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An innovative phase 2 chronic pain master protocol design to assess novel mechanisms in multiple pain types

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Abstract

Introduction: The phase 2 chronic pain master protocol (CPMP) presented here provides a construct to accelerate the investigation of novel analgesics, broadly referred to here as mechanisms. Designed to address historical challenges in analgesic research and development, such as the choice of indication, this protocol enables the efficient evaluation of potential therapeutics with different mechanisms of action in 3 pain types: nociceptive pain (osteoarthritis), neuropathic pain (diabetic peripheral neuropathic pain), and mixed pain (chronic low back pain).

Methods: The study design was determined before the identification of any specific molecule. Statistical simulations were conducted to optimize the methodology and design, the culmination of which were submitted to and accepted by the Complex Innovative Trial Design Pilot Meeting Program, a unique collaboration with the United States Food and Drug Administration. Benefits of the CPMP include limiting the number of study participants exposed to placebo and reducing the total sample size over time by leveraging placebo data across studies within a pain type and efficacy data across pain types for a specific molecule. The CPMP design enables: (1) efficient evaluation of multiple novel mechanisms of action; (2) the study of multiple molecules simultaneously or serially; (3) direct statistical comparison of molecules within a pain type; and (4) efficient planning and conduct of clinical studies. ClinicalTrials.gov ID NCT05986292.

Perspective: By evaluating novel mechanisms across different pain types, therapeutic potential can be assessed more efficiently compared with traditional individual clinical studies.

Keywords: Analgesics, Clinical study, Master protocol, Pain

1. Introduction

Chronic pain is a public health crisis, with over 20% of adults in the United States estimated to live with some form of pain lasting 3 or more months.[21] The efficient discovery and development of novel analgesics are urgently needed to address this crisis; however, progress has been challenging, with a probability of approval by the U.S. Food and Drug Administration (FDA) of only 0.7% for novel analgesics that have completed phase 1 studies compared with an overall probability of 6.5% for novel drugs across all diseases.[28] This low rate of FDA approval of novel analgesics may be due, in part, to the overinterpretation of preclinical data and application of traditional clinical trial designs.[3,12,13,16,17,25,26,29]

This article describes a chronic pain master protocol (CPMP) aimed at addressing 4 key challenges in analgesic drug development, namely: (1) the high number of novel analgesics, broadly referred to here as mechanisms, that warrant clinical investigation; (2) differences in efficacy measures between animals in preclinical studies and humans in clinical studies; (3) the high response rate to placebo in analgesic clinical studies; and (4) the choice of clinical population.

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One approach to addressing these challenges is a master protocol designed to maximize the amount of data gained while simultaneously accelerating the drug development process.[31] A master protocol can facilitate investigation of multiple novel mechanisms in multiple indications or pain types using one overall study design. As the individual studies share key design elements, comprehensive data can be gathered more quickly compared with traditional individual clinical studies (see Supplementary Video 1). Innovative statistical approaches incorporated into master protocols, including placebo borrowing, have the additional benefit of decreasing the number of participants assigned to placebo, thereby minimizing allocations to ineffective treatment arms, and reducing the overall size and cost of clinical studies. Furthermore, this approach enables the simultaneous evaluation of novel mechanisms in multiple pain types.

The phase 2 CPMP presented here aims to improve evaluation of novel mechanisms of action by conducting studies in 3 pain types: nociceptive pain (osteoarthritis), neuropathic pain (diabetic peripheral neuropathic pain), and mixed pain (chronic low back pain).

2. Methods

2.1. Study design

The rationale for this CPMP is illustrated in **Figure 1**. Rapid and simplified evaluations of molecules with novel mechanisms of action were paramount in this CPMP. The objective was to evaluate novel mechanisms in multiple pain conditions using a protocol design that could accommodate undiscovered molecules. This required maximum flexibility in how the protocol was envisaged and executed, given its potential to test an unknown number of therapeutics.

The overarching CPMP trial alias, H0P-MC-CPMP (ClinicalTrials.gov ID NCT05986292), represents a multicenter, randomized, double-blind, placebo-controlled, phase 2, proof-of-concept (POC) platform trial to assess the safety and efficacy of multiple novel analgesics in 3 pain conditions: osteoarthritis pain, diabetic peripheral neuropathic pain, and chronic low back pain. The CPMP is structured in 3 levels as shown in **Figure 2**. The master protocol level establishes baseline entry criteria for the program, outlines the randomization scheme, sets the study duration, and defines the primary outcome for all studies. The disease-specific addenda (DSA) specify the 3 indications under study and contain study elements specific to each target population, such as unique efficacy scales. The intervention-specific appendices (ISAs) represent a specific investigational compound of a defined mechanism of action to be tested in each DSA. The ISAs include study elements specific to a given intervention including dosing regimen, unique eligibility criteria based on the safety and tolerability profile, and options for interim analyses if required. Each level is complementary to the others to offer maximum flexibility, but neither the DSAs nor the ISAs can contradict the overarching master protocol.

2.2. Eligibility criteria

Key inclusion criteria for the CPMP include a visual analog scale pain value of ≥40 and <95 before randomization with a history of daily pain for ≥12 weeks and a value of ≤30 on the pain catastrophizing scale. Key exclusion criteria include: second- or third-degree atrioventricular heart block or dissociation or history of ventricular tachycardia; permanent sensory loss procedure within the last 6 months; planned surgery; acute, serious, or unstable medical condition; cancer within 2 years of randomization; fibromyalgia; substance use disorder; and intolerance to acetaminophen or paracetamol, which is used as a rescue medication.

2.3. Primary objective and endpoint

The primary objective of the CPMP is the efficacy of each study intervention vs placebo, measured by the mean change from baseline assessment to the endpoint for average pain intensity using a Numeric Rating Scale (NRS). Using a take-home device, participants complete the following NRS item daily: "Please rate your pain by selecting the one number (0–10) that describes your AVERAGE level of (foot, low back, knee) pain during the past 24 hours." To minimize potential rating bias, the NRS data are blinded to the sites. All 3 disease states are required to use this common primary endpoint to maintain the master structure, even if it is not the typical primary endpoint for registration across all indications.

2.4. Secondary objectives and endpoints

The secondary objectives at the master level include additional efficacy measures, physical functioning assessments, overall improvement, and emotional functioning. Disease state–specific assessments are also included as secondary endpoints at the DSA level, specifically, the Western Ontario and McMaster Universities Osteoarthritis Index for osteoarthritis pain,[30] the Roland–Morris Disability Questionnaire for chronic lower back pain,[22] and the Brief Pain Inventory–Short Form for diabetic peripheral neuropathic pain.[5,6] Visual analog scale data are also collected as a secondary endpoint, and these data are not blinded.

Figure 1. Master protocol rationale for chronic pain. Master protocol designs have been used successfully in rare diseases where it is difficult to find appropriate participants or in biomarker-based studies. Chronic pain is not a rare disease but not all chronic pain types are the same.

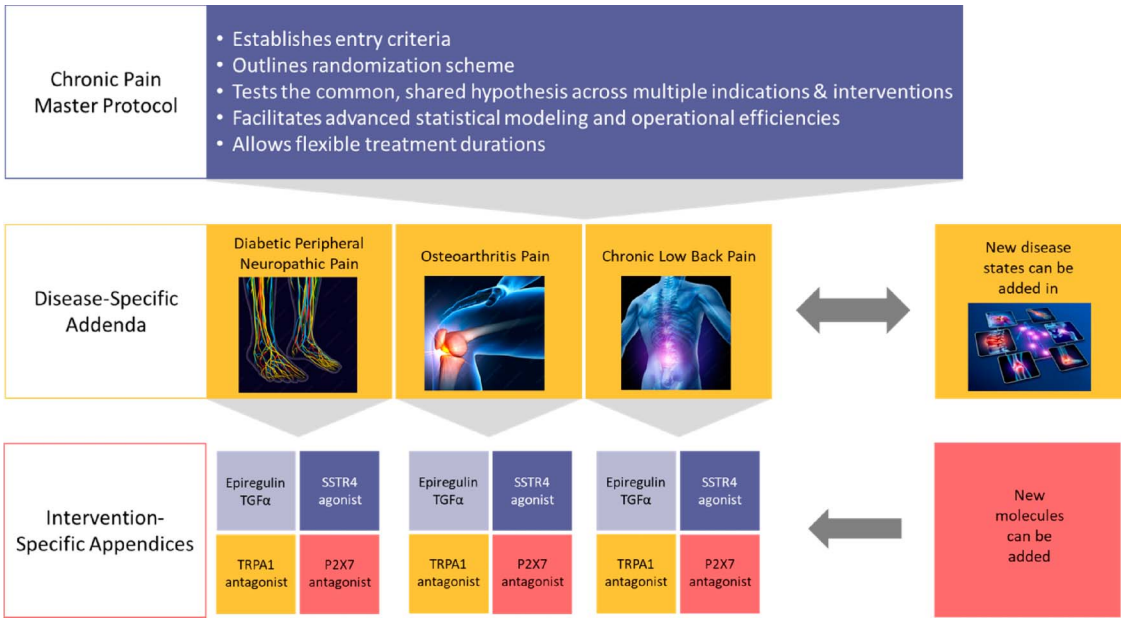

Figure 2. Chronic pain master protocol 3-tiered document structure. P2X7, purinoceptor 7; SSTR4, somatostatin receptor type 4; TGFα, transforming growth factor alpha; TRPA1, transient receptor cation channel subfamily A member 1. Diabetic peripheral neuropathic pain illustration from medejaja (stock illustration ID 394116595), Shutterstock, July 19, 2024; osteoarthritis pain illustration from Axel_Kock (stock illustration ID 1857461167), Shutterstock, July 19, 2024; chronic low back pain illustration from Lightspring (stock illustration ID 94983727), Shutterstock, July 19, 2024; new disease states illustration from Lightspring (stock illustration ID 1533836189), Shutterstock, July 19, 2024; all illustrations licensed and used with permission.

2.5. Disease-specific addenda

The DSAs define the 3 chronic pain disease states under study. Additional inclusion and exclusion criteria specific to a disease state are included at the DSA level; however, the inclusion criteria cannot be broadened beyond those defined at the master level.

2.6. Intervention-specific appendices

Each ISA is a multicenter, randomized, double-blind, placebo-controlled, POC trial to compare phase 2 pain interventions vs placebo. However, individual ISAs cannot stand alone and are required to be conducted as an appendix to the CPMP. Because of the flexibility built into the CPMP design, the ISAs can start and

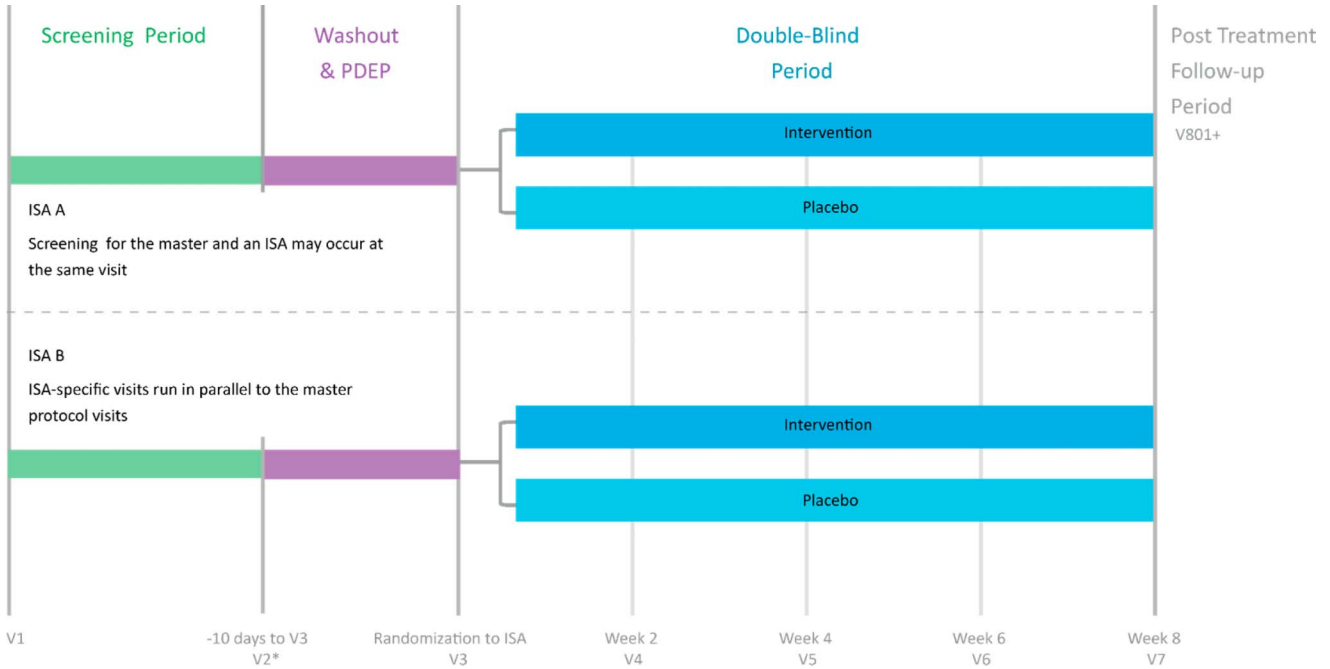

Figure 3. ISA study design schema. Several aspects of the study design are blinded to investigators and clinical staff. Depending on the ISA design, an ethical review board supplement may be used. Optional follow-up periods beyond the 8-week double-blind period may be specified in an individual ISA. *Medication washout and preliminary data entry period begins. ISA, intervention-specific appendix; PDEP, preliminary data entry period; V, visit.

end independently of one another as new analgesics become available for clinical testing.

Figure 3 displays the ISA study design schema. Each ISA includes an 8-week, double-blind treatment period in which participants are randomized at a 2:1 ratio (intervention:placebo), irrespective of how many ISAs are simultaneously active. Visit 3 is the common point of randomization for each ISA, and visits occur at every 2 weeks throughout the double-blind period. Additional visits may be added to enable any unique procedural requirements. Depending on the ISA design, a blinded ethical review board supplement may be used.

2.7. Complex Innovative Trial Design Meeting Program participation

The CPMP was accepted as part of the FDA's Complex Innovative Trial Design (CID) Pilot Meeting Program in June 2019. The CID, included as part of the FDA Reauthorization Act of 2017, under the Prescription Drug User Fee Act VI, sought to facilitate and advance the use of complex adaptive, Bayesian, and other novel clinical trial designs.[8] After 2 in-person consultations with the FDA-assigned review division and biometrics experts, statistical simulations and methods were discussed and modified before finalization of the CPMP. Program participation was successfully completed in January 2020, and the CPMP currently serves as the first master protocol case study.[9] Consistent with the CID program objectives, the FDA has disclosed this design and learnings.[19]

2.8. Statistical modeling

The primary efficacy objective is to evaluate whether each analgesic in the CPMP is superior to placebo in the respective chronic pain condition. The primary efficacy analyses are performed using a Bayesian mixed-model repeated-measures method to evaluate the efficacy of each analgesic on the overall mean change of average pain intensity from baseline to the endpoint as measured by an NRS during the 8-week, double-blind treatment period.

A Bayesian critical success factor (CSF), defined for each ISA in the master protocol, is used to assess whether the ISA meets its primary endpoint at the conclusion of the double-blind portion of the study. The CSF has the general form: *probability (treatment effect* $<$ *effect of interest)* $>$ *probability threshold*. *Treatment effect* is defined as the mean treatment difference (study intervention − placebo) from baseline to endpoint. The *effect of interest*, typically found through a literature search or based on clinical judgment, is often set near the minimal clinically important difference. The *probability threshold* is set to have the desired operating characteristics or risk level under a range of plausible, assumed drug-effect scenarios of truth. Additional CSFs to the primary endpoint can also be considered because of various factors, such as multiplicity from an interim analysis, inclusion of additional treatment arms, or a specific placebo-borrowing approach if used.

The synchronized design elements of the CPMP, such as the same investigative sites, the standardized battery of scales across ISAs, common visit schedules, homogeneity within the pain-specific populations, and similarity in the inclusion/exclusion criteria, facilitate borrowing of placebo information across the ISAs within a specific pain type. The CPMP uses a 2:1 randomization scheme (intervention:placebo) for each ISA, and the design allows the opportunity to add multiple doses. From the placebo-borrowing perspective, a key advantage of using 2:1 randomization is that, after completion of a few ISAs, there may be a sufficiently large bolus of placebo participants with the respective pain type to use in the primary efficacy analysis. Benefits of borrowing placebo information between interventions within a disease state also include the opportunity for increased power to detect a treatment effect or the possibility of needing fewer participants randomized to placebo for an ISA to maintain the same power.

Various methods have been proposed to leverage placebo data from other similar studies. The choice of the method depends on key factors such as the number of historical data sources, potential exchangeability, and commensurability of the placebo data between the historical and current ISAs. At the early stage of the CPMP, limited data are available to borrow and a fixed amount of borrowing is accomplished through borrowing all (pooling) or a prespecified fraction (power prior) of placebo participants from the available ISAs. In a situation where data from multiple ISAs are available, borrowing of placebo information within a DSA is accommodated through implementing a dynamic borrowing approach, such as a Bayesian hierarchical model or mixture priors approach, where the amount of borrowing is adapted based on the similarity of the placebo data between the historical and current ISAs. In the Bayesian hierarchical model, a hierarchical framework is developed for the mean placebo response that allows for adaptive placebo borrowing under the assumption that placebo participants are within the same disease state. The mixture priors approach provides an alternative dynamic method that can adapt the level of borrowing depending on the similarity of the placebo response.

The novel framework of the CPMP provides a unique opportunity to study an analgesic for multiple pain types. In addition to the opportunity to borrow placebo data within a pain type, the framework allows for leveraging the treatment effect information across the pain types for the same analgesic. There is often a considerable amount of uncertainty regarding the efficacy of an intervention in one pain type vs another. However, some pain conditions are more closely related than others, and network meta-analyses can be performed on existing literature to determine the overall similarity between the disease states. The advantages of borrowing treatment effect information from other pain types may include increased efficiency of estimates, adjusted treatment effect estimates for a pain type based on data from other pain types, and an increased understanding of the relatedness of the intervention between pain types. A dynamic borrowing approach, such as a commensurate prior, can be used to improve the decision-making process and better understand the efficacy of each intervention within a pain type.

An extensive battery of simulation studies was conducted to evaluate the key operating characteristics of the CPMP (Supplementary File 2, available at http://links.lww.com/PR9/A257). Each ISA can have its own unique sample size and powering assumptions, and thus simulations will be conducted on an ongoing basis throughout the trial. The simulations are necessary to understand the potential impact of placebo borrowing and treatment-effect borrowing on the power and overall performance of the trial. Key factors to evaluate by simulation for each ISA include: (1) the amount of placebo data information that is available from completed and ongoing ISAs; (2) the understanding of the observed or potential treatment effects between pain types for an analgesic; (3) any potential placebo "drift" that could occur over the course of the trial because of time or modifications to the conduct of the trial; and (4) the impact of different routes of intervention administration.

3. Discussion

The primary goal of using a CPMP is to simultaneously address 4 key challenges in analgesic drug development, namely: (1) the high number of novel mechanisms that warrant clinical investigation; (2) differences in efficacy measures between animals in preclinical studies and humans in clinical studies; (3) the high response rate to placebo in analgesic clinical studies; and (4) the choice of clinical population. Although future CPMPs could make different design choices, the guiding principle for this CPMP is to achieve POC across 3 indications while realizing multiple operational efficiencies. The first 4 drugs investigated using the CPMP have enrolled over 1700 participants to date.

With rare exception, chronic pain conditions are the result of complex biological, social, and psychological factors and few monogenic conditions have been identified. The target validation datasets are typically comparable, with some combination of preclinical model data and human genetic or tissue expression data, and thus, no clear prioritization framework exists to advance molecules with the highest probability of conferring clinical efficacy. However, investigating each of these targets with traditional POC approaches is not sustainable given the time and cost. Even though a master protocol has not historically been leveraged outside rare or biomarker-driven diseases, it can be engineered to solve the challenge of evaluating an expanse of suitable molecules if significant operational efficiencies are realized. In this case, the number of molecules to be tested was unknown at the time of the master design; therefore, the infrastructure needed to be flexible enough to evaluate additional molecules by the simple addition of an ISA.

The trial features stipulated at the master level include the primary and some secondary endpoints, trial duration, and eligibility criteria. The CPMP is uniquely designed to allow for standardized study conduct and ensure the data collected remain relevant across the ISAs. Given the inherent differences in the 3 disease states included in the DSAs, the choice of primary endpoint is not necessarily the most acceptable endpoint for each condition. This is most obvious in osteoarthritis pain, where the Western Ontario and McMaster Universities Osteoarthritis Index is the accepted regulatory endpoint but is not the primary endpoint across the CPMP. As average pain intensity is typically assessed in each pain clinical trial, even if not designated the primary endpoint, it was chosen as the primary objective at the CPMP level. Because the data from these POC studies are not intended for registration purposes, other endpoints more appropriate for a disease state can still be assessed within an ISA as a secondary objective. Furthermore, the totality of evidence in a trial can be leveraged for decision making. In the case that a primary endpoint is not met, further development decisions can be made based on the combined efficacy and safety data.

Trial duration for typical registration studies is specified at 12 weeks.[10] However, focusing on signal-seeking studies vs phase 3-enabling designs allows for more flexibility in the trial duration. Because the molecules under evaluation are mechanistically novel, it is important to quickly determine if they are clinically relevant. An 8-week trial duration was determined to provide sufficient time for an onset of action while minimizing the time patients received placebo with a low probability of analgesic benefit.

High-level eligibility criteria are set at the master level. POC trials often focus on a specified, homogeneous population to maximize the chance of observing efficacy, yet this is often cited as a reason why trials do not replicate from phase 2 to phase 3. Thus, the decision was taken to streamline the inclusion and exclusion criteria and include a range of pain severities within each pain type. Of note, the CPMP allows for additional exclusion criteria at a specific disease-state level to provide additional restrictions beyond those included in the CPMP; however, the inclusion criteria cannot be broadened beyond those allowed at the master level.

As with all clinical trials, the potential to amend the CPMP exists; however, a goal of minimizing amendments was set at the outset to preserve the ability to borrow participants over time. In addition, the potential to add or replace clinical trial populations (DSAs) exists as the CPMP continues.

As novel analgesics are added to the CPMP, some degree of analgesic-specific customization can occur at the ISA level. As an example, the overall trial duration and the associated visit structure is 8 weeks, yet if a particular analgesic does not have sufficient toxicology data to allow for 8 weeks of dosing, it is possible to dose for a shorter duration, either in a blinded or unblinded fashion, while maintaining the same visit structure. Similarly, participants can be followed up for longer than 8 weeks of dosing. The route of administration is another parameter that can be set at the ISA level, which is an important feature given the uncertainty of which and how many analgesics will be evaluated.

The second major challenge a master design helps mitigate is the difference in efficacy measures between preclinical and clinical studies. Although significant efforts have been made to augment the evoked endpoints traditionally measured in behavioral assays,[14,18,23] the reality is that no model will recapitulate the chronic pain experience or report of pain intensity in humans. Thus, once a preclinical data package has been generated wherein the hypothesized attenuation of pain signaling can be demonstrated, an adequate and predictable pharmacokinetic/pharmacodynamic relationship exists to set the dose clinically, and an adequate safety package is generated, evaluating efficacy in humans is the only true test of a novel analgesic. Preclinical models are leveraged to optimize drug properties, but expansive profiling across multiple model types is minimized. Given the verbal endpoint is only relevant in humans, speeding the clinical evaluation is paramount.

In addition to the rich phenotypic data collected across the various efficacy scales, genetic and biomarker data are also collected. The genetic data will be leveraged over time to potentially identify genetic factors influencing susceptibility for developing chronic pain or identify subpopulations that may respond preferentially to a particular mechanism. Other genomic data may be used in a similar way to identify markers of drug response or disease severity. The digital biomarker data are planned to be used to improve accuracy in study patient selection and possibly outcome measurements.

The third challenge of a high placebo response in analgesic clinical trials has led to significant efforts to better understand the causes of placebo response and minimize it. Identical protocols across analgesics allow for a contemporary assessment of placebo response and, importantly, enable reduced sample sizes. This is accomplished by direct borrowing of placebo participant data to minimize the number of participants needed to adequately power the trial.

The choice of chronic pain populations to include in the CPMP is based on multiple factors, including unmet need, diversity of underlying pathophysiology, and as a representative of each type of chronic pain: osteoarthritis pain as nociceptive, diabetic peripheral neuropathic pain as neuropathic, and chronic lower back pain as mixed. Each of these conditions represents a significant unmet need, the data for this being previously reported.[1,11,24,27] However, it is uncertain at study initiation which

population will respond to each novel analgesic or if an analgesic will be effective in multiple chronic pain types, as was observed with duloxetine and pregabalin.[7,15] Therefore, limiting evaluation to a single population raises the risk that the incorrect population is chosen or that the full breadth of efficacy is delayed or ultimately unknown. As such, each indication is evaluated independently of the outcome of the other two. It is expected that studies for each indication should read out at a similar time, but in the event one is lagging, it would still run to completion. That said, any analgesic that is ineffective across all 3 pain types is likely to have development halted, enabling testing of other more promising analgesics.

The intentional consistency of the study schedule and endpoints lends itself to borrowing of information using a Bayesian approach. The primary analysis model is analogous to the frequentist mixed-model repeated-measures method, a flexible and robust model to analyze continuous longitudinal outcomes, with the additional flexibility to incorporate prior information when available from completed ISAs to make efficient use of the available accrued data. After fitting the model, the posterior Markov chain Monte Carlo method is used to specify the treatment effect parameter for each primary objective to ensure robust and appropriate use of information within the platform.

In addition to addressing the challenges inherent in analgesic discovery, this CPMP enables operational benefits previously observed in other master protocols.[2,4,20] By partnering with sites capable of evaluating multiple assets in all 3 indications simultaneously, significantly reduced administrative costs and time associated with starting up new trial sites for each analgesic should be realized.[12] The use of common sites also minimizes the complexity associated with site readiness and clinical trial material requirements. Enrollment periods should also be significantly reduced, beginning with the first analgesic and decreasing with each subsequent analgesic. Participant screening occurs at the master level vs the asset level in a stand-alone POC trial. This translates to participants potentially qualifying for multiple ISAs, such that once a new asset is activated, participants are already known and can be randomized assuming they continue to meet eligibility requirements.

The CPMP can also increase data quality and efficiency through its shared and reusable infrastructure.[12] Sites repeat the overall study visit structure across each analgesic and thus realize efficiencies with each subsequent analgesic. The common data acquisition construct also enables head-to-head comparison of analgesics over time. Additional benefits related to evaluating multiple analgesics across 3 indications should also be realized because this is a dataset that does not exist to date. Examples include a contemporary placebo dataset by indication and the concordance of endpoints that seemingly measure the same endpoint, and how these patient-reported outcomes relate to digital biomarker data.

The concept of a master protocol for 3 indications in phase 2 of development, however, requires some design tradeoffs vs the goals of traditional signal-seeking studies. The ability to evaluate analgesics in 3 populations requires greater upfront resource investment, albeit less overall resources, compared with 3 independent POC studies. Part of the rationale for enrolling heterogenous phase 3-like populations is to improve translatability, but an operational consideration of ensuring an expedited enrollment period is also a driver. The choice of a 2:1 randomization ratio is another parameter that was chosen to reduce enrollment periods. Similarly, because of the signal-seeking design, the total number of participants per trial has to be kept to the minimum to detect a difference from placebo at the specified effect size. However, small sample sizes could decrease the magnitude of treatment effect and potential responder identification. Additional tradeoffs include an inherent risk of increasing placebo response because of 2:1 randomization and the lack of benefit of placebo borrowing to the first analgesic tested (except in retrospect).

As the CPMP is a balance of scientific goals with operational efficiencies, dynamic tensions are constant between individual program objectives and optimizing for the whole. Given the unmet need in chronic pain, the ongoing opioid epidemic, and the paucity of new treatments for patients, the need to validate and develop novel analgesics more efficiently and in less time has never been greater.

Disclosures

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