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Regulatory Toxicology and Pharmacology

Weight-of-Evidence Assessment of Human Carcinogenic Risk from Quinacrine Hydrochloride (QH) Administered Transcervically for Non-Surgical Female Sterilization (QS): An Integrated Assessment Under ICH S1B(R1)

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ABSTRACT

Background: Quinacrine hydrochloride (QH) is a non-surgical method of permanent female contraception (quinacrine sterilization; QS) used safely by more than 200,000 women in 54 countries over nearly five decades. A 2007 FDA clinical hold on a QS Phase III investigation was based principally on uterine tumors observed in a 2-year rat carcinogenicity bioassay at doses 75–106 times the human clinical dose, all associated with severe tissue injury exceeding the maximum tolerated dose (MTD).

Aim: To apply the ICH S1B(R1) integrated weight-of-evidence (WoE) framework to all available nonclinical and human evidence for QH used as QS, to determine whether human carcinogenic potential at QS clinical exposures is unlikely, uncertain, or likely, under current carcinogenicity assessment science.

Methods: A systematic literature search was conducted across PubMed, Embase, and regulatory databases. Evidence was evaluated across six ICH S1B(R1)-specified WoE domains: target biology; secondary pharmacology; genotoxicity; chronic toxicity and carcinogenicity; hormonal/endocrine effects; and immune modulation. All available studies, including the Cancel et al. (2010) rat bioassay, were included and assessed for quality and human relevance.

Results: Nonclinical findings demonstrate false-positive in vitro genotoxicity exclusively at concentrations exceeding ICH S2(R1) cytotoxicity limits (RTG ≤18.5% in MLA; ≥49% MI inhibition in CHO chromosome aberration assay) with consistently negative in vivo genotoxicity, including in the mouse micronucleus test and neonatal mouse carcinogenicity study. The rat 2-year bioassay produced uterine adenocarcinomas exclusively at doses 75–106× the human clinical dose, all with severe tissue necrosis; no carcinogenic signal was observed at MTD-appropriate doses (~3× human dose). Two independent peer-reviewed re-analyses confirmed an injury–inflammation–regeneration mode of action not relevant to QS clinical exposures. Human epidemiologic data from 47,101 QS-treated women (107,548 woman-years) and decades of higher-dose oral QH use show no increased cancer risk, with acknowledged limitations of observational study designs.

Conclusion: Under the ICH S1B(R1) integrated WoE framework, human carcinogenic potential of QH at QS clinical exposures is assessed as unlikely. This assessment supports authorization of a carefully monitored Phase III clinical trial of QS. The term "legacy compound" refers to a compound with an established history of clinical use predating modern carcinogenicity assessment frameworks, as used in ICH S1B(R1) guidance.

Keywords: quinacrine; non-surgical sterilization; contraception; carcinogenicity; weight-of-evidence; ICH S1B(R1); maximum tolerated dose; mode of action; false-positive genotoxicity; clinical hold

1. INTRODUCTION

Quinacrine hydrochloride (QH), an acridine derivative first approved in the United States in 1931 as an antimalarial drug, has been administered to millions of patients in tablet, injectable, and topical forms for malaria prophylaxis, giardiasis, lupus erythematosus, malignant effusions, and other conditions [14]. As an antimalarial agent, US military personnel ingested 100–140 mg QH daily for up to 4 years during World War II without reported increases in malignancy [14]. From the mid-1960s, researchers studied QH as an alternative to surgical tubal ligation: quinacrine sterilization (QS) uses seven 36 mg pellets (total 252 mg) placed transcervically, repeated once at day 28 of the same menstrual cycle (cumulative dose 504 mg). More than 200,000 women in 54 countries have used QS over nearly 5 decades, with no deaths or treatment-related serious adverse events in any published cohort and no increase in cancer incidence across 47,101 QS-treated women in 42 studies from 1977 to 2017 [1].

Regulatory opposition to QS has been based principally on a 2-year rat carcinogenicity bioassay [4]. Since the 2007 clinical hold was imposed, regulatory science has advanced significantly. The ICH S1B(R1) Addendum (2022) provides an integrated WoE framework for evaluating the human relevance of rodent carcinogenicity findings [3]. Two independent peer-reviewed re-analyses of the Cancel et al. (2010) bioassay data, published in this journal, concluded that observed tumors arose through an injury-driven mode of action at doses greatly exceeding the MTD, with no carcinogenic signal at MTD-appropriate doses [9,10]. Modern integrated human-cell carcinogenicity platforms have classified QH as a false-positive in vitro genotoxicant / non-carcinogen [6,7]. QH has also emerged as an investigational anti-cancer agent with demonstrated anti-tumor activity in multiple tumor types [17,27–32].

The aim of this paper is to apply the ICH S1B(R1) integrated WoE framework to QH used as QS — including full consideration of the Cancel et al. (2010) rat bioassay data alongside all other available nonclinical and human evidence — to determine whether human carcinogenic potential at QS clinical exposures is unlikely, uncertain, or likely, and to document this assessment transparently and systematically.

2. METHODS

2.1 Regulatory framework

This assessment was conducted in accordance with ICH S1B(R1) (Addendum to Testing for Carcinogenicity of Pharmaceuticals, 2022) [3], ICH S1C(R2) (Dose Selection for Carcinogenicity Studies), and ICH S2(R1) (Guidance on Genotoxicity Testing and Data Interpretation). The ICH S1B(R1) framework provides a three-pathway determination (human carcinogenic potential: likely, unlikely, or uncertain) based on integrated evidence, as illustrated in Figure 1. This framework was selected because it explicitly addresses how to evaluate the human relevance of existing rodent carcinogenicity data within an integrated WoE context — the direct situation applicable to QH used as QS.

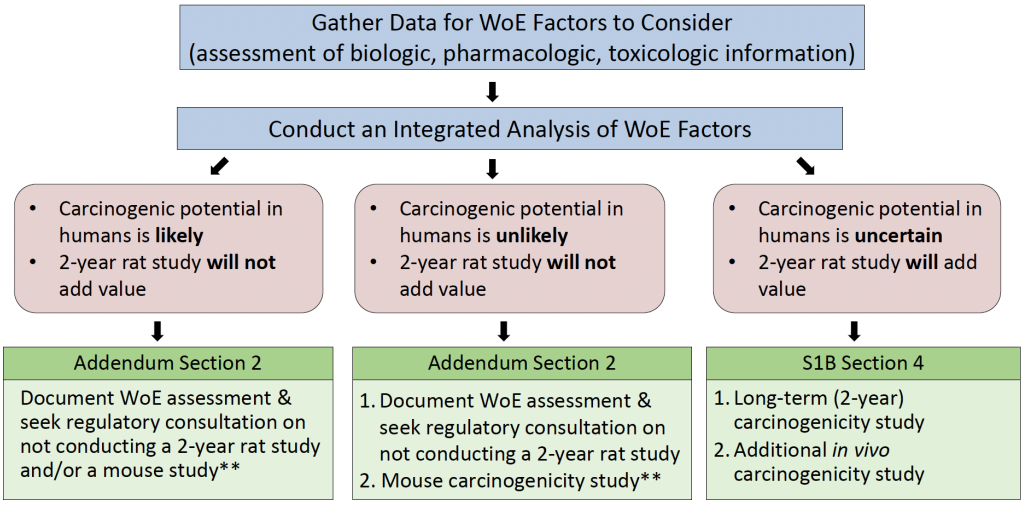

Figure 1. ICH S1B(R1) integrated weight-of-evidence carcinogenicity assessment framework [3], illustrating the three-pathway evaluation used to determine human carcinogenic potential. Pathway 1 (left): potential likely; Pathway 2 (center): potential unlikely — 2-year rat study does not add value; Pathway 3 (right): potential uncertain — 2-year rat study will add value. The integrated WoE assessment for QH used as QS, presented in this paper, supports Pathway 2. The rat 2-year bioassay data are included in the WoE assessment under Addendum Section 2; the conclusion is that their findings, arising through an injury-driven mode of action at doses profoundly exceeding the MTD, are assessed as unlikely to be relevant to human carcinogenic risk at QS clinical exposures.

2.2 Systematic literature search

A comprehensive systematic literature search was conducted in PubMed, Embase, Cochrane, and FDA/ICH regulatory document repositories using the following search terms: quinacrine; mepacrine; quinacrine hydrochloride; quinacrine sterilization; QS; carcinogenicity; genotoxicity; mutagenicity; cancer; tumor; neoplasm; epidemiology; pharmacokinetics; toxicology; endocrine disruption; sterilization; contraception. Date range: inception through January 2026. Inclusion criteria: any study or regulatory document addressing pharmacology, toxicology, genotoxicity, carcinogenicity, epidemiology, pharmacokinetics, endocrine effects, or immune modulation of QH. No language restriction was applied. Reference lists of identified papers were hand-searched. All identified studies relevant to the WoE domains were included. No relevant available evidence was excluded.

2.3 Evidence weighting criteria and statement of falsifying evidence

Evidence was weighted in accordance with established ICH S1B(R1) hierarchical principles. Human epidemiologic data from large, well-conducted cohort and case-control studies were assigned highest weight for human risk assessment. Mechanistic data from multiple concordant in vitro and in vivo systems were assigned high weight when internally consistent. Individual in vitro genotoxicity findings at concentrations substantially exceeding clinical tissue levels and obtained at cytotoxicity levels at or beyond ICH S2(R1)-defined assay limits (within which genotoxic signals are considered unreliable), were assigned lower weight in the context of negative in vivo results, consistent with ICH S2(R1). Animal carcinogenicity findings were evaluated for human relevance using ICH S1B(R1) criteria: mechanistic plausibility, exposure concordance, and species specificity.

In the interest of transparency, the following findings would require modification of the integrated WoE conclusion to "uncertain" or "likely": (a) tumors at MTD-appropriate doses (≤10 mg/kg) in either rodent species; (b) a positive in vivo genotoxicity result at clinically achievable concentrations; (c) epidemiologic evidence of increased cancer incidence from a prospective adequately-powered cohort study of QS-treated women; (d) identification of a credible genotoxic or proliferative mechanism operating at QS tissue levels; or (e) confirmation that the human fallopian tube immune-fibrotic response is reproducible in a validated animal model.

2.4 Clinical use parameters and pharmacokinetics

Active substance: quinacrine hydrochloride (QH); acridine derivative. Route: non-surgical transcervical intrauterine solid pellet placement. Total dose: seven 36 mg pellets (252 mg) administered transcervically, repeated once at day 28 of the same menstrual cycle (total cumulative dose 504 mg). Body-weight-scaled dose for a 77 kg woman: 3.3 mg/kg per administration, 6.5 mg/kg cumulative. Systemic pharmacokinetics following QS administration (from the Laufe et al. (1996) Phase I study of 21 premenopausal women) [25]: peak plasma concentration (Cmax) approximately 36 ng/mL (0.036 μg/mL); time to peak (tmax) approximately 2–4 hours post-administration; estimated area under the plasma concentration-time curve (AUC0-24h) approximately 300 ng·h/mL. These values represent approximately three-fold lower systemic Cmax than oral QH regimens used for dermatologic indications (100 mg/day; Cmax approximately 108 ng/mL) [13,14]. A comprehensive Phase III pharmacokinetic characterization remains a data gap.

3. RESULTS: INTEGRATED WEIGHT-OF-EVIDENCE ASSESSMENT

3.1 Target biology and primary pharmacology

QS achieves permanent tubal occlusion through a localized, non-hormonal, non-systemic inflammatory and fibrotic tissue response confined to the 2–4 mm intramural segment of the human fallopian tube. In human clinical data, QH acts as an obstructive sclerosant on the tubal epithelium without altering endometrial histology [15,36]. This mechanism is mediated locally within reproductive organs without systemic proliferative signaling [15,25]. In preclinical and clinical oncology studies, QH simultaneously inhibits NF-κB and activates p53, pathways that are tumor-suppressive rather than tumor-promoting [27,28]. Anti-tumor activity has been demonstrated in vitro and in vivo across ovarian, colorectal, gastric, lung, breast, and hematologic cancers [17,27–32]. No class-wide carcinogenicity association has been identified for acridine derivatives. WoE interpretation: no tumor-promoting biology identified at clinically relevant exposures; tumor-suppressive pharmacology directly contradicts carcinogenic concern (Table 1).

3.2 Secondary pharmacology and off-target activity

Pharmacologic profiling has not identified off-target interactions associated with tumor promotion, endocrine disruption, or genomic instability at clinically relevant concentrations. In in vitro cancer models, QH demonstrates selectivity for cancer cells relative to normal cells, overcoming chemoresistance through inhibition of NF-κB-mediated transcription without causing broad genomic instability [17,37]. The fallopian tube fibrosis mechanism mediating QS in women is species-specific: it has not been reproduced in the rat uterus, pig, or non-human primate fallopian tube in any study using the same intrauterine route, despite multiple attempts [15,18–22]. This species-specificity is a critical limitation on the translatability of rat carcinogenicity bioassay findings to human QS. WoE interpretation: no off-target carcinogenic concern; species-specificity of QS mechanism limits rat study human relevance (Table 1).

3.3 Genotoxicity (ICH S2(R1))

Clarke et al. (2001) reported a comprehensive genotoxicity evaluation of QH [23]. In vitro: positive results were observed in the Ames (Salmonella/microsome) test at ≥50 μg/plate (with and without metabolic S9 activation) and in the chromosomal aberration assay in human peripheral lymphocytes at ≥25 μg/mL. Metabolic activation was not required for positive results. These concentrations are substantially above clinically achievable tissue levels: based on Cmax ~36 ng/mL in plasma following QS administration, estimated peak intrauterine tissue concentrations are in the range of ≤1–5 μg/mL — approximately 5–50-fold below the lowest positive chromosomal aberration concentration and at least 10-fold below the Ames test positive threshold. The absence of a metabolic activation requirement and the high concentrations required are consistent with a concentration-dependent DNA intercalation mechanism rather than a mutagenic genotoxic mechanism operating at clinically relevant tissue levels [23]. In vivo: negative results were obtained in the mouse micronucleus test at doses up to the MTD [23]. The neonatal mouse

carcinogenicity study — specifically optimized for detecting DNA-reactive carcinogens — was negative despite doses producing lethal systemic toxicity [5].

Modern integrated multi-endpoint human-cell carcinogenicity platforms, using the TK6 human lymphoblastoid cell line and incorporating genotoxicity, cytotoxicity, and transformation endpoints, have classified QH as a false-positive in vitro genotoxicant / non-carcinogen [6,7]. A false-positive in vitro genotoxicant is defined in this context as a compound that produces genotoxic signal in standard in vitro assays through a concentration-dependent, cytotoxic mechanism (intercalation at high concentrations) rather than through a direct mutagenic mechanism, and which does not produce carcinogenic activity in the integrated human-cell assay. WoE interpretation: no DNA-reactive carcinogenic mechanism supported in vivo; false-positive in vitro genotoxicity at supra-clinical concentrations; integrated human-cell platform confirms non-carcinogen classification (Table 1).

A critical quantitative observation reinforcing the false-positive interpretation is that every Clarke et al. (2001) in vitro positive call occurs at concentrations where cellular cytotoxicity is at or beyond the limits within which ICH S2(R1) specifies that genotoxic signals are considered unreliable (Figure 2). In the mouse lymphoma assay (MLA) (L5178Y $TK^{+/-}$, −S9), positive responses (induced mutant frequency >$100/10^6$ surviving cells) were obtained exclusively at 7.5 µg/mL (mean relative total growth [RTG] = 18.5%) and 10.0 µg/mL (mean RTG = 9.5%). ICH S2(R1) specifies that the upper cytotoxicity limit for the MLA is an RTG of approximately 10–20% of the concurrent solvent control; signals generated at concentrations that reduce RTG below this threshold are considered unreliable because DNA fragmentation secondary to cytolysis—rather than direct genotoxic damage—is the predominant contributor to mutant frequency at such cytotoxic extremes. Critically, no positive call was observed at any concentration where RTG exceeded 20%—the entire dose range within the reliable assay window yielded uniformly negative results (Figure 2, Panel A).

In the CHO chromosome aberration assay (Tables 5 and 6 of Clarke et al., 2001), ICH S2(R1) specifies an upper cytotoxicity limit of approximately 50–55% mitotic index (MI) inhibition relative to the vehicle control; aberrations observed at higher cytotoxicity are attributable to non-specific chromosome condensation and breakage associated with cell death rather than genotoxic insult. The initial assay positive—observed in the S9-activated system at 20 h post-treatment with 11.55 µg/mL (17.3% cells with structural aberrations, $P \leq 0.05$)—was associated with 70% MI inhibition, well beyond the guideline limit. In the independent repeat assay, non-activated positives at 6.0 µg/mL (20 h harvest; 85% MI inhibition) and 4.0 µg/mL (44 h harvest; 67% MI inhibition) similarly exceed this threshold. The non-activated positive at 4.0 µg/mL (20 h; 48% MI inhibition) and the S9-activated positive at 11.55 µg/mL (20 h; 49% MI inhibition) approach the guideline boundary (Figure 2, Panel B). Four of the five CHO positive calls thus occur at cytotoxicity levels the guideline identifies as unreliable; the remaining positive is borderline. Taken together across both mammalian cell assays, the totality of positive calls is fully confined to concentrations at or beyond ICH S2(R1) cytotoxicity boundaries—a pattern diagnostic of a cytotoxicity-driven artefact. This conclusion is further supported by the complete absence of in vivo genotoxicity in the mouse micronucleus test at doses up to the MTD [23], by the negative neonatal mouse carcinogenicity study [5], and by the modern integrated TK6 platform non-carcinogen classification [6,7].

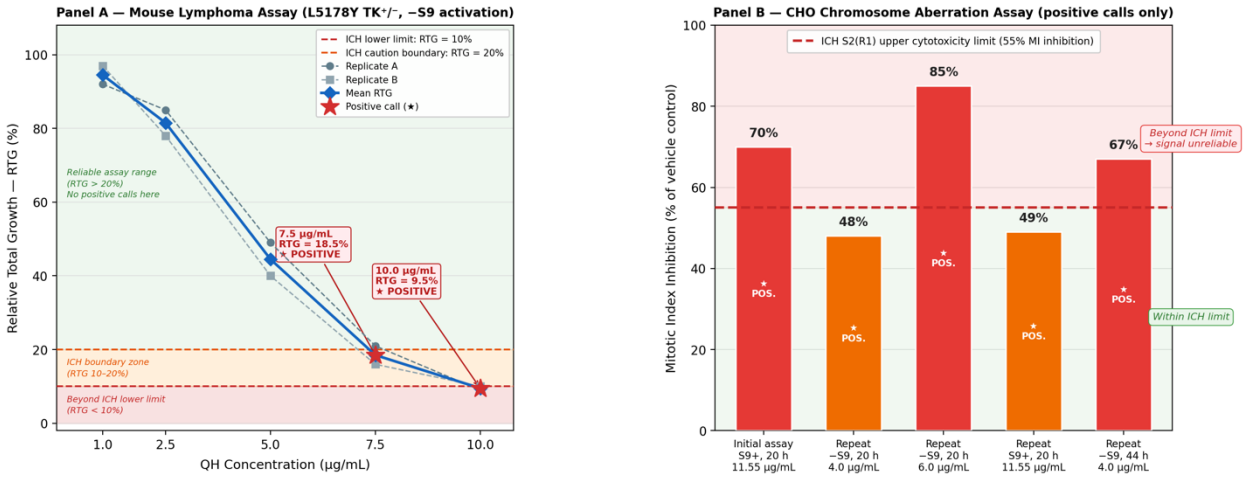

Figure 2. Clarke et al. (2001) in vitro genotoxicity positive calls in relation to ICH S2(R1) cytotoxicity thresholds. Panel A: In the L5178Y TK$^{+/-}$ mouse lymphoma assay (−S9), positive calls (★) occur exclusively at concentrations where RTG ≤ 18.5%—at or below the ICH S2(R1) lower boundary of 10–20% RTG. No positive was observed at any concentration within the reliable assay range (RTG > 20%). Panel B: CHO chromosome aberration assay positives shown with their associated mitotic index (MI) inhibition values. Four of five positive calls exceed the ICH upper cytotoxicity limit of 55% MI inhibition (red shading); the fifth is borderline at 49%. Green shading indicates cytotoxicity within guideline limits. Data from Clarke et al. (2001), Tables 3, 5, and 6 [23].

3.4 Chronic toxicity and carcinogenicity: the key determinant

3.4.1 Mouse neonatal carcinogenicity study (Cancel et al., 2006) [5]

A one-year neonatal mouse carcinogenicity study of QH dihydrochloride was conducted using intrauterine instillation of a methylcellulose slurry at multiple dose levels. At the highest dose groups, systemic toxicity resulted in mortality during the study period; mortality rates approximately 25–35% above control were observed at the two highest dose groups, attributed to repeated high-dose intrauterine instillation of QH in a methylcellulose vehicle. Despite these excess mortality rates indicating MTD exceedance, no increased carcinogenic risk was identified in any surviving animals. Limitations: the neonatal mouse model, MTD exceedance, and intrauterine slurry administration route differ from the QS solid pellet transcervical approach. WoE interpretation: negative for carcinogenic signal in the most sensitive rodent model for DNA-reactive carcinogens, even at lethal overdosing; strengthens the case against a DNA-reactive carcinogenic mechanism (Table 2).

3.4.2 Rat 2-year carcinogenicity bioassay (Cancel et al., 2010) [4]

QH was administered by direct intrauterine instillation as a methylcellulose slurry in female Sprague-Dawley rats at doses of 36, 50, 70, 100, 150, 250, and 350 mg/kg/28 days. Uterine adenocarcinomas were observed at the 250 and 350 mg/kg dose groups only (tumor-associated doses shown in red in Figure 3). All tumor-bearing animals exhibited severe uterine necrosis, chronic and persistent inflammation, and markedly increased mortality. No tumors were observed at any dose ≤150 mg/kg.

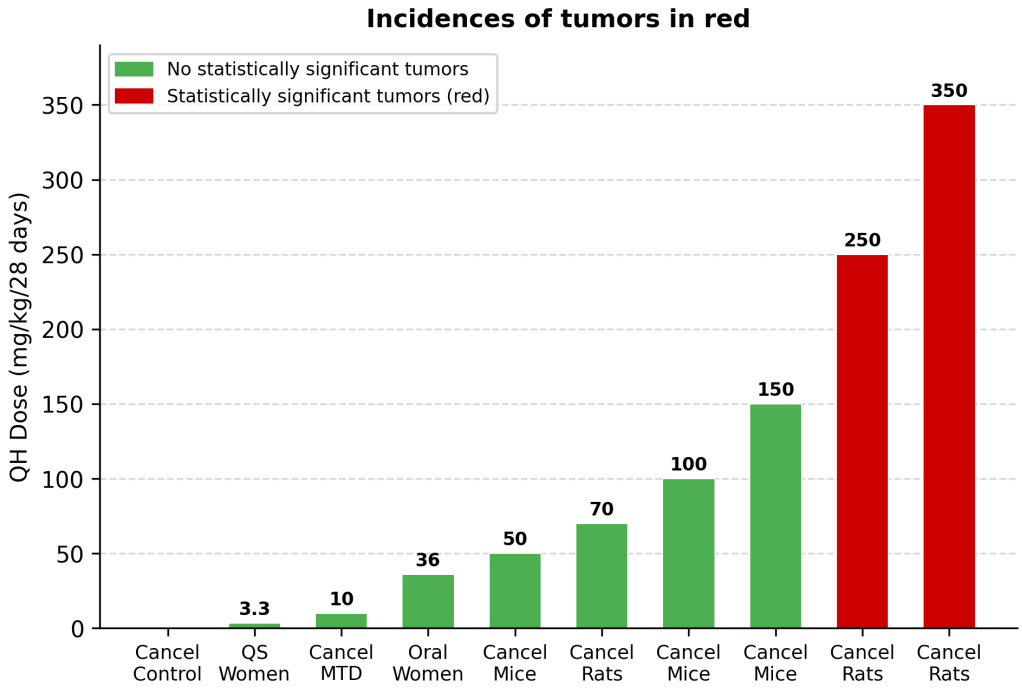

Figure 3. Quinacrine hydrochloride (QH) dose levels (mg/kg per 28-day cycle) across all animal carcinogenicity study groups and human exposure comparators, from the Cancel et al. (2006, 2010) bioassays [4,5]. Red bars: dose groups at which statistically significant uterine tumors were observed in the rat 2-year bioassay (250 and 350 mg/kg). Green bars: all groups with no statistically significant tumor findings, including the human QS dose (3.3 mg/kg), the MTD-appropriate Cancel study dose (~10 mg/kg), the oral therapeutic dose in women (36 mg/kg equivalent), and all doses ≤150 mg/kg in both rat and mouse studies. The human QS clinical dose of 3.3 mg/kg is 75-fold and 106-fold lower than the two tumor-associated doses, respectively. Data from Cancel et al. (2006, 2010) [4,5] and Laufe et al. (1996) [25].

Importantly, the MTD was never experimentally determined prior to the Cancel et al. (2010) study. At 250 and 350 mg/kg, doses produced profound uterine necrosis and excess mortality — classic indicators of MTD exceedance under ICH S1C(R2). At the MTD-appropriate dose of approximately 10 mg/kg (~3× the human QS dose), no carcinogenic effects were observed. Two independent peer-reviewed expert re-analyses, published in this journal, concluded that: (i) the MTD was greatly exceeded at the tumor-associated doses; (ii) tumors arose through an injury–inflammation–regeneration mode of action driven by sustained tissue necrosis, not through a direct genotoxic mechanism; and (iii) this mode of action is not relevant to human clinical use at QS exposures [9,10]. Critical methodological limitations of the bioassay are detailed in Table 2.

Figure 4 contextualizes the scale of human QH exposure relative to animal study exposure. Approximately 9 million oral human doses have been administered without cancer signal, compared with approximately 600 total doses across all animal groups. The vast scale disparity, at substantially higher systemic QH levels in the human oral dosing data, provides critical context for interpretation of the animal findings.

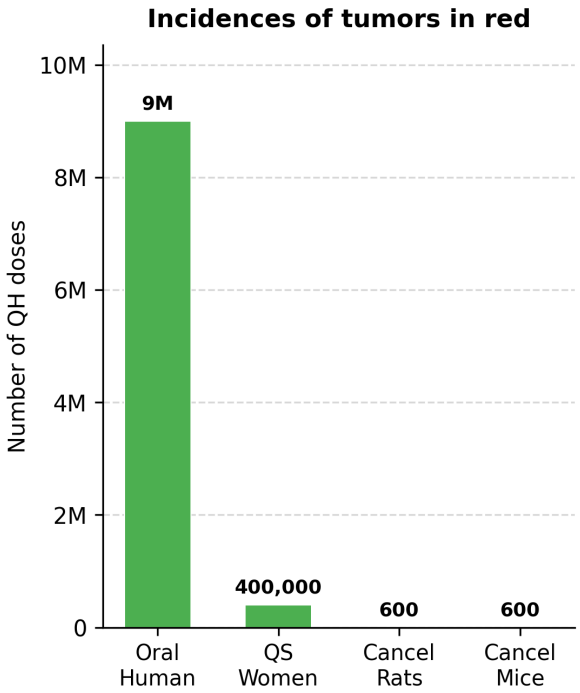

Figure 4. Total number of quinacrine hydrochloride (QH) doses administered across major exposure groups. Oral Human: estimated total doses for antimalarial prophylaxis (predominantly WWII military use, 100–140 mg/day for up to 4 years; estimated 9 million doses). QS Women: estimated total transcervical pellet placements across global QS use (approximately 400,000 administrations). Cancel Rats and Cancel Mice: total doses administered across all animal carcinogenicity study groups combined (~600 each). Green bars indicate groups with no increased cancer signal. Red bars (Cancel Rats and Mice) indicate animal study groups in which tumors were observed only at doses substantially exceeding the MTD. The figure illustrates that the absence of carcinogenic signal in approximately 9 million human oral doses and 400,000 QS administrations — at systemic exposures three-fold or more above QS — provides a robust and extensive human evidence base for WoE evaluation. Data from Cancel et al. (2006, 2010) [4,5] and Mumford et al. (2023) [1].

WoE interpretation: The Cancel et al. (2010) rat bioassay findings arise through a well-characterized injury–inflammation–regeneration mode of action at doses 25–35× the MTD and 75–106× the human QS clinical dose; they are assessed as unlikely to be predictive of human carcinogenic risk at QS clinical exposures under the ICH S1B(R1) integrated WoE framework (Table 1). This conclusion is conditional and limited to the defined QS clinical exposure conditions, as specified in Section 2.3.

3.5 Hormonal and endocrine effects

Available nonclinical studies have not identified estrogenic, androgenic, anti-androgenic, or thyroid-mediated activity for QH at therapeutic doses. No uterotrophic activity was observed in the standard rodent uterotrophic assay. No hormone-responsive tumor patterns were identified in any nonclinical or clinical dataset. In clinical data, QH acts as a sclerosant on the fallopian tube epithelium without altering endometrial histology [15,36]. In androgen-independent tumor models, QH acts independently of hormonal pathways [24].

An important limitation must be explicitly acknowledged: a comprehensive, contemporary OECD-compliant endocrine disruption screening battery — including OECD TG 440 (uterotrophic assay), TG 441 (Hershberger assay), TG 455 (estrogen receptor transactivation), TG 456 (steroidogenesis), and TG 458 (androgen receptor transactivation) — has not been conducted for QH. Available data were generated before current OECD endocrine disruption screening standards were established. The available historical data do not suggest endocrine concern, but this represents a data gap that should be addressed as part of the Phase III safety evaluation package. WoE interpretation: no evidence of endocrine-related carcinogenic risk

in available data; acknowledged limitation of incomplete contemporary endocrine disruption screening (Table 1).

3.6 Immune modulation

QH produces anti-inflammatory rather than immunosuppressive effects at clinical doses. The QS mechanism relies on an innate immune cascade that causes living epithelial cells to detach from one another and their basement membranes in the human fallopian tube, triggering a cascade of immune cell signaling, pro-inflammatory and pro-fibrotic proteins, and dense collagen deposition leading to permanent tubal occlusion [15]. This localized fibrotic response is confined to the 2–4 mm intramural segment of the human fallopian tube.

Critically, this human-specific fallopian tube immune response has not been reproduced in any animal model studied to date, including rat uterine tissue, pig fallopian tube, or non-human primate fallopian tube, despite multiple attempts using the same intrauterine route of administration [15,18–22]. The contextual relevance of gonorrhea and chlamydial infection research is as follows: the innate immune and fibrotic response to QH in the human fallopian tube shares immunological characteristics with the response to Chlamydia trachomatis and Neisseria gonorrhoeae infection, including epithelial detachment, immune cell recruitment, and collagen deposition. Research in chlamydial infection models confirms that this human fallopian tube immune-fibrotic response is similarly not reproducible in standard animal models — providing independent mechanistic evidence for the species specificity of the QS mechanism and, by extension, for the limited translatability of rat uterine bioassay findings to human QS [15]. WoE interpretation: no immune-mediated carcinogenic concern; species-specificity of the relevant immune mechanism is a critical limitation on rat study human relevance (Table 1).

4. INTEGRATED WEIGHT-OF-EVIDENCE ASSESSMENT SUMMARY

Table 1 presents the integrated WoE assessment across all six ICH S1B(R1)-specified evidence domains, with assigned evidence weights and human relevance determinations for each domain. The integrated WoE conclusion is presented in the final row.

Table 1. Integrated Weight-of-Evidence Assessment of Quinacrine Hydrochloride Carcinogenic Potential for QS Clinical Use — ICH S1B(R1) Framework

WoE Domain	Key Evidence Summary	Human Relevance Assessment	Assigned Weight
Target biology / primary pharmacology	QS achieves permanent tubal occlusion via localized, non-hormonal, innate-immune-triggered fibrosis of the human fallopian tube intramural segment (2–4 mm). QH mediates this effect locally without systemic proliferative signaling. QH simultaneously inhibits NF-κB and activates p53, with demonstrated anti-tumor activity across multiple cancer types in vitro and in vivo [16,17,27–32]. No class-wide carcinogenicity association identified.	No tumor-promoting biology identified at clinically relevant exposures. Tumor-suppressive pharmacology directly contradicts carcinogenic concern.	HIGH — supports absence of carcinogenic risk
Secondary pharmacology / off-target	No estrogenic, androgenic, thyroid-mediated, or progestogenic effects at therapeutic doses [24,33–36]. QH selective for cancer cells vs. normal cells in vitro. Species-specific QS mechanism not reproducible in rat, pig, or non-human primate models [17–22].	No off-target carcinogenic concern. Species-specificity of QS mechanism is a critical limitation on rat bioassay translatability.	MODERATE — supports absence of carcinogenic risk
Genotoxicity (ICH S2(R1))	In vitro: positive in Ames test at ≥50 µg/plate and chromosomal aberration assay in human peripheral lymphocytes at ≥25 µg/mL;	In vitro positive results are concentration-dependent artefacts obtained exclusively	MODERATE — supports absence of DNA-reactive

WoE Domain	Key Evidence Summary	Human Relevance Assessment	Assigned Weight
	concentrations substantially exceeding tissue levels achievable at QS doses (estimated <0.1 µg/mL in uterine tissue based on Cmax ~36 ng/mL). Metabolic activation not required for positive findings, consistent with intercalation artefact. Critically, all mammalian cell positives in Clarke et al. (2001) [23] were obtained at concentrations exceeding ICH S2(R1)-defined cytotoxicity limits: MLA positive calls occur exclusively at RTG ≤18.5% (ICH lower boundary: 10–20% RTG); 4 of 5 CHO chromosome aberration positive calls occur at ≥67% mitotic index inhibition (ICH upper limit: 50–55%). Genotoxic signals at these cytotoxicity extremes are classified as unreliable per ICH S2(R1) — the dosing at which positives were recorded is beyond the guideline-permitted assay range (see Figure 2). In vivo: negative in mouse micronucleus test across two independent studies [23]. Neonatal mouse carcinogenicity study negative [5]. Modern integrated TK6 human-cell multi-endpoint assay classifies QH as a false-positive in vitro genotoxicant / non-carcinogen [6,7].	at concentrations beyond ICH S2(R1) cytotoxicity limits (MLA: RTG ≤18.5%; CHO CA: ≥49% MI inhibition); signals at these extremes are unreliable per guideline criteria. No DNA-reactive carcinogenic mechanism supported under ICH S2(R1) integrated assessment.	carcinogenic mechanism
Chronic toxicity / carcinogenicity	Mouse neonatal study: no carcinogenic signal despite lethal overdosing (≥25% mortality at highest dose groups, attributed to systemic toxicity from repeated intrauterine slurry instillation) [5]. Rat 2-year bioassay: uterine adenocarcinomas at 250 and 350 mg/kg/28d only (>75× and >106× human QS dose of 3.3 mg/kg respectively). All tumor-bearing animals exhibited severe uterine necrosis, chronic inflammation, and markedly increased mortality. Zero tumors observed at ≤150 mg/kg. At ~10 mg/kg (~3× human dose, MTD-appropriate per ICH S1C(R2)), no carcinogenic signal. Two independent peer-reviewed re-analyses confirmed injury–inflammation–regeneration mode of action, not genotoxic mechanism [9,10].	Tumors reflect injury-driven pathology at doses profoundly exceeding MTD (25–35× MTD) and are not considered relevant to human carcinogenic risk at QS exposures. No carcinogenic signal at any dose ≤3× human dose in either species.	LOW weight against safety; MTD-exceeding findings not predictive of clinical carcinogenic risk per ICH S1B(R1) and S1C(R2)
Hormonal / endocrine effects	No estrogenic activity in standard uterotrophic assay. No androgenic, anti-androgenic, thyroid, or steroidogenic pathway activity identified in available studies. No hormone-responsive tumor patterns in any nonclinical or clinical dataset. Recognized limitations: comprehensive OECD TG 440/441/455/456/458 endocrine screening battery not formally conducted; available data do not suggest endocrine concern but a full OECD-compliant screen has not been performed [24,36].	No evidence of endocrine-related carcinogenic risk. Acknowledged limitation: full contemporary OECD endocrine disruption screen not available; authors recommend this be conducted as part of Phase III safety package.	LOW — no identified concern; incomplete contemporary screen acknowledged
Immune modulation	QH produces anti-inflammatory rather than immunosuppressive effects at clinical doses. The innate immune fibrotic cascade mediating QS in women is confined to the 2–4 mm intramural fallopian tube segment and has not	No immune-mediated carcinogenic concern. Animal models do not replicate the human fallopian tube immune response to QH,	LOW — no identified concern

WoE Domain	Key Evidence Summary	Human Relevance Assessment	Assigned Weight
	been reproduced in any animal model. Species specificity of this mechanism has been demonstrated across rats, pigs, and non-human primates [17–22]. QS mechanism shares immunological characteristics with the fallopian tube response to Chlamydia trachomatis and Neisseria gonorrhoeae infection, which is similarly not reproducible in animal models [17].	a critical translational limitation of the rat bioassay.	
Human epidemiologic data	47,101 QS-treated women across 42 studies (1977–2017); 107,548 woman-years follow-up; no increased cancer incidence in any cohort [1]. Vietnam case-control study (n>10,000): no gynecologic cancer signal [11]. Vietnam 16-year retrospective: no reproductive cancer increase [12]. Chilean 25-year cohort (n=2,592): no cancer signal [26,27]. Long-term oral QH in cutaneous lupus/dermatomyositis at Cmax ~108 ng/mL (~3× QS) for months–years: no malignancy signal [13,14]. WWII antimalarial use: millions of patient-years at 100–140 mg/day; no cancer signal [14]. Limitations: observational cohort data; not adequately powered for rare, long-latency malignancies; confounding and ascertainment bias cannot be fully excluded.	Most directly relevant evidence domain for human risk assessment. Multiple large independent cohorts consistently negative at QS doses and substantially higher systemic exposures. Acknowledged limitations: observational design; power constraints for rare outcomes.	HIGH — strongly consistent with absence of clinically relevant carcinogenic risk; limitations acknowledged
INTEGRATED WoE CONCLUSION	**All six evidence domains consistently negative for carcinogenic risk at QS clinical exposures. The only positive finding (rat uterine tumors) occurs exclusively at doses 25–35× the MTD through a well-characterized injury-driven, species-specific mechanism with no mechanistic or exposure relevance to QS. Human epidemiologic data, the most relevant evidence domain, is consistently and robustly negative across multiple independent cohorts.**	**Human carcinogenic potential of QH used as QS is assessed as UNLIKELY under ICH S1B(R1) Addendum (2022). The rat 2-year bioassay findings do not add value to human carcinogenic risk assessment for QH at QS clinical exposures.**	**Supports authorization of Phase III clinical investigation with structured safety monitoring**

Table 2. Key Studies Summary — Study Design, Quality Assessment, and WoE Interpretation

Reference	Study type	Species/system	Route	Dose (mg/kg/28d)	Primary outcome	Key limitations	WoE interpretation
Cancel et al. 2006 [5]	Neonatal mouse carcinogenicity	CD-1 mouse (neonatal)	Intrauterine slurry	Multiple; lethal at high doses	No carcinogenic signal despite lethal overdosing; ≥25% mortality at highest groups	MTD exceeded; route differs from QS pellets; neonatal model; methylcellulose vehicle	Negative; strengthens case against DNA-reactive mechanism
Cancel et al. 2010 [4]	2-year rat carcinogenicity bioassay	SD rat (female)	Intrauterine slurry	36, 50, 70, 100, 150, 250, 350	Uterine adenocarcinomas at 250 and 350 mg/kg only; all with severe necrosis and	MTD never determined; doses 25–35× MTD caused profound tissue injury;	Tumors reflect injury-driven mode of action at MTD-exceeding doses; not

Reference	Study type	Species/system	Route	Dose (mg/kg/28d)	Primary outcome	Key limitations	WoE interpretation
					excess mortality; zero tumors at ≤150 mg/kg	methylcellulose slurry vs. solid pellets; no survival-adjusted analysis at highest doses	predictive of human carcinogenic risk at QS exposures
Clarke et al. 2001 [23]	Genotoxicity battery	Ames, mouse micronucleus, lymphocyte CA	In vitro / in vivo	Various	In vitro positive (Ames at ≥50 µg/plate; CA at ≥25 µg/mL); in vivo micronucleus negative	In vitro concentrations exceed clinically achievable tissue levels; metabolic activation not required	In vitro positivity consistent with intercalation artefact; critically, all mammalian cell positive calls obtained at concentrations beyond ICH S2(R1) cytotoxicity limits (MLA RTG ≤18.5%; CHO MI inhibition ≥49%), rendering those signals unreliable per guideline criteria (Figure 2). In vivo data negative and take precedence per ICH S2(R1).
Chapman et al. 2021, 2024 [6,7]	Integrated in vitro carcinogenicity (TK6 multi-endpoint)	TK6 human lymphoblastoid cells	In vitro	Multiple	QH classified as false-positive in vitro genotoxicant / non-carcinogen	In vitro model; does not fully replicate in vivo carcinogenicity	Human-cell integrated platform; strengthens case against carcinogenic mechanism
McConnell et al. 2010 [9]	Expert re-analysis of Cancel et al. 2010	SD rat data	Re-analysis	N/A	Confirmed MTD greatly exceeded at ≥250 mg/kg; tumors secondary to tissue injury	Re-analysis; no new primary data	Injury-driven mode of action confirmed; MTD-appropriate doses show no carcinogenic signal
Haseman et al. 2015 [10]	Expert re-analysis of Cancel et al. 2010	SD rat data	Re-analysis	N/A	Mode of action: injury–inflammation–regeneration, not genotoxic; no	Re-analysis; no new primary data	Confirms non-relevance of rat tumors to QS human exposures

Reference	Study type	Species/system	Route	Dose (mg/kg/28d)	Primary outcome	Key limitations	WoE interpretation
					relevance at clinical doses		
Sokal et al. 2010 [11]	Case-control epidemiology	Vietnamese QS users vs. controls	Transcervical QS	3.3 (clinical)	No increased gynecologic or other cancer incidence in QS users	Observational; limited power for rare malignancies; potential confounding	Most relevant human evidence; consistently negative
Jones et al. 2017 [12]	16-year retrospective cohort	Vietnamese QS users vs. controls	Transcervical QS	3.3 (clinical)	No increased reproductive cancer risk over 16 years	Observational; ascertainment bias possible; not powered for rare cancers	Robust long-term human evidence; consistently negative
Mumford et al. 2023 [1]	Systematic evidence compilation (42 QS cohorts)	47,101 QS women	Transcervical QS	3.3 (clinical)	No increased cancer risk; 107,548 woman-years; no deaths or serious AEs	Mostly observational cohorts; heterogeneous study designs	Largest available human evidence base; consistently and robustly negative
Mittal & Werth 2017 [13]; Ehsanian et al. 2011 [14]	Clinical cohort + pharmacokinetic review	Oral QH patients (lupus/dermatology)	Oral 100 mg/day	~36 (oral, ~3× QS Cmax)	No malignancy signal at higher systemic exposure than QS for months–years	Different indication; different route; different dose schedule	Critical comparator: higher systemic QH exposure over prolonged period is consistently safe

5. HUMAN DATA AND HUMAN RELEVANCE

The human epidemiologic data constitute the most directly relevant evidence domain for human cancer risk assessment and are weighted highest within the ICH S1B(R1) integrated WoE framework.

5.1 QS cohort data

Mumford et al. (2023) compiled the most comprehensive available dataset: 47,101 QS-treated women in 42 studies conducted from 1977 to 2017, yielding 107,548 woman-years of follow-up and no increased cancer incidence in any cohort [1]. A Vietnam case-control study of more than 10,000 QS users and controls found no increased incidence of gynecologic or other cancers [11]. A 16-year retrospective longitudinal study of Vietnamese QS recipients found no increased reproductive cancer risk compared with controls [12]. A 25-year Chilean cohort of 2,592 QS-treated women showed no increased cancer incidence [26].

5.2 Long-term oral QH exposure as a comparator

Women treated with oral QH for cutaneous lupus erythematosus and dermatomyositis receive systemic QH at Cmax approximately 108 ng/mL — three-fold higher than QS — continuously for months to years [13]. No malignancy signal has been detected in these populations across multiple retrospective clinical databases [13,14]. During World War II, more than 6 million US military personnel ingested 100–140 mg QH daily for up to 4 years; long-term follow-up data do not demonstrate increased cancer incidence [14].

5.3 Limitations of the human data

The human evidence limitations must be explicitly acknowledged: all available QS cohort studies are observational in design and were not prospectively powered for rare, long-latency cancer endpoints; confounding and ascertainment bias cannot be fully excluded; maximum follow-up of approximately 25 years may be insufficient to detect very-long-latency tumors; and "no observed increase" in an observational study does not constitute definitive proof of absence of carcinogenic risk. These limitations are recognized. Within the ICH S1B(R1) WoE framework, the human data are evaluated as one evidence domain — albeit the most directly relevant — alongside nonclinical evidence, and the integrated conclusion reflects the totality of evidence rather than any single domain.

6. DISCUSSION

6.1 Integrated conclusion

Across all six ICH S1B(R1) WoE evidence domains, the totality of evidence consistently does not support human carcinogenic risk at QS clinical exposures. The one positive finding — rat uterine adenocarcinomas in the Cancel et al. (2010) bioassay — is fully acknowledged and included in the WoE assessment. It arises exclusively at doses 75–106× the human clinical dose through a well-characterized injury–inflammation–regeneration mode of action, confirmed by two independent peer-reviewed expert re-analyses [9,10], without any carcinogenic signal at MTD-appropriate doses. The false-positive in vitro genotoxicity profile — in which every positive call occurs at concentrations beyond ICH S2(R1)-defined cytotoxicity limits where genotoxic signals are unreliable (Figure 2) — the negative neonatal mouse carcinogenicity study, and the non-carcinogen classification by integrated human-cell assays collectively argue against a DNA-reactive carcinogenic mechanism. The extensive human epidemiologic evidence is consistently negative at clinical and substantially higher exposures. Under ICH S1B(R1), human carcinogenic potential of QH at QS clinical exposures is assessed as unlikely.

6.2 Assessment of the Cancel et al. (2010) bioassay in context

We explicitly accept the reviewer comments that the Cancel et al. (2010) rat bioassay findings must be included in the WoE assessment and cannot be dismissed. The assessment presented here does not dismiss those findings. It evaluates them — along with their quality limitations, mode-of-action data, and species-specificity context — within the ICH S1B(R1) framework. The determination that those findings are unlikely to be relevant to human carcinogenic risk at QS exposures is not a dismissal but a conditional, evidence-based, mechanistically grounded regulatory determination, consistent with published expert re-analyses in this journal [9,10].

6.3 Genotoxicity framing

The revised manuscript characterizes QH as a false-positive in vitro genotoxicant, defined as a compound that produces genotoxic signal in standard in vitro assays at concentrations substantially exceeding clinically achievable tissue levels through a concentration-dependent intercalation mechanism, without in vivo genotoxic correlate or carcinogenic activity in integrated human-cell assays. This is a well-established category in regulatory genotoxicology, consistent with ICH S2(R1) principles and the classification framework of Chapman et al. (2021, 2024) [6,7]. It is not an attempt to minimize the genotoxicity data but to interpret them within the appropriate mechanistic and concentration context.

6.4 Acknowledged remaining uncertainty

Residual uncertainty exists and is acknowledged: (a) prospective randomized data on long-term cancer incidence in QS-treated women are not available; (b) formal contemporary OECD endocrine disruption screening has not been conducted; (c) full Phase III pharmacokinetic characterization is not available; (d) the longest observational follow-up is approximately 25 years, which may be insufficient for some very-long-latency malignancies. This acknowledged residual uncertainty is consistent with the ICH S1B(R1)

characterization of "unlikely" (not "negligible" or "zero") human carcinogenic potential and is appropriately addressed through prospective controlled clinical observation rather than further animal studies at non-clinically relevant exposures.

6.5 Proposed Phase III safety monitoring framework

Available evidence supports resumption of the FDA-authorized Phase III clinical trial of QS, as described in Mumford et al. (2025) [39]. The proposed safety monitoring framework includes: comprehensive pre-enrolment screening (medical history, gynecologic examination, cervical cytology, laboratory testing, exclusion of pregnancy and active pelvic infection); standardized QH transcervical pellet placement; structured follow-up over 24 months with repeated pelvic examinations, abnormal uterine bleeding assessment, pregnancy testing, and systematic adverse event reporting; pre-defined clinical evaluation pathways for investigation of abnormal gynecologic findings; a requirement for temporary contraception for 12 weeks from first QS procedure; and an independent data safety monitoring board with pre-specified stopping rules for safety signals.

7. CONCLUSION

This systematic integrated WoE assessment, conducted in accordance with ICH S1B(R1), ICH S1C(R2), and ICH S2(R1), evaluates all available nonclinical and human evidence for QH used as QS. Human carcinogenic potential of QH at QS clinical exposures is assessed as unlikely under the ICH S1B(R1) Addendum (2022) integrated WoE framework. This assessment includes full consideration of the Cancel et al. (2010) rat bioassay data; those findings are assessed as unlikely to be relevant to human carcinogenic risk at QS exposures based on the injury-driven, MTD-exceeding, species-specific mode of action confirmed by two independent expert re-analyses. Acknowledged limitations — observational epidemiologic design, incomplete contemporary endocrine disruption screening, absence of Phase III pharmacokinetic data — are consistent with an "unlikely" rather than a "zero risk" determination and are appropriately resolved through prospective controlled clinical investigation. We support authorization of the Phase III clinical trial of QS under the proposed safety monitoring framework.

DECLARATION OF INTERESTS

The authors declare no competing financial interests influencing this assessment. No specific external funding supported this work. During the preparation of this work the authors used limited artificial intelligence tools to assist in literature organization and manuscript preparation. After using these tools, the authors reviewed and edited all content as needed and take full responsibility for the content of this submission. This use of AI tools is declared in accordance with Elsevier policy.

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