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Tissue Biopsy Collections in Nonhuman Primates During Toxicology Studies: A Comparison of Findings with Animals Not Sampled

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ABSTRACT

Background and purpose: The collection of biopsies for biodistribution in toxicology studies is an essential component of several drug modalities, especially gene therapy, for identifying biomarkers and evaluating efficacy. It is imperative to understand whether the biopsy sample collection procedure in nonhuman primates (NHPs) has any impact on test article safety and efficacy assessments.

Methods: We retrospectively reviewed the pre- and post-biopsy (skin, liver, or muscle) data collected at our facility to evaluate the effect on clinical condition, bodyweight, hematology, and serum chemistry parameters. We also compared data from biopsy studies with parameters from studies where biopsy procedures were not performed in NHPs (n=22).

Results: Data was reviewed from a total of 30 cynomolgus monkeys that had at least one biopsy collection. A total of 106 biopsies (14 muscle, 20 liver, 72 skin) were evaluated. The analysis of biopsy samples to understand the biodistribution and pharmacological effect of the test article was a primary study endpoint in 4 of 7 studies. The primary endpoint in 3 of 7 studies with biopsy procedures was to evaluate the potential toxicity of the test article. Mild swelling or the presence of a wound, was observed at the biopsy site, post-sample collection in 4 of 30 (13%) animals, which all resolved with veterinary treatment. There were no significant changes in bodyweight, clinical signs, hematology or serum chemistry parameters in animals with biopsy procedures, as compared to pre-biopsy animals or animals without sample collection by biopsy.

Conclusions: The addition of minimally invasive and precise biopsy procedures in nonclinical safety studies is a valuable approach to combine toxicological and biodistribution assessments, without impacting the quality of data and animal well-being. This approach enables a reduction in the number of animals used for toxicology studies, which is an approach that aligns with the 3Rs of experimental animal welfare (Replacement, Reduction, and Refinement).

INTRODUCTION

Nonhuman primates (NHPs), which are phylogenetically close to humans, are often thought of as an “ideal” nonrodent species for nonclinical research. Biodistribution and toxicity studies in NHPs are a vital part of the safety assessment of various drug modalities, including gene therapy, prior to clinical entry. Repeated collection of tissue samples by biopsy during distribution studies are an integral part of study design, to predict clinical efficacy and safety.

The purpose of this poster was to investigate whether the biopsy sample collection procedure in NHPs has any impact on test article safety and efficacy assessments.

MATERIAL AND METHODS

Table 1. Test System

	Toxicity studies	Biodistribution/Efficacy studies
Number of studies screened	3	4
Species/strain	*Purpose-bred cynomolgus monkey*	*Purpose-bred cynomolgus monkey*
Age	2 - 4 years	2 - 4 years
Body weight	1.6 - 3 kg	1.6 - 3 kg
Total number of animals	10 Males and 6 Females	7 Males and 7 Females
Total number of biopsy	2 (Liver), 8 (Muscle), 72 (Skin)	18 (Liver), 6 (Muscle), 0 (Skin)

All animal-related procedures were approved by Altasciences IACUC.

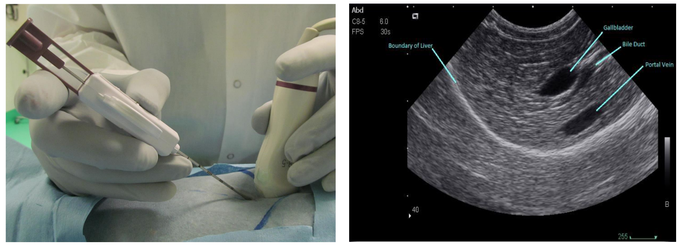

Figure 1. 2D ultrasound image of the liver (solid white line), gall bladder, and large vasculature structures (black oval areas)

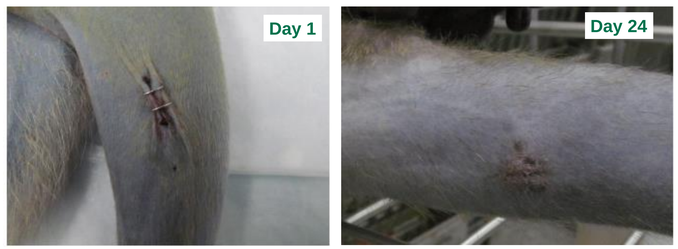

Figure 2. Vastus lateralis (muscle) immediately and on day 24 following the sample collection

RESULTS AND DISCUSSION

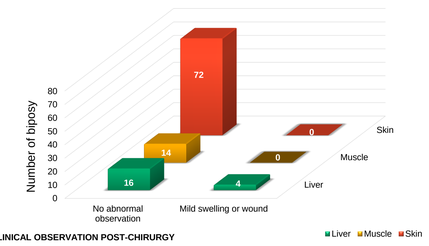

Figure 3. Clinical observation in animals after either liver, muscle, or skin biopsy.

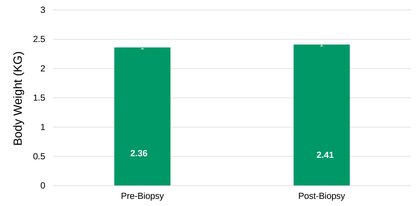

Figure 4. Body weights in animals before and after either liver, muscle, and/or skin biopsy.

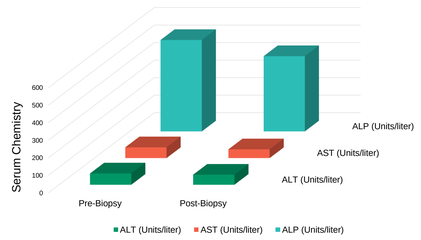

Figure 5. Serum chemistry parameters in animals before and after either liver, muscle, and/or skin biopsy.

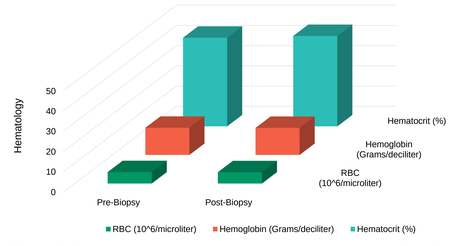

Figure 6. Serum chemistry parameters in animals before and after either liver, muscle and/or skin biopsy.

DISCUSSION AND CONCLUSION

Biopsies are routinely used in minimally invasive procedures in nonclinical studies, and needle placement is highly accurate when biopsies are performed with imaging guidance, such as an ultrasound. Whenever a needle is inserted into the body, there is a risk for adverse events, such as pain, infection, or bleeding. Thus, it is imperative to understand whether biopsy sample collection procedures in NHPs have any impact on test article safety and efficacy assessments.

In pharmacology and toxicology studies, performed at Altasciences in NHPs, we found that liver, skin, or muscle sample collection by biopsy procedure had a 100% success rate, without any major complication. The biopsy procedure performed to monitor the efficacy of test articles in conjunction with toxicity or biodistribution endpoints, did not have an impact on the overall well-being of animals, and did not interfere with hematology and serum chemistry-related parameters.

This analysis suggests that research biopsies performed at an experienced testing facility offer acceptable safety/tolerability for animals, and demonstrate that adequate tissue samples for molecular studies can be collected without impacting test article efficacy/safety assessment.

REFERENCES

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