Public Summary of the QSPainRelief Project at the End of the Project (30 June 2025)

1.1 Summary of the context and overall objectives of the project

Chronic pain affects one in five Europeans, yet many patients gain little relief from current medicines or suffer severe side effects. QSPainRelief addresses this unmet need by developing a **Quantitative Systems Pharmacology (QSP) *in silico* platform** to identify promising drug combinations for pain treatment. Using computer-based models - faster and more affordable than clinical trials - the platform predicts the benefit-risk balance of novel drug combinations before patient testing. The consortium integrated pharmacokinetic, receptor-binding, cellular signalling, and neural circuit models, and data aiming to tailor predictions to patient subgroups. Together, these efforts provide a foundation for better pain management and a deeper understanding of chronic pain and drug action.

1.2 Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

QSPainRelief achieved its overarching objectives and delivered an *in silico* platform ready for further exploitation.

WP1 – Project management

Strong coordination ensured smooth project delivery. Two major QSPainRelief project meetings were held (one on-site, one virtual), and regular Steering Committee calls secured alignment across partners. The independent Scientific and Ethical Advisory Board (SEAB) was actively engaged, with patient representatives providing valuable input.

WP2 – QSPainRelief platform development

The QSPainRelief model platform substantially improved. The latest *in silico* models of analgesia, sedation, drug abuse liability, and cognitive impairment contain the main targets involved to make testable predictions based on pharmacological properties and define neuronal network parameters. Connected with the improved CNS drug distribution and target site binding kinetic models, these models were applied to more than thirty augmentation drugs, combined with morphine. Their predictions identified nortriptyline as the most promising partner drug for morphine in neuropathic pain, leading to the design of a prospective patient trial.

WP3 – Data management

Supporting these efforts, the QSPainRelief database was populated with data from preclinical and clinical studies, which were checked for quality and made available for cross-validation of the models. To facilitate the communication of results, an interactive web-based application was developed, allowing clinicians, regulators, and industry partners to explore different weighting of outcomes and patient subgroups.

WP4 – *In silico* computation and benefit-risk analysis

Using multivariate models and the Clinical Utility Index (CUI), drug combinations were ranked by benefit versus risk. A dedicated Shiny app was developed for interactive visualization, making results accessible to clinicians and stakeholders. An online questionnaire to capture patient preferences regarding drug effects was also developed and piloted, recognising the importance of including patients' voices in treatment optimisation.

WP5 – Cellular signalling

Mechanistic insights were advanced through *in vitro* cellular signalling studies, which confirmed the predicted existence of MOR–CB1 receptor heteromers, shedding new light on opioid–cannabinoid interactions. *In vitro* and computational studies also clarified how drug-receptor binding and biased signalling evolve over time.

WP6 – Preclinical *in vivo* validation

In vivo animal studies tested morphine in combination with pregabalin, THC, and fluvoxamine. The sedative effect of morphine interfered with the behavioural responses to pregabalin and TCH. Therefore, a non-contingent experimental approach was implemented for morphine and fluvoxamine. Morphine was highly effective in preventing neuropathic injury-induced hypersensitivity, while fluvoxamine had limited and transient effects.

WP7 – Clinical studies in healthy volunteers

The clinical trial in healthy volunteers investigated morphine +/- pregabalin (NovelA study) showing that the combination produces analgesic synergy in healthy subjects. The morphine +/- fluvoxamine (NovelB study) showed that while fluvoxamine alone was not analgesic, the combination with morphine produced enhanced and additive pain relief compared to morphine alone.

WP8 – Patient studies and platform calibration

Patient studies, although challenged by the COVID-19 pandemic and recruitment difficulties (opioid and non-opioid drug combination prescribing are uncommon in routine care) provided important biomarker data. In addition, a complementary study in thoracotomy patients yielded valuable insights into mechanisms underlying the development of persistent post-surgical pain. A REDcap-based platform was successfully implemented for patient data collection, laying the foundation for future trials.

WP9 – Dissemination, training, and exploitation

Dissemination and training activities remained strong throughout the final period. Many scientific publications, conference presentations, and educational events were delivered. A major white paper was prepared about the "*In silico* prediction of new effective combinational treatment of chronic pain in individual patients", and two key reports were produced: One identifying promising drug combinations for further clinical development, and another one highlighting combinations that should be avoided due to a poor risk-benefit balance. Also, a final exploitation plan outlines our market access strategy, and a briefing book (to receive regulatory advice) was submitted to the European Medicines Agency (EMA). Patient engagement was strengthened through events and active involvement of Pain Alliance Europe (PAE), ensuring that project outcomes were communicated clearly to those most affected.

WP10 & WP11 – Ethics

All ethical approvals were secured for preclinical and clinical studies. Regular ethical monitoring reports were submitted. Patient involvement strengthened oversight.

1.3 Progress beyond the state of the art, expected results until the end of the project and potential impacts (including the socio-economic impact and the wider societal implications of the project so far)

QSPainRelief has significantly advanced the state of the art in pain research and drug development. It is the first project worldwide to deliver a fully integrated, mechanism-based QSP platform capable of predicting the benefit vs. risk profile of analgesic drug combinations. The confirmation of receptor heteromers and the incorporation of time-dependent signalling dynamics represent major scientific advances. The clinical studies provided proof of concept that certain drug combinations, such as morphine with pregabalin or fluvoxamine, can offer improved pain relief, while the identification of combinations with unfavourable profiles provides equally important results.

The interactive modelling platform, the accompanying clinical utility app, and key reports on safe and unsafe drug combinations are tangible outputs that will support physicians, patients, regulators, and industry in making better-informed decisions. In the future, pharmaceutical companies can use these tools to prioritise combinations most likely to succeed, reducing development costs.

QSPainRelief successfully paved the way towards more personalised, safer, and more effective treatments for chronic pain patients. This has the potential to reduce the burden of ineffective treatments, minimise side effects, and improve quality of life for millions of patients. At the same time, the project strengthens Europe's leadership in computational pharmacology, supports innovation in drug development, and demonstrates the societal value of integrating modelling with experimental and clinical research.