SUCCESS STORY

Novartis
Operating in 140 countries with global headquarters in Basel, Switzerland, Novartis offers a wide range of healthcare products through Pharmaceuticals, Vaccines and Diagnostics, Sandoz and Consumer Health Divisions. Nearly 100,000 people are working at Novartis to help discover, develop and successfully market innovative products to prevent and cure diseases, to ease suffering and to enhance the quality of life.

Industry: **Pharmaceutical**
Geography: **Global**

Deployment Summary
Spotfire is used for safety data assessment and interactive data exploration in preclinical and clinical studies at Novartis. Workflows based on Spotfire are a substantial step forward from traditional manual processes which include reworking of data in multiple iterations between stakeholder communities.

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"Interactive graphical data exploration provides an efficient, powerful and flexible tool to improve both detection and systematic assessment of safety signals,"

Michael Merz, MD, Head Safety Networks, Novartis Institutes for BioMedical Research Basel

Using TIBCO Spotfire for Exploratory Data Analysis and Safety Assessment in Preclinical and Clinical Studies

Exploratory data analysis is performed at different levels In the Novartis research and development environment, beginning at the individual study level. During a clinical study, monitoring safety biomarker trends and incidences of adverse events over time can be crucial to detect relevant safety signals as early as possible and decide on potential risk management and risk minimization steps. After completion of a study, the cross-functional project team may benefit from jointly and interactively querying safety data to further explore any signals and start to generate mechanistic hypotheses suited to explain any relevant safety observation.

At the same time, the team can select the most suitable graphical displays of safety information to be included in final study reports or submission documents.

Across an entire project, systematic data exploration may help to further assess the relevance of putative signals, identify dose-response relationships, if any, and screen for risk factors in the target population.

Finally, at a broader level comparing effects across different indications, exploratory graphical data analysis can support teasing out disease and population specific differences in safety profiles of a drug candidate.

Challenges

Current standard practice in clinical drug safety assessment still are summary tables and data listings, and, sometimes, graphs produced by expert statisticians or programmers. The typical process usually looks like this:

- a project team including expert statisticians jointly plans a clinical study
- the clinical team generates the respective data either in-house or via contract research organizations
- programmers produce standard tables/listings/graphs summarizing the data to help the research or clinical team exploring the study results
- in case the data provide evidence for safety signals and suggest certain mechanisms underlying the findings, the team requests further in depth analyses, hypothesis testing, and production of more specific graphical displays

Thus, depending on size and complexity of a given dataset,

- the time from first getting the study results in-house to final interpretation of the data may include one or more iterations of such “team <> data analyst” communication loops, a process that can easily take several weeks to complete, and
- safety signals may be overlooked by just using standard analysis approaches, which predominantly are of univariate nature, whereas adverse biological effects often consist of subtle changes in multi-dimensional patterns of markers and measurements.

Clinical and Preclinical Safety Assessment with Spotfire

A workflow for exploratory clinical safety data analysis using Spotfire enterprise analytics may start with frequency distributions of key safety variables, comparing shape of distributions across treatment groups as shown in Figure 1:

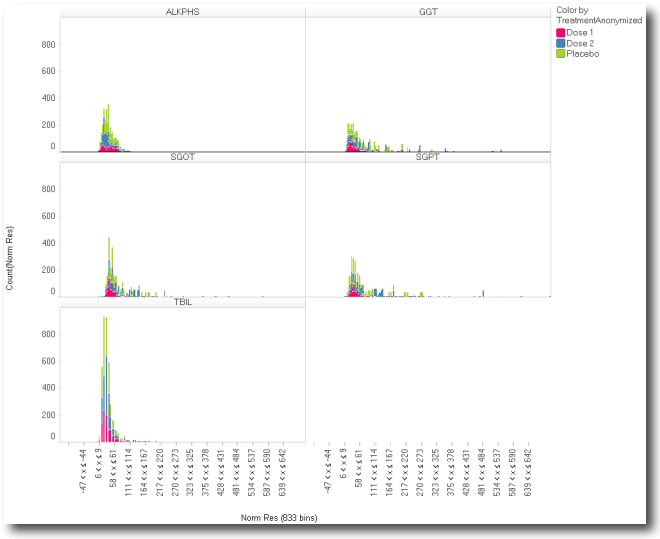

Figure 1: Frequency distributions of liver biomarkers (normalized values). Color coding is by treatment. For ALT (SGPT), AST (SGOT), and GGT, there seems to be a trend for higher values with active treatment.

Second step may be a comparison of shifts from baseline for those parameters that showed relevant findings in frequency distributions in step 1, as shown in Figure 2:

Figure 2: Scatterplot of maximum postbaseline vs baseline values across liver biomarkers, lipids, and white blood cell count (normalized values). Color coding is by gender. Relevant increases from baseline can be observed for ALT (SGPT), AST (SGOT), and, to a lesser extent, for alkaline phosphatease (ALKPHS).

Time profiles of e.g. liver enzymes can easily be checked for presence of "Hy's law" cases, i.e. elevation of ALT (SGPT) exceeding 3 x ULN, and total bilirubin exceeding 2 x ULN, using Spotfire software linked line plots and marking all profiles exceeding 3 x ULN for ALT. The respective profiles for total bilirubin are then highlighted in parallel (Figure 3):

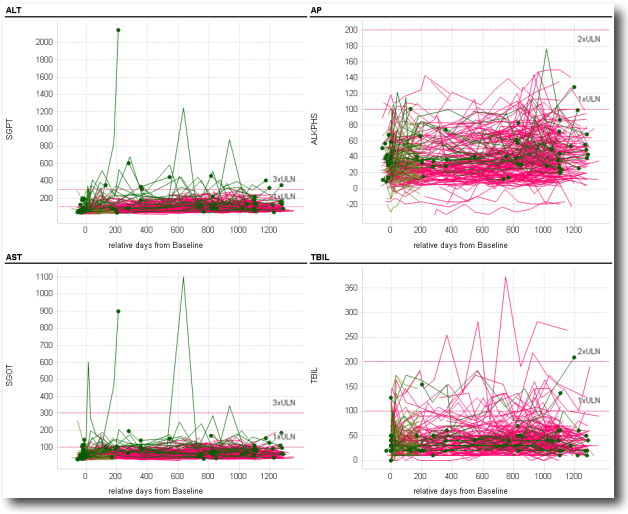

Figure 3: Line plots for liver biomarkers. All ALT (SGPT) profiles exceeding 3 x ULN have been marked. Profiles for the other biomarkers corresponding to the same patients are highlighted. There seems to be one patient potentially fulfilling Hy's law criteria.

Enzyme profiles over time in relation to treatment discontinuation may be checked using Trellis line plots with one panel per patient, and treatment end indicated by a vertical line (Figure 4):

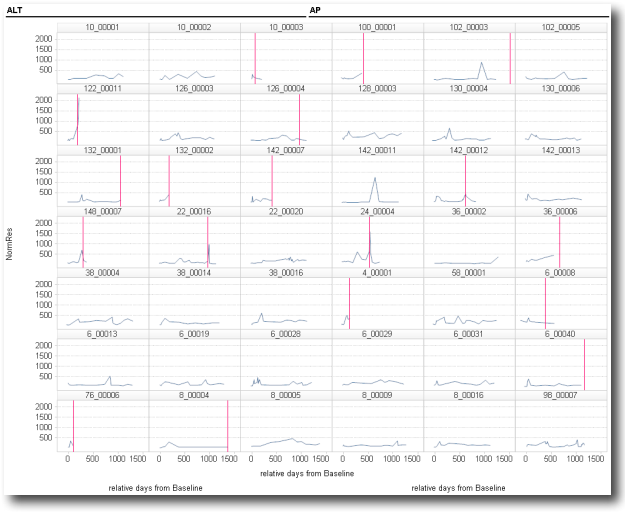

Figure 4: Time profiles of normalized ALT for selected patients. Treatment end indicated by vertical red line. Several panels show a transient response; elevations are short-lived and levels return to normal without stopping the treatment.

Finally, plotting time profile of biomarkers of interest along the same time axis as adverse events and concomitant medications facilitates identification of potential associations and may suggest alternative explanations for certain biomarker changes.

In the preclinical setting, associations between clinical pathology changes and histopathology findings can be easily assessed using a combination of line and scatter plots (Figure 5):

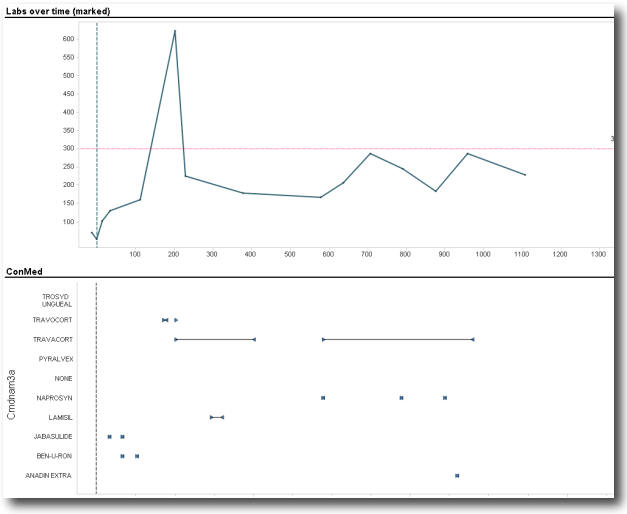

Figure 5: Time profile of normalized ALT along with intake of concomitant medication. ALT peak occurred shortly after intake of paracetamol, which may have been causally related to the enzyme elevation.

The analysis flow presented above is highly interactive in Spotfire. Graphs show population and sub-population trends, and can also be used to identify subjects with out-of-range measurements on a variety of responses. The user can easily drill down to subject-level information for all of these cases. This flow enables data quality to be assessed in an ongoing basis, and provides insights in to root causes and relations between the individual data components and elements.

Solutions

Using interactive graphical data analysis, experimental results can be explored either by individual scientists or in interactive team sessions, providing an opportunity to search for multi-dimensional changes in safety biomarkers, test assumptions, generate and pre-test hypotheses, and define a set of plots optimally suited to display relevant safety findings. With that type of output provided to the statistician, further in-depth analyses can be performed in a much more focused way, and a set of high quality plots based on the templates identified during the exploratory phase can be compiled to go into final study reports and submission documents.

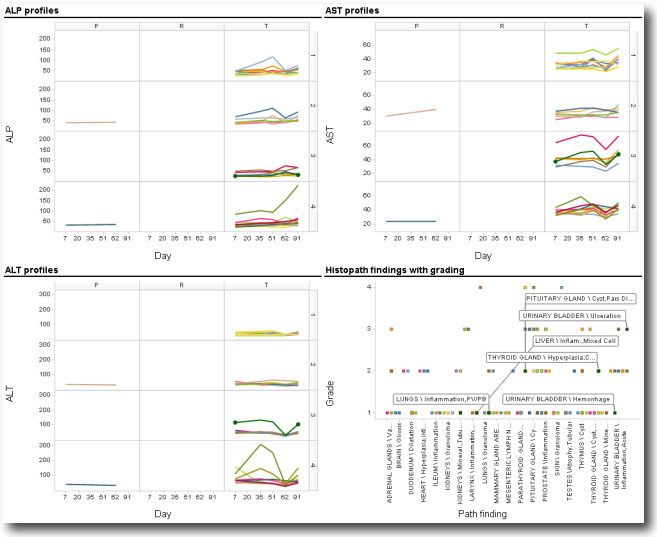

Figure 6: Plots of liver biomarker profiles across dose groups and histopathology from an animal experiment show the correlation between clinical pathology and histopathology. In Spotfire software, marking a specific profile in one panel (green in this example) displays all pathology findings with labels to identify the tissue and severity, linking together clinical pathology and histopathology.

Results

At Novartis, Spotfire enterprise analytics is being used as one of the key tools for interactive graphical data analysis for both preclinical and clinical studies. "Interactive graphical data exploration provides an efficient, powerful and flexible tool to improve both detection and systematic assessment of safety signals," says Michael Merz, Clinical Pharmacologist and Head of Safety Networks Preclinical Safety at Novartis.

Spotfire enterprise analytics enables project teams to efficiently address questions such as

- Is there any dose–response relationship for certain effects?
- Are there any specific subgroups at increased risk?
- Do any patient groups show higher incidences for certain adverse events or deviating safety biomarker values, possibly associated with factors such as age, gender, race, body mass index, smoking status, or alcohol consumption?
- Which parameters show relevant shifts from baseline?
- What do time profiles of individual markers look like?
- Are there any obvious patterns that change in a treatment related fashion?

Project teams may use Spotfire software to look at parameters such as liver enzymes, muscle enzymes, markers of inflammation, and the like. Merz states, "Plotting a large amount of data using a small set of suitable displays can quickly show if there is any difference in response between compounds or across patient groups. It can be extremely difficult or sometimes impossible to make sense of such a large amount of complex data by just looking at data listings or tabular summaries."

"Spotfire is suited to support interactive data exploration in a project team setting, facilitating both hypothesis generation and testing, and reducing analysis time," says Merz. "I have been using this tool for several years and have become an enthusiast for it and for the potential of interactive graphical data analysis in general."

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