THE DIFFERENCE IS IN THE DATA®

mmsholdings.com

Case Study

Evaluating Biomarkers

Establishing biomarkers of treatment efficacy in liver disease

KerusCloud® is a revolutionary simulation-guided study design tool that ensures clinical trials are designed effectively to collect the right data, in 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 Software

KerusCloud® allows multiple study uncertainties to be explored simultaneously, in minutes, within a virtual environment. Study outcomes are visualized with an interactive heatmap where detailed results help identify the pros and cons of different design options. This allows the key drivers of study success to be pinpointed rapidly so that the best design and analysis approach can be selected, first time.

Diverse information and data types inform the simulations with sources including the scientific literature, disease registries, historical trials and real-world data. These data are captured in the platform as synthetic data sets, avoiding privacy constraints, and used to build virtual patient populations to answer 'what if' study scenarios questions.

KerusCloud's synthetic data driven simulations are uniquely informative. They best represent the complexity found in real studies by accurately mimicking the quirks found in real patient-level data, like missingness. Therefore, KerusCloud® provides exceptional advanced analytical insights able to deliver the smarter studies needed to address today's complex clinical research challenges.

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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?

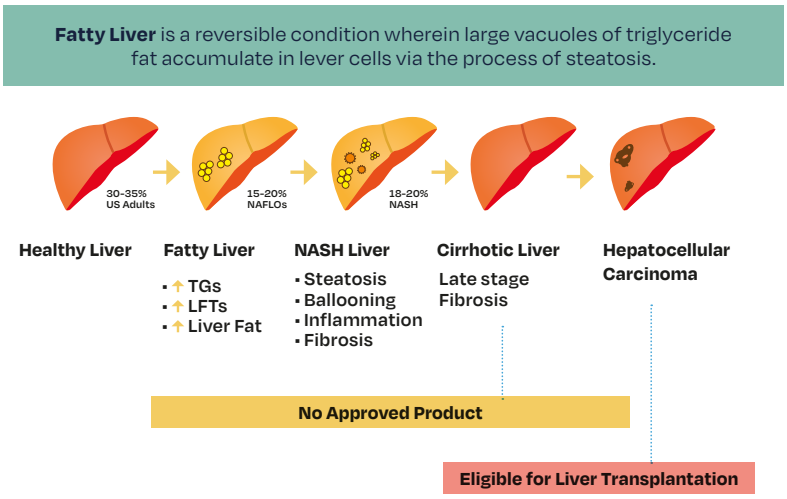

Figure 1. Liver disease progression, where fibrosis is categorised by severity of liver scarring

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The Approach

To support the assessment:

- Extensive literature searches were carried out by the Data Science team to identify and collate information on the five biomarkers e.g., expected response in the untreated target population and expected level of variability.
- The data sourced was standardised and synthesized to generate virtual patient level synthetic datasets within KerusCloud® to inform study simulations of numerous 'what if' scenarios of interest (Figure 2).
- Different study scenarios were used to explore the six key questions of interest for the Sponsor and anticipate issues such as variability that was larger than expected or treatment effect that was smaller than expected. Scenario outcomes were viewed via interactive KerusCloud® heatmaps (Figure 3) where they could be explored in detail.

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The Results

Exploration of multiple scenarios indicated 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.**

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The Impact

KerusCloud® enabled the Sponsor to use quantitative based evidence to make decisions regarding the design of the study. Using KerusCloud® established 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.

Using the biomarker PRO-C3 would give the best chance of success in clinical trials.

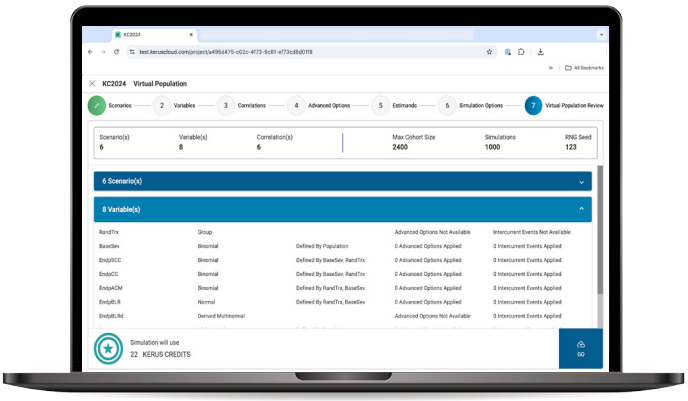

Figure 2. Construction of a virtual population in KerusCloud®

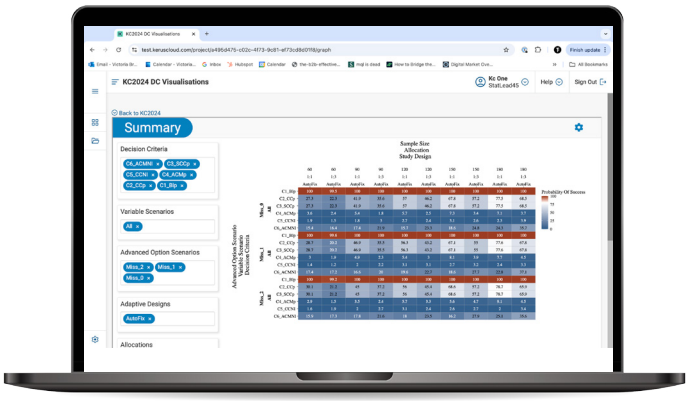

Figure 3. A typical results heatmap in KerusCloud®

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Why MMS?

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 programs 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 biostatistics 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 MMS can help to generate strong evidence packages to support regulatory engagement or investment, accelerating development timelines and increasing the value of pipelines.

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 our website: mmsholdings.com

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