

ORIGINAL ARTICLE

Multimethod quantitative benefit-risk assessment of treatments for moderate-to-severe osteoarthritis

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Objective: Demonstrate how benefit-risk profiles of systemic treatments for moderate-to-severe osteoarthritis (OA) can be compared using a quantitative approach accounting for patient preference.

Study design and setting: This study used a multimethod benefit-risk modelling approach to quantifiably compare treatments of moderate-to-severe OA. In total four treatments and placebo were compared. Comparisons were based on four attributes identified as most important to patients. Patient Global Assessment of Osteoarthritis was included as a favourable effect. Unfavourable effects, or risks, included opioid dependence, nonfatal myocardial infarction and rapidly progressive OA leading to total joint replacement. Clinical data from randomized clinical trials, a meta-analysis of opioid dependence and a long-term study of celecoxib were mapped into value functions and weighted with patient preferences from a discrete choice experiment.

Results: Lower-dose **NGFi** had the highest weighted net benefit-risk score (0.901), followed by higher-dose NGFi (0.889) and **NSAIDs** (0.852), and the lowest score was for **opioids** (0.762). Lower-dose NGFi was the highest-ranked treatment option even when assuming a low incidence (0.34% instead of 4.7%) of opioid dependence (ie, opioid benefit-risk score 808) and accounting for both the uncertainty in clinical effect estimates (first rank probability 46% vs 20% for NSAIDs) and imprecision in patient preference estimates (predicted choice probability 0.26, 95% confidence interval [CI] 0.25-0.28 vs 0.21, 95% CI 0.19-0.23 for NSAIDs).

Conclusion: The multimethod approach to quantitative benefit-risk modelling allowed the interpretation of clinical data from the patient perspective while accounting for uncertainties in the clinical effect estimates and imprecision in patient preferences.

KEYWORDS

benefit-risk assessment, nerve growth factor inhibitor, opioid, osteoarthritis, patient preference

ClinicalTrials.gov identifiers: NCT02697773, NCT02709486 and NCT02528188.

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1 | INTRODUCTION

Osteoarthritis (OA) is a disease for which several systemic pharmacological treatment options are available with notably different risk profiles. Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors, are effective,¹ but they can increase cardiovascular risk, especially myocardial infarction (MI),² and can cause gastrointestinal toxicity and renal insufficiency.³ Opioids may be used to treat patients who do not respond to NSAIDs or other analgesics, although opioid dependence is a major public health concern.^{4,5}

Several targeted agents are now in development for the treatment of OA.⁶ Tanezumab, a humanized antinerve growth factor monoclonal antibody⁷ (ie, NGF inhibitor, NGFi), has demonstrated efficacy in clinical trials of patients with moderate-to-severe OA and inadequate responses to standard analgesics. However, it can increase the risk of rapidly progressive OA type 2 (RPOA 2), an adverse drug reaction that, in some cases, requires total joint replacement.^{8–12}

Benefit-risk assessment provides information on how a medical product, including an emerging treatment option, can fit within the current product landscape, particularly within a marketing application. The standard approach for comparing the benefits and risks of different treatments is a qualitative benefit-risk assessment.^{13,14} However, qualitative approaches do not systematically integrate patient preferences, which are increasingly sought to help inform policy and clinical decision making.¹⁵ Patient preferences are especially important when the benefit-risk balance is preference-sensitive,^{16–21} as in the case of OA, where treatment decisions may depend on patient preferences for different characteristics of the treatment.²²

Quantitative benefit-risk (qBR) approaches allow for patient preferences to be incorporated,^{23–25} but their application has been hampered by the lack of representative utility weights, and difficulty in incorporating patient preferences due to imprecision/variability in patient preference data and inherent statistical variability in clinical effect estimates.^{26–28} In the current study, we used a multimethod assessment that couples a structured benefit-risk approach¹⁷ with multicriteria decision, stochastic multicriteria acceptability (to address variability in clinical effect estimates) and predicted choice probability analyses (to address variability in patient preferences) to quantitatively rank profiles of selected benefit and risks corresponding to NGFis, NSAIDs and opioids in the treatment of moderate-to-severe OA. In addition to demonstrating the use of this qBR through generating comparative benefit-risk profiles for these treatments, this work is part of a case study to inform the development of guidelines on the incorporation of patient preferences in decisions on medicinal products by the Innovative Medicines Initiative.²⁹ We hypothesized that patient preferences combined with clinical trial data would provide a meaningful way to differentiate benefit-risk profiles of alternative treatments for moderate-to-severe OA.

2 | METHODS

This study used a multimethod qBR approach to quantifiably compare NGFi, NSAIDs and opioids in the treatment of moderate-to-

What is already known about this subject

- Interest has grown in using quantitative methods to evaluate the benefit-risk balance of treatments, but this has been hampered in part by the difficulty getting agreed on preference weights into the analysis.

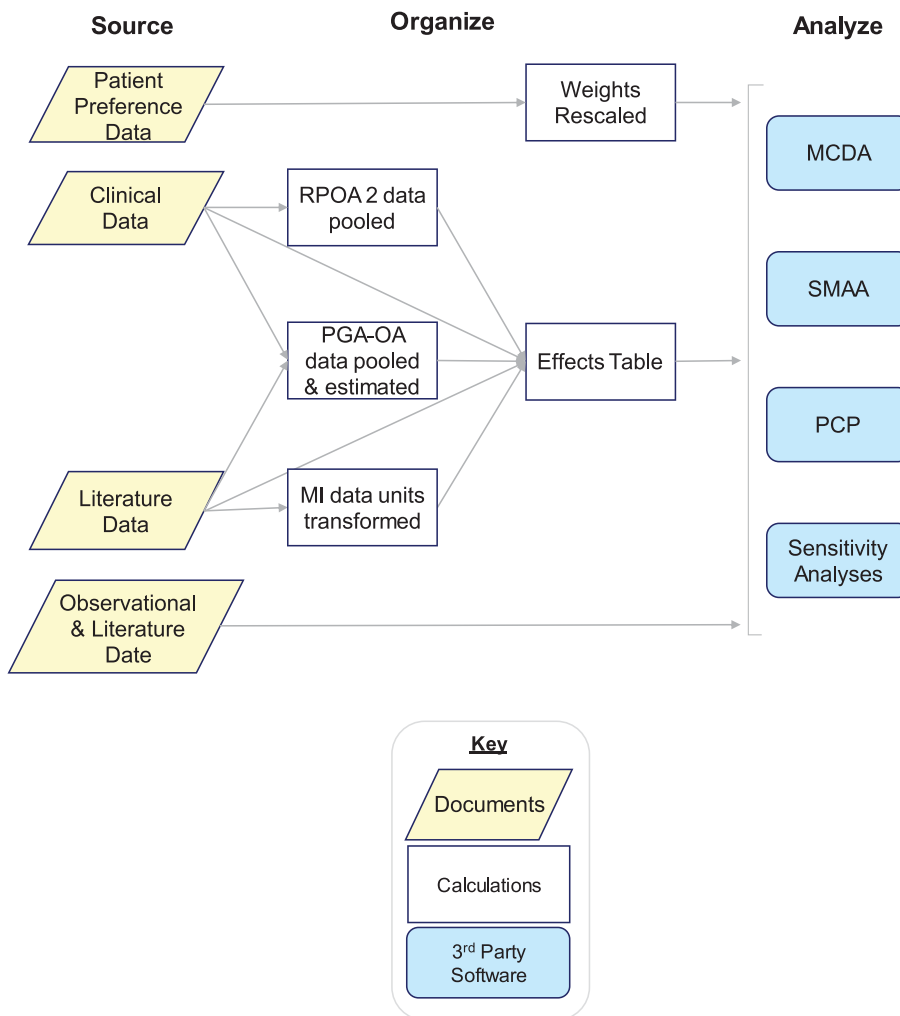
What this study adds

- This study demonstrated how quantitative benefit-risk assessment incorporating patient preferences into the analysis can be used to compare systemic treatments for moderate-to-severe osteoarthritis with differing benefit-risk profiles.
- Benefit-risk profiles of treatments for moderate-to-severe osteoarthritis can be quantitatively compared using patient preferences, while addressing uncertainty in clinical data and imprecision in preference data.
- The multimethod approach described here provides additional support for benefit-risk conclusions and may be included in regulatory submissions.

severe OA. NSAIDs and opioids were selected as comparators for NGFi because they are systemic pharmacological treatments commonly used in the clinic, recommended by at least two major OA guidelines^{30–35} as monotherapies and not specifically limited to 1–2 months of use per labelling. Representative agents from each class (opioids and NSAIDs) were selected to simplify data collection and result interpretation by reducing the number of comparisons. Potential differences in clinical performance between the drugs of each class were accounted for with a range of sensitivity analyses.

Clinical data on efficacy and safety from randomized clinical trials,^{10–12,36,37} a meta-analysis of opioid dependence³⁸ and a long-term study of celecoxib³⁷ were weighted with preferences from a discrete choice experiment in patients with OA only, chronic lower back pain only or both.³⁹ The overall analysis approach for the qBR was adapted from Postmus et al¹⁷ (Figure 1). As a first step, using structured benefit-risk assessment principles and attribute preferences elicited from a representative population, attributes were selected that could differentiate the included treatment options. Next, source data were extracted from published articles^{10–12,36–38} and the discrete choice experiment,³⁹ organized using the effects table framework⁴⁰ and mapped into clinical value scores. Finally, qBR assessment was performed using multicriteria decision, stochastic multicriteria acceptability and predicted choice probability analyses.

FIGURE 1 Schematic of the comparative benefit-risk approach. The overall analysis approach for the quantitative benefit-risk assessment was adapted from Postmus et al.¹⁷ First, based on structured benefit-risk assessment principles and using attribute preferences elicited from a representative population, favourable (PGA-OA) and unfavourable (opioid dependence, nonfatal MI and joint safety [RPOA 2]) attributes were selected that can differentiate the included treatment options. Next, source data were extracted from published articles and the discrete choice experiment, and organized in the effects table framework, with favourable and unfavourable attributes mapped into clinical value scores for efficacy (OA symptom relief) and safety (dependence, cardiovascular safety and joint safety). Finally, quantitative benefit-risk assessment was performed using multicriteria decision, stochastic multicriteria acceptability and predicted choice probability analyses. CV, cardiovascular; MI, myocardial infarction; OA, osteoarthritis; PGA-OA, Patient Global Assessment of Osteoarthritis; RPOA 2, rapidly progressive osteoarthritis type 2



2.1 | Selecting the attributes

Favourable and unfavourable attributes for the qBR were identified in focus groups with 32 patients as being the most important when choosing a treatment for chronic pain³⁹ and following good practice.⁴¹ Briefly, Patient Global Assessment of Osteoarthritis (PGA-OA) was included as a favourable effect because it was a co-primary endpoint in the pivotal NGFi trials¹⁰⁻¹² and because it includes all aspects of how the disease and treatment affect OA patients, including pain and function. Opioid dependence, nonfatal MI and RPOA 2 leading to total joint replacement (RPOA 2) were included as risks because they are the main drivers of the benefit-risk balance for opioids, NSAIDs and NGFis.⁴²⁻⁴⁴ The description of each attribute that was presented to patients in the preference elicitation survey is included in the Supporting Information.³⁹

2.2 | Selecting the data

Clinical data on the four selected favourable (PGA-OA) and unfavourable (opioid dependence, nonfatal MI and RPOA 2) attributes

for the five treatment options and the scale ranges that were calibrated for valuing clinical data and supporting sensitivity analyses are summarized in Table 2.

PGA-OA data were derived as much as possible from studies of similar design, namely, tanezumab studies NCT02697773, NCT02709486 and NCT02528188 for NGFi, using the weighted mean treatment effects of the summed data, and NCT02528188 for NSAIDs. These studies were phase 3 randomized, double-blind, controlled, multicenter studies of the long-term safety and efficacy of tanezumab in subjects with osteoarthritis of the hip or knee.

As there was insufficient PGA-OA data for opioids within the NGFi clinical program, the equivalent of PGA-OA data for opioids was obtained from the literature. The literature review identified only one high-quality published study in a similar trial population of a similar duration that reported high-quality efficacy data for oxycodone in moderate to severe OA pain. Oxycodone is commonly prescribed for moderate-to-severe OA pain and was therefore selected to represent opioid efficacy. The most important unfavourable effect of NGFi to patients was joint safety, the primary safety risk for tanezumab. Clinical performance data for RPOA 2 were obtained from pooled, exposure-adjusted, tanezumab OA studies NCT02697773,

NCT02709486 and NCT02528188, which included adjudicated RPOA 2 outcomes.

The most important unfavourable effect of NSAIDs was nonfatal MI. NSAIDs data on nonfatal MIs were obtained from the Adenoma Prevention with Celecoxib trial.³⁷ Celecoxib was used to represent NSAID clinical performance because this study provided long-term, placebo-controlled, cardiovascular safety data from a population of patients without elevated risk for cardiovascular events, like OA. An extensive survey of available published data did not identify alternative data that were of higher quality, and findings from other studies were consistent with cardiovascular data from this trial. Pooled results from celecoxib 200 mg BID and 400 mg BID regimens were used. An assumption was made that nonfatal MI rates for tanezumab and opioids were similar to the general population because these treatments are not associated with increased risk of cardiovascular events. The placebo rate in the colorectal adenoma prevention trial was used to approximate the nonfatal MI rates for tanezumab and opioids.

Opioid dependence data for the primary analysis were based on a pooled meta-analysis³⁸ of 12 homogenous studies measuring dependence or abuse in the pain population. A sensitivity analysis explored other possible dependence rates informed by Vowles et al⁴⁵ and a retrospective observational cohort study (data on file). The cohort study used only 2008-2018 electronic claims from Optum Clinformatics Data Mart, an integrated US research database of enrollment, inpatient and outpatient medical claims, pharmacy claims and laboratory results. This study did not access medical records. The study population ($n = 81,909$) was defined as patients diagnosed with OA who have used at least two different nonopioid analgesics and the absence of any opioid medication (opioid cohort) or absence of diclofenac dispensation 24 months prior to the index date (nonopioid cohort).

Patient preference data were collected with a discrete choice experiment (DCE) reported elsewhere.³⁹ The patient preference study included both OA and CLBP patients, but the study population was similar to NGFi pivotal clinical trials in terms of demographics and clinical characteristics. Preferences did not significantly differ across baseline disease state, namely, OA only, chronic lower back pain only or both.³⁹ Preference data from the overall population were therefore used for this quantitative benefit-risk analysis.

2.3 | Estimating clinical value

Clinical data for the selected favourable and unfavourable attributes were mapped to value scores using value functions (see Supporting Information for details). For each attribute, the value function measured the clinical relevance of data on a scale from 0 (least) to 1 (most) for the performance for each drug treatment.

Values scores ranged between 0 and 1, where 0 reflected the least and 1 reflected the most value. Scale ranges for each value function were calibrated to encompass the range of clinical data needed for sensitivity analysis.⁴⁵ Preference weightings from the patient preference study³⁹ were rescaled by normalizing weightings to sum to

unity. Linear value functions were selected because they approximated results from the patient preference study. This process mapped attribute performance into value scores such that:

- a greater reduction in PGA-OA generates a higher OA symptom relief score
- a lower incidence of RPOA 2 generates a higher joint safety score
- a lower incidence of dependence generates a higher dependence safety score
- a lower incidence of nonfatal MI generates a higher cardiovascular safety score.

Weightings were derived in two steps: (i) rescaling and (ii) calculating proportional weightings for each attribute. DCE results were rescaled to ease interpretation of the qBR results without changing the actual trade-offs expressed by the weightings. This needs to be done because the attribute levels in the DCE spanned a wider range than the clinical data. Details of the scale mappings per attribute were as follows:

- The PGA-OA scale was reduced from the three-step DCE scale (ie, from “poor” to “very good”) to a one-step value scale (ie, from “poor” to “fair”) that assumed that the baseline PGA-OA was “poor” (ie, $-1-0$) for all patients.
- The joint safety scale was reduced from the DCE scale (ie, 0-4%) to the scale used for the qBR (ie, 0-1.5%).
- MI was not rescaled because the DCE scale (0-0.5%) aligned with the clinical data (0.14-0.44%).
- The dependency scale was reduced from the DCE scale (ie, 0-25%) to the scale used for the qBR (ie, 0-15%).

Patient weightings were derived by calculating the proportion of the attribute's importance relative to the total amount of importance placed on all attributes shown in Table 1.

2.4 | Analysing quantitative benefit-risk

Preference weightings were combined with clinical value scores to assess the patients' weighted net benefit-risk of the treatment options.¹⁷ The weighted net benefit-risk computation used a simple additive model that summed the product of each attribute's weightings and value.²⁸ This gave the partial benefit-risk contribution for each treatment effect. The weighted net benefit-risk was the sum of the partial contributions from all attributes.

Three sensitivity analyses were performed on the clinical data, preference data and the definition of pain and symptom relief. A one-way sensitivity analysis was performed on the opioid dependence rate. Opioid dependence was isolated for sensitivity analysis because reported rates varied widely, from 0.337% (data on file) to 9.8%.⁴⁵ A one-way sensitivity analysis on patient preference weighting of joint safety was performed to identify the weight needed to change the most preferred treatment from lower dose NGFi to opioid. A structural sensitivity analysis was performed by changing the definition of

TABLE 1 Patient characteristics at baseline

Characteristic	Full preference study population n = 602 ^e	OA only preference study population n = 201	NGFi clinical trial population ^b		
			NCT 02697773 ^b n = 696	NCT 02709486 ^c n = 849	NCT 02528188 ^d n = 2996
Age (years), mean	63.7	65.7	60.8	64.9	60.6
Sex, %					
Male	40.9	34.8	34.9	30.9	34.8
Female	59.1	65.2	65.1	69.1	65.2
Ethnicity, %					
African American	3.7	2.5	22.0	0.0	17.2
Asian	1.5	1.5	3.7	12.5	10.1
Caucasian/White	94.0	94.0	72.4	87.2	70.0
Other	4.5	7.0	1.9	0.4	2.7
WOMAC pain subscale score, mean	6.4	6.6	7.2	6.6	7.0
Disease duration (years), mean	9.3	7.5	8.8
OA diagnosed ≥5 years ago, (%)	50.0	53.2
PGA-OA, n (%)	n = 537	n = 179	n = 696	n = 847	n = 2996
Very good	5 (0.9)	0 (0.0)	0 (0.0)	1 (0.1)	0.1
Good	26 (4.8)	9 (5.0)	1 (0.1)	1 (0.1)	0.5
Fair	157 (29.2)	56 (31.3)	403 (57.9)	413 (48.8)	57.5
Poor	229 (42.6)	70 (39.1)	255 (36.6)	375 (44.3)	37.0
Very poor	120 (22.3)	44 (24.6)	37 (5.3)	57 (6.7)	5.0

Abbreviations: NGFi, nerve growth factor inhibitor; OA, osteoarthritis; PGA-OA, Patient Global Assessment of Osteoarthritis; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

^aBaseline values.

^bSource: Schnitzer et al.¹⁰

^cSource: Berenbaum et al.¹¹

^dSource: NCT02528188¹²

^eSource: Turk et al.³⁹

pain and symptom relief from PGA-OA to the Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain and WOMAC Physical Function Subscales,¹ which were co-primary efficacy endpoints in the clinical trials.^{10,11}

Two additional stochastic analyses were performed to assess the effects of the inherent statistical variability in clinical effect estimates and imprecision in patient preference data. First, a multiway sensitivity analysis on all clinical data using a stochastic multicriteria acceptability approach²⁸ was applied to calculate the probability of rankings for the treatment options. For the stochastic multicriteria acceptability approach, 10 000 iterations were run, providing 0.01 precision with 95% confidence for the rank probabilities.²⁸ The first rank probability describes the chances of a given treatment having the highest weighted benefit-risk score for the average patient, while accounting for uncertainty in the clinical effect estimates. The distributions used for the stochastic multicriteria acceptability analysis are shown in

Supporting Information Table S2. Second, the effect of imprecision in patient preference data was assessed by estimating predicted choice probabilities, which describe the probabilities of an average patient preferring treatment profiles consisting of mean clinical effects, while accounting for imprecision in the patient preference estimates.⁴⁶

3 | RESULTS

3.1 | Patient characteristics

The preference study was completed by 601 patients of which 201 had OA only. All patients had complete data as only fully completed preference surveys were considered for analysis. The NGFi clinical programme included studies NCT02697773 (n = 696 patients), NCT02709486 (n = 849 patients) and NCT02528188 (n = 2996 patients). In all studies, the mean age was 60-65 years, the majority of patients were female (59-69%), mean WOMAC Pain Subscale scores were 6.4-7.2 (indicating moderate to severe pain⁴⁷), most patients (>94% in each study) had a fair to poor PGA-OA and most were

TABLE 2 Preference weighting and clinical value scores for each treatment option

Clinical measure	DCE scale	Quantitative benefit-risk scale	Proportional weighting ^{a,b}	NGFi lower dose	NGFi higher dose	NSAID	Placebo	Opioid
Benefits								
PGA-OA, LS mean \pm SE change from baseline at week 16 ^b	Poor to very good	OA symptom relief: fair (-1) to poor (0) ^b	0.486	-0.90 \pm 0.03 ^{c,d,e}	-0.94 \pm 0.03 ^{c,d,e}	-0.94 \pm 0.04 ^e	-0.64 \pm 0.05 ^{c,d}	-0.80 \pm 0.05 ^{c,d,f,h}
Risks								
RPOA 2	0-4%	Joint safety: 0-1.5%	0.050	0.42 ^{c,d,e,g}	1.36 ^{c,d,e}	0.10 ^e	0 ^{c,d}	0
Nonfatal myocardial infarction	0-0.5%	Cardiovascular safety: 0-0.5% ^g	0.131	0.14 ⁱ	0.14 ⁱ	0.44 ^j	0.14 ⁱ	0.14 ⁱ
Opioid dependence	0-25%	Dependence: 0-15%	0.333	0	0	0	0	4.70 ^k

Abbreviations: DCE, discrete choice experiment; LS, least squares; NGFi, nerve growth factor inhibitor; NSAID, nonsteroidal anti-inflammatory drug; PGA-OA, Patient Global Assessment of Osteoarthritis; RPOA 2, rapidly progressive osteoarthritis type 2; SE, standard error.

^aSource: Turk et al.³⁹

^bProportional weightings for an improvement from worst to best score in each attribute were derived by calculating the proportion of the attribute's importance relative to the total amount of importance placed on all attributes.

^cAssumed a baseline PGA-OA of "poor" for all patients.

^dSource: NCT02697773¹⁰

^eSource: NCT02709486¹¹

^fSource: NCT02528188¹²

^gExposure-adjusted.

^hSource: Afiliato et al.³⁶

ⁱM1 risk was not rescaled because the scale used in the discrete choice experiment (0-0.5%) aligned with the clinical data (0.14-0.44% of patients).

^jSource: Solomon et al.³⁷

^kSource: Higgins et al.³⁸

FIGURE 2 Net benefit-risk scores of osteoarthritis treatment options (Supporting Information Table S1). Safer, more efficacious treatments score higher than treatments with less safety and efficacy. The contribution to net benefit from a given attribute is the same when two treatments' comparative clinical performance on that attribute is equal. MI, myocardial infarction; NGFi, nerve growth factor inhibitor; NSAID, nonsteroidal anti-inflammatory drug; PGA, Patient Global Assessment; RPOA 2, rapidly progressive osteoarthritis type 2

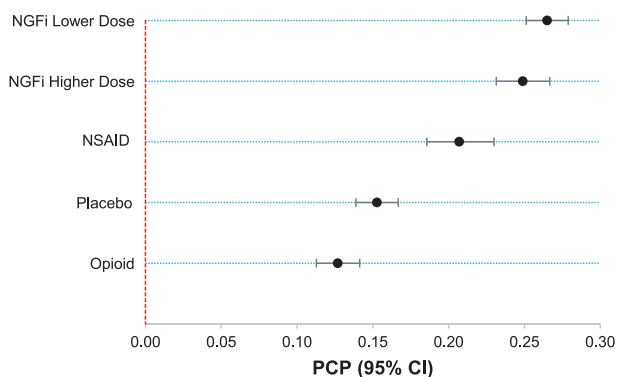
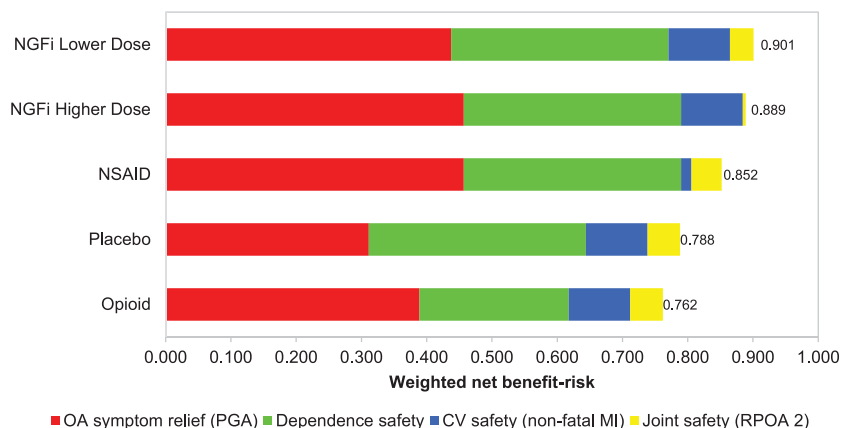


FIGURE 3 Sensitivity analysis: effect of imprecision in patient preference estimates. One-way sensitivity analysis was conducted on patient preference weighting of joint safety (rapidly progressive osteoarthritis type 2). CI, confidence interval; NGFi, nerve growth factor inhibitor; NSAID, nonsteroidal anti-inflammatory drug; PCP, predicted choice probability

white/Caucasian, although the proportions were lower in the three clinical trials (70-87%) than in the preference study (94.0%) (Table 1).

3.2 | Quantitative benefit-risk analysis

Clinical data for the selected favourable (PGA-OA) and unfavourable attributes (rates of opioid dependence, RPOA 2 and nonfatal MI) were mapped to clinical value scores (OA symptom relief, dependence, cardiovascular safety and joint safety) to represent the value of a given clinical performance on a scale ranging from 0 (no value) to 1 (maximum value) (Table 2). Treatments with the same clinical performance have equal scores on those attributes, like cardiac safety for non-NSAIDs and dependence safety for nonopioid treatments. Scores were then weighted with preference weightings to calculate the net benefit-risk scores presented in Figure 2 and Supporting Information Table S1. The highest weighted net benefit-risk score (0.901) was for lower-dose NGFi and the lowest (0.762) was for opioids. The score was higher for lower-dose NGFi than opioids because of more

favourable efficacy (least-squares mean change from baseline at week 16: 0.9 vs -0.8) and dependence risk (incidence rate 0% vs 4.7%), which countered the higher unfavourable joint safety rate (incidence rate 0.42% vs 0%). Sensitivity analysis showed that the benefit-risk score for lower-dose NGFi was stable over a wide range of patient weightings for joint safety and that the weighting for joint safety would need to increase by 7.2-fold before opioids would outrank lower-dose NGFi (Supporting Information Figure S1). Lower-dose NGFi was the highest ranked treatment alternative, predicted choice probability of 0.26 (95% confidence interval [CI] 0.25-0.28) vs 0.21 (95% CI 0.19-0.23) for NSAIDs, even when accounting for imprecision in all patient preference estimates (Figure 3) or assuming a low incidence of opioid dependence (Supporting Information Figure S2).

Sensitivity analysis for uncertainty in clinical data showed that lower-dose NGFi had the highest probability (46%) of being the highest ranked treatment and a 75% chance of being the highest or second-highest ranked treatment (Figure 4). NSAIDs had the second-highest probability (20%) of being the highest ranked, whereas opioids had a 0% chance of being the highest ranked. Replacing PGA-OA with the WOMAC Pain Subscale or the WOMAC Physical Function Subscale resulted in a similar ordering of the treatment alternatives and little change in the relative differences between them (Supporting Information Figure S3). When using the WOMAC Pain Subscale or the WOMAC Physical Function Subscale as the favourable attribute, the weighted net benefit-risk score of lower-dose NGFi remained stable over a wide range of patient weightings for joint safety (Supporting Information Figure S4).

4 | DISCUSSION

This study used a multimethod qBR approach to show how patient preference data and clinical data can be combined to rank treatment options with differing benefit-risk profiles to supplement medical product decision making. The study also showed that the multimethod approach can address the limitations and uncertainties of the data, including variability in clinical data and imprecision in preference data.²⁶⁻²⁸

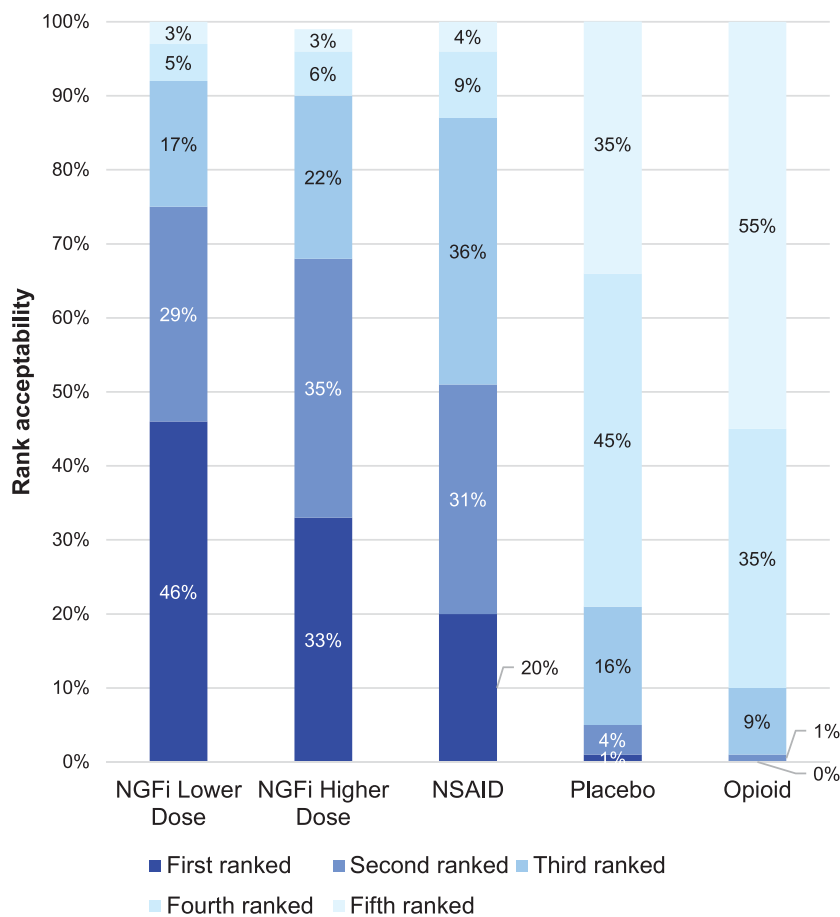


FIGURE 4 Sensitivity analysis: uncertainty in clinical effect estimates. Uncertainty in all clinical data was tested simultaneously using stochastic multicriteria acceptability analysis. Shown are the probabilities of each ranking for each treatment. NGFi, nerve growth factor inhibitor; NSAID, nonsteroidal anti-inflammatory drug

As a first step of the multimethod qBR, standard approaches were used to select the favourable and unfavourable attributes that were most important to patients. For the current study, PGA-OA was selected over WOMAC, another efficacy endpoint used in the OA clinical trials,⁴⁸ because it captured pain and function in a single measure. Opioid dependence, nonfatal MI and joint safety were included as unfavourable attributes because they are the primary safety concern for the three treatment options⁴²⁻⁴⁴ and because they were identified in focus groups and a quantitative preference study as being most important to patients.³⁹

A strength of the current analysis is that the preference weights that inform the analysis were collected from a large patient preference study in a similar patient population and do not rely on assumptions made by healthcare professionals. This approach enables clinical performance data to be interpreted from the patient perspective which can be informative for drug approval decision making. A potential limitation is that the analysis included only one unfavourable attribute from each treatment class, possibly missing other attributes that may be important to other stakeholders. The preference study identified the most important attributes to patients. Had other attributes been included, data requirements would increase without contributing insights to the model because the other attributes were of minor importance to patients. Additionally, other types of attributes, such as convenience or mode of

administration, which can inform the benefit-risk assessment of a drug, were not included in this analysis.

Another potential limitation of the analysis was the lack of head-to-head data. The clinical safety data for the different treatments were from multiple studies with different designs, durations, comparators and endpoints. In particular, the reported rates of opioid dependence vary widely. However, the multimethod qBR described here allows the effect of such uncertainties to be explored systematically in sensitivity analyses. Sensitivity analyses showed that the conclusions were stable across a wide range of reported rates of opioid dependence and when simultaneously considering the inherent statistical variability in all clinical effect estimates.

The study demonstrated that a multimethod qBR assessment (a combination of structured benefit-risk assessment,¹⁷ multicriteria decision, stochastic multicriteria acceptability and predicted choice probability analyses) enabled a holistic comparison of treatment alternatives by taking into account uncertainties and imprecision in clinical performance and weights informed by one stakeholder, the patient. The results are applicable to other stakeholders, for example regulators for whom quantitative approaches are increasingly being used to inform benefit-risk decision-making.⁴⁹⁻⁵¹ Rather than replacing human judgment or dictating a solution, these methods aggregate information to foster deliberation and support equitable and transparent benefit-risk decision making.

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CONTRIBUTORS

All authors helped to write or made substantive comments on the manuscript, approved the final version submitted and agreed to be accountable for it. In addition, J.D.M. contributed to study interpretation, T.T. contributed to study design and interpretation, J.M., E.W. and R.J. contributed to study conception, design, conduct, analysis and interpretation, K.B. contributed to study conception, design, conduct, data collection and interpretation, and B.H. contributed to the collection of the patient preference data and interpretation.

DATA AVAILABILITY STATEMENT

Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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