

Effects on Endochondral Ossification in Young Adult Cynomolgus Monkeys in a Toxicology Study

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WORLDWIDE RESEARCH & DEVELOPMENT



Background

- A 3.75 year old, 5 kg sexually mature male cynomolgus monkey (Mauritian origin) was administered a biologic fusion molecule weekly (slow IV bolus) for 6 weeks as part of a general toxicology study.
- This study was conducted in accordance with the current guidelines for animal welfare (National Research Council Guide for the Care and Use of Laboratory Animals, 2011; Animal Welfare Act (AWA), 1966, as amended in 1970, 1976, 1985, and 1990, and the AWA implementing regulations in Title 9, Code of Federal Regulations, Chapter 1, Subchapter A, Parts 1-3). The procedures used in this study were reviewed and approved by the Institutional Animal Care and Use Committee.

Background, continued

- Blood was collected on Days -20 and 44 for hematology, clinical chemistry, and metabolic and bone biomarkers and urine was collected on Day 44 for urinalysis.
- Exposure to the test article was confirmed on Study Days 1 and 36.
- During the dosing phase, body weight decreased (0.86x) in this animal compared with 3 age-matched control male monkeys whose body weight increased (1.07x to 1.10x).
- A complete necropsy was performed on Study Day 44, 1 day after the final dose. There were no relevant gross observations.

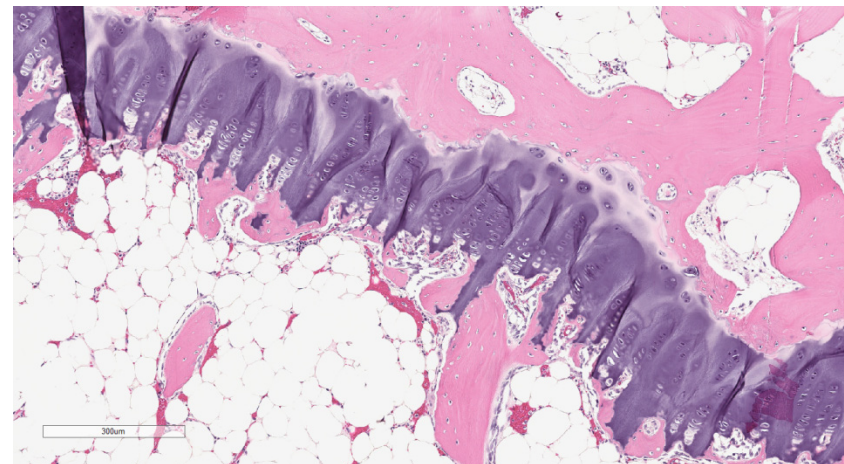
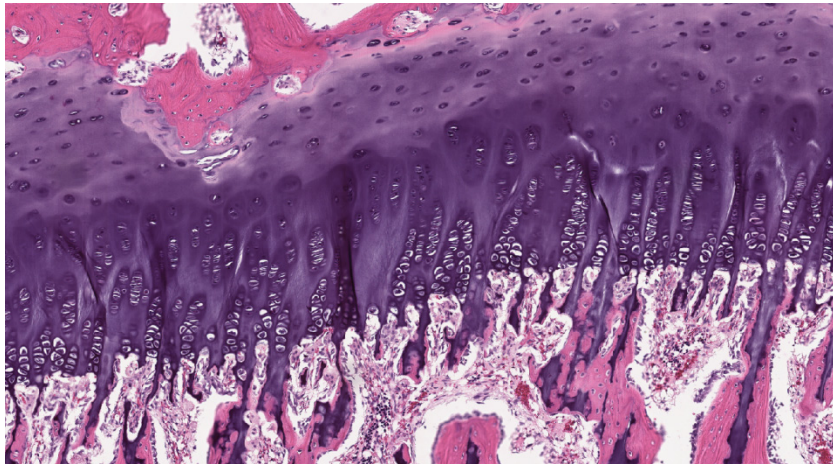
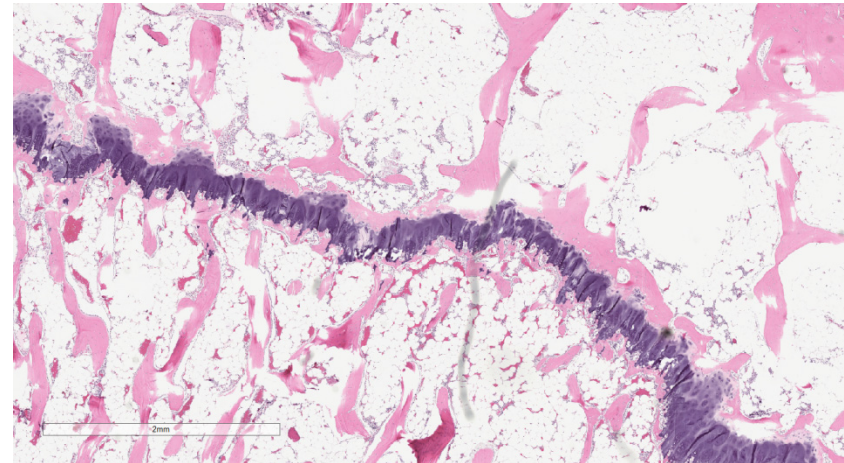
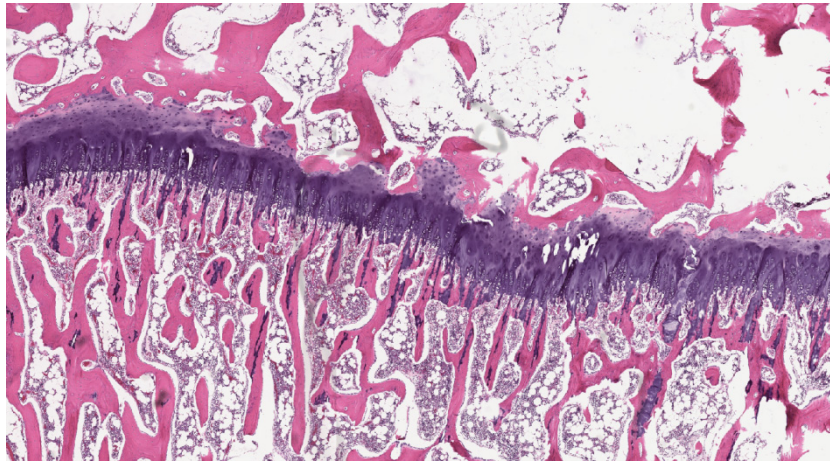
Key Clinical Pathology Findings (Day 44 compared to Day -20):

- Decreased: glucagon (0.37x), osteocalcin (0.85x), PINP (0.58x), and lymphocyte count (0.65x).
- Increased: adiponectin (3.02x), ketone bodies (1.71x), cortisol (1.86x), ALT (1.87x), AST (2.31x), and fibrinogen (1.37x).

Key Microscopic Findings

- Bone (Tibia):
 - Physeal dystrophy, grade 2
 - Physeal dystrophy was characterized by a thinner physis and fewer (but frequently thicker) primary spongiosa compared with controls. Affected physes were characterized by fewer proliferating and hypertrophic chondrocytes in the thinner physis
- Costochondral junction (rib):
 - Physeal dystrophy, grade 3
 - Increased adiposity, grade 3
- Liver:
 - Vacuolation: hepatocyte, midzonal, multifocal, grade 2
- Adrenal Gland:
 - Hypertrophy: zona fasciculata, multifocal, unilateral, grade 1
- Pancreas:
 - Decreased zymogen content, diffuse, grade 1

Proximal Tibia Growth Plate & Metaphysis, Control Male (left) vs Test-article treated Male (right)



Discussion:

- In this study, the finding of physal dystrophy in several animals correlated with decreased osteocalcin, PINP, and IGF-1 and was considered adverse because of the negative effect on longitudinal bone growth. The impact of this finding on the clinical development of the test article was minimal because the intended patient population was adult with closed growth plates; if a pediatric indication had been considered additional investigative work would have been very likely required by regulatory agencies. The interpretive challenge in this case was trying to separate a direct test article-related effect on cartilage and bone cells from an effect due to weight loss.
- The other clinical pathology and microscopic findings provided were consistent with the mechanism of action of the test article.

References:

- Axelsson I, Pita JC, Howell DS et al. Kinetics of proteoglycans and cells in growth plate of normal, diabetic and malnourished rats.
- Heinrichs C, Colli M, Yanovski JA, et al. Effects of fasting on the growth plate: systemic and local mechanisms. *Endocrinology*, 138 (12): 5359-5365, 1997.



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