyses corresponding to the effect of top dose vs placebo, low dose vs placebo and the effect of the single factor of treatment in an analysis of covariance. Red indicates low Probability of Success (PoS), green a PoS > 80%.

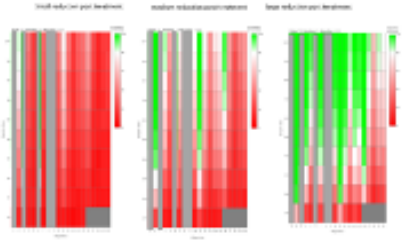
1:2:2 allocation. Low dose defined at 50% effect of high dose. Low correlation between baseline and post-treatment.



1:2:2 allocation. Low dose defined at 50% effect of high dose. High correlation between baseline and post-treatment.



1:2:2 allocation. Low dose defined at 90% effect of high dose Low correlation between baseline and post treatment.



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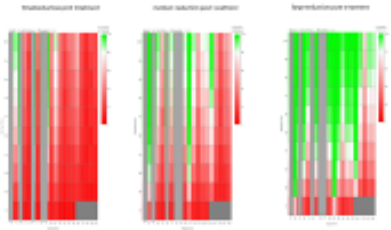

Figure 2.

A series of heatmaps evaluating the effect of different treatment allocation ratios across the five different biomarkers.

The Impact

With **KerusCloud** simulation it was possible to determine that:

- **Analysis of covariance including baseline was the most powerful analysis.**
- **Using PRO-C3 biomarker would lead to the greatest probability of success; with around 35 subjects required to observe a reduction of 50% with 80% probability of success.**
- **YKL-40 required more subjects to achieve the same level of success as PRO-C3; with over 60 subjects required to observe a reduction of 50% with 80% probability of success.**
- **A substantial increase in the number of subjects was required if a smaller clinical effect was evident; an increase from 35 to 85 subjects was required if a 33% reduction was observed.**
- **When moving from a treatment allocation ratio 1:1 to 1:2 to 1:3, the probability of success decreased. This varied according to sample size and biomarker.**

KerusCloud demonstrated that the inclusion of a panel of biomarkers as secondary endpoints in an early-phase trial with safety and PK as primary endpoints provided a realistic chance of observing a clinically-relevant treatment effect.