

The ICHS1 Regulatory Testing Paradigm of Carcinogenicity in rats.

Status Report 2019

Jan Willem van der Laan (EC, Europe; Regulatory Chair), Todd Bourcier (FDA, United States), Tania Cavaliero (Swissmedic, Switzerland), Tim McGovern (FDA, United States), Akiyoshi Nishikawa (MHLW/PMDA, Japan), Mizuho Nonaka (MHLW/PMDA, Japan), Kumiko Ogawa (MHLW/PMDA, Japan), Markku Pasanen (EC, Europe), Geoffrey Ebere (Health Canada, Canada).

Introduction

The ICH-S1 Expert Working Group (EWG) convened in Charlotte, NC in November 2018 to discuss the status of the prospective evaluation study which started in August of 2013 with the publication of the Regulatory Notice Document (RND). This status report provides a brief overview of the study's progress and summary analysis of submitted 2yr rat study outcomes in relation to their respective carcinogenicity assessment documents (CADs). This third update also presents case examples of CADs and study outcomes that supported Category 2, 3a, and 3b designations.

Background: The RND hypothesis and the Prospective Evaluation Study

The Regulatory Notice Document (RND) posted to the ICH website in August 2013 announced the start of a prospective evaluation study whereby sponsors voluntarily submit CADs. A CAD addresses the carcinogenic potential of an investigational pharmaceutical using a weight-of-evidence approach and, based on the level of certainty of carcinogenic risk and its potential human relevance, a company is expected to indicate the need for and additional value of conducting a 2yr rat study. Each participating Drug Regulatory Agency (DRA) independently reviews the submitted CADs and the rationale for concurrence or non-concurrence with the sponsor's assessment is documented. As the 2yr rat studies are completed and results submitted to the DRAs, the study's outcome is then checked against the weight-of-evidence assessment in the respective CAD. Results on the accuracy of prospective assessments and the degree of concordance among all parties are anticipated to help define the conditions under which a weight-of-evidence evaluation sufficiently characterizes the risk of human carcinogenicity without conducting a 2-yr rat carcinogenicity study.

In December 2017, the S1 EWG met in Montreal to conduct an interim analysis of 14 rat study outcomes and their respective CADs. No cases were identified that clearly and meaningfully differed between the 2yr study outcome and the prospective weight of evidence provided in the corresponding CAD.

In November 2018, the S1 EWG met in Charlotte to discuss a second cohort of an additional 14 rat study outcomes in relation to their corresponding CADs. While recognizing the complexity of some cases, no cases were identified as clear failures of the prospective CAD to provide an adequate carcinogenicity assessment without the results of the 2yr rat studies. The EWG concluded that the interim analysis supported the continued acceptance of final study reports towards a decisional analysis once the dataset reaches a minimum of 20 Category 3a/b cases.

State of the Prospective Evaluation Study (Feb 2019)

Part 1: Update on CAD and Final Study Report Submissions

The acceptance period for CAD submissions closed on 31 Dec 2017. A total of 48 CADs submitted by 22 sponsors are now reviewed and categorized by DRAs. For the corresponding final rat study reports, the DRAs received 35 submissions among which 28 were evaluated by the full S1 Expert Working Group. As stated in the 2016 RND revision, a threshold of 20 complete category 3 cases (i.e., CAD + study report) is necessary to allow a decisional analysis by the EWG. To date, DRAs received 15 complete category 3 cases among which 12 were reviewed by the EWG.

CAD Categories and Concordance

The RND directs Sponsors to classify their investigational compound into one of the following categories:

- *Category 1: Highly likely to be carcinogenic in humans, such that rodent carcinogenicity studies would not add value.*
- *Category 2: Uncertain carcinogenic potential, such that rodent carcinogenicity studies are likely to add value.*
- *Category 3a: Highly likely to be carcinogenic in rats through prior established and well-recognized mechanisms known to be human irrelevant, such that a rat carcinogenicity study would not add value.*
- *Category 3b: Highly unlikely to be carcinogenic in both rats and humans, such that a rat carcinogenicity study would not add value.*

Table 1 summarizes the Categories designated by the Sponsors and the corresponding category designation by the DRAs after review of the 48 CADs. Sponsors designated Category 3a or 3b for 32 of the 48 CADs submitted (67%). Overall, the DRAs concurred with the Sponsor's designation of Category 3a/b in 25 of these cases (78%). As not all Category 3a/b designations by DRAs were unanimous, Table 2 summarizes the extent of concordance among the participating DRAs in

agreeing with the Sponsor’s designation of Category 3a/b. The DRAs were unanimous in concurring with a Category 3a/b designation in 11 cases (34%) but remained split, typically between Categories 2 & 3, in 14 cases (56%). The unanimous concordance on Category 3a/b for 11 cases is of particular interest, as these cases may be most instructive in defining support for a Category 3 designation with the least probability of regulatory discordance.

Table 1: Category designation by Sponsors and DRAs for CADs

	Sponsor	DRAs
Cat 1	3	3
Cat 2	13	20
Cat 3a/b	32	25
Total:	48	48

Table 2: Concordance among DRAs on Sponsor-proposed Category 3a/b designations.

Category	Sponsor designation	DRA designation		
		Unanimous	Split	DRA Total
3a	15	7	6	13
3b	17	4	6	10
2/3a/3b	--	--	2	2
Totals:	32	11	14	25

Part 2: Interim analysis of CADs in relation to Rat Carcinogenicity Study Outcome:

As of Jan 2019, the DRAs received a total of 34 Final Summary Reports (FSRs) from completed 2yr rat studies. The S1 EWG has jointly discussed 28 of these cases in Montreal (2017) and Charlotte (2018). The Sponsor and DRA-designated categories of the 28 cases are shown in Table 3. Twelve of the 28 cases are considered Category 3a/3b by the DRAs, and the majority of other cases are considered Category 2. An additional 9 of the 14 outstanding Category 3a/3b FSRs must be received and reviewed by the DRAs to reach the decisional target ≥ 20 Category 3a/3b cases.

Table 3: CAD category designations of 28 reviewed studies

Category	Sponsor	DRAs
1	2	2
2	8	14
3a or 3b	18	12 (6 unanimous, 6 split)

Case Studies

The intent of the following case studies is to briefly illustrate the process by which the DRAs have assessed CADs submitted by participating Sponsors and to highlight key observations that contributed to categorization of CADs and their concordance with the study outcomes.

Each case provides the rationale for category designation by the Sponsor and DRAs, describes the outcome of the 2yr rat study, and addresses concordance between the CAD and the study outcome. Factors within the weight of evidence that proved particularly relevant are highlighted for each case.

Category 3B: Case F28/FST

- *Category 3b: Highly unlikely to be carcinogenic in both rats and humans, such that a rat carcinogenicity study would not add value.*

CAD designation: Case F28/FST involved an antiviral drug with a non-mammalian target. The Sponsor classified F28 as Category 3B, stating that the current pharmacological and toxicological dataset suggests the absence of carcinogenic potential in rats and in humans. Given the lack of rodent carcinogenicity of other marketed drugs in this class, as well as the non-host target, F28 was predicted to be negative for carcinogenicity in the 2 year rat bioassay and would not add substantial value to the overall WOE-based risk assessment.

DRA's unanimously agreed with this classification based upon the lack of a mammalian target coupled with high compound target selectivity. Toxicology studies of 26 weeks duration in rats did not show any drug-related histological lesions with or without preneoplastic characteristics. A single high dose female exhibited mammary carcinoma at week 13 in the chronic study, but this was judged to be independent of treatment as no other females showed any adverse histology of mammary tissue. There was no evidence of hormonal disturbances or genotoxic potential, and compounds with similar pharmacodynamic effects did not induce carcinogenic effects in rat bioassays.

2yr rat study outcome: Both the sponsor and the DRAs concluded that no drug-related tumors were observed at any dose level, and that non-neoplastic findings were unremarkable in the study.

Comments: In this case, the CAD and study outcome were in complete agreement. The case was identified as an ideal Category 3B scenario based on the lack of a mammalian target, absence of any concerning off-target activity, and experience with other drugs in the same class.

Category 3A: Case F17/FSO

- *Category 3a: Highly likely to be carcinogenic in rats through prior established and well-recognized mechanisms known to be human irrelevant, such that a rat carcinogenicity study would not add value.*

CAD Designation: Case F17/FSO involved a small molecule inhibitor of a solute co-transporter (F17). The Sponsor classified F17 as Category 3A, and cited the following at-risk tissues for neoplasia: tubule cells in the kidney, Leydig cells in the testis, and medullary cells in the adrenal. Histological changes observed in these tissues in the chronic rat study included renal proximal tubular hypertrophy with mineralization, dilatation, and increased kidney weight, and adrenal hypertrophy and increased adrenal weight with vacuolation of the zona glomerulosa. No adverse histology was described for the testes. The Sponsor's assessment that this potential tumor outcome in rats would be irrelevant to human risk was largely based on published reports of results from 2yr rat bioassays with other members of this pharmaceutical class. At therapeutic levels of exposure to F17, it was argued that the key mechanistic events underlying tumorigenesis in rats would not be engaged or only minimally engaged in human subjects, and therefore present minimal carcinogenic risk to humans. In further support, the sponsor noted that inactivating mutation of F17's target in both rats and humans is not known to be associated with a tumorigenic phenotype. The Sponsor additionally described F17 as non-genotoxic and being devoid of endocrine and immunosuppressive properties as assessed in standard genotoxicity and general toxicity studies conducted in support of clinical trials.

The DRAs unanimously agreed with key arguments in the Sponsor's WOE assessment. The DRAs took particular note of F17's toxicological and pharmacological similarity with other members of the class for which published and non-published information regarding the tumorigenic mode of action and outcome in rats was available. Human irrelevance of the potential tumor outcome was based on exposure considerations (i.e., tumorigenic MOA would not be sufficiently engaged at therapeutic exposure).

2yr rat study outcome: The Sponsor and the DRAs concluded that F17 increased the incidence of benign adrenal pheochromocytoma in male rats. No drug-related neoplasia was observed in the predicted at-risk tissues of the testis or kidney, nor in other examined tissues. Non-neoplastic findings in predicted at-risk tissues included tubule degeneration/dilatation in the kidneys and a minor increase (2/6) in testicular interstitial hyperplasia.

Comments: In this case, the tumor outcome in rats partially agreed with the Sponsor's and DRA's assessment in the CAD. Adrenal pheochromocytoma was both predicted in the CAD and observed in the study outcome, whereas neoplasia of the renal tubule cells and Leydig cells were predicted in the CAD but not observed in the rat bioassay. It was recognized that an absence of neoplasia in the kidney and testis is not necessarily inconsistent with identification of neoplastic risk in these tissue as presented in the CADs, particularly in the context of the information available for this pharmacological class of compounds. However, this case also emphasizes the utility of a reasonably established tumorigenic profile of an existing drug class in building a persuasive weight-of-evidence for a Category 3 designation.

Category 3A: Case F6/FSE

- *Category 3a: Highly likely to be carcinogenic in rats through prior established and well-recognized mechanisms known to be human irrelevant, such that a rat carcinogenicity study would not add value.*

CAD designation: Case F6/FSE involved another antiviral drug with a non-mammalian target (F6). The Sponsor classified F6 as Category 3A citing rodent-specific bladder tumors as a possible outcome in the 2yr rat bioassay. This was based on the presence of needle-like crystals in urine in the chronic rat toxicology study, albeit without evidence of histological disruption to the urothelium. F6 was not genotoxic by standard testing and did not exhibit hormonal or immunosuppressive attributes in the nonclinical program. F6 tested negative for drug-related neoplasms in a six-month study conducted in Tg.Ras H2 mice. A survey of 2yr rat bioassays conducted with compounds in the same pharmacological class indicated either an absence of drug-related tumors or an increase in rodent-specific liver neoplasms. DRAs unanimously agreed with the Sponsor's arguments and with a Category 3A designation.

2yr rat study outcome: An increase in bladder tumors as anticipated in the CAD were not observed at any dose, including the maximum dose that was associated with urinary crystals in the prior 6-month study. However, the combination of thyroid parafollicular C-cell adenoma and carcinoma increased in females with statistical significance by both trend- and pairwise statistical testing for a common tumor. The Sponsor interpreted this signal as unrelated to drug for the following primary reasons: 1) the tumor incidence remained within the range of historical controls, 2) the tumors were not associated with related histological changes to the thyroid (e.g., hyperplasia), 3) the signal was observed only in females but not in males, and 4) there is no apparent pharmacological basis to suspect causality for F6.

The DRAs agreed on the absence of bladder tumors but disagreed in part on interpretation of the study outcome in light of the thyroid C-cell neoplasms. One view is that the overall weight-of-evidence, such as presented by the Sponsor, supports the interpretation that the 2yr rat study was negative for drug-related tumors. Another view is that statistical significance by trend and pairwise testing supports the interpretation of a positive 2yr rat study for C-cell neoplasms. In this latter view, drug-relatedness and clinical relevance is an evaluation that occurs after the study is concluded as ‘negative’ or ‘positive’ based on pre-specified statistical thresholds. Despite this difference in analytical approach, the DRAs generally agreed that consideration of WOE factors beyond statistical testing indeed supports the conclusion that the C-cell neoplasms in female rats are unlikely related to F6.

Comments: In this case, the 2yr study outcome was, overall, consistent with the CAD of F6. As with the unrealized expectation of renal and testicular neoplasms in Case F17/FSO, the expectation of bladder tumors in the current Case was not realized in the 2yr rat study, again indicating that identification of at-risk tissues does not translate with high confidence to tumor emergence in those tissues. The partial disagreement among DRAs regarding interpretation of the study outcome in light of the parafollicular neoplasms reflects primarily a regional difference in the analytical approach to rodent carcinogenicity studies. While all DRAs generally agreed that the statistical increase in parafollicular neoplasms is unlikely drug-related based on the totality of the data, the fact of achieving pre-specified thresholds for statistical significance can have implications for drug labeling in some regulatory regions, particularly in the US.

Category 2: Case P1/PSD

- *Category 2: Uncertain carcinogenic potential, such that rodent carcinogenicity studies are likely to add value.*

CAD Designation: Case P1/PSD is a small molecule ion channel ligand (P1) classified by the Sponsor as Category 3B. The sponsor cited the following as most pertinent to this proposed categorization: 1) Proliferative and hypertrophic changes in the forestomach and liver of rats in

the chronic study at high exposures (50x human exposure), 2) hypertrophy of the detrusor muscle and transitional epithelium of the bladder, while present at all dose levels, reflects P1 pharmacology and is not relevant to cancer risk, 3) persistent estrus in a fertility study was not associated with histological changes to reproductive organs in the chronic study indicating minimal hormonal disruption of no consequence, 4) P1 is non-genotoxic and non-immunosuppressive, and 5) rat neoplasms reported with some other class compounds (e.g., pancreatic and vascular) are not relevant to human risk.

The DRAs unanimously disagreed with the Sponsor's assessment and designated Category 2 on the argument that the tumor outcome in the rat study could not be confidently predicted based on the existing WOE. In particular, the DRAs disagreed that human irrelevance of the neoplasms reported with other class compounds had been persuasively demonstrated. Moreover, the tumor profile was not consistent among different compounds of the same pharmacological class, which precludes confident prediction of outcome for P1 and indicates an appropriate need for compound-specific evaluation of carcinogenic potential.

2yr rat study outcome: The Sponsor reported an increased incidence of urinary bladder urothelial cell papilloma in males that was statistically significant by trend and pair-wise testing, although the absolute incidence was low and consistent with historical controls. The Sponsor concluded, however, that the increased incidence of papilloma does not reflect a direct carcinogenic effect of P1 based on the following observations: 1) no coincident hyperplasia or mucosal thickening/necrosis of the bladder urothelium, and 2) some evidence of urinary crystals in a 1 month study though without significant Ki67 staining in the 6 month study.

The DRAs partially disagreed on interpretation of this study outcome. While recognizing the statistical significance of the increase in papilloma, some DRAs did not consider the outcome clearly positive or related to drug, whereas other DRAs voiced concern for even an equivocal tumor outcome which would require further follow-up studies.

Comments: In this case, the DRAs initially disagreed that the WOE for P1 was sufficient to confidently predict the outcome of a rat bioassay or provided an adequate assessment of carcinogenic risk without rat bioassay results. This view was driven primarily by the inconsistent tumor profile of the drug class with unresolved human relevance, which suggested the need for compound-specific assessments. Some DRAs therefore considered any study outcome with P1, whether negative, equivocal, or positive, as adding value to the overall WOE assessment of carcinogenic risk. Other DRAs suggested that an inconsistent tumor profile of a drug class alone might not be an appropriate rationale for requiring a rat bioassay for all subsequent members of the drug class; rather, additional compound-specific WOE factors should be considered in judging the potential value of a rat bioassay in such cases.

Category 2: Case F11/FSP

- *Category 2: Uncertain carcinogenic potential, such that rodent carcinogenicity studies are likely to add value.*

CAD Designation: Case F11/FSP is a first-in-class small molecule agonist of pro-angiogenic signaling pathways (F11) designated by the Sponsor and all DRAs as Category 2. The sponsor described several lines of evidence in support of this categorization: 1) the target pharmacology increases activity of growth factors implicated in tumor progression, 2) known mutations in upstream regulatory proteins are associated with a variety of tumors in humans and rodents, 3) F11 being first-in-class. The Sponsor noted that therapeutic exposure to F11 was not associated with an increase in plasma growth factors exceeding normal variation and therefore minimal carcinogenic potential is expected; however, establishment of dose response information for tumor outcome would add value to the risk assessment. F11 resulted in multi-organ toxicity in rodents and non-rodents which was mostly attributed to excessive pharmacology. F11 did not show evidence of hormonal or immunosuppressive activity and was considered non-genotoxic. The carcinogenic potential of a disproportionate human metabolite was to be addressed in a spiking study conducted in mice.

2yr rat study outcome: The Sponsor reported no increase in F11-related tumor incidence in the 2yr rat study. The DRAs noted a numerical imbalance in mammary fibroadenoma in males that did not reach statistical significance, but agreed with the Sponsor's conclusion of a negative tumor outcome for F11. Non-neoplastic findings of note included cardiomyopathy with atrial thrombosis and stomach ulceration with thrombosis which were consistent with prior findings in the chronic toxicology study.

Comments: In this case, the 2yr study outcome provided relevant exposure-response information that the Sponsor and DRAs considered valuable for an adequate assessment of F11's carcinogenic potential. A primary issue of concern was the pharmacology of F11 which is associated with known carcinogenic signaling pathways, including associative evidence of genetic mutations in this pathway and emergence of tumors in rats and humans. Being a first-in-class small molecule, relevant information regarding exposure-response for pharmacological activity and carcinogenic outcome was lacking. Clear evidence of pharmacological activity for F11 was observed only at the highest dose in the 2yr rat study; however, no drug-related tumors were observed at the pharmacologically active dose which also provided a high multiple to human therapeutic exposure. Therefore, this outcome met the anticipated value of the 2yr rat study in a practical manner by identifying a pharmacologically active yet non-carcinogenic exposure to F11 that can be weighed against human therapeutic activity and exposure. Additionally, this case demonstrated the value of quantitative exposure-response information for tumor outcome for a compound that would otherwise be viewed as a carcinogenic hazard to human subjects.

Concluding Remarks

The 28 cases reviewed by the EWG have yielded a number of examples where all parties unanimously agreed that results from a 2-yr bioassay would be necessary for an adequate assessment of human carcinogenic risk. Other examples, though more limited in number, illustrate scenarios where all parties unanimously agreed that the existing WOE was sufficiently informative of human carcinogenic risk that a 2-yr bioassay would not add substantial value to the assessment. Given the unanimity of scientific opinion, these cases may be the most instructive for defining the characteristics of a pharmaceutical that could support a Category 3a/b designation with the least probability of regulatory discordance.

In approximately two-thirds of all cases, at least one DRA agreed with a sponsor's Category 3 designation and the case is therefore 'counted' as Category 3, but it is important to note that the DRAs did not unanimously agree on the designation. Missing or incomplete information in the CAD often contributed to this lack of unanimity but, not infrequently, it also reflects differences in scientific judgement among the DRAs; this should be expected given the complexity of information included in a comprehensive WOE document.

In a limited number of cases, interpretation of the 2-yr study outcome also differed amongst DRAs which complicated the primary assessment of whether study results (positive or negative) were predicted by the CAD. This is more difficult to address as there is no international standard for study interpretation; for example, one DRA may conclude a study 'positive' based on predefined statistical thresholds alone, whereas another DRA may conclude the same study 'negative' after additional consideration of historical incidence data. Despite this difference amongst DRAs, the overall approach to assessing clinical relevance of tumor incidence data appears in general consistent, with all DRAs ascribing weight to exposure margins, biological plausibility, known class-related effects, and any other relevant information.

Outcomes of the 2-yr studies for each case are proving instructive for re-evaluating the concerns a DRA may have had during review of the CAD and, conversely, for re-evaluating the CAD for evidence that might explain an unexpected outcome observed in the 2yr study. Thus, pharmacological and toxicological attributes are being identified that may be exclusionary of a WOE CAD option, and other attributes initially tagged as a concern but do not yield a tumorigenic outcome are also being identified. This prospective study is a learning process and each case has provided a new lesson or has reinforced lessons learned from prior cases; therefore, it is necessary that the EWG receive and evaluate all 20 Category 3 cases as a minimal dataset prior to drawing final conclusions. Ideally, this analytical approach will yield sufficiently instructive criteria for when a WOE option would be preferable to a 2-yr bioassay in a development program, thereby improving assessment of human carcinogenic risk of pharmaceuticals and minimizing regulatory discordance across regions.