April 2017

OECD ADVERSE OUTCOME PATHWAY

Project Submission Form

If you require further information please contact the OECD Secretariat Delrue (Nathalie.delrue@oecd.org)
Return completed forms to our generic account (env.tgcontact@oecd.org), and Nathalie

PROJECT TITLE

GLP-1 receptor activation leading to thyroid C-cell tumors

SUBMITTED BY (Country / European Commission / Secretariat)

Japan

DATE OF SUBMISSION TO THE SECRETARIAT

Nov.14th, 2018

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	Japan
Agency/ministry/Other:	Japan Pharmaceutical Manufacturers Association
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PROJECT CATEGORY

☒ Development of an AOP - applicable to a chemical category

Select the development tool to be used
☒ AOP-Wiki ☐ Effectopedia

☐ Guidance document related to AOP development including its evaluation

☐ Knowledge management tool for supporting AOP development including its evaluation

☐ Other, please specify below

If other category, please specify:

PROJECT DESCRIPTION

Please provide sufficient information to facilitate the review of the project submission by the OECD secretariat and the Extended Advisory Group with respect to its suitability to be included in the workplan of the AOP programme.

During the decades of drug development with rodent carcinogenicity studies, some classes of pharmaceuticals are known to induce tumors with non-genotoxic mechanisms based on their on-target or off-target pharmacology as well as toxicity; some are mostly common in rodents and the others might be extrapolated to humans. One of these non-genotoxic carcinogenesis is glucagon-like peptide-1 (GLP-1) receptor activation-induced thyroid C-cell tumors and we propose to develop the AOP.

GLP-1 receptor agonists are reported to promote thyroid C-cell tumor formation in the rodent two-year carcinogenicity studies [1][2]. GLP-1 receptors are expressed in thyroid C cells and their agonists stimulate GLP-1 receptors to increase cAMP level in the C cells, thereby, enhance their calcitonin (CT) synthesis and release, which increases the blood calcitonin level [3][4]. Persistent C-cell stimulation for calcitonin secretion induces C-cell proliferation to promote the formation of focal C-cell hyperplasia and following C-cell tumors [3][4][5].

The risk of GLP-1 receptor activation-induced thyroid C-cell tumor formation in humans deems to be low compared with rodents considering that the expression of GLP-1 receptor in human C cells is much less than those observed in rodents [3][6][7][8].

Note: For AOP Development projects please indicate the extent of the pathway to be described (i.e. the anchor points), the intermediate events that are likely to be addressed, the state of current development**,** the degree to which this pathway is already understood and described in the literature, and the expectation on the availability of evidence to support the AOP. Proposers should also indicate if and how the AOP is associated to any regulatory toxicological endpoints (e.g. acute or chronic toxicity, toxicity to reproduction etc.) Please provide references, links or attachments for supplementary information.

PROJECT PLANNING

In this section, please provide an indication of when the project is likely to commence and the expected duration. Please also make reference to any particular milestones or external factors that will influence project planning, and if the project is linked to programmes of particular organisations or consortia.

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The Japanese Pharmaceutical Manufacturers Association (JPMA) will develop several AOPs for non-genotoxic carcinogenesis based on our survey on the pharmacology-induced modes of action of carcinogenesis in the next four years under the cooperation with Dr. Kumiko Ogawa (National Institute of Health Sciences).

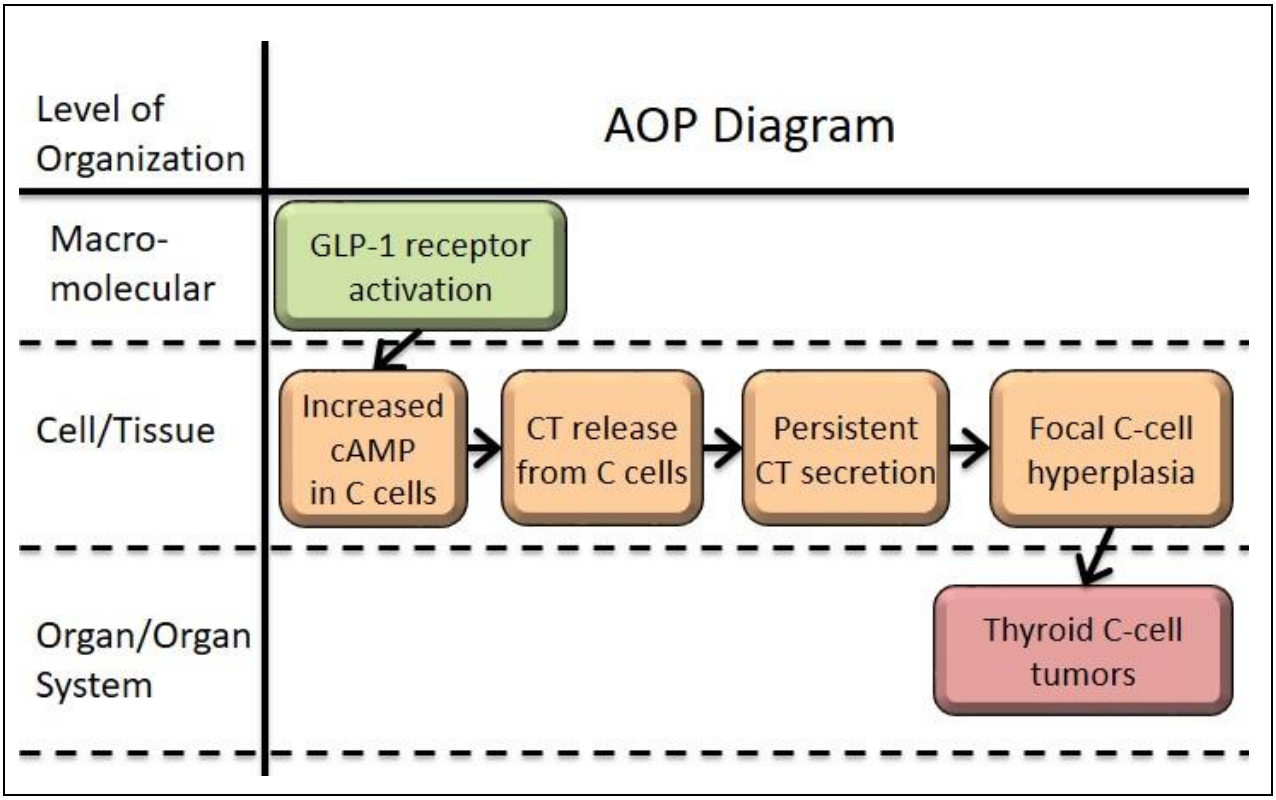
The timeline of the development of the present AOP is as follows:

Nov., 2018: to submit the AOP SPSF

Jun., 2019: to complete AOP Wiki input and wiki input and request an internal review by EAGMST

FLOW DIAGRAM

In this section, please provide a flow diagram of the proposed AOP, including the MIE, KEs at the various stages (molecular interaction, cellular response, organ response) and the AO.



References

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   https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf
2. US Package Insert (BYETTA®)
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3. Knudsen LB, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ. (2010) Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 151(4):1473-86.

   http://www.ncbi.nlm.nih.gov/pubmed/20203154

4. Parola A. (2009) Liraglutide: Advisory Committee Nonclinical Briefing Document.

5. Madsen LW, Knauf JA, Gotfredsen C, Pilling A, Sjögren I, Andersen S, Andersen L, de Boer AS, Manova K, Barlas A, Vundavalli S, Nyborg NC, Knudsen LB, Moelck AM, Fagin JA. (2012) GLP-1 receptor agonists and the thyroid: C-cell effects in mice are mediated via the GLP-1 receptor and not associated with RET activation. Endocrinology. 153(3):1538-47.

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7. Waser B, Beetschen K, Pellegata NS, Reubi JC. (2011) Incretin receptors in non-neoplastic and neoplastic thyroid C cells in rodents and humans: Relevance for incretin-based diabetes therapy. Neuroendocrinology 94:291-301.

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8. Waser B, Blank A, Karamitopoulou E, Perren A, Reubi JC. (2015) Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. Mod Pathol 28(3):391-402.

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