Supplementary files

1. **GRIPP2 short form50.**

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| Section and topic | Item | Reported on page No |
| 1: Aim | Report the aim of PPI in the study | Introduction – under ‘Objectives’ |
| 2: Methods | Provide a clear description of the methods used for PPI in the study | Methods – ‘Co-production’ |
| 3: Study results | Outcomes—Report the results of PPI in the study, including both positive and negative outcomes | Discussion – ‘Reflections on the process of triangulation’ |
| 4: Discussion and conclusions | Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects | Discussion –‘Potential limitations and future directions’ and ‘Reflections on the process of triangulation’ |
| 5: Reflections/critical perspective | Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience | Discussion –‘Potential limitations and future directions’ |

PPI=patient and public involvement

1. **Agenda for GALENOS – Triangulation meeting, February 15th 2024**

**LSR:** TAAR1 agonists for psychosis (<https://wellcomeopenresearch.org/articles/8-365>)

**Chair**: JH

**Research questions:**

* What are the effects of TAAR1 agonists on psychosis, considering both behavioural measures from animal studies and symptoms in human studies?
* What are the side-effects (and tolerability) of TAAR1 agonists in psychosis, considering both animal studies and human studies?
* What are the effects of TAAR1 agonists on neurobiological measures relevant to psychosis such as dopaminergic, glutamatergic and serotonergic signaling in preclinical animal experiments and human studies on psychosis, and their underlying mechanism?

**Agenda:**

10.00 – 10.15 Introductions and potential conflict of interest

10.15 – 10.30 Presentation of human data, Summary of Evidence and interpretation of findings (SS)

10.30 – 10.35 Specific questions on humans (All)

10.35 – 10.50 Presentation of non-human data, Summary of Evidence and interpretation of findings (MM)

10.50 – 10.55 Specific questions on non-humans (All)

10.55 – 11.40 Discussion of evidence for animals and humans (All)

11.40 – 11.50 COFFEE BREAK

11.50 – 13.00 Discussion (triangulating the evidence)

13.00 – 13.30 LUNCH

13.30 – 14.45 Discussion (triangulating the evidence)

14.45 – 15.00 COFFEE BREAK

15.00 – 16.00 Recommendations

**Notes:**

1. We will ask people attending the triangulation meeting to study the material about the LSR that will be circulated in advance (the presentations in the morning will assume that attendees have already familiarized themselves with the studies/review).
2. At the end of the morning presentations of human and non-human studies, we may spend some time discussing/digging deeper into the available evidence before we move to the discussion about triangulation of evidence
3. **Examples of areas of clarification requested by the panel**

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| Clarifications requested by the panel | Response from the GALENOS expert group |
| **Presentation of human studies** |
| What were the patient populations studied? | *Patients with schizophrenia (efficacy), healthy controls (acceptability and safety)* |
| Were Phase II trials included? | *Yes, the team had access to some data from all the Phase I, II and III trials, but could not access all the available data* |
| Would the LSR team want to include other populations (depression) in further iterations ? | *Yes, possibly* |
| **Presentation of animal studies** |
| Why was hyperlocomotion used and not other models of psychosis e.g. sensorimotor gating in the pre-pulse inhibition model? | *There is limited data on prepulse inhibition, and limited data in models of cognitive impairments* |
| Is there data that is unpublished by the companies? | *Yes: agreement that one of the weaknesses in animal data is the gaps in the data* |
| Is there data on the effects of licensed antipsychotics? | *No published data, one PhD study has found a significant effect on locomotor activity which is consistent with published data for the same behavioural readout.*  |
| The validity of animal models in human psychosis was questioned. Studies focused on attenuation of a drug-induced locomotor activity which is a task validated to predict dopamine2-receptor antagonist-like drugs. May not be most relevant for TAAR1 or drugs acting via novel mechanisms. Alternative methods are currently limited – for example, ketamine-induced psychosis in animals is a model used for agitation in humans, but this addresses only one symptom of psychosis and may not be a valid model of the agitation seen in psychosis. Also, cognitive impairment can be a key symptom in psychosis – is there any animal model for this?  | *Few of the animal studies looked at the so-called ‘negative’ symptoms (e.g. lack of motivation, social withdrawal, or reduced cognitive function) of psychosis.* *Some of the studies had some tests that aim at proxies for negative symptoms but there was not enough material for a systematic review.**Limited studies on effects on different cognitive domains.* |