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# OPPONENT'S REVIEW

**Title of the dissertation thesis:** Research on ghrelin mechanisms for the prevention of relapse in cannabinoid addiction

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**Supervisor:** doc. PharmDr. Magdaléna Šustková, CSc.

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Dissertation thesis of dr. Chrysostomos Charalambous summarizes the results of his experimental work during his doctoral study of Pharmacology and toxicology. The structure and length of the thesis are standard; the main text consists of approximately 50 pages and 107 references covering both recent and historical scientific literature.

The thesis is well-written, and the structure is logical. The theoretical part explains the public health risks, regulatory principles, and epidemiology of cannabinoid abuse. The text further elaborates on the neurobiology of addiction and involvement of ghrelin signalling in addiction is described in detail, focusing on the therapeutic potential of ghrelin receptor antagonists. Finally, a brief overview of major behavioral techniques is explained.

The thesis has a well-supported theoretical background. The hypotheses are clearly stated and reflect the aims. The methods are concise but informative, I particularly like the graphical overview of the experimental designs. The results are nicely described and easy to follow.

The discussion is balanced, detailed, and well supported by the results and available literature. The conclusion adequately summarizes the results and their significance.

One key paper provides the base for the thesis published in an excellent Journal. This Journal belongs to the MDPI publishing house, but despite a general notion against MDPI Journals, this one is known in the field, and it received the first IF in 2014 and has had an increasing (or stable) trend ever since. Chrysostomos is the first author of this paper and his contribution to the preclinical research of drug addiction is evident from other published papers as well. Despite his position as a Ph.D. student, he could generate an impressive citation record (currently 105 citations, 80 without self-citations, and an H index of 6).

From the formal point of view, it would be nice to have the key paper available as an annex, but it is surely no problem to find it. I was informed, that there is a certain overlap of the texts

between the previous dissertation and the original paper. I served as opponent of the previous thesis as well and I do not find any merit for suspecting plagiarism.

The quality of the scientific content in the thesis is undeniable. The experiments were well-designed and revealed new evidence regarding the potential therapeutic effect of JMV2959 in drug addiction.
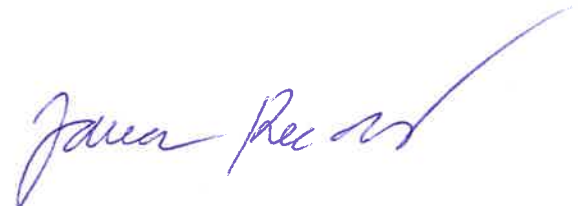
I have the following questions:

JMV2959 decreased cannabinoid intake as well as relapse in two behavioral paradigms, which is an excellent result. However, in human most of the pharmacological interventions are chronic. Is there any evidence that the anti-addiction effect of JMV2959 is stable in time?

I would worry about which strain to select for WIN 55,212-2 IVSA. There is a nice paper reporting that LH and LE rats are reliable but not SD rats (10.1016/j.neuropharm.2006.09.007). Please, can you comment on the selection of the experimental animals?

Do you believe that GHS-R1A will reach the clinical field? Are there any constraints like toxicity or adverse effects?

PharmDr. Chrysostomos Charalambous showed extensive knowledge of the field of addiction and the ability to perform experimental studies and report their results independently. The scientific content of the thesis is excellent and brings new promising evidence in the field of treatment of drug addiction. Therefore, I do recommend the dissertation thesis for public defense as a basis for the successful termination of the doctoral study and awarding the Ph.D. degree.

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