

Definiens enables early decision making in pre-clinical study

CASE STUDY

ALTANA Pharma AG

ALTANA Pharma AG is a part of Nycomed, a leading European pharmaceutical company with operations all over the world. ALTANA employs around 8,600 people and provides a range of innovative pharmaceutical products with a focus on prescription drugs for gastrointestinal and respiratory diseases.

In a pre-clinical safety study of a new compound, a Definiens' application identified a clear proliferation of bile ducts in monkey livers indicating potential toxicity. The application automatically took measurements of the size and area of the bile ducts and even the number of nuclei they contained. As a result of the study, ALTANA chose not to proceed with an expensive clinical trial using the compound.

Background

ALTANA owns a valuable ATPase inhibitor, marketed under the trade name Pantoprazole. Annual sales of the drug are €1.4 billion worldwide. The compound comes off patent in 2010 and ALTANA is keen to find a replacement.

The Challenge

The Institut für Präklinische Arzneimittelsicherheit (IPAS) is the preclinical site of ALTANA and conducts in silico, in vitro and in vivo safety studies for drug candidates.

IPAS was engaged in a safety assessment of a new compound from a pCAP-Inhibitor class for the rapid treatment of gastric ulcers. The study involved examining the proliferation of bile ducts in the liver of monkeys as an indicator of toxicity. 44 animals were studied, divided into four groups. Three of the groups were given different levels of dosage while the control group received no dose.

Working with a slide taken from each monkey's liver, the IPAS team isolated three images from different parts of each slide. These 132 images formed the basis of the study.

The challenge was to identify the bile ducts within the images and take the following measurements:

- › The number of bile ducts
- › The length and width of each bile duct
- › The area of each bile duct
- › The distance between bile ducts

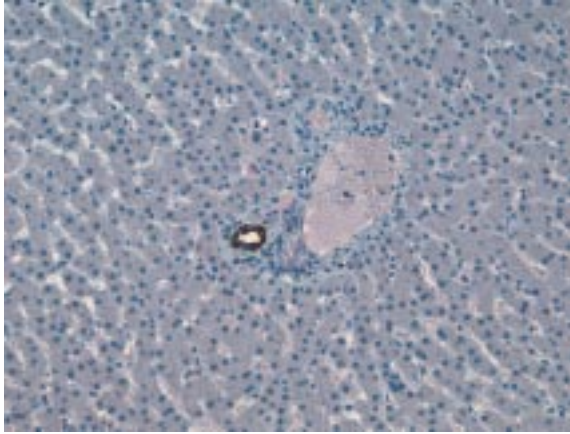
The Approach

The study used the IHC stain CK18 to highlight the bile ducts and haematoxylin to counterstain the nuclei. Because of the variability of the staining process, the bile ducts could appear red, brown or purple. While a pathologist could easily handle such variation, this presented a major challenge for any automated or semi-automated image analysis system.

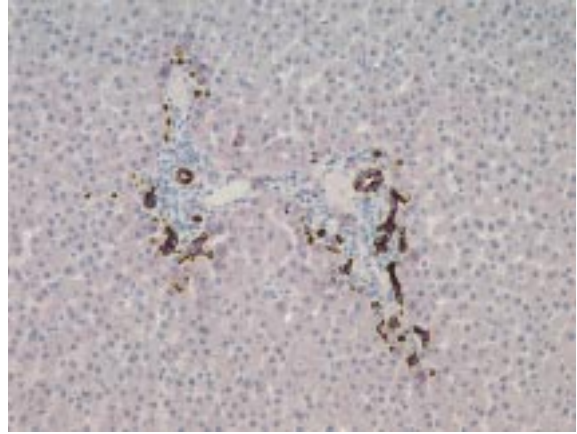
IPAS recognized that if an image analysis system could overcome this challenge, the results would be far more consistent and delivered much faster. The study provided an ideal opportunity to test Definiens' technology.

IPAS supplied Definiens with the 132 images together with detailed specifications of the identifying characteristics of bile ducts. These included their shape, color, size and relationship to the background and other objects. The Definiens' team encoded these characteristics into an application that could detect the bile ducts and measure the required parameters.

The application was calibrated so that it could handle the wide variation in the color and intensity of the stain. It was also able to identify and discount artifacts caused by over-staining.



A Normal bile duct in monkey liver



B Proliferation of bile ducts in high dose treated monkeys

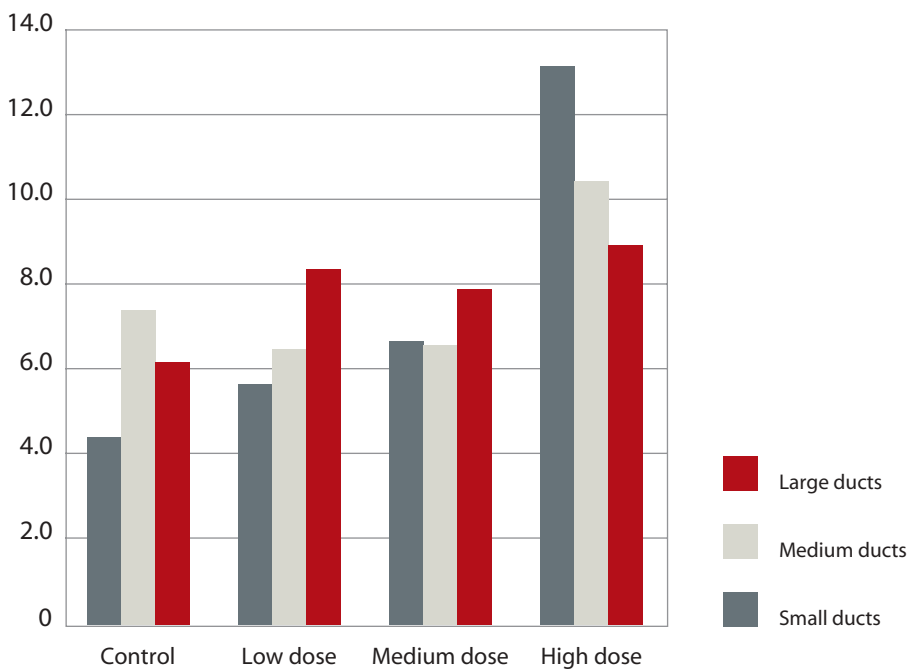
Since the number of images was relatively small, IPAS chose to develop a semi-automated solution that could be built quickly. The application identified regions of interest which were checked by a pathologist. Following this, the required measurements were performed automatically.

The Results

A total of 1032 bile ducts were identified and measured in the study. The bile ducts were divided into three categories – small, medium and large. The mean number of bile ducts per category was calculated for each group of monkeys, giving the following results:

The results clearly showed that the number of bile ducts was greatly increased with a high dose

Prof. Germann, Head of IPAS, was impressed by the accuracy of the results. “In less than 3% of cases, a bile duct was overlooked or an artifact was incorrectly identified as a bile duct. This level of accuracy was considerably higher than would be expected if pathologists had manually examined the images.”



Number of monkey liver bile ducts for low, medium and high dose groups.

IPAS conducts further analysis

Following the initial results, IPAS decided to investigate the bile ducts in greater detail. Using the same 132 images, it sought to count the number of nuclei in each bile duct. In just two days, the Definiens team created new ruleware to perform this task and the analysis was immediately available to IPAS.

The results of the study indicated that the compound had potentially toxic side effects. As a result, ALTANA decided not to submit the compound for a clinical trial which, had it proceeded, would have cost millions of euros.

The benefits of Definiens

IPAS found that Definiens' technology was superior to all other known image analysis applications for four reasons:

- The Definiens' application was able to handle the wide variation in stain color and intensity. Even the variable quality of the images themselves did not affect the application's ability to recognize bile ducts and take accurate measurements.
- Considerable costs were saved by dividing the analysis into three stages – bile duct identification, manual correction and measurement. The manual correction by a pathologist saved time calibrating the application, reducing the overall cost of development.

- When IPAS decided to make further investigations using the same images, it was easy to develop new ruleware to count the number of nuclei in the bile ducts that had already been identified.
- The Definiens' application delivered much more consistent results than manual analysis. IPAS was convinced that if it ran a larger study, the application could be calibrated to run in a fully-automatic mode with an even higher degree of accuracy. This would greatly reduce the time and cost of the study.

ALTANA adopts Definiens

As a result of the study, Definiens' technology has become an integral part of the process of evaluating drug candidates at ALTANA.

"Definiens is our supportive assessment tool of choice and is applied in selected routine toxicologic pathology assessments," explains Prof. Germann. "It enables an automatic extraction of regions of interest to discriminate changes in the histological slides of organs investigated."

"Definiens' technology underpins ALTANA's move towards integrated image assessment which will advance even further now that ALTANA belongs to the new NYCOMED organization."

DEEPER INSIGHTS • FASTER RESULTS • BETTER DECISIONS

Definiens is the number one Enterprise Image Intelligence™ company for analyzing and interpreting images on every scale, from microscopic cell structures to satellite images.

The patented Definiens Cognition Network Technology®, developed by Nobel Laureate Prof. Gerd Binnig and his team, emulates human cognitive processes of perception to extract intelligence from images. If you are interested in learning more about how Definiens could address the challenges you face, please contact us at info@definiens.com or visit our website at

www.definiens.com

Corporate Headquarters

Definiens AG
Trappentreustrasse 1
80339 München
Germany
Tel +49 (0)89 231180-0

Americas Headquarters

Definiens Inc
55 Madison Avenue
Suite 400 Morristown, NJ 07960
USA
Tel +1-973-285-3291

Copyright ©2007 Definiens AG. Definiens and Definiens eCognition are trademarks, registered trademarks, or service marks of Definiens in the United States, the European Community, or certain other jurisdictions.

All registered trademarks, pending trademarks, or service marks are property of their respective owners. The information in this document is subject to change without notice and should not be construed as a commitment by Definiens AG. Definiens AG assumes no responsibility for any errors that may appear in this document.

CSL-0002-01-030507