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Methadone administration and QT interval prolongation: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Methadone is a long-acting opioid used to treat opioid use disorder, cancer pain and provide perioperative analgesia. Methadone administration has been associated with QTc interval prolongation and consequently an increased risk of ventricular arrhythmias. This mechanism appears to be mediated by HERG channel inhibition, drug–drug interactions and genetic susceptibility. This protocol describes the methodology for a systematic review and meta-analysis aiming to evaluate the association between methadone administration and QTc prolongation and estimate the odds of major cardiac events. Our leading hypothesis is that methadone exerts a dose-dependent and time-dependent effect on QT prolongation.

Methods and analysis We will conduct a systematic literature search of randomised controlled trials, prospective and retrospective cohort studies and case–control studies involving adult or paediatric patients receiving oral or intravenous methadone for opioid use disorder, cancer-related pain and surgical pain. Searches will be performed in Ovid MEDLINE, Ovid Embase, Cochrane CENTRAL, Web of Science and ClinicalTrials.gov. The primary outcome will be QTc interval length (in milliseconds). Secondary outcomes will include odds of clinically significant QTc prolongation and major adverse cardiac events. Comparator groups will include baseline pre-methadone QTc measurements and an external control group not exposed to methadone. Random-effects meta-analyses will be conducted, reporting mean differences with 95% CIs. Prespecified subgroup analyses based on methadone dose and duration of exposure will be performed when feasible. Risk of bias will be assessed using the Cochrane Risk of Bias 2 tool for randomised studies and Risk Of Bias In Non-Randomised Studies-of Interventions for non-randomised studies. The certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Ethics and dissemination Ethical approval is not required. We will include data obtained exclusively from previously published peer-reviewed studies available in reputable databases. The results of this study are intended for dissemination via publication in a peer-reviewed journal.

PROSPERO registration number CRD420251143441.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To enhance clinical interpretability and avoid inappropriate pooling, analyses will be stratified by methadone clinical indication (opioid use disorder, cancer pain and surgical pain), acknowledging fundamental differences in dosing, duration of exposure and patient populations.
⇒ Evaluating the QTc interval as a continuous outcome allows more precise quantification of methadone cardiac electrophysiological effects, while secondary outcomes using pre-established QTc thresholds improve clinical relevance.
⇒ Prespecified subgroup analyses based on methadone dose and duration of exposure directly address the primary biological hypothesis of dose-dependent and time-dependent QTc prolongation and may strengthen causal inference.
⇒ Much of the existing literature consists of retrospective or non-randomised studies with limited adjustment for confounding, which may introduce bias and require downgrading the overall certainty of the evidence.
⇒ Important modifiers of QTc prolongation risk, including drug interactions and pharmacogenomic variability, are inconsistently reported across studies and represent a challenge to be incorporated into the analysis.

INTRODUCTION

Methadone is an μ-opioid receptor agonist with a prolonged half-life that has remained the standard of care for maintenance therapy of opioid use disorder (OUD) since the 1960s.[1–4] Methadone is effective in reducing withdrawal symptoms,[5] reducing opioid abuse[6] and improving mortality rates.[7] Due to its pharmacological activity as a μ-opioid agonist, N-methyl-D-aspartate receptor antagonist and serotonin transporter antagonist, methadone has also been used to treat chronic cancer pain.[8] In more recent decades, the indication of methadone has expanded to treating surgical pain.[9–15]

Methadone has been associated with an increased risk of QTc interval prolongation and subsequent development of ventricular arrhythmias.[16] Krantz *et al* published in 2002 a case series of 17 patients treated

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with methadone who experienced torsade de pointes.[17] Another study, including 247 hospitalised patients with active or past history of intravenous drug use, found that patients on chronic methadone therapy (median dose 100 mg/day) had a significantly higher prevalence of QTc greater than 500 ms, compared with controls not receiving the medication (16.2% vs 0%).[18] In that report, 3.6% of the methadone treated patients presented in-hospital torsades de pointes.[18] Based on those and other published reports, expert guidelines have emphasised periodic electrocardiographic monitoring in patients receiving chronic methadone therapy because of the association with QT prolongation and an increased risk of ventricular arrhythmias.[17–21] Contrarily, studies investigating lower methadone dosages have shown no clinically relevant increase in QTc interval.[22 23] A recent systematic review by Mercadante reported that evidence of methadone-induced QTc prolongation in patients with cancer chronic pain is limited and that doses usually used to treat chronic pain may not require electrocardiographic monitoring.[24]

Because of the limitations of the current evidence, a systematic review and meta-analysis will offer a rigorous approach to evaluate the association of methadone and QTc prolongation. It will also serve to estimate the risk of major cardiac events in patients treated with methadone. Our leading hypothesis is that methadone exerts an effect on QT prolongation, which is dose-dependent and time-dependent.

METHODS

Protocol and registration

This protocol for a systematic review and meta-analysis follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. A prospective version of the protocol was registered in PROSPERO (CRD420251143441), and any modifications will be updated through this online register.

Eligibility criteria

Our study will include inpatient and outpatient adult and paediatric patients receiving oral or intravenous methadone for OUD, cancer pain, surgical pain and any other indication. We will use two comparator groups: (1) an internal control in which baseline measurements prior to methadone initiation will be used as the control group, and (2) an external control group comprising patients not receiving methadone, including other opioids or a placebo. The primary outcome is QTc interval length (in milliseconds). The secondary outcome is the odds of major cardiac events (defined as ventricular tachycardia, ventricular fibrillation or sudden cardiac death) and the odds of clinically relevant QT interval prolongation (defined as QTc >500 ms, > 25% increase from baseline or >60 ms increase from baseline).[25]

Studies eligible for inclusion will be randomised controlled trials (RCTs), prospective and retrospective cohort studies, and case–control studies reporting the primary or secondary outcome in adult or paediatric patients receiving methadone, compared with either baseline QT interval prior to methadone initiation or with patients not receiving methadone (ie, other opioids or placebo). Both studies providing raw data and those reporting effect estimates will be considered eligible for inclusion. We will exclude preclinical studies, case reports, case series, abstracts, studies without full-text availability in English or Spanish, and non-peer-reviewed studies.

Information sources and search strategy

We performed a comprehensive systematic search adhering to the PRISMA-S1 for Searching checklist. We searched Ovid MEDLINE, Ovid EMBASE, Cochrane Central, Web of Science and ClinicalTrials.gov from 1 January 1970 to 21 October 2025. Search strategies, subject headings and keywords were tailored to each database by a medical research librarian with expertise in systematic reviews, in consultation with the clinical study team. The full search strings are available in tables 1–3. Searches were limited to human studies and English or Spanish language articles. Deduplication of references was performed manually in EndNote.

Selection process and data collection

Covidence software will be used to perform study screening and selection. To identify eligible studies, two investigators will independently conduct initial screening of titles and abstracts, followed by a full-text review of eligible reports. Disagreements will be resolved by a third reviewer. A PRISMA flow diagram will be used to summarise the study selection process.

Data from individual studies will be collected by two authors using a pre-elaborated Excel spreadsheet, including: (1) Study characteristics (first author, year of publication, study design and country of origin), (2) sample characteristics (sample sizes, age and sex in both the methadone and control groups), (3) methadone administration characteristics (methadone indication, methadone dose and length of methadone administration), (4) QTc interval measurement characteristics (QTc formula used; Bazett or Fridericia and method of QTc measurement; manual or automated), (5) results of included studies (QTc length) and (6) secondary outcomes (odds of QTc prolongation and odds of malignant arrythmias or sudden cardiac death). A third author will perform a validity assessment of the data extraction process.

Risk of bias and quality of evidence assessment

Two investigators will independently assess the risk of bias. The Cochrane Risk of Bias 2 (RoB 2) tool[26] will be used for RCTs, and the Risk Of Bias In Non-Randomised Studies-of Interventions (ROBINS-I)[27] tool for observational studies. The RoB 2 tool will be used to assess biases related to randomisation, deviations in interventions, missing outcome data, outcome measurement and

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Table 1 Ovid Embase search string

Ovid Embase search string	
1	QTc Interval/
2	("QT-interval*" or "long QT syndrome" or "long QT" or "prolonged QT" or "QT prolongation" or "QTc prolongation").ti,ab.
3	((QT or QTc) ADJ (abnormal or assessment or changes or effect* or extend* or interval* or lengthen* or prolonged or prolongation or time)).ti,ab.
4	QTC.ti.
5	OR/1-4
6	Methadone/
7	(methadon* or dolophine or physeptone or symoron or methaddict or adanon or phenadone or amidone or heptadon or ketalgin or miadone or metasedin or wesadone).ti,ab.
8	OR/6-7
9	(exp Animal/ or exp Animal Model/ or exp Animal Experiment/ or Experimental Animal/ or Nonhuman/ or "In Vitro Study"/) not exp Human/
10	(amphibian* or animal? or bird or birds or bovine or canine or cat or cats or cattle or cow or cows or dog or dogs or ferret* or fish or frog* or "guinea pig*" or hamster* or horse* or "in vitro" or lambs or llama* or marmoset* or mice or monkey* or mouse or murine or pig or pigs or piglets or porcine or primate or primates or rabbit* or rat or rats or sheep or swine or trout* or veterinar* or zebra*).ti.
11	OR/12-13
12	11 OT 14
13	Abstract.pt. or Overall/ (a collection of abstracts)
14	Abstract Report/ (used incorrectly)
15	Book/ or Book.pt.
16	Exp Biography/ or biograph*.ti.
17	(book and review*).ti.
18	AND/5,8
19	Limit 9 to (English or Spanish)
20	Limit 10 to yr="1970-current"
21	Case Report/ or Case Reports/
22	Chapter/ or Chapter.pt.
23	Conference/ or Conference.pt.
24	Conference Paper/ or Conference Paper.pt.
25	Conference Review.pt.
26	Exp "Congresses as Topic"/
27	Consensus Development/
28	Exp Clinical Protocol/ or Clinical Trial Protocol/
29	Exp Conference Abstract/ or Conference Abstract.pt.
30	Exp Conference Paper/
31	Editorial/ or Editorial.pt.
32	Feasibility Study/
33	Exp Interview/
34	Exp Practice Guideline/
35	Exp Review/ or review.pt.
36	Short Survey/
37	Validation Study/
38	(abstract* or "annual meeting" or "case report" or "case series" or comment* or conference or congress or editor* or feasibility or "in vitro" or letter or "meta-analysis" or meeting or paper* or poster* or proceeding* or protocol or symposium or validation).ti.
39	OR/16-38
40	15 NOT 39 (retrieves 218)
41	("19392907" or "16801510" or "16877186" or "15857742" or "20597697" or "25644980" or "18071169").pm.
42	40 and 41

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Table 2 Ovid MEDLINE search string

Ovid MEDLINE search string	
1	Long QT Syndrome/
2	("QT-interval*" or "long QT syndrome" or "long QT" or "prolonged QT" or "QT prolongation" or "QTc prolongation").ti,ab.
3	((QT or QTc) ADJ (abnormal or assessment or changes or effect* or extend* or interval* or lengthen* or prolonged or prolongation or time)).ti,ab.
4	QTC.ti.
5	OR/1-4
6	Methadone/
7	(methadon* or dolophine or physeptone or symoron or methaddict or adanon or phenadone or amidone or heptadon or ketalgin or miadone or metasedin or wesadone).ti,ab.
8	OR/6-7
9	AND/5,8
10	Limit 9 to (English or Spanish)
11	Limit 10 to yr="1970-current"
12	(exp Animals/ NOT humans.sh.)
13	(amphibian* or animal? or bird or birds or bovine or canine or cat or cats or cattle or cow or cows or dog or dogs or ferret* or fish or frog* or "guinea pig*" or hamster* or horse* or "in vitro" or lambs or llama* or marmoset* or mice or monkey* or mouse or murine or pig or pigs or piglets or porcine or primate or primates or rabbit* or rat or rats or sheep or swine or trout* or veterinar* or zebra*).ti.
14	OR/12-13
15	11 OT 14
16	Case reports/
17	Clinical Trial Protocol/
18	Exp Congress/
19	Exp "Congresses as Topic"/
20	Editorial/
21	English Abstract/
22	Exp Historical Article/
23	Overall/
24	Exp Review/
25	Validation Study/
26	Video-Audio Media/
27	(abstract* or "annual meeting" or "case report" or "case series" or comment* or conference or congress or editor* or feasibility or "in vitro" or letter or "meta-analysis" or meeting or paper* or poster* or proceeding* or protocol or symposium or validation).ti.
28	OR/16-27
29	15 NOT 28 (retrieves 218)
30	("19392907" or "16801510" or "16877186" or "15857742" or "20597697" or "25644980" or "18071169").ui.
31	29 and 30

Table 3 Web of Science and Cochrane search strings

Database	Search string
Web of Science	**Title:** (QT or QTc) AND (abnormal or assessment or changes or effect* or extend* or interval* or lengthen* or long or prolonged or prolongation or syndrome or time) **AND** methadon* or dolophine or physeptone or symoron or methaddict or adanon or phenadone or amidone or heptadon or ketalgin or miadone or metasedin or wesadone
Cochrane	**Title, Abstract, Keyword:** (QT or QTc) AND (abnormal or assessment or changes or effect* or extend* or interval* or lengthen* or long or prolonged or prolongation or syndrome or time) **AND** methadon* or dolophine or physeptone or symoron or methaddict or adanon or phenadone or amidone or heptadon or ketalgin or miadone or metasedin or wesadone

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reported results. Domain 4 of the RoB 2 tool and Domain 6 of the ROBINS-I tool, which evaluate bias arising from outcome measurement, will allow assessing the risk of bias for studies relying on automated QTc measurements, given their potential susceptibility to measurement inaccuracy.[28] Overall risk of bias will be categorised as low, moderate or high, based on the highest risk rating among individual domains. Discrepancies will be resolved by a third reviewer.

One investigator will grade the quality of evidence using the Evidence-based Practice Center programme guidelines.[29] A second investigator will review the assessment, and any disagreement will be resolved through discussion.

Statistical analysis

We will perform a quantitative analysis using R (V.4.2.3, Comprehensive R Archive Network). Studies will be grouped and analysed separately according to methadone indication: (1) OUD, (2) cancer pain, (3) surgical pain and (4) any other indication. For the primary outcome, QTc interval will be studied as a continuous variable (in milliseconds) and estimates will be reported as mean difference (MD) with corresponding measure of variance, comparing: (1) within-group changes from baseline (post–pre) in methadone-treated participants and (2) between-group differences between methadone users and controls not receiving methadone. We will perform a random-effects meta-analysis using a restricted maximum likelihood estimator to pool study-level mean changes in QTc interval following methadone administration and, where available, pooled MDs between methadone and control group, accounting for study heterogeneity among included studies. Studies evaluating the QTc interval using the Bazett correction formula and those using the Fridericia correction formula will be analysed separately.

Risk of bias will be incorporated into the meta-analysis by adjusting the contribution of each study according to its overall risk of bias. Specifically, multiplicative adjustment factors will be applied to the inverse-variance weights, with factors of 1.0, 0.5 and 0.25 assigned to studies classified as low risk, some concerns and high risk of bias, respectively.[30 31]

When primary studies provide raw data on mean QTc interval length, the MD will be calculated directly to include in the pooled analysis. If studies report exclusively the change in QTc interval or the corresponding MD, these effect estimates will be extracted directly and incorporated into the pooled analysis. When primary studies report continuous outcomes as medians and measures of spread (range and/or IQR) without means and SD, we will apply established transformation methods to estimate the sample mean and SD for inclusion in the meta-analysis. Specifically, we will use the approach of Wan *et al*[32] to estimate SD from median, range and/or IQR, and the method of Luo *et al*[33] to estimate the sample mean from the available quantile information.

Subgroup analysis considering methadone dosing for the methadone indications will be performed (<50 mg/day, 50–100 mg/day, >100 mg/day for OUD[34 35] and ≤0.1 mg/kg, 0.11–0.2 mg/kg, >0.2 mg/kg for surgical pain) and length of methadone administration (<1 month and >1 month for cancer pain and OUD).[36]

For the secondary outcomes, the odds of major cardiac events will be studied as a dichotomous variable. We will calculate ORs, incorporating prospective and retrospective studies, with 95% CIs using a random-effects model. We will also use ORs to evaluate the odds of prolonged QTc (defined as >500 ms, >25% increase from baseline or an absolute increase of >60 ms from baseline).

Results will be interpreted in the context of pooled effect estimates and considering heterogeneity of studies included in the analysis. Statistical heterogeneity will be assessed using the I^2 statistic and Cochran's Q test, with heterogeneity interpreted descriptively and considered potentially important when I^2 exceeds 25% or when the Cochran's Q test yields $p<0.1$. Publication bias will be assessed using a funnel plot, the Egger's regression test and the trim-and-fill method will be applied to assess the potential impact of small-study effects on the pooled estimates.[37]

When quantitative synthesis is not possible due to limited data to pool results or substantial clinical heterogeneity among included studies, data extracted from individual studies will be summarised in evidence tables in accordance with the Synthesis Without Meta-analysis reporting guideline.[38] Studies will be grouped according to methadone indication (OUD, cancer pain, surgical pain or other indications) and comparator used (baseline measurements or non-methadone controls). Both primary and secondary outcomes will be reported, depending on the available evidence. Intervention effects will be included as presented in the original studies. The result synthesis will focus on the direction and magnitude of effect, statistical significance and consistency of findings across studies. Risk of bias will be included for each study and clinical and methodological heterogeneity will be described narratively. Evidence tables will be provided as online supplemental material, with key findings described in the main manuscript.

Planned timeline

The PICOT question was formulated in August 2025. Since, we have completed the literature search, study selection, data extraction and data synthesis. The data analysis and quality assessments will proceed in the following 2 months, with an additional month designated for final revisions, author review and approval prior to submission. We plan to submit the manuscript for publication by September 2026.

Patient and public involvement

None.

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Ethics and dissemination

This systematic review and meta-analysis will exclusively use data from previously published investigations and use reputable databases. Therefore, ethical approval is not required. Our results will be published in a peer-reviewed journal.

DISCUSSION

This systematic review and meta-analysis will evaluate the association of methadone with QTc interval prolongation and ventricular arrhythmias in the different clinical indications of the medication. The findings of our evaluation will provide evidence to guide the use of intravenous methadone in the perioperative period, which is typically given at low dosages, and provide information on dose-dependent effects, mainly in the context of chronic pain and OUD therapy, when dose escalation is frequently involved. We also expect to identify gaps in current research that need to be incorporated in future prospective and retrospective studies.

The design of this systematic review and meta-analysis will account for substantial heterogeneity in the existing literature, particularly regarding: (1) the definitions and thresholds used for clinically relevant QTc prolongation; (2) the choice of QT correction formula (Bazett vs Fridericia); and (3) the method of QTc measurement (automated vs manual). In our study, the primary outcome was the QTc interval (in milliseconds) as a continuous variable. This will allow us to quantify the effect of methadone on the QTc interval compared with baseline. The odds of clinically relevant QTc prolongation, ventricular arrhythmias and sudden cardiac death will be explored as a secondary outcome. Although biological sex differences may warrant the use of sex-specific thresholds for clinically relevant QTc interval prolongation,[39 40] we decided on implementing QTc >500 ms, as this criterion applies to both sexes, increases specificity and is also commonly used across studies evaluating this outcome. Furthermore, we have included an additional definition of QTc prolongation, defined as either a >25% increase from baseline or an absolute increase of >60 ms from baseline,[25] to capture all potential clinically relevant cases of methadone-induced QTc prolongation. Given methodological differences between QT correction formulas,[25] studies using Bazett and Fridericia corrections will be analysed separately. We will also document the method of QTc measurement (automated vs manual). Risk of bias assessment will allow downgrading the quality of evidence for studies relying on automated QTc measurements, which are susceptible to inaccuracy.[28]

Individual studies suggest methadone-induced QTc prolongation is associated with methadone dosing and duration of use. In a randomised controlled study of 154 patients with OUD, the proportion of subjects receiving methadone at stable doses that experienced prolonged QTc (defined as >470 ms for males and 490 ms for females) increased significantly over time (2% at 4 weeks, 6% at 8 weeks and 21% at 16 weeks).[21] Similarly, a cross-sectional study of 450 patients receiving methadone for OUD found a significant association between methadone dose and QTc interval length (R^2=0.28 in men and R^2=0.12 in women).[41] However, in paediatric cardiac surgical patients, no dose-dependent effect was identified in patients receiving a single intraoperative intravenous methadone dose.[42] The prespecified subanalyses in our study, which account for methadone dose and duration of exposure, will enable evaluation of potential dose-dependent and time-dependent effects across clinical contexts. We do not anticipate performing dose-based subgroup analyses for cancer pain due to highly individualised dosage initiation and titration,[43] and lack of characterisation of dose–response relationship in the QTc interval in patients with cancer pain in the current evidence.[44]

A recent systematic review and meta-analysis evaluated the association between methadone maintenance therapy for OUD and QTc interval prolongation, including 22 observational studies.[45] The authors reported a 34% pooled prevalence of QTc prolongation and a 2% incidence of torsades de pointes. However, their analysis did not include a baseline comparator group nor a control without methadone exposure. Second, QTc interval was not evaluated as a continuous variable, limiting assessment of the magnitude of QTc changes associated with methadone therapy. Our study protocol aims to address these limitations by evaluating both continuous and dichotomous QTc outcomes and by incorporating appropriate control groups. Furthermore, our analysis will include patients receiving methadone for a broader range of indications (ie, surgical pain and chronic pain).

Investigating methadone effect on the QT interval should also consider potential drug interactions. In a case–control study by Antoniou *et al* of 2925 patients who presented sudden cardiac death or ventricular arrhythmia, serotonin reuptake inhibitor use was associated with increased risk of the outcome in patients receiving methadone, compared with those not receiving methadone.[46] This consideration is particularly relevant in the OUD population, where concomitant prescribed medications and substance use may further increase the risk of QTc prolongation.[47] Also, relevant to surgical patients who receive multiple hypnotic medications, sympathomimetics, antibiotics, antihistamines and neuromuscular blocking agents.[48]

We anticipate several limitations in this study. First, heterogeneity in methadone dosing regimens, duration of exposure, QTc measurement techniques and the timing of QTc assessment relative to methadone administration may complicate the pooling and interpretation of the results. To address these limitations, we have prespecified definitions and data extraction procedures for these variables in the current protocol. Additionally, potential sources of heterogeneity, including pooling adult and paediatric patients and outpatient and inpatient populations across studies, will be summarised narratively to

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facilitate interpretation of the pooled estimates. Second, given the nature of the outcome, we will have to carefully evaluate the risk of positive publication bias, as specified in the methods section. Third, evidence for QTc prolongation following methadone administration is mainly derived from non-controlled prospective observational studies or retrospective studies with inadequate reporting or matching of confounding variables will limit the ability to establish causal inference and therefore will downgrade the quality of evidence of our results.

Lastly, we will not be able to incorporate known variables associated with this mechanism, including CYP2B6 or CYP2C19 metabolism phenotype, NOS1AP variants and KCNH2 polymorphism.[49–52] In a cohort study of 179 patients receiving methadone for OUD (mean dose 145 mg/day and mean treatment duration 61 months), individuals with slow CYP2B6 metabolic activity had a longer QTc than extensive metabolisers (439 vs 421 ms).[53] A network meta-analysis may be considered in future research, to evaluate the effect of methadone in the presence of concomitant medications and explore potential drug–drug interactions, including those mediated through cytochrome P450 enzyme competition.

Despite these limitations, we anticipate that this systematic review and meta-analysis will advance understanding of methadone-associated QTc prolongation, provide an objective synthesis of the available evidence and identify critical areas requiring further investigation to optimise the safe administration of methadone across clinical settings.

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Competing interests EDK serves on an Independent Data Monitoring Committee for Vertex Pharmaceuticals, unrelated to the content of this article. All other authors have no competing interest to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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