

RESEARCH MONOGRAPH . COMPOUND PROFILE

Verteporfin

A second-generation benzoporphyrin derivative photosensitizer approved for ocular photodynamic therapy, distinguished from first-generation porphyrins by rapid clearance, selective vascular targeting, and a pharmacologically independent capacity to disrupt the YAP-TEAD transcriptional complex implicated in Hippo pathway dysregulation and solid tumor progression.

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ABSTRACT

Verteporfin (benzoporphyrin derivative monoacid ring A, BPD-MA, CL 318952) is a semi-synthetic chlorin-class photosensitizer derived from protoporphyrin IX and approved by the United States Food and Drug Administration since April 2000 for the photodynamic therapy of predominantly classic subfoveal choroidal neovascularization secondary to age-related macular degeneration, pathologic myopia, and presumed ocular histoplasmosis syndrome. Marketed as Visudyne by QLT PhotoTherapeutics (subsequently Bausch and Lomb), the compound represented the first pharmacological intervention for neovascular age-related macular degeneration and established ocular photodynamic therapy as a standard of care prior to the introduction of anti-vascular endothelial growth factor agents. The photodynamic mechanism operates through selective accumulation in neovascular endothelium via lipoprotein-mediated uptake, followed by activation with 689 nm non-thermal laser light to generate reactive oxygen species (singlet oxygen and superoxide) that produce localized vascular endothelial damage, thrombosis, and vessel occlusion without thermal injury to the overlying neurosensory retina.

Independent of its photosensitizing activity, verteporfin was identified in 2012 by Liu-Chittenden et al. as a small-molecule inhibitor of the Yes-associated protein (YAP) and transcriptional enhanced associate domain (TEAD) protein-protein interaction, a critical effector node of the Hippo tumor suppressor pathway [1]. This discovery initiated a substantial and expanding preclinical oncology literature demonstrating that verteporfin, without

photoactivation, suppresses YAP-driven transcription, inhibits proliferation and invasion, and produces survival benefit in xenograft and orthotopic models of glioblastoma, pancreatic ductal adenocarcinoma, ovarian carcinoma, hepatocellular carcinoma, colorectal carcinoma, melanoma, and retinoblastoma [2, 3, 4, 5]. The YAP-TEAD inhibitory mechanism involves direct binding to YAP that alters its conformation and prevents association with TEAD transcription factors, upregulation of 14-3-3 sigma (stratifin) that sequesters YAP in the cytoplasm, and suppression of downstream targets including connective tissue growth factor (CTGF) and cysteine-rich angiogenic inducer 61 (CYR61) [6, 7].

Pharmacokinetics following the approved intravenous dose of 6 mg per square meter of body surface area are characterized by biexponential disposition with a distribution phase of 1 to 3 hours and a terminal elimination half-life of 5 to 6 hours. Verteporfin is 90 percent associated with plasma lipoproteins (principally low-density lipoprotein) and approximately 6 percent with albumin. Metabolism is limited and occurs through liver and plasma esterases to the diacid metabolite BPD-DA; cytochrome P450 enzymes do not contribute meaningfully to elimination. Excretion is predominantly fecal as unchanged drug, with less than 0.01 percent recovered in urine [8, 9].

This monograph reviews the chemistry, synthesis, and photophysics of verteporfin; the dual mechanism encompassing photodynamic vascular occlusion and light-independent YAP-TEAD inhibition; the comprehensive pharmacokinetic record; the clinical evidence base across ophthalmic and investigational oncologic indications; sourcing and quality verification for research applications; reconstitution and handling protocols;

stack-interaction considerations; adverse-event signal including photosensitivity; and a comparative assessment of five alternative photosensitizers or YAP pathway inhibitors against verteporfin on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Verteporfin.

Marketed name: Visudyne (QLT PhotoTherapeutics/Novartis Ophthalmics, subsequently Bausch and Lomb/Valeant Pharmaceuticals, currently Bausch and Lomb).

Development codes: CL 318952 (CIBA-Geigy/Novartis); BPD-MA (benzoporphyrin derivative monoacid ring A, the principal identifier in the early photobiology literature).

Chemical Abstracts Service registry number: 129497-78-5.

International Union of Pure and Applied Chemistry name: The compound is a 1:1 mixture of two regioisomers. Regioisomer I: methyl (3aS,14bS)-9-[2-(methoxycarbonyl)ethyl]-3a-ethyl-14b-methyl-2,3,3a,4,5,14b-hexahydro-1H-benzo[b]porphyrin-13-propanoate. Regioisomer II: the 13-methyl ester positional isomer. The formal IUPAC designations for the two regioisomers are 9-methyl and 13-methyl trans-(plus or minus)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-benzo[b]porphine-9,13-dipropanoate.

DrugBank identifier: DB00460.

United States Pharmacopeia: Verteporfin monograph exists in the USP-NF for the injectable preparation.

1.2 Structural class and chemistry

Verteporfin belongs to the chlorin structural class, a reduced porphyrin macrocycle containing one pyrroline ring (one reduced pyrrole nitrogen), which confers a strong absorption band in the red region of the visible spectrum (approximately 689 nm) and distinguishes chlorins from the fully conjugated porphyrins that absorb maximally near 630 nm. Within the chlorin class, verteporfin is a benzopor-

phyrin derivative: the macrocycle bears a fused cyclohexadiene (benzo) ring that extends conjugation and shifts the long-wavelength absorption band to 689 nm with high molar extinction coefficient (approximately 34,000 M⁻¹ cm⁻¹) [10].

Molecular formula: C₄₁H₄₂N₄O₈.

Molecular weight: 718.79 g/mol.

Physical properties: Dark green to dark blue-green solid. Soluble in dimethyl sulfoxide; sparingly soluble in methanol and ethanol; essentially insoluble in water as the free acid. The clinical formulation (Visudyne) is supplied as a liposomal preparation containing verteporfin in egg phosphatidylglycerol and dimyristoylphosphatidylcholine to achieve aqueous dispersibility for intravenous administration.

Stereochemistry: The compound contains two stereocenters at the 4a and 3 positions of the reduced pyrroline ring and is supplied as the racemic trans diastereomer. The clinical material is a 1:1 mixture of the two positional regioisomers (I and II) differing in the location of the methyl ester on the propionic acid side chains at positions 9 and 13 of the macrocycle [11].

Photophysical properties: Absorption maximum 689 nm (Q-band) in the therapeutic window for tissue penetration; singlet oxygen quantum yield approximately 0.7 to 0.8 in organic solvents; triplet state lifetime approximately 10 microseconds in deoxygenated solution. These properties underwrite the photodynamic efficacy: efficient absorption of clinically deliverable 689 nm laser light, efficient intersystem crossing to the triplet state, and efficient energy transfer to molecular oxygen to generate cytotoxic singlet oxygen [10].

1.3 Synthesis

Verteporfin is synthesized from protoporphyrin IX dimethyl ester through a Diels-Alder cycloaddition strategy. The principal synthetic route proceeds through the following stages [12, 13]:

1. Retro-Diels-Alder activation of the vinyl group at position 3 or 8 of protoporphyrin IX dimethyl ester to generate a reactive diene system on the macrocyclic periphery.

2. Diels-Alder [4+2] cycloaddition with dimethyl acetylenedicarboxylate (DMAD) as the dienophile, producing the fused cyclohexadiene ring characteristic of the benzoporphyrin derivative scaffold. This reaction generates four possible regioisomers and diastereomers; the trans diastereomer at the ring junction is the desired product.
3. Selective monohydrolysis of one of the two methyl ester groups on the fused ring to yield the monoacid (ring A) derivative. The hydrolysis is regioselective under controlled basic conditions, producing predominantly the BPD-MA regioisomer mixture rather than the diacid (BPD-DA) or the ring B monoacid.
4. Purification by chromatography (silica gel or reverse-phase HPLC) to separate the ring A monoacid from the ring B monoacid and the diacid. The final product is a 1:1 mixture of the two regioisomers (positions 9 and 13), which is the defined drug substance.

The liposomal formulation is prepared by dissolving verteporfin in the lipid components (egg phosphatidylglycerol and dimyristoylphosphatidylcholine in a defined molar ratio), hydrating the lipid film with aqueous buffer, and sizing by extrusion or homogenization to produce unilamellar vesicles of defined diameter (approximately 100 to 200 nm). The formulation is lyophilized for storage stability and reconstituted at the time of use.

2. Abstract

Verteporfin (BPD-MA, CL 318952, Visudyne) is a second-generation benzoporphyrin derivative photosensitizer approved for ocular photodynamic therapy and an emergent pharmacological tool for light-independent inhibition of the YAP-TEAD transcriptional complex, the principal effector of the Hippo tumor suppressor signaling cascade. The compound occupies a unique position in contemporary pharmacology as a clinically validated drug with an established safety database that has been repurposed through mechanistic discovery into a broadly studied oncology research tool.

The photodynamic application exploits the photophysical properties of the chlorin macrocycle (strong 689 nm absorption, high singlet oxygen quantum yield) in combination with selective vascular accumulation through lipoprotein-mediated endothelial uptake to produce targeted vascular occlusion of choroidal neovascular membranes. The Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) registration trials demonstrated statistically significant reduction in the risk of moderate and severe visual acuity loss at 12 and 24 months in patients with predominantly classic subfoveal choroidal neovascularization [14, 15].

The YAP-TEAD inhibitory application, discovered by Liu-Chittenden et al. in 2012 through a chemical library screen [1], operates independently of photoactivation and involves direct binding to YAP protein, conformational disruption of the YAP-TEAD interaction surface, upregulation of the cytoplasmic sequestration factor 14-3-3 sigma, and transcriptional suppression of YAP-TEAD target genes including CTGF and CYR61 [6, 7]. Preclinical evidence spans glioblastoma, pancreatic adenocarcinoma, ovarian carcinoma, hepatocellular carcinoma, colorectal carcinoma, retinoblastoma, and melanoma, with demonstrated anti-proliferative, anti-invasive, and pro-apoptotic effects in cell lines and xenograft models at concentrations achievable without photoactivation [2, 3, 4, 5].

Pharmacokinetics are characterized by rapid lipoprotein association (90 percent bound to LDL and other lipoproteins), biexponential elimination with a terminal half-life of 5 to 6 hours, limited metabolism through plasma and hepatic esterases, and predominantly fecal excretion as unchanged drug [8, 9]. The compound pro-

duces transient photosensitivity (48 hours post-infusion), injection site reactions, and rare infusion-related back pain as principal adverse events at the approved dose of 6 mg per square meter [16].

3. Discovery and Development History

3.1 Origin and photobiology context

The benzoporphyrin derivatives were first synthesized in the laboratory of David Dolphin at the University of British Columbia in the 1980s as part of a systematic effort to develop second-generation photosensitizers with improved photophysical and pharmacokinetic properties relative to the first-generation hematoporphyrin derivative (Photofrin) [12]. The design objectives were a strong absorption band in the red spectral region (greater than 680 nm) for improved tissue penetration, rapid systemic clearance to minimize prolonged photosensitivity, and selective uptake by neovascular tissue. The Diels-Alder approach to fusing a benzo ring onto the porphyrin macrocycle achieved the spectral shift; the monoacid modification achieved the lipophilicity profile required for lipoprotein association and vascular targeting.

3.2 Preclinical photodynamic characterization

QLT PhotoTherapeutics, Inc. (Vancouver, British Columbia) licensed the benzoporphyrin derivative technology from the University of British Columbia and advanced BPD-MA through preclinical characterization in the late 1980s and early 1990s. Key preclinical findings included selective accumulation in neovascular endothelium within minutes of intravenous injection, efficient photodynamic vascular occlusion at 689 nm laser activation, and rapid clearance producing a photosensitivity window of only 24 to 48 hours (compared to 4 to 6 weeks for Photofrin) [17]. The compound was characterized in animal models of choroidal neovascularization, demonstrating selective closure of neovascular membranes with preservation of the overlying neurosensory retina.

3.3 Clinical development and regulatory approval

QLT partnered with CIBA Vision (subsequently Novartis Ophthalmics) for the clinical development program. The pivotal registration trials were:

The TAP (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy) Study, a multicenter randomized double-masked placebo-controlled trial enrolling 609 patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration [14]. At 12 months, 67 percent of verteporfin-treated patients lost fewer than 15 letters of visual acuity compared to 39 percent of placebo-treated patients (p less than 0.001). The benefit was sustained at 24 months.

The VIP (Verteporfin in Photodynamic Therapy) Study extended the indication to occult-only subfoveal neovascularization and to pathologic myopia [15]. Both trials supported the regulatory submissions.

Regulatory approvals: Switzerland (December 1999), United States FDA (April 12, 2000), European Union (July 2000), Japan (October 2003). Verteporfin was the first pharmacological treatment approved for neovascular age-related macular degeneration and remained a standard of care until the introduction of ranibizumab (Lucentis, 2006) and bevacizumab (Avastin, off-label) anti-VEGF therapies shifted treatment paradigms.

3.4 Identification of YAP-TEAD inhibitory activity

In 2012, Liu-Chittenden et al. at Johns Hopkins University reported the results of a chemical library screen for inhibitors of the YAP-TEAD protein-protein interaction [1]. The screen identified verteporfin as a compound that disrupted YAP-TEAD complex formation in a mammalian two-hybrid assay and suppressed YAP-dependent transcription in cell-based reporter systems. Critically, the YAP inhibitory activity was demonstrated in the absence of light activation, establishing that the effect was pharmacological rather than photodynamic.

This discovery initiated a second research life for the compound. The subsequent decade has produced over 200 publications characterizing verteporfin as a YAP-TEAD inhibitor across multiple tumor types, establishing molecular mechanism, and exploring combination strategies with conventional chemotherapy and targeted agents.

3.5 Current status

The compound remains approved and marketed as Visudyne for ocular photodynamic therapy, though its clinical use has diminished substantially with the dominance of anti-VEGF therapy for neovascular age-related macular degeneration.

Photodynamic therapy with verteporfin retains a role in central serous chorioretinopathy, polypoidal choroidal vasculopathy, and selected cases of choroidal neovascularization unresponsive to anti-VEGF agents [18]. The YAP-TEAD inhibitory application remains preclinical; no registration trial of verteporfin as a systemic oncologic agent has been completed.

4. Mechanism of Action

Verteporfin possesses two mechanistically distinct pharmacological activities: a photodynamic mechanism requiring light activation and a transcriptional inhibitory mechanism operating independently of light.

4.1 Photodynamic mechanism

The photodynamic mechanism proceeds through three essential components: the photosensitizer (verteporfin), light of the appropriate wavelength (689 nm), and molecular oxygen in the target tissue.

Upon intravenous infusion, verteporfin rapidly associates with plasma lipoproteins, predominantly low-density lipoprotein (LDL). Neovascular endothelial cells, which overexpress LDL receptors to support their high metabolic demands, internalize the lipoprotein-drug complex through receptor-mediated endocytosis. This produces selective accumulation of verteporfin in neovascular tissue within 15 to 20 minutes of infusion [17].

Activation with 689 nm non-thermal diode laser light (delivered at 600 mW per square centimeter for 83 seconds, producing a light dose of 50 J per square centimeter) excites verteporfin from the ground state (S_0) to the first excited singlet state (S_1). Rapid intersystem crossing (facilitated by the heavy-atom effect of the nitrogen atoms and the extended conjugation) populates the longer-lived triplet state (T_1). The triplet state transfers energy to molecular oxygen through a Type II photodynamic mechanism, generating singlet oxygen (1O_2), the principal cytotoxic species [10].

Singlet oxygen has a diffusion radius of approximately 20 nm and a lifetime of approximately 3 microseconds in biological media. Its destructive action is therefore strictly localized to the immediate vicinity of the photosensitizer. In the context of verteporfin PDT, singlet oxygen damages endothelial cell membranes, basement membrane proteins, and intracellular organelles, producing endothelial cell death, platelet activation, thrombosis, and vascular occlusion. The neurosensory

retina overlying the treated neovascular membrane is spared because the photosensitizer is concentrated in the vascular compartment and the laser parameters are non-thermal [19].

A secondary Type I mechanism (electron transfer rather than energy transfer) generates superoxide radical anion and hydroxyl radicals, contributing to the oxidative damage profile but constituting a minority of the photodynamic effect under clinical conditions.

4.2 YAP-TEAD transcriptional complex inhibition

The Hippo signaling pathway is a conserved kinase cascade (MST1/2, LATS1/2, MOB1, SAV1) that phosphorylates the transcriptional co-activator YAP (Yes-associated protein) and its paralog TAZ (transcriptional co-activator with PDZ-binding motif), promoting their cytoplasmic retention and proteasomal degradation. When Hippo signaling is attenuated, unphosphorylated YAP translocates to the nucleus and binds TEAD family transcription factors (TEAD1-4), activating target genes that promote proliferation (CTGF, CYR61, BIRC5), epithelial-mesenchymal transition, and stemness maintenance. Dysregulation of the Hippo-YAP axis is implicated in the majority of human solid tumors [20].

Verteporfin inhibits this pathway at the YAP-TEAD protein-protein interaction step through at least two characterized mechanisms:

1. Direct binding to YAP: Verteporfin binds YAP and induces a conformational change that disrupts the interface required for TEAD association. The binding abrogates YAP-TEAD2 complex formation in co-immunoprecipitation and mammalian two-hybrid assays at concentrations of 1 to 10 micromolar [1].
2. Upregulation of 14-3-3 sigma (stratifin): Verteporfin increases the expression of 14-3-3 sigma, a cytoplasmic scaffolding protein that binds phosphorylated YAP and promotes its cytoplasmic sequestration. This mechanism reinforces the direct binding disruption by reducing the nuclear availability of YAP even if some YAP-TEAD complexes form [7].

Downstream consequences include transcriptional suppression of CTGF, CYR61, survivin (BIRC5), and other YAP-TEAD target genes; induction of cell cycle arrest (predominantly G1 arrest); induction of apoptosis through mitochondrial pathway activation; suppression of epithelial-mesenchymal transition markers; and inhibition of cell migration and invasion [2, 3, 4, 5].

4.3 Additional light-independent mechanisms

Beyond YAP-TEAD inhibition, verteporfin has been reported to modulate additional signaling pathways without photoactivation:

Autophagy suppression: Verteporfin inhibits autophagic flux at concentrations of 2 to 10 micromolar, potentially through disruption of autophagosome-lysosome fusion or through direct effects on autophagy-related proteins [21].

Wnt/beta-catenin pathway modulation: Several reports indicate cross-talk between verteporfin-mediated YAP suppression and Wnt pathway activity, with indirect suppression of beta-catenin-dependent transcription in colorectal cancer models [22].

NF-kappaB suppression: Verteporfin has been reported to suppress NF-kappaB signaling in selected cell models, though the specificity and directness of this effect relative to YAP-TEAD inhibition remain incompletely characterized.

4.4 Dose-mechanism relationships

At the approved clinical dose for photodynamic therapy (6 mg per square meter, producing peak plasma concentrations of approximately 1 to 2 micrograms per milliliter or 1.4 to 2.8 micromolar), free drug concentrations available for YAP-TEAD inhibition are limited by the 90 percent lipoprotein binding. Effective free concentrations for YAP-TEAD disruption in cell-based assays (1 to 10 micromolar total, producing effective free concentrations of approximately 0.1 to 1 micromolar) overlap the lower end of achievable systemic exposure at the approved dose, suggesting that modest YAP-TEAD inhibitory activity may occur even at the standard photodynamic therapy dose. However, the preclinical oncology literature typically employs higher concentrations (5 to 50 micromolar in vitro) than those achievable with the current clinical formulation and dosing regimen, representing a translational gap that has not been bridged by a systemic oncology clinical trial.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and administration

Verteporfin is administered exclusively by the intravenous route in clinical practice. The compound is not orally bioavailable in a therapeutically relevant formulation owing to its high molecular weight (718.79 g/mol), poor aqueous solubility, and susceptibility to degradation in the gastrointestinal environment. The clinical formulation is a lyophilized liposomal preparation reconstituted and diluted immediately before intravenous infusion.

The standard intravenous dose is 6 mg per square meter of body surface area, administered as an infusion over 10 minutes at a rate of 3 mL per minute using a syringe pump with an in-line filter (1.2 micrometer pore size) [23].

5.2 Distribution

Following intravenous infusion, verteporfin exhibits biexponential pharmacokinetics with a distribution phase of approximately 1 to 3 hours. The compound is 90 percent associated with plasma lipoprotein fractions (predominantly low-density lipoprotein, with contributions from very-low-density lipoprotein and high-density lipoprotein) and approximately 6 percent associated with albumin [8]. The lipoprotein association is the molecular basis for the selective vascular targeting: LDL receptor-mediated endocytosis concentrates the drug in metabolically active endothelial cells.

Peak plasma concentrations following the standard 6 mg per square meter dose are approximately 1 to 2 micrograms per milliliter, achieved at or near the end of the 10-minute infusion [9].

The apparent volume of distribution has not been extensively characterized in published pharmacokinetic analyses owing to the liposomal formulation complicating standard compartmental modeling.

5.3 Metabolism

Metabolism of verteporfin is limited. The principal metabolic transformation is ester hydrolysis of the methyl ester on the propionic acid side chain, catalyzed by plasma and hepatic esterases, to produce the diacid metabolite BPD-DA. The extent of metabolite formation is less than 10 percent of administered dose as assessed by area-under-the-curve ratios [8, 9].

Cytochrome P450 enzymes do not contribute meaningfully to verteporfin metabolism. In vitro studies with NADPH-dependent liver enzyme systems (including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) demonstrated negligible transformation, indicating that the compound is unlikely to participate in CYP-mediated drug-drug interactions as either a substrate, inhibitor, or inducer [9].

5.4 Elimination

Elimination is predominantly fecal as unchanged drug, consistent with biliary excretion of the large, highly protein-bound molecule. Less than 0.01 percent of an administered dose is recovered in urine [8]. The terminal elimination half-life is 5 to 6 hours.

5.5 Special populations

Elderly patients (greater than 65 years): Mean C_{max} and AUC values are modestly higher than in younger patients, attributed to age-related changes in lipoprotein metabolism and hepatic blood flow. These differences are not considered clinically significant and do not require dose adjustment [9].

Hepatic impairment: In patients with mild hepatic impairment (Child-Pugh A), the elimination half-life is prolonged by approximately 20 percent. Data in moderate to severe hepatic impairment are limited; caution is recommended.

Renal impairment: Given the negligible renal contribution to elimination (less than 0.01 percent), renal impairment is not expected to alter pharmacokinetics significantly.

Pediatric patients: Pharmacokinetic data in pediatric populations are limited to case series of photodynamic therapy for pediatric choroidal conditions; no formal pediatric pharmacokinetic study has been published.

5.6 Photosensitivity pharmacokinetics

The duration of cutaneous photosensitivity correlates with plasma drug levels. Photosensitivity testing at 1.5 hours post-infusion shows a high frequency of positive reactions; by 24 hours the frequency has decreased substantially, and by 48 hours most patients are no longer photosensitive. The 48-hour sunlight avoidance recommendation in the prescribing information reflects this pharmacokinetic-pharmacodynamic relationship [16].

6. Preclinical Pharmacology

6.1 Photodynamic therapy models

Verteporfin photodynamic therapy has been extensively characterized in animal models of choroidal neovascularization, including laser-induced choroidal neovascularization in non-human primates and rodents, and in spontaneous models. The compound produces dose-dependent and light-dose-dependent vascular occlusion with selectivity for neovascular tissue over normal choroidal vasculature at optimized dosing parameters [17, 19].

Additional preclinical photodynamic applications include Barrett's esophagus (canine model), skin cancer (murine melanoma and squamous cell carcinoma), prostate cancer, and pancreatic cancer. In each model, the photodynamic mechanism produces localized tumor ablation with minimal systemic toxicity.

6.2 YAP-TEAD inhibition: in vitro oncology

The YAP-TEAD inhibitory activity has been characterized across a broad spectrum of tumor cell lines:

Glioblastoma: Verteporfin at 2 to 10 micromolar suppresses proliferation, induces G1 arrest and apoptosis, and inhibits invasion in U87, U251, and patient-derived glioblastoma stem cell lines. Anti-invasive efficacy is demonstrated at sub-cytotoxic concentrations (1 to 2 micromolar), suggesting that YAP-TEAD-mediated transcriptional reprogramming of invasion occurs at lower drug exposure than frank cytotoxicity [2].

Pancreatic ductal adenocarcinoma: Verteporfin suppresses PANC-1 and BxPC-3 cell proliferation, arrests cells in G1, induces apoptosis, and inhibits angiogenesis and vasculogenic mimicry through disruption of the YAP-TEAD complex at 1 to 5 micromolar [3].

Ovarian carcinoma: Dose- and time-dependent inhibition of proliferation, migration, and invasion in SKOV3, OVCAR3, and A2780 cell lines at 2 to 10 micromolar [4].

Retinoblastoma: The clinically used photosensitizer verteporfin inhibits YAP-TEAD interaction and retinoblastoma cell growth in vitro without light activation at 1 to 5 micromolar, establishing the compound as a potential therapeutic for this pediatric malignancy [5].

Hepatocellular carcinoma: Suppression of HepG2 and Huh7 proliferation and colony formation; synergy with sorafenib in combination experiments [24].

6.3 YAP-TEAD inhibition: in vivo oncology

Xenograft studies have demonstrated anti-tumor efficacy of systemically administered verteporfin without photoactivation:

Glioblastoma: Intraperitoneal verteporfin (100 mg/kg) in orthotopic U87 xenograft-bearing mice produced significant survival benefit and reduced tumor invasiveness compared to vehicle-treated controls [2].

Pancreatic cancer: Subcutaneous PANC-1 xenografts treated with verteporfin showed dose-dependent growth suppression [3].

Ovarian cancer: Intraperitoneal verteporfin reduced peritoneal dissemination in orthotopic ovarian cancer models [4].

The doses employed in these preclinical studies (typically 50 to 100 mg/kg in mice) translate by allometric scaling to substantially higher human-equivalent doses than the approved 6 mg per square meter photodynamic therapy dose, representing the principal translational barrier to clinical oncology application.

7. Clinical Evidence Base

7.1 Age-related macular degeneration

The TAP Study (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy) was the pivotal Phase 3 registration trial [14]. In 609 patients with predominantly classic subfoveal choroidal neovascularization randomized to verteporfin PDT or placebo PDT, 67 percent of verteporfin-treated patients avoided moderate visual loss (fewer than 15 letters lost) at 12 months compared to 39 percent of placebo patients (p less than 0.001). At 24 months, the benefit was sustained: 53 percent versus 38 percent.

The VIP Study extended efficacy data to patients with occult-only subfoveal neovascularization and to patients with pathologic myopia-associated choroidal neovascularization [15]. At 24 months, verteporfin-treated eyes were significantly less likely to experience moderate visual loss.

Meta-analyses of the TAP and VIP data (combined safety population of 948 verteporfin-treated patients and 475 placebo-treated patients) established the safety profile described in the adverse events section and confirmed the efficacy signal across the approved indications [16].

7.2 Central serous chorioretinopathy

Following the decline in verteporfin PDT use for age-related macular degeneration with the advent of anti-VEGF agents, photodynamic therapy was repositioned for central serous chorioretinopathy (CSC), a condition characterized by serous retinal detachment from choroidal vascular hyperpermeability. Reduced-fluence (half-dose or half-fluence) verteporfin PDT has become a standard treatment for chronic CSC, supported by multiple randomized controlled trials demonstrating superior subretinal fluid resolution compared to observation or sham treatment [18, 25].

The PLACE trial (2018), a multicenter randomized controlled non-inferiority trial comparing half-dose PDT with micropulse laser for chronic CSC, demonstrated superiority of PDT for anatomic and functional outcomes at 6 months [26].

7.3 Polypoidal choroidal vasculopathy

Verteporfin PDT remains a first-line or combination therapy for polypoidal choroidal vasculopathy, particularly in Asian populations where this condition constitutes a substantial proportion of neovascular macular disease. The EVEREST II trial demonstrated that combination therapy (verteporfin PDT plus ranibizumab) produced superior polyp regression compared to ranibizumab monotherapy [27].

7.4 Investigational oncology applications

Clinical translation of verteporfin as a systemic YAP-TEAD inhibitor for oncology remains in early stages. The VERTPAC-01 and VERTPAC-02 studies investigated ultrasound-guided verteporfin photodynamic therapy for locally advanced pancreatic cancer, combining the photodynamic mechanism with the YAP-TEAD inhibitory mechanism through direct intratumoral light delivery [28]. Results demonstrated feasibility and safety but have not produced registration-quality efficacy data.

No Phase 2 or Phase 3 trial of systemic verteporfin as a light-independent YAP-TEAD inhibitor for solid tumors has been initiated, and the translational gap between preclinical effective doses (50 to 100 mg/kg in mice) and the approved human dose (6 mg per square meter, approximately 0.16 mg/kg) remains a significant barrier to clinical oncology development.

8. Sourcing and Quality Verification

8.1 Pharmaceutical-grade sources

The pharmaceutical-grade preparation is Visudyne (Bausch and Lomb), supplied as a lyophilized powder for reconstitution in single-use glass vials containing 15 mg of verteporfin. The formulation includes egg phosphatidylglycerol, dimyristoylphosphatidylcholine, ascorbyl palmitate, and butylated hydroxytoluene as antioxidants. Pharmaceutical-grade material is available in all jurisdictions where the product is registered (United States, European Union, Japan, Canada, Australia, and others).

8.2 Research-grade sources

Research-grade verteporfin is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich/MilliporeSigma, MedChemExpress, Cayman Chemical, Selleckchem, Tocris, Abcam, InvivoChem, and others) at purity greater than 95 percent by HPLC. Supply is in milligram to gram quantities as the free acid. Pricing is moderate to high relative to simple small molecules, reflecting the complexity of porphyrin synthesis; typical pricing is \$100 to \$500 per 100 mg of greater than 98 percent purity material at the time of monograph preparation.

8.3 Quality verification

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (target greater than 95 percent; ideally greater than 98 percent for mechanistic studies)
- UV-visible absorption spectroscopy confirming the characteristic Q-band at 689 nm and the Soret band near 430 nm
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 719.3)
- Nuclear magnetic resonance spectroscopy (1H NMR) for structural confirmation, particularly verification of the regioisomer ratio

- Assessment of photodegradation: verteporfin is photolabile; lots stored or handled in ambient light may contain photodegradation products that confound biological assays

8.4 Light protection requirements

Verteporfin is photosensitive. All handling, storage, and experimental procedures with the compound must be conducted under reduced light conditions or amber/red-filtered lighting. Solutions must be protected from ambient room light and direct sunlight. Failure to protect from light produces rapid photodegradation with loss of both photodynamic and YAP-TEAD inhibitory activity.

9. Reconstitution and Handling

9.1 Clinical reconstitution (Visudyne)

The Visudyne lyophilized cake is reconstituted by adding 7.0 mL of sterile water for injection to the vial, producing 7.5 mL of a 2.0 mg/mL solution [23]. The reconstituted solution is opaque and dark green. The required volume is withdrawn and diluted in 5 percent dextrose injection to a total infusion volume of 30 mL. The diluted solution must be used within 4 hours of reconstitution and must be protected from light during storage and administration.

Administration is by intravenous infusion over 10 minutes at a rate of 3 mL per minute using a syringe pump and an in-line filter with 1.2 micrometer pore size. Extravasation must be avoided; the compound causes severe photosensitivity reactions in tissue exposed to light [23].

9.2 Research reconstitution

For in vitro research, verteporfin is typically dissolved in dimethyl sulfoxide (DMSO) at stock concentrations of 10 to 50 mM (7.2 to 36 mg/mL). The stock solution is aliquoted in amber or foil-wrapped tubes and stored at minus 20 degrees Celsius, protected from light. Working concentrations for cell-based YAP-TEAD inhibition assays are typically 0.5 to 20 micromolar in complete cell culture medium.

For in vivo research (murine models), verteporfin is formulated in DMSO/polyethylene glycol/saline vehicles or in liposomal preparations mimicking the clinical formulation. Intraperitoneal or intravenous routes are employed at doses of 10 to 100 mg/kg.

9.3 Stability considerations

The lyophilized solid is stable at 2 to 8 degrees Celsius protected from light for the duration of the labeled shelf life (typically 3 years for pharmaceutical-grade Visudyne). Reconstituted solutions are stable for 4 hours at room temperature pro-

tected from light. DMSO stock solutions are stable for at least 6 months at minus 20 degrees Celsius protected from light; repeated freeze-thaw cycles should be minimized.

Photodegradation is the principal stability concern. Exposure to ambient fluorescent room lighting for as little as 15 to 30 minutes produces measurable photodegradation. All experimental protocols involving verteporfin should specify light protection at every step, and light-exposed controls should be included in experimental designs to distinguish photodynamic from pharmacological effects.

10. Stack Interactions and Combinations

10.1 Photosensitizing agents

Concurrent use of other photosensitizing agents (aminolevulinic acid, porfimer sodium, temoporfin, methoxsalen) produces additive photosensitivity risk. Temporal separation of at least 2 weeks between photosensitizing treatments is recommended in clinical practice.

10.2 Calcium channel blockers and vasoconstrictors

Agents that alter choroidal blood flow (calcium channel blockers, vasoconstrictors) may affect the accumulation of verteporfin in choroidal neovascular tissue and the efficacy of photodynamic therapy. These interactions are primarily relevant to the photodynamic application rather than the YAP-TEAD mechanism.

10.3 Anti-VEGF agents

Combination of verteporfin PDT with intravitreal anti-VEGF agents (ranibizumab, bevacizumab, aflibercept) is established clinical practice for polypoidal choroidal vasculopathy and selected cases of age-related macular degeneration [27]. The combination exploits the complementary mechanisms of vascular occlusion (PDT) and angiogenic suppression (anti-VEGF).

10.4 Conventional chemotherapy (oncology research context)

Preclinical combination studies have demonstrated synergy between verteporfin (as a YAP-TEAD inhibitor) and several chemotherapeutic agents:

Sorafenib: Synergistic growth inhibition in hepatocellular carcinoma models; verteporfin suppresses the YAP-mediated resistance mechanism that limits sorafenib efficacy [24].

Gemcitabine: Additive or synergistic effects in pancreatic cancer models, attributed to verteporfin suppression of YAP-driven survival signaling that mediates gemcitabine resistance [3].

Cisplatin: Enhanced cytotoxicity in ovarian cancer cell lines when combined with verteporfin, attributed to suppression of YAP-mediated DNA damage repair pathway activation [4].

10.5 Targeted kinase inhibitors

Verteporfin has been studied in combination with EGFR inhibitors, BRAF inhibitors, and MEK inhibitors in preclinical models, with reported synergistic effects attributed to suppression of the YAP-TEAD pathway as a resistance escape mechanism following kinase inhibitor exposure [29].

10.6 CYP-mediated interactions

Verteporfin does not undergo meaningful CYP-mediated metabolism and has not demonstrated inhibition or induction of major CYP isoforms in vitro. The potential for pharmacokinetic drug-drug interactions through CYP mechanisms is considered low [9].

10.7 Thromboembolic risk

Given the mechanism of photodynamic action (vascular thrombosis), concurrent anticoagulant or antiplatelet therapy may theoretically reduce PDT efficacy. Conversely, prothrombotic states may enhance the occlusive effect. These considerations are specific to the photodynamic application.

11. Adverse Events and Safety

11.1 Common adverse events (photodynamic therapy application)

The principal adverse events reported in the TAP and VIP registration trials (combined safety population) were [16]:

- Injection site reactions: 13.1 percent versus 5.6 percent placebo (pain, edema, inflammation, hemorrhage, discoloration, and rarely extravasation injury)
- Visual disturbances: 10 to 30 percent (blurred vision, visual field defects, decreased visual acuity). Acute severe visual acuity decrease (loss of 4 or more lines within 7 days of treatment) occurred in 0.7 percent (TAP) to 4.9 percent (VIP) of treated patients
- Photosensitivity reactions: 2.4 percent versus 0.3 percent placebo (sunburn-like reactions upon unprotected sun exposure within 48 hours of treatment)
- Infusion-related back pain: approximately 2 percent (mechanism unclear; possibly related to complement activation or liposomal formulation effects)
- Nausea: 1 to 5 percent
- Asthenia: 1 to 5 percent
- Hypercholesterolemia: 1 to 5 percent (possibly related to the liposomal lipid load)

11.2 Rare and serious adverse events

- Severe chest pain and vasovagal reactions: rare (less than 1 percent); can occur during or shortly after infusion
- Hypersensitivity reactions including anaphylaxis: rare
- Severe extravasation injury with tissue necrosis upon light exposure: reported in cases where infusion extravasated into surrounding tissues
- Atrial fibrillation and other arrhythmias: rare, reported in postmarketing surveillance

11.3 Photosensitivity management

The photosensitivity window extends approximately 48 hours post-infusion. During this period, patients must avoid direct sunlight and bright indoor lighting on exposed skin. Conventional UV-blocking sunscreens are not protective because photoactivation occurs in the visible spectrum (689 nm and shorter wavelengths visible light); only physical barriers (clothing, dark environments) provide protection [16].

If inadvertent light exposure occurs during the photosensitivity window, clinical presentation is similar to severe sunburn and may include erythema, edema, and blistering of exposed skin. Treatment is supportive.

11.4 Ocular safety

Subretinal hemorrhage, retinal pigment epithelial tears, and transient choroidal ischemia have been reported following verteporfin PDT, predominantly in patients with large neovascular lesions or with underlying conditions predisposing to these complications [14, 15].

11.5 Safety in the context of YAP-TEAD inhibition research

No clinical trial has administered verteporfin at the higher doses that would be required for systemic YAP-TEAD inhibition in oncology. The safety profile at such doses is unknown. Preclinical toxicology data at high doses (50 to 100 mg/kg in mice) have not demonstrated dose-limiting non-photodynamic toxicities, but the absence of human data at these exposures represents a significant gap in the safety characterization for potential oncologic applications.

11.6 Pregnancy and lactation

Animal reproduction studies have demonstrated teratogenicity at doses 40-fold the recommended human dose (rat) and embryoletality at 67-fold the recommended human dose (rabbit). The compound is classified as pregnancy category C (risk cannot be ruled out). Use during pregnancy is recommended only if the potential benefit justifies the potential risk to the fetus. Excretion in human milk is unknown; caution is recommended in nursing women.

12. Comparative Assessment

This section presents a structured comparative assessment of five compounds against verteporfin, evaluated across five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators span both the photodynamic therapy domain and the YAP-TEAD inhibition domain, reflecting verteporfin's dual mechanistic identity.

12.1 Porfimer sodium (Photofrin)

Mechanism: First-generation hematoporphyrin derivative photosensitizer. Photodynamic mechanism identical in principle (singlet oxygen generation upon light activation) but with substantially different photophysical properties: absorption maximum at 630 nm with low molar extinction coefficient, requiring higher light doses and limiting tissue penetration relative to verteporfin.

Clinical status: FDA-approved for esophageal cancer, non-small cell lung cancer, Barrett's esophagus, and endobronchial cancer. The first photosensitizer to achieve regulatory approval (1995).

Novelty: Low. First-generation photosensitizer chemistry; the compound is the historical reference for photodynamic therapy.

Effect size: Demonstrated clinical efficacy in approved indications (esophageal and endobronchial tumor ablation). Not applicable to neovascular macular degeneration (never developed for this indication due to poor photophysical properties for retinal application).

Promising potential: Low for new applications. The compound has been superseded by second-generation photosensitizers (verteporfin, temoporfin, talaporfin) in most active research programs.

Side-effect profile: The principal limitation is prolonged photosensitivity (4 to 6 weeks), attributable to slow clearance and cutaneous retention. This contrasts sharply with verteporfin's 48-hour photosensitivity window and was a primary driver of second-generation photosensitizer development.

Overall validation: High for the historical contribution to photodynamic therapy; low for contemporary research utility.

Comparison to verteporfin: Verteporfin is superior in photophysical properties (longer wavelength absorption, higher extinction coefficient, greater tissue penetration), pharmacokinetic profile (rapid clearance, short photosensitivity window), and selectivity (lipoprotein-mediated vascular targeting). Porfimer sodium lacks YAP-TEAD inhibitory activity. Verteporfin has replaced porfimer sodium in essentially all applications where both compounds were candidates.

12.2 Talaporfin sodium (Laserphyrin, NPe6)

Mechanism: Second-generation chlorin photosensitizer. Mono-L-aspartyl chlorin e6. Absorption maximum at 664 nm; singlet oxygen generation upon photoactivation.

Clinical status: Approved in Japan (2003) for early-stage endobronchial lung cancer; approved in Japan (2013) for malignant brain tumors (intraoperative photodynamic therapy). Under investigation for esophageal cancer and other solid tumors.

Novelty: Moderate. Improved photophysical properties relative to first-generation sensitizers; the chlorin macrocycle (like verteporfin) provides longer-wavelength absorption. However, the 664 nm absorption is intermediate between porfimer (630 nm) and verteporfin (689 nm).

Effect size: Demonstrated clinical efficacy in approved Japanese indications (endobronchial and brain tumor ablation). The photodynamic effect is comparable in principle to verteporfin at matched light doses.

Promising potential: Moderate. Active clinical research programs, particularly in Japan, for brain tumor and esophageal applications. Not developed for ophthalmic indications.

Side-effect profile: Photosensitivity window of approximately 2 weeks, intermediate between porfimer sodium (4 to 6 weeks) and verteporfin (48 hours). Other adverse events are similar to the photodynamic therapy class (local tissue effects, injection site reactions).

Overall validation: Moderate. Approved in Japan with active clinical programs; limited global registration.

Comparison to verteporfin: Verteporfin has superior pharmacokinetic properties (shorter photosensitivity window, more rapid clearance) and the additional YAP-TEAD mechanism. Talaporfin has the advantage of Japanese regulatory approval for solid tumor indications (brain, lung) where verteporfin has not achieved registration. The two compounds serve different clinical niches within the photodynamic therapy field.

12.3 Super-TDU (peptide YAP-TEAD inhibitor)

Mechanism: Cell-permeable peptide derived from the VGLL4 (vestigial-like family member 4) protein that competes with YAP for TEAD binding. The mechanism directly mimics the endogenous tumor suppressor function of VGLL4 by occupying the TEAD transcription factor binding surface [30].

Clinical status: Preclinical only. No clinical development reported.

Novelty: High. Peptide-based competitive inhibition at the TEAD binding surface represents a mechanistically distinct approach from verteporfin's allosteric disruption of YAP conformation.

Effect size: Demonstrated anti-tumor efficacy in gastric cancer xenograft models with suppression of TEAD-dependent transcription comparable in magnitude to verteporfin at effective doses [30].

Promising potential: Moderate. The peptide nature limits oral bioavailability and systemic stability; clinical translation would require formulation advances (stapled peptides, lipid nanoparticle delivery, or peptidomimetic redesign).

Side-effect profile: Preclinical only. Theoretical advantage of mechanism specificity (direct TEAD competition without the photodynamic activity of verteporfin).

Overall validation: Low. Preclinical research tool only; no clinical validation.

Comparison to verteporfin: Super-TDU is more mechanistically specific (direct TEAD competition without photosensitizing activity) but lacks the clinical validation, safety database, and regulatory path that verteporfin possesses. Verteporfin's dual mechanism (photodynamic plus YAP-TEAD) is either an advantage (broader applicability) or disadvantage (non-specific effects confound mechanism interpretation) depending on the research context.

12.4 CA3 (CIL56 analog)

Mechanism: Small-molecule YAP-TEAD inhibitor identified through structure-activity relationship optimization of the CIL56 scaffold [31]. Inhibits YAP/TAZ-TEAD transcriptional activity and suppresses downstream target gene expression.

Clinical status: Preclinical only. Early-stage research compound.

Novelty: Moderate to high. Purpose-designed small-molecule YAP-TEAD inhibitor with improved potency relative to verteporfin in some cell-based assays [31].

Effect size: Demonstrated anti-proliferative and anti-tumor efficacy in mesothelioma and other YAP-driven cancer models at low micromolar concentrations. Direct comparisons with verteporfin in matched assay systems suggest comparable or slightly superior potency [31].

Promising potential: Moderate. The compound addresses the limitations of verteporfin (photosensitivity, non-specific effects) through purpose-designed YAP-TEAD inhibition. However, the absence of clinical safety data or any regulatory path limits near-term translational potential.

Side-effect profile: Preclinical only. No photosensitizing activity (a theoretical advantage over verteporfin for systemic oncology applications).

Overall validation: Low. Research tool without clinical validation.

Comparison to verteporfin: CA3 is a more specific YAP-TEAD inhibitor without the photosensitizer burden that complicates verteporfin interpretation in dark (non-light-activated) experiments. Verteporfin retains the advantages of clinical validation, known human pharmacokinetics, and established safety data. For mechanistic research requiring specificity of YAP-TEAD inhibition, CA3 may be preferred; for translational research leveraging existing clinical infrastructure, verteporfin is preferred.

12.5 TEADi (IK-930, TEAD palmitoylation inhibitor)

Mechanism: Small-molecule inhibitor targeting the TEAD autopalmitoylation pocket, a lipid-binding site required for TEAD stability and transcriptional activity. Inhibition of palmitoylation destabilizes TEAD proteins and suppresses YAP/TAZ-

TEAD transcriptional output [32]. This mechanism targets TEAD directly rather than YAP, distinguishing it from verteporfin.

Clinical status: Phase 1 clinical trial initiated (IK-930, Ikena Oncology) for advanced solid tumors with Hippo pathway alterations including mesothelioma and NF2-mutant tumors [32].

Novelty: High. The TEAD palmitoylation pocket is a recently validated druggable site; the mechanism is distinct from all prior YAP-TEAD inhibition strategies.

Effect size: Preclinical efficacy in NF2-deficient mesothelioma models demonstrates potent suppression of TEAD-dependent transcription and anti-tumor activity. Human clinical data are not yet available.

Promising potential: High. Active Phase 1 clinical trial with a defined patient population (NF2-altered tumors) and a rationale mechanism-based strategy. This represents the most advanced clinical program specifically targeting the Hippo-YAP-TEAD axis for oncology.

Side-effect profile: Phase 1 safety data not yet reported. Theoretical advantages include absence of photosensitizing activity and mechanism specificity for TEAD.

Overall validation: Low to moderate. Phase 1 clinical trial in progress; no efficacy readout available.

Comparison to verteporfin: TEADi/IK-930 represents the next generation of Hippo pathway therapeutics, designed specifically as oncology agents rather than repurposed photosensitizers. If Phase 1 data are favorable, this class will likely supersede verteporfin as the research and clinical tool for YAP-TEAD pathway inhibition in oncology. Verteporfin retains advantages of immediate availability, known safety at the photodynamic therapy dose, and utility as a preclinical reference compound for YAP-TEAD biology while purpose-designed agents advance through clinical development.

12.6 Comparator summary

The five comparators span two pharmacological domains. In the photodynamic therapy domain, **porfimer sodium** is the historical first-generation reference with inferior pharmacokinetics, and **talaporfin sodium** is a contemporary second-generation chlorin with intermediate properties and Japanese regulatory approval for

solid tumor applications. In the YAP-TEAD inhibition domain, **Super-TDU** is a mechanistically elegant peptide tool, **CA3** is a purpose-designed small molecule with improved specificity, and **TEADi/IK-930** represents the most advanced clinical strategy targeting the Hippo pathway directly through TEAD destabilization.

Verteporfin occupies a unique bridging position: it is the only compound with both regulatory approval and established clinical safety data that also possesses validated YAP-TEAD inhibitory activity. Its limitations are the photosensitizing activity (which complicates non-photodynamic applications), the translational dose gap for systemic YAP-TEAD oncology (preclinical effective doses far exceed the approved photodynamic therapy dose), and the non-specificity of its YAP-TEAD mechanism relative to purpose-designed inhibitors. Its strengths are immediate clinical and research availability, extensive human safety data, applicability to both photodynamic and dark (non-photoactivated) experimental designs, and the existing regulatory infrastructure that could support repurposed clinical investigation.

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