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A Prospective ICH S1B(R1) Weight-of-Evidence Carcinogenicity Assessment for GLP-1 Receptor Agonists and Two-Year Rat Bioassays

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Background and Purpose: Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are peptide drugs used to treat type 1 diabetes and obesity in adults. Across the category of GLP-1RA drugs, consistent findings of thyroid C-cell adenoma/carcinoma in 2-year carcinogenicity studies in rodents have been reported. Notably, the clinical relevance of these findings remains unclear. The ICH S1B(R1) "Testing for Carcinogenicity of Pharmaceuticals" guideline describes a robust weight-of-evidence (WoE) approach to determine the utility of conducting traditional long-term *in vivo* rodent carcinogenicity studies (ICH, 2022). The approach described in ICH S1B(R1) involves assessing six key WoE factors specific to the drug or drug class to generate a network of evidence and conclude whether proceeding with 2-year rat carcinogenicity studies would contribute significantly to the human carcinogenicity risk assessment. This study applied the ICH S1B(R1) WoE framework to evaluate the pharmacology and biology of GLP-1RA class drugs to determine if 2-year rat bioassays are expected to add value to human carcinogenicity risk assessment.

Methods: The following GLP-1RA drugs were evaluated: the short-acting Adlyxin (lixisenatide) and Byetta (exenatide), and the long-acting Trulicity (dulaglutide), Ozempic (semaglutide), Mounjaro (tirzepatide), Victoza (liraglutide), and Tanzeum (albiglutide). For these GLP-1RA drugs, new drug applications (NDAs) and/or biological license applications (BLAs) were reviewed and information was extracted to evaluate the six WoE factors outlined in the S1B(R1) guidance document – target biology, secondary pharmacology, histopathology from chronic studies, hormonal effects, genotoxicity, and immune modulation – in relation to the GLP-1RA drug class. These findings were compiled and used to evaluate corresponding implications for GLP-1RA use and cancer risk in humans in accordance with best practices outlined in Bassan *et al.* (2024) and Bourcier *et al.* (2024) on applying the WoE framework. Each factor was analyzed and the preponderance of evidence across all six factors was then used to identify the GLP-1RA Carcinogenicity Risk Category (1, 2, 3a, or 3b) as defined by Bourcier *et al.* (2024).

Results: *Target Biology/Primary Pharmacology:* The major mechanism of action of these drugs is the binding of GLP-1R, which results in synthesis and secretion of insulin, thereby inhibiting the release of glucagon. GLP-1RAs also promote the survival of pancreatic beta cells, facilitating optimal regulation of blood glucose levels, appetite, and, ultimately, body mass. Since the biological activity of these drugs is well understood, this WoE factor suggests that conducting a 2-year rat bioassay is less likely to add value to a human carcinogenicity risk assessment.

Secondary Pharmacology: The major off-target effects of concern for GLP-1RAs in humans include clinical symptoms associated with gastrointestinal (GI) disturbances, for which chronic rodent studies are not likely to generate additional information of importance. Accordingly, this factor suggests that 2-year rat bioassays would be of limited value.

Histopathology from Chronic Studies: Histopathological results from sub-chronic and chronic studies of GLP-1RA in rodent models demonstrate consistent findings. Most long-acting GLP-1RAs have been associated with an increased risk of thyroid C-cell adenomas and carcinomas in 2-year rodent bioassays,

as well as non-specific diffuse and localized C-cell hyperplasia in sub-chronic and chronic repeated-dose studies in mice and rats, but not in non-human primates and dogs. However, no thyroid tumor findings were observed in 6-month rasH2/Tg-rasH2 mouse studies. Consequently, these findings have been used to set the regulatory requirement for a boxed carcinogenicity warning for risk of medullary thyroid cancer, despite limited translational evidence and species-specific differences in thyroid cancer related to C-cell GLP-1RA expression in rodents when compared to monkeys, dogs, and humans. Since these findings have been shown to have limited human relevance, this WoE factor indicates less value in conducting a 2-year rat bioassay.

Hormonal Effects: Although the primary mechanism of action for GLP-1RAs involves modulation of hormone signaling, these drugs have not been implicated consistently in adverse hormonal effects that would increase the risk of developing cancer. GLP-1RAs have not been shown to induce significant gross or microscopic alterations in endocrine or reproductive organs, disruptions in cancer-associated hormone signaling (*e.g.*, estrogen and its receptors), or modulation of nuclear receptors known to be involved in carcinogenesis (*e.g.*, PPAR-α, AhR). Accordingly, findings related to this WoE factor also suggests that conducting 2-year rat bioassays is of limited value.

Genotoxicity: ICH S6 standard genotoxicity battery testing, including *in vitro* Ames assays, chromosome aberration, and *in vitro* rat micronucleus tests, conducted with GLP-1RAs have demonstrated consistently a lack of genotoxic potential for this class of drugs. Likewise, this WoE factor indicates that a 2-year rat bioassay is unlikely to add significant value in determining human carcinogenicity risk.

Immune Modulation: GLP-1RAs can induce alterations in tissue-resident and circulating lymphocyte population ratios and other markers of global immune status; however, these alterations are frequently cited as being beneficial outcomes reflective of treatment-related reductions in obesity-mediated inflammation. Although additional studies are needed to elucidate an accurate association between GLP-1RAs and immunomodulation, there are no strong non-clinical signals in immune cell populations that would suggest clinically relevant immunosuppression of antitumor regulatory T-cell and natural killer cell populations. Consequently, a 2-year rat bioassay is less likely to add value to a carcinogenicity risk assessment based on this WoE factor.

Based on the network of evidence generated by applying the WoE carcinogenicity assessment framework to the GLP-1RA drug class collectively, it can be concluded that conducting additional long-term cancer studies in rodents is unlikely to contribute significantly to human carcinogenicity risk assessments. Accordingly, a Carcinogenicity Risk Category of 3a is proposed, signifying that these drugs are "highly likely to be tumorigenic in rats, but not in humans, through prior established and well recognized mechanisms known to be human irrelevant, such that a 2-year rat study would not add value," per Bourcier *et al*. (2024).

Conclusions: Overall, these findings related to the six major WoE categories defined in ICH S1B(R1) indicate that future 2-year rat bioassay studies for GLP-1RAs are not likely to generate evidence that will contribute significantly to the human carcinogenicity risk assessments for the specific agents within this drug class.