− APPLICATION −

Background and Rationale

GLP-1 receptor agonists have shown incredible promise for longevity and healthspan but until Orforglipron we have only had peptides which require injection which is a serious increase in cost and work to test in animals compared to orally bioavailable compounds.

Now with the advent of Orforglipron, we have access to a small-molecule, orally bioavailable GLP-1 receptor agonist. If it demonstrates promising lifespan benefits in mice, this would justify the higher cost and effort of testing injectable GLP-1 receptor agonists for lifespan effects, and support subsequent studies in higher mammals.

Assuming this has similar effects to semaglutide, liraglutide and other singular GLP-1RA drugs it will impact mTOR and have a wide range of positive metabolic regulatory effects which are correlated with increased longevity and healthspan. Information on these effects are detailed in the references section.

Suggested Treatment Protocol

Orforglipron is a chemically stable, non-peptide small-molecule GLP-1 receptor agonist and is suitable for incorporation into rodent chow. As a low-molecular-weight organic compound, it is expected to remain stable in pelleted feed under standard vivarium conditions. Feed should be stored protected from excessive heat and light.

Based on published mouse efficacy studies demonstrating metabolic activity at oral exposures between approximately 1 and 10 mg/kg body weight/day, a concentration of 18 ppm in food is recommended. Using the ITP conversion factor (1 mg/kg body weight/day ≈ 6 ppm in food), 18 ppm corresponds to approximately 3 mg/kg body weight/day, which lies within the established pharmacologically active range in mice.

This dose is expected to achieve sustained GLP-1 receptor engagement while minimizing the risk of excessive weight suppression that could confound lifespan interpretation.

The expected pharmacological effects of Orforglipron can be monitored primarily through non-invasive measures. Weekly body weight monitoring during early treatment, followed by monthly tracking, along with cage-level food intake measurements, should be sufficient to confirm GLP-1 receptor engagement, as this class of agents reliably reduces food intake and body weight in mice.

If biochemical confirmation is desired, fasting glucose may be measured 4 to 8 weeks after treatment initiation. HbA1c measurement is optional. Both parameters can be assessed non-terminally using standard mouse blood collection techniques.

No routine sacrifice or internal tissue collection is required. The proposed monitoring approach is low cost and does not require specialized equipment beyond standard colony management tools and an optional glucometer.

There is no clear reason to deviate from standard ITP initiation. Orforglipron acts through metabolic pathways that are fully established in adult mice, and earlier initiation could confound results due to effects on growth.

Treatment should begin at 4–6 months of age, consistent with standard ITP practice. A slightly broader window of 4–8 months would also be biologically acceptable if needed.

Safety Information

Orforglipron has been evaluated in rodent preclinical models and in multiple human clinical trials. In published rodent studies of weeks to months duration, pharmacologically active oral doses produced expected metabolic effects without reports of acute organ toxicity or lethal outcomes.

In human Phase 1 through Phase 3 studies, adverse events were consistent with the established GLP-1 receptor agonist class. The most common effects were gastrointestinal, including nausea, diarrhea, constipation, vomiting, and abdominal discomfort. These events were generally dose dependent and most frequent during early treatment or dose escalation. While many participants experienced improvement over time, a subset discontinued treatment due to intolerance.

As with other agents in this class, potential risks include pancreatitis and gallbladder-related events, although these appear infrequent in available clinical data. GLP-1 receptor agonists also reduce appetite and body weight, which represents a primary pharmacologic effect rather than toxicity. However, in a lifespan study, sustained reductions in food intake or excessive weight loss could confound interpretation and therefore warrant careful monitoring.

There are no publicly reported LD50 or TD50 values for this compound, and no published evidence of lethal toxicity at doses used in animal efficacy studies or in human clinical trials. Nonetheless, given its metabolic activity, routine monitoring of body weight and general condition in treated mice would be appropriate.

While no published lifespan-specific toxicity data are available for Orforglipron, routine monitoring of body weight, food intake, and general condition is recommended to identify potential confounding effects.

Costs

Orforglipron is commercially available from InvivoChem at an estimated cost of $28,500 for 38 g, covering the total compound needed for 18 ppm in 2,100 kg of food. Smaller quantities are also available from MedChemExpress (100 mg for USD 880), though bulk pricing is pending and likely higher than InvivoChem.

The compound can be delivered as a solid powder and incorporated directly into chow under standard handling conditions. No specialized formulation or storage beyond standard laboratory precautions is required. If a cost-sharing arrangement with the ITP is necessary, this estimate provides a realistic basis for budgeting.

References

Studies on Orforglipron:

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2. Effect of Food Consumption on the Pharmacokinetics, Safety, and Tolerability of Once-Daily Orally Administered Orforglipron (LY3502970), a Non-peptide GLP-1 Receptor Agonist https://doi.org/10.1007/s13300-024-01554-1
3. Orforglipron: A Comprehensive Review of an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity and Type 2 Diabetes https://doi.org/10.3390/ijms27031409
4. Orforglipron: A Novel Oral GLP-1 Agonist for the Treatment of Obesity and Diabetes https://doi.org/10.1097/CRD.0000000000001139
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Studies on other GLP-1RAs:

7. GLP-1RAs improve mitochondrial ATP production by utilizing more glucose and fatty acids, promote the growth and division of mitochondria, reduce ROS and protect against mitochondrial damage. https://doi.org/10.1089/ars.2021.0113
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9. Stimulates autophagy by AMPK/mTOR pathway. https://doi.org/10.1152/ajpendo.00195.2019
10. GLP-1 has positive effects on stem cells including proliferation, differentiation, migration and more. https://doi.org/10.1038/nrendo.2009.285
11. Improves cardiovascular disease risk factors such as dyslipidemia, weight and hypertension. Potentially improves endothelial function and mitigates heart failure. https://doi.org/10.1155/2018/4020492
12. Improves hypertension https://doi.org/10.1016/j.bbrc.2009.01.003
13. May have a positive impact on the cognitive impairment brought on by diabetes or obesity, enhancing memory and learning https://doi.org/10.3389/fnins.2019.01112
14. Long term use of GLP-1 should reduce prostate, colon and lung cancer risk https://doi.org/10.1080/07435800.2021.1955255
15. Liraglutide administration combatted skeletal muscle atrophy in rodents, leading to enhanced muscular function https://doi.org/10.1016/j.metabol.2019.154044
16. Liraglutide reduced cartilage degradation through anti-catabolic effect at in-vitro, and in-vivo it targets cartilage inflammation, its breakdown and reduced pain https://doi.org/10.1038/s41598-022-05323-7
17. Liraglutide reduced neuroinflammation, decreased AMD symptoms and protected retinal ganglion cells https://doi.org/10.1038/s41598-019-52295-2
18. Improved cognitive and non-cognitive function within the central nervous system
19. https://doi.org/10.1016/j.bcp.2020.114187
20. No association was observed between cognitive changes and alterations in body mass index, blood pressure, or glycemic control. This means these effects were independent. https://doi.org/10.1161/JAHA.120.020734
21. Neuronal differentiation and cell proliferation are caused by activating the GLP- 1R signaling pathway https://doi.org/10.1111/j.1471-4159.2010.06731.x and https://doi.org/10.1007/s00018-010-0398-3
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Applicant (and Co-Applicant) Biosketch or CV

− STATEMENT OF UNDERSTANDING −

In submitting this proposal, I agree to the following:

- I understand that all information presented in the proposal can be freely shared with members of the ITP Steering Committee and Access Panel during their evaluation of proposals but will otherwise be considered confidential.
- If my proposal, or a modification of it (such as altered dosage or frequency of administration), is accepted for inclusion in a research protocol, I will be asked to help evaluate the data and to prepare the data for written and oral publications, on each of which I will be offered co-authorship. I understand the ITP intends to submit the results of all ITP-supported studies for publication – regardless of whether they produce data showing positive or negative effects on health status in mice.
- I understand that data generated by ITP-supported experiments using the compound/diet proposed will be made publicly available and can be used by anyone in applications for further research support. I also will be free to use ITP-generated data in the context of my applications for research support or for any other purpose.
- **If applicable:** The compound/diet proposed makes use of materials that are not yet freely available and whose production depends on proprietary or unpublished methods. If my application is approved for incorporation in the ITP, a mutually acceptable Materials Transfer Agreement that would permit me to provide the ITP with the compound(s) needed for the experimentation will be developed with the Institutions involved in this program.

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Applicant Signature

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Co-Applicant Signature