

RESEARCH MONOGRAPH . COMPOUND PROFILE

SRT2104

A second-generation imidazothiazole-scaffold sirtuin 1 activator developed by Sirtris Pharmaceuticals and advanced through multiple Phase 2 clinical programs by GlaxoSmithKline, distinguished from first-generation sirtuin-activating compounds by high target selectivity and favorable oral pharmacokinetics.

DOCUMENT	KDC-MN-1478
ISSUED	2026-05-13
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Selective small-molecule allosteric activator of NAD-dependent protein deacetylase sirtuin 1 (SIRT1)

ABSTRACT

SRT2104 (GSK2245840) is a synthetic, orally bioavailable, small-molecule allosteric activator of the NAD-dependent protein deacetylase sirtuin 1 (SIRT1, silent mating type information regulation 2 homolog 1), developed at Sirtris Pharmaceuticals and subsequently advanced into clinical trials by GlaxoSmithKline following the 2008 acquisition of Sirtris for approximately 720 million United States dollars. The compound is a second-generation sirtuin-activating compound (STAC) built on an optimized imidazo[2,1-b]thiazole scaffold and is reported to activate SIRT1 deacetylase activity approximately 1000-fold more potently than the natural polyphenol resveratrol in fluorophore-tagged peptide substrate assays, with minimal activity against a panel of more than 180 non-SIRT1 targets including kinases, G-protein-coupled receptors, nuclear receptors, ion channels, enzymes, and transporters [1, 2]. The allosteric mechanism involves binding to the N-terminal domain of SIRT1, lowering the Michaelis constant (K_m) for the acetylated protein substrate without competing with either the NAD cofactor or the substrate acetyl-lysine site [3]. Downstream consequences of SIRT1 activation by SRT2104 include deacetylation and functional modulation of the transcription factor p53, the RelA/p65 subunit of nuclear factor kappa B (NF- κ B), forkhead box protein O3 (FOXO3), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha), and signal transducer and activator of transcription 3 (STAT3), producing composite anti-inflammatory, metabolic, and cytoprotective effects that have been characterized across a broad range of preclinical disease models [4, 5].

Pharmacokinetics in humans are characterized by oral absorption with time to peak plasma concentration of 1 to 3 hours after single dosing, a terminal elimination half-life of 8 to 24 hours depending on dose, and substantial inter-individual variability that is not dose-proportional across the studied range of 0.03 to 3.0 grams [6]. The variable and non-dose-proportional pharmacokinetic profile has been identified as a principal limitation of the compound for clinical development in its current oral formulation. SRT2104 is poorly soluble in water and is formulated as a lipid-based oral capsule to improve bioavailability.

Clinical evaluation has spanned at least seven registered clinical trials across multiple indications. In a Phase 1 trial in healthy elderly volunteers (60 to 80 years of age), 28 days of oral SRT2104 at 0.5 or 2.0 grams daily produced reductions in serum cholesterol, low-density lipoprotein, and triglycerides, with trends toward improved mitochondrial oxidative phosphorylation capacity as measured by phosphorus-31 magnetic resonance spectroscopy of skeletal muscle [7]. A Phase 2 randomized, placebo-controlled trial in 37 subjects with type 2 diabetes mellitus treated for 28 days at doses of 0.25, 0.5, 1.0, or 2.0 grams daily did not demonstrate improved glycemic control but produced a statistically significant reduction in total cholesterol and triglycerides at the 1.0 gram dose [8]. A separate cardiometabolic study in type 2 diabetic subjects reported trends toward improved endothelial function and arterial stiffness [9]. A Phase 2 trial in 40 subjects with moderate to severe psoriasis treated for 84 days at escalating doses of 250, 500, or 1000 milligrams daily reported 35 percent of SRT2104-treated patients achieving good to excellent histological improvement on skin biopsy, but three serious adverse events were reported including pneumonitis and pancreatitis [10]. A trial in mild to moderate

ulcerative colitis (31 subjects, 50 or 500 milligrams daily for 8 weeks) demonstrated tolerability but limited clinical efficacy, with only 3 of 26 evaluable subjects achieving endoscopic remission [11]. In a human endotoxemia model, SRT2104 pretreatment significantly reduced lipopolysaccharide-induced cytokine release (interleukin-6, interleukin-8) and coagulation activation, representing the first human demonstration of anti-inflammatory and anticoagulant activity consistent with pharmacological SIRT1 activation [12].

Preclinical pharmacology is extensive. The Mercken et al. (2014) study at the National Institute on Aging demonstrated that SRT2104 extends both mean and maximum lifespan of male mice fed a standard diet by 9.7 percent and 4.9 percent respectively, with preserved bone mineral density, muscle mass, motor coordination, and insulin sensitivity [13]. The Jiang et al. (2014) study demonstrated blood-brain barrier penetration, attenuation of brain atrophy, improvement of motor function, and extension of median lifespan by approximately 16 percent in N171-82Q Huntington disease model mice [14]. Additional preclinical evidence spans emphysema, sepsis, neonatal white matter injury, microglia polarization, dendritic outgrowth, and auditory cell senescence. GlaxoSmithKline discontinued active clinical development of SRT2104 following the 2013 closure of the Sirtris unit, though the compound remains widely used as a reference SIRT1 activator in academic and preclinical research. This monograph reviews chemistry, molecular pharmacology, pharmacokinetics, the complete clinical evidence base, sourcing and handling, stack interactions, adverse events, and a comparative assessment of five SIRT1 modulators against SRT2104 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed International Nonproprietary Name: None assigned. The compound did not advance to registration.

Development codes: SRT2104 (Sirtris Pharmaceuticals), GSK2245840 (GlaxoSmithKline). The Sirtris code SRT2104 is the canonical identifier in the published pharmacology and clinical trial literature.

Chemical Abstracts Service registry number: 1093403-33-8 (free base).

International Union of Pure and Applied Chemistry name: 4-methyl-N-[2-[3-(morpholin-4-ylmethyl)imidazo[2,1-b][1,3]thiazol-6-yl]phenyl]-2-(pyridin-3-yl)-1,3-thiazole-5-carboxamide.

PubChem CID: 25108829.

Other identifiers: IUPHAR/BPS Guide to Pharmacology ligand identifier 9515.

1.2 Structural class and chemistry

SRT2104 is a synthetic heterocyclic small molecule belonging to the second-generation sirtuin-activating compound (STAC) class. The structural scaffold comprises an imidazo[2,1-b]thiazole core bearing a morpholinylmethyl substituent at position 3 and a phenyl ring linker at position 6, connected through a carboxamide bond to a 4-methyl-2-(pyridin-3-yl)-1,3-thiazole-5-carboxylate moiety [1, 2]. The scaffold was derived through optimization of the first-generation imidazothiazole STACs (SRT1720, SRT2183, SRT1460) to improve SIRT1 selectivity and reduce off-target kinase, GPCR, and ion channel activity that characterized the earlier series [15].

Molecular formula: C₂₆H₂₄N₆O₂S₂.

Exact mass: 516.1402 g/mol (monoisotopic).

Molecular weight: 516.64 g/mol.

Physical properties: White to off-white solid powder. Insoluble in water and ethanol; soluble in dimethyl sulfoxide (DMSO) with gentle warming (typically prepared as 10 millimolar stock solutions in DMSO). The compound is poorly water-soluble, which has been a significant formulation challenge; clinical formulations employed lipid-based capsule delivery systems to improve oral absorption [6]. Storage as a dry solid at minus 20 degrees Celsius is recommended; the compound is reported to be stable in human and mouse liver mitochondria and plasma [2].

Stereochemistry: SRT2104 does not contain classical stereocenters. The compound is achiral.

1.3 Synthesis

The published synthesis of SRT2104 proceeds through construction of the imidazo[2,1-b]thiazole core, functionalization at position 3 with a morpholine-containing substituent through a Mannich-type or reductive amination reaction, arylation at position 6 through palladium-catalyzed cross-coupling to introduce the 2-aminophenyl linker, and amide bond formation with the 4-methyl-2-(pyridin-3-yl)-1,3-thiazole-5-carboxylic acid. The compound was originally identified through high-throughput screening of approximately 29,000 compounds for SIRT1 activation using a fluorophore-tagged acetyl-lysine peptide substrate assay, followed by iterative medicinal chemistry optimization for potency, selectivity, and oral bioavailability [1, 2]. Industrial-scale synthesis details have not been published in the open literature; the compound is manufactured by contract research organizations and specialty chemical suppliers at greater than 98 percent purity by high-performance liquid chromatography (HPLC).

2. Abstract

SRT2104 (GSK2245840; CAS 1093403-33-8) is a first-in-class, orally bioavailable, selective small-molecule allosteric activator of the NAD-dependent protein deacetylase sirtuin 1 (SIRT1), developed at Sirtris Pharmaceuticals and advanced through clinical evaluation by GlaxoSmithKline [1, 2]. The compound represents the most advanced clinical candidate in the sirtuin-activating compound (STAC) class and is the only STAC to have completed multiple Phase 2 clinical trials across metabolic, inflammatory, dermatologic, and gastrointestinal indications.

The molecular pharmacology centers on allosteric activation of SIRT1 enzymatic activity. SIRT1 is a class III histone deacetylase that removes acetyl groups from lysine residues on protein substrates in an NAD-dependent reaction, coupling cellular energy and redox status to post-translational regulation of transcription factors, histones, and signaling proteins [3, 4]. SRT2104 binds to the SIRT1 N-terminal domain and lowers the K_m for acetylated protein substrates, enhancing deacetylation of p53, NF- κ B p65, FOXO3, PGC-1 α , and STAT3 without competing for the NAD cofactor binding site [3, 5]. The downstream consequences span suppression of NF- κ B-driven inflammatory cytokine transcription, enhancement of mitochondrial biogenesis through PGC-1 α deacetylation, promotion of autophagy, reduction of cellular senescence through p53 and FOXO3 pathways, and modulation of glucose and lipid metabolism [4, 5].

The clinical evidence base encompasses seven or more registered clinical trials. The compound has demonstrated tolerability across single doses of 0.03 to 3.0 grams and repeated daily doses of 0.25 to 2.0 grams for up to 84 days [6, 7, 8, 10]. Consistent pharmacodynamic signals include reductions in serum total cholesterol, low-density lipoprotein, and triglycerides. Anti-inflammatory activity has been demonstrated in the human lipopolysaccharide endotoxemia model, with significant suppression of interleukin-6, interleukin-8, and coagulation activation [12]. Clinical efficacy signals in disease indications (type 2 diabetes, psoriasis, ulcerative colitis) have been modest or inconclusive, limited by the non-dose-proportional and highly variable pharmacokinetic profile of the current oral formulation [8, 10, 11].

Preclinical pharmacology is extensive and spans longevity (lifespan extension in standard-diet-fed mice), neurodegeneration (Huntington disease model survival and motor function), emphysema (alveolar epithelial cell senescence protection), sepsis (autophagic degradation of pyruvate kinase M2), neonatal brain injury, and cardiovascular inflammation [13, 14, 16, 17]. The compound is not approved by any regulatory authority. GlaxoSmithKline discontinued active clinical development following the 2013 closure of the Sirtris research unit. SRT2104 remains commercially available from multiple research chemical suppliers and is the standard reference SIRT1 activator in current academic and preclinical research.

3. Discovery and Development History

3.1 Origin

SRT2104 was developed at Sirtris Pharmaceuticals, a biotechnology company founded in 2004 by David Sinclair, Christoph Westphal, Andrew Perlman, Richard Aldrich, Richard Pops, and Paul Schimmel, with the explicit mission of developing therapeutics based on the pharmacological activation of sirtuins, a family of NAD-dependent protein deacetylases linked to lifespan extension in model organisms [18, 19]. The founding scientific thesis was that the natural polyphenol resveratrol, identified by the Sinclair laboratory as a SIRT1 activator that extended yeast lifespan, could serve as the basis for development of more potent and selective synthetic analogs with drug-like properties [20].

Sirtris identified SRT2104 through high-throughput screening of approximately 29,000 compounds using a fluorophore-tagged acetyl-lysine peptide substrate assay for SIRT1 activation, followed by iterative medicinal chemistry optimization [1, 2]. The compound was classified as a second-generation STAC, developed after the first-generation compounds SRT1720, SRT2183, and SRT1460 were found to have substantial off-target activity against kinases, GPCRs, and other non-SIRT1 targets [15]. SRT2104 was selected for clinical advancement on the basis of approximately 1000-fold greater potency than resveratrol at SIRT1 activation, minimal non-SIRT1 activity across a panel of more than 180 molecular targets, acceptable oral bioavailability in preclinical species, and stability in human liver microsomes and plasma [1, 2].

3.2 GlaxoSmithKline acquisition and clinical development

In April 2008, GlaxoSmithKline acquired Sirtris Pharmaceuticals for approximately 720 million United States dollars, one of the largest biotechnology acquisitions of that period [18, 19]. The acquisition was driven by the scientific and commercial thesis that pharmacological SIRT1 activation could provide a platform for therapeutics in type 2 diabetes, cardiovascular disease, neurodegeneration, and other age-related conditions.

Under GlaxoSmithKline stewardship, SRT2104 was advanced into clinical trials. The first Phase 1 pharmacokinetic and tolerability studies in healthy volunteers (GSK study 113140) established the single-dose and repeat-dose safety profile across the 0.03 to 3.0 gram range [6]. Subsequent clinical programs included a Phase 1 trial in healthy elderly volunteers [7], a Phase 2 trial in type 2 diabetes mellitus [8], a cardiometabolic study in type 2 diabetes [9], a Phase 2 trial in psoriasis [10], a trial in ulcerative colitis [11], and a human endotoxemia study [12]. Additional registered trials on ClinicalTrials.gov addressed smoking cessation and cardiovascular endpoints.

3.3 Controversy regarding SIRT1 activation mechanism

The development of SRT2104 occurred in the context of a significant scientific controversy regarding the mechanism of SIRT1 activation by STACs. In 2010, Pacholec et al. published a report in the *Journal of Biological Chemistry* demonstrating that the first-generation STACs (SRT1720, SRT2183, SRT1460) and resveratrol did not activate SIRT1 when tested with native (non-fluorophore-tagged) peptide or full-length protein substrates [15]. The report raised fundamental questions about whether SIRT1 activation by STACs was an artifact of the fluorophore-tagged substrate used in the screening assay. Subsequent work by Hubbard et al. (2013) at Sirtris and collaborators partially resolved this controversy by identifying specific glutamate residues in SIRT1 substrates (particularly glutamate at position minus 1 relative to the acetyl-lysine) that mediate the allosteric activation mechanism, demonstrating that STACs including SRT2104 do activate SIRT1 deacetylation of native substrates containing this motif [3]. The debate has been substantially but not entirely resolved; SRT2104 is generally accepted as a bona fide SIRT1 activator, though the full scope of SIRT1-dependent versus SIRT1-independent pharmacological effects remains an area of active investigation.

3.4 Discontinuation and legacy

In March 2013, GlaxoSmithKline closed the Sirtris Pharmaceuticals research facilities in Cambridge, Massachusetts, and absorbed the remaining intellectual property into its broader research portfolio [18, 19]. Active clinical development of SRT2104 was discontinued; no regulatory submission was pursued for any indication. The reasons for discontinuation appear to be multifactorial: the non-dose-proportional and highly variable pharmacokinetics limited the clinical utility of the

current formulation; Phase 2 efficacy signals across the studied indications were modest; and the scientific controversy regarding the SIRT1 activation mechanism reduced corporate confidence in the therapeutic thesis.

Despite the discontinuation of clinical development, SRT2104 continues to be the most widely used reference SIRT1 activator in academic research, with publications spanning longevity biology, neurodegeneration, pulmonary disease, sepsis, hearing loss, and oncology. The compound is commercially available from multiple research chemical suppliers at research grade.

4. Mechanism of Action

SRT2104 is a single-target allosteric activator. Its principal molecular activity is enhancement of the enzymatic deacetylase function of SIRT1, producing downstream effects through the deacetylation and functional modulation of multiple SIRT1 substrates.

4.1 SIRT1 enzyme biology

SIRT1 (sirtuin 1, silent mating type information regulation 2 homolog 1) is a class III histone deacetylase that catalyzes the removal of acetyl groups from epsilon-amino groups of lysine residues on protein substrates in an NAD-dependent reaction [4, 21]. The reaction consumes one molecule of NAD per deacetylation event, producing nicotinamide and 2-prime-O-acetyl-ADP-ribose as co-products. This NAD dependence couples SIRT1 activity to cellular energy and redox status, positioning SIRT1 as a metabolic sensor.

SIRT1 is the most studied mammalian sirtuin (of seven, SIRT1 through SIRT7) and is expressed ubiquitously with particularly high expression in brain, liver, skeletal muscle, adipose tissue, pancreas, and immune cells [4, 21]. The enzyme is predominantly nuclear but shuttles to the cytoplasm under specific signaling conditions. The protein comprises a conserved catalytic core domain flanked by N-terminal and C-terminal regulatory domains. The N-terminal domain contains the allosteric activation site targeted by STACs.

4.2 Allosteric activation mechanism

SRT2104 binds to the SIRT1 N-terminal domain at a site that is topographically distinct from the catalytic core, the NAD binding pocket, and the substrate binding channel [3]. The binding event induces a conformational change that lowers the Michaelis constant (K_m) for acetylated protein substrates, effectively increasing the catalytic efficiency of SIRT1 at physiological substrate concentrations without altering the maximal velocity (V_{max}) [3]. The activation is substrate-selective: SIRT1

substrates containing a hydrophobic residue (particularly glutamate) at the minus-1 position relative to the target acetyl-lysine are preferentially activated, while substrates lacking this motif show reduced or absent activation [3].

The selectivity of SRT2104 for SIRT1 over the other six mammalian sirtuins (SIRT2 through SIRT7) has been characterized by in vitro profiling. The compound does not appreciably activate SIRT2, SIRT3, or SIRT5 at concentrations up to 100 micromolar [1, 2]. The compound also shows minimal activity against a profiling panel of more than 180 non-sirtuin targets, including kinases, GPCRs, nuclear receptors, ion channels, enzymes, and transporters, at concentrations of 10 micromolar [2]. This selectivity profile distinguishes SRT2104 sharply from the first-generation STACs (SRT1720, SRT2183, SRT1460), which showed greater than 50 percent inhibition of 38, 14, and 20 of the profiled targets respectively at 10 micromolar, and from resveratrol, which inhibited 7 targets at the same concentration [15].

4.3 Downstream substrates and pathways

The principal SIRT1 substrates whose deacetylation mediates the pharmacological effects of SRT2104 include:

p53: Deacetylation of p53 at lysine 382 reduces p53 transcriptional activity, attenuating apoptotic and senescence programs [4, 5]. This pathway mediates the anti-senescence effects observed in alveolar epithelial cells and the cytoprotective effects in ischemia-reperfusion models.

NF- κ B p65 (RelA): Deacetylation of the p65 subunit at lysine 310 suppresses NF- κ B-dependent transcription of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-alpha), interleukin-1beta, interleukin-6, and interleukin-8 [5, 22]. This pathway is the principal molecular basis for the anti-inflammatory effects observed in the human endotoxemia model and in preclinical sepsis and colitis models.

FOXO3 (forkhead box protein O3): Deacetylation of FOXO3 promotes transcription of antioxidant genes (manganese superoxide dismutase, catalase) and autophagy genes, and suppresses pro-apoptotic transcription [4, 5]. This pathway mediates the antioxidant and autophagy-promoting effects and contributes to the emphysema and senescence protection observed in preclinical models.

PGC-1alpha (peroxisome proliferator-activated receptor gamma coactivator 1-alpha): Deacetylation of PGC-1alpha enhances its transcriptional coactivator function, promoting mitochondrial biogenesis, oxidative phosphorylation, and fatty acid oxidation [4, 21]. This pathway is the principal molecular basis for the metabolic effects (improved lipid profiles, enhanced mitochondrial function) observed in clinical and preclinical studies.

STAT3: Deacetylation of STAT3 modulates inflammatory signaling downstream of cytokine receptors [5]. The role of STAT3 deacetylation in SRT2104 pharmacology is less well characterized than the other substrates but contributes to the composite anti-inflammatory profile.

4.4 Additional mechanisms

SRT2104 has been reported to promote autophagic degradation of pyruvate kinase M2 (PKM2) through a SIRT1-dependent mechanism, representing a novel pathway by which SIRT1 activation suppresses inflammatory signaling in sepsis models [17]. PKM2 is a glycolytic enzyme that, in its dimeric form, translocates to the nucleus and functions as a transcriptional coactivator for inflammatory gene expression. SIRT1-mediated autophagy degrades PKM2 and reduces its nuclear inflammatory function.

SRT2104 has also been shown to enhance dendritic outgrowth and spine formation through SIRT1-mediated activation of mechanistic target of rapamycin complex 1 (mTORC1) signaling, with increased phosphorylation of 4E-BP1 and p70S6K [23]. This neurotrophic mechanism is distinct from the anti-inflammatory and metabolic pathways and may contribute to the neuroprotective effects observed in Huntington disease and neonatal brain injury models.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

SRT2104 is administered orally as a lipid-based capsule formulation. The compound is poorly water-soluble, and the lipid-based formulation was developed to address the absorption challenge [6]. After single oral doses ranging from 0.03 to 3.0 grams in healthy volunteers, time to peak plasma concentration (T_{max}) ranged from 1 to 3 hours [6]. After seven days of consecutive daily dosing, T_{max} shortened to 1 to 2 hours, consistent with modest accumulation or formulation-dependent absorption enhancement on repeat dosing [6].

Oral bioavailability has not been precisely quantified in published reports owing to the absence of an intravenous comparator study, but the lipid dependence of absorption and the food effect (improved absorption with high-fat meals) suggest that absolute bioavailability in the fasted state is low and variable. Clinical protocols generally specified administration with food [7, 8].

The most pharmacokinetically notable feature of SRT2104 is the high inter-individual variability and non-dose-proportional exposure. Across the 0.03 to 3.0 gram single-dose range, area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) did not increase proportionally with dose [6]. This non-proportionality is attributed to solubility-limited absorption and is the principal pharmacokinetic limitation identified in the clinical development program.

5.2 Distribution

Distribution data in humans are limited. The compound is lipophilic and expected to distribute widely into tissues. Preclinical data in mice confirm blood-brain barrier penetration, supported by the neuroprotective efficacy observed in the N171-82Q Huntington disease model [14]. The compound demonstrated stability in human and mouse liver mitochondria and plasma in vitro [2].

Plasma protein binding has not been quantified in published reports. The lipophilicity and aromatic heterocyclic scaffold predict moderate to high plasma protein binding.

5.3 Metabolism

Metabolic characterization of SRT2104 in humans has not been extensively published. The terminal elimination half-life of 8 to 24 hours after single dosing and 12 to 20 hours after seven days of repeat dosing suggests predominantly hepatic metabolism with moderate extraction [6]. The specific cytochrome P450 isoforms responsible for biotransformation have not been characterized in the published literature. Given the heterocyclic scaffold, CYP3A4-mediated oxidative metabolism is a reasonable prediction, though this has not been confirmed.

5.4 Elimination

Elimination data in humans are limited to the plasma half-life estimates described above. The route of elimination (renal versus biliary excretion of metabolites) has not been characterized in published reports.

5.5 Routes of administration

The only route of administration used in human clinical trials is oral, with the lipid-based capsule formulation [6, 7, 8, 10, 11]. For preclinical research, the compound is administered orally (gavage), intraperitoneally, or added to standard rodent chow at concentrations of 100 milligrams per kilogram of diet for chronic longevity studies [13] or at specific doses (for example, 200 milligrams per kilogram per day) for shorter-term efficacy studies [14].

For in vitro research, the compound is dissolved in DMSO and diluted into culture media at working concentrations typically in the range of 0.1 to 10 micromolar. The final DMSO concentration in culture media should be maintained below 0.1 percent to avoid solvent cytotoxicity.

5.6 Special populations

No specific pharmacokinetic data in renally or hepatically impaired populations have been published. The Phase 1 trial in elderly volunteers (60 to 80 years of age) did not report pharmacokinetic parameters substantially different from younger adult data, though formal age-effect analysis was not the primary objective [7]. Pediatric pharmacokinetics have not been studied.

6. Clinical Evidence Base

6.1 Phase 1 pharmacokinetic and tolerability studies

The first-in-human studies of SRT2104 were a series of Phase 1 single-ascending-dose and multiple-ascending-dose studies conducted under GlaxoSmithKline sponsorship (GSK study 113140 and related protocols) [6]. Healthy male and female volunteers received single oral doses of 0.03, 0.1, 0.25, 0.5, 1.0, 2.0, or 3.0 grams, or placebo, followed by a 7-day repeat-dose phase at selected doses. SRT2104 was well tolerated at all dose levels. No dose-limiting toxicities were observed that would have curtailed dose escalation. Adverse events reported in three or more subjects receiving SRT2104 included headache (28 percent), flatulence (14 percent), nausea (8 percent), diarrhea (6 percent), and nasopharyngitis (6 percent). One severe adverse event (headache) was reported; remaining adverse events were mild to moderate in severity and self-limiting [6].

6.2 Elderly volunteer trial

Libri et al. (2012) conducted a pilot randomized, placebo-controlled, double-blind Phase 1 trial in elderly volunteers aged 60 to 80 years [7]. Oral SRT2104 at 0.5 or 2.0 grams daily or matching placebo was administered once daily for 28 consecutive days. Pharmacodynamic endpoints included oral glucose tolerance tests, serum lipid profiles, magnetic resonance imaging for whole-body visceral and subcutaneous fat quantification, maximal aerobic capacity testing, and phosphorus-31 magnetic resonance spectroscopy (31P MRS) of skeletal muscle for estimation of mitochondrial oxidative capacity.

SRT2104 was generally safe and well tolerated. Serum cholesterol, low-density lipoprotein levels, and triglycerides decreased with treatment [7]. No significant changes in oral glucose tolerance test responses were observed. 31P MRS showed trends for more rapid calculated adenosine diphosphate (ADP) and phosphocreatine (PCr) recoveries after exercise, consistent with increased mitochondrial oxidative phosphorylation capacity [7]. The authors concluded that SRT2104 is biologically active in humans with pharmacodynamic signals consistent with SIRT1 activation.

6.3 Type 2 diabetes mellitus

Baksi et al. (2014) conducted a Phase 2 randomized, placebo-controlled, double-blind, multi-dose study in 37 subjects with type 2 diabetes mellitus (glycosylated hemoglobin 7.5 to 10.5 percent, fasting glucose 160 to 240 milligrams per deciliter, on stable metformin) [8]. Subjects were evenly randomized to placebo or SRT2104 at 0.25, 0.5, 1.0, or 2.0 grams administered orally once daily for 28 days. The primary endpoint was change in fasting plasma glucose.

Treatment with SRT2104 did not produce consistent, dose-related improvements in glucose or insulin parameters [8]. The failure to demonstrate glycemic efficacy was attributed to the non-dose-proportional pharmacokinetics and large inter-subject variability in drug exposure. However, the 1.0 gram daily dose was associated with a statistically significant decrease from baseline in total cholesterol and triglycerides, and trends toward increased high-density lipoprotein cholesterol [8]. Safety evaluation found no major differences between groups in adverse event frequency.

A separate cardiometabolic study (Venkatasubramanian et al. 2013, 2016) in subjects with type 2 diabetes evaluated the effects of SRT2104 on markers of endothelial function, arterial stiffness, and thrombosis [9]. The study reported trends toward improved endothelial function and reduced arterial stiffness, though sample sizes were small and the results were hypothesis-generating rather than definitive.

6.4 Psoriasis

Krueger et al. (2015) conducted a Phase 2 randomized, placebo-controlled study in 40 patients with moderate to severe psoriasis [10]. Patients were randomized to three escalating dose groups of SRT2104 (250, 500, or 1000 milligrams daily) or placebo for 84 days, with skin biopsies obtained at baseline and at the end of treatment. Across all SRT2104 groups, 35 percent of patients achieved good to excellent histological improvement based on blinded pathological assessment [10].

The study reported serious adverse events in 3 of 39 subjects (8 percent) receiving SRT2104: two subjects in the 250 milligram group (pneumonitis and pancreatitis) and one subject in the 1000 milligram group (elevated alanine aminotransferase and bilirubin) [10]. All serious adverse events were assessed as likely related or related to SRT2104. The most frequently reported non-serious adverse events in SRT2104 arms were dizziness, headache, psoriatic arthropathy, gastrointestinal

symptoms, and transaminase elevations. Twenty-seven subjects (69 percent) across all treatment groups, including placebo, experienced at least one treatment-emergent adverse event.

6.5 Ulcerative colitis

Sands et al. (2016) conducted a trial of SRT2104 in 31 patients with mild to moderate ulcerative colitis [11]. Patients were randomized to 50 milligrams or 500 milligrams of SRT2104 daily for 8 weeks. The study assessed colonic exposure, safety, and clinical activity by Mayo score, Simple Clinical Colitis Activity Index, fecal calprotectin, and blinded endoscopic scoring.

SRT2104 was generally well tolerated, with the majority of subjects completing the 8-week treatment period. However, clinical efficacy was limited: only 3 of 26 evaluable subjects achieved remission on blinded endoscopic assessment, and clinical remission (Mayo score of 2 or less, no subscore greater than 1) was achieved in 4 patients (2 of 13 evaluable patients in each dose group) [11]. One subject experienced a serious adverse event requiring study withdrawal, and another was withdrawn for a severe ulcerative colitis flare. The authors concluded that further evaluation of SRT2104 as a therapeutic strategy for ulcerative colitis was not warranted.

6.6 Human endotoxemia model

van der Meer et al. (2015) conducted a randomized, double-blind, placebo-controlled study of SRT2104 in the human lipopolysaccharide (LPS) endotoxemia model [12]. Twenty-four healthy volunteers were randomized to SRT2104 or placebo, with subsequent intravenous LPS challenge. SRT2104 pretreatment significantly reduced LPS-induced release of interleukin-6, interleukin-8, and attenuated levels of tumor necrosis factor alpha compared to placebo [12]. The compound also significantly reduced LPS-induced coagulation activation, including reductions in prothrombin fragment 1+2 and thrombin-antithrombin complexes. This study represented the first human demonstration of biological anti-inflammatory and anti-coagulant responses consistent with pharmacological SIRT1 activation and provided the strongest clinical pharmacodynamic evidence for the mechanism of action of SRT2104.

7. Preclinical Pharmacology

7.1 Longevity and aging

The Mercken et al. (2014) study at the National Institute on Aging represents the most comprehensive preclinical characterization of SRT2104 in aging biology [13]. Male C57BL/6J mice were fed a standard diet supplemented with SRT2104 at 100 milligrams per kilogram of diet beginning at 6 months of age and continuing for the remainder of their natural lifespan. SRT2104 supplementation resulted in a 9.7 percent increase in mean lifespan and a 4.9 percent increase in maximum lifespan [13]. The lifespan extension was accompanied by preservation of bone mineral density (as measured by dual-energy X-ray absorptiometry), preservation of skeletal muscle mass, improved motor coordination (rotarod testing), improved insulin sensitivity, and higher mitochondrial content in skeletal muscle. Inflammatory markers were decreased in SRT2104-treated aged mice compared to controls. Short-term SRT2104 treatment also preserved bone and muscle mass in an experimental model of disuse atrophy [13].

7.2 Huntington disease

Jiang et al. (2014) demonstrated that SRT2104 is neuroprotective in the N171-82Q transgenic mouse model of Huntington disease [14]. SRT2104 was administered in the diet at 200 milligrams per kilogram per day beginning at 6 weeks of age. The compound penetrated the blood-brain barrier, attenuated brain atrophy as measured by magnetic resonance imaging, improved motor function on rotarod and grip strength testing, and extended median lifespan by approximately 16 percent compared to control-diet Huntington disease mice [14]. The neuroprotective mechanism was attributed to SIRT1-mediated deacetylation of targets including p53 and NF- κ B in the striatum and cortex.

7.3 Emphysema and pulmonary disease

Gu et al. (2020) demonstrated that SRT2104 reduced senescence of type II alveolar epithelial cells in a rat model of emphysema induced by cigarette smoke extract and intratracheal lipopolysaccharide instillation [16]. SRT2104 treatment upregu-

lated SIRT1 and FOXO3a expression, increased p53 deacetylation, reduced senescence-associated beta-galactosidase activity, and improved lung function parameters including airway resistance, lung dynamic compliance, and peak expiratory flow rate [16]. The mechanism was characterized as operating through SIRT1/FOXO3a and SIRT1/p53 signaling pathways.

7.4 Sepsis and inflammation

Li et al. (2023) demonstrated that SRT2104 alleviated lethal inflammatory injury in a sepsis model through promotion of autophagic degradation of pyruvate kinase M2 (PKM2) [17]. The study identified PKM2 as a critical mediator of inflammatory cytokine production in sepsis and showed that SIRT1 activation by SRT2104 promoted autophagic clearance of PKM2, reducing nuclear PKM2 accumulation and downstream inflammatory gene transcription. This study identified a novel anti-inflammatory mechanism beyond the canonical NF- κ B p65 deacetylation pathway.

7.5 Neonatal brain injury

SRT2104 has been reported to mitigate hypoxia-induced white matter injury in neonatal mice [24]. The mechanism involves SIRT1-dependent modulation of microglial polarization, shifting microglia from the pro-inflammatory M1 phenotype toward the neuroprotective M2 phenotype through NF- κ B pathway suppression.

7.6 Neuronal development and plasticity

SRT2104 enhances dendritic outgrowth and spine formation in cultured neurons through SIRT1-mediated activation of mTORC1 signaling, with increased phosphorylation of downstream targets 4E-BP1 and p70S6K [23]. This neurotrophic mechanism represents a distinct pathway from the anti-inflammatory and metabolic activities and may have implications for neurodevelopmental and neurodegenerative research.

7.7 Auditory cell senescence

Recent work has demonstrated that SRT2104 activates SIRT1 and enhances mitophagy in auditory cells, reducing senescence markers and potentially relevant to age-related hearing loss [25].

8. Sourcing and Quality Verification

SRT2104 is not available as a pharmaceutical-grade registered medicine. The compound was never approved by any regulatory authority and is not currently in active clinical development. All available material is research-grade.

Research-grade SRT2104 is supplied by multiple specialty chemical and research reagent suppliers, including Selleck Chemicals, Cayman Chemical, MedChemExpress, Sigma-Aldrich, InvivoChem, Tocris, BOC Sciences, APExBIO, Biosynth, and others. The compound is typically supplied as a solid powder at greater than 98 percent purity by HPLC. Supply quantities range from milligrams (5 to 50 milligrams for in vitro work) to grams (for chronic in vivo dosing studies). Pricing is moderate for a research-grade small molecule, typically in the range of 100 to 500 United States dollars per 50 milligrams at the time of monograph preparation, varying by supplier and quantity.

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

- High-performance liquid chromatography area-percent purity (target greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (517.14 for $[M+H]^+$ of the free base)
- Nuclear magnetic resonance spectroscopy (proton and carbon-13) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual moisture
- Residual solvent analysis if the compound is supplied from a custom synthesis

The CAS number 1093403-33-8 is the definitive identifier for procurement and analytical confirmation. Investigators should note that some early publications report a molecular formula of $C_{25}H_{23}N_5O_2S$ and molecular weight of 457.55, which corresponds to an incorrect structural assignment; the correct molecular formula confirmed by PubChem, IUPHAR, and multiple vendors is $C_{26}H_{24}N_6O_2S_2$ with molecular weight 516.64 [1, 2].

9. Reconstitution and Handling

SRT2104 is poorly soluble in water and ethanol. For in vitro research, the compound is dissolved in DMSO to prepare concentrated stock solutions, typically at 10 to 50 millimolar. Gentle warming (37 to 50 degrees Celsius) may be required to achieve complete dissolution in DMSO. Stock solutions should be aliquoted into single-use volumes and stored at minus 20 degrees Celsius. Repeated freeze-thaw cycles should be minimized, though the compound appears stable through at least 3 to 5 freeze-thaw cycles in DMSO.

For cell culture experiments, DMSO stock solutions are diluted directly into culture media at the working concentration (typically 0.1 to 10 micromolar). The final DMSO concentration in the culture medium should not exceed 0.1 percent (volume per volume) to avoid solvent effects on cell viability and gene expression. Vehicle controls containing equivalent DMSO concentrations should be included in all experiments.

For in vivo oral administration in rodents, SRT2104 can be incorporated into standard rodent chow at concentrations of 100 to 200 milligrams per kilogram of diet for chronic studies [13, 14]. For acute dosing by oral gavage, the compound is suspended in vehicle solutions containing methylcellulose (0.5 percent) with Tween 80 (0.1 percent) or in corn oil. Intraperitoneal administration is typically in DMSO-containing vehicles at volumes not exceeding 10 milliliters per kilogram.

Solid compound should be stored at minus 20 degrees Celsius in a desiccated, light-protected container. The compound is reported to be stable under these conditions for at least 2 years. Room-temperature handling during weighing and formulation preparation is acceptable for short periods.

10. Stack Interactions and Combinations

SRT2104 interacts with several drug and compound classes through its SIRT1-mediated mechanism and through pharmacokinetic considerations. Investigators conducting research with SRT2104, especially in combination studies, should consider:

NAD precursors (nicotinamide riboside, nicotinamide mononucleotide): SIRT1 enzymatic activity is NAD-dependent. Co-administration with NAD precursors represents a mechanistically rational combination that may enhance the pharmacological effects of SIRT1 activation by increasing the availability of the enzymatic co-substrate. This combination has been explored in preclinical research and is a common research paradigm, though additive or synergistic effects have not been formally characterized for SRT2104 specifically.

Resveratrol and other polyphenolic SIRT1 activators: Concurrent administration with resveratrol is pharmacologically redundant for the SIRT1 activation mechanism, as both compounds target the same allosteric activation site [3, 20]. The combination may produce additive SIRT1 activation at low individual doses but offers no mechanistic advantage over dose escalation of either agent alone. Resveratrol has substantially lower potency and selectivity than SRT2104 and introduces off-target activities (cyclooxygenase inhibition, estrogen receptor modulation, AMP-activated protein kinase activation) that complicate interpretation of combination experiments.

Metformin: Metformin activates AMP-activated protein kinase (AMPK), which in turn activates SIRT1 through increased NAD levels [21]. The combination of SRT2104 with metformin represents a convergent activation of the SIRT1 pathway through complementary mechanisms. The type 2 diabetes clinical trial required stable metformin therapy, and no pharmacokinetic interaction was identified [8].

Caloric restriction mimetics (rapamycin, spermidine): SRT2104 and caloric restriction share overlapping downstream pathways through SIRT1, AMPK, mTOR, and FOXO signaling. Co-administration with rapamycin (an mTOR inhibitor) could produce complementary or antagonistic effects depending on the specific pathway and tissue context. The combination has not been systematically characterized.

CYP3A4 substrates and inhibitors: Although the specific CYP isoforms metabolizing SRT2104 have not been published, the heterocyclic scaffold suggests CYP3A4 involvement. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) may increase SRT2104 exposure, and strong inducers (rifampin, carbamazepine, phenytoin) may reduce it. Investigators should consider this potential interaction when designing combination studies.

Nicotinamide: Nicotinamide is a product inhibitor of SIRT1; at high concentrations (millimolar range), nicotinamide inhibits SIRT1 deacetylase activity by occupying the nicotinamide binding pocket [21]. Co-administration of SRT2104 with high-dose nicotinamide (as distinct from nicotinamide riboside or nicotinamide mononucleotide) could partially antagonize the SIRT1 activation and should be avoided in research protocols.

Anti-inflammatory agents: SRT2104 suppresses NF- κ B-mediated inflammatory signaling. Combination with other anti-inflammatory agents (corticosteroids, non-steroidal anti-inflammatory drugs, biologics targeting TNF- α or interleukins) may produce additive immunosuppression. No specific pharmacodynamic or pharmacokinetic interactions have been characterized.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events observed across SRT2104 clinical trials at doses of 0.25 to 2.0 grams daily for up to 84 days are:

- Headache (reported in approximately 28 percent of subjects in Phase 1 studies) [6]
- Gastrointestinal symptoms including flatulence (14 percent), nausea (8 percent), and diarrhea (6 percent) [6]
- Nasopharyngitis (6 percent) [6]
- Dizziness (reported in psoriasis and other trials) [10]
- Transaminase elevations (mild, generally clinically insignificant) [10]

These adverse events are generally mild to moderate in severity and self-limiting. No dose-limiting toxicities were identified across the dose-escalation range in Phase 1 studies [6].

11.2 Serious adverse events

Three serious adverse events were reported in the psoriasis Phase 2 trial, all assessed as likely related or related to SRT2104 [10]:

- Pneumonitis (one subject, 250 milligram dose group)
- Pancreatitis (one subject, 250 milligram dose group)
- Elevated alanine aminotransferase and bilirubin (one subject, 1000 milligram dose group)

The pneumonitis and pancreatitis events are notable and raise potential safety signals that would require further characterization in any future clinical development. The hepatic signal (transaminase and bilirubin elevation) is consistent with the pharmacological activity of SIRT1 in hepatic metabolism and requires monitoring in chronic dosing.

In the ulcerative colitis trial, one subject experienced a serious adverse event requiring study withdrawal, and another was withdrawn for a severe disease flare [11].

11.3 Tolerability in chronic dosing

The 28-day (type 2 diabetes, elderly volunteers) and 56-day (ulcerative colitis) and 84-day (psoriasis) chronic dosing studies did not reveal progressive or cumulative toxicity beyond the events described above [7, 8, 10, 11]. The overall safety profile across the clinical program is broadly acceptable for a research-stage compound, with the pneumonitis and pancreatitis signals as the principal areas of concern.

11.4 Preclinical safety

Chronic dietary administration to mice at 100 milligrams per kilogram of diet for the natural lifespan (approximately 2 to 3 years) did not produce clinically evident toxicity [13]. Body weight was maintained, and no treatment-related mortality was observed.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five SIRT1 modulators against SRT2104, evaluated against five competency standards: novelty, effect size, promising potential (current state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal SIRT1-targeting compounds with substantive published pharmacology or clinical data.

12.1 Resveratrol

Mechanism: Natural polyphenolic SIRT1 activator. Trans-3,5,4'-trihydroxystilbene, a phytoalexin found in grape skins, red wine, and several other plant sources. Resveratrol was identified by the Sinclair laboratory as the first SIRT1 activator and was the scientific starting point for the entire STAC field [20]. However, resveratrol is a promiscuous compound with established activity at cyclooxygenase-1 and cyclooxygenase-2, estrogen receptors, AMP-activated protein kinase, phosphodiesterases, and multiple other targets.

Novelty: Low. Resveratrol is the original and most extensively studied SIRT1 activator. Thousands of publications document its pharmacology across virtually every disease model. The novelty as a SIRT1 activator is historical rather than current.

Effect size: Variable and modest in clinical trials. The RECSAM trial and other human studies have reported inconsistent metabolic effects, with some showing improvements in glucose handling and inflammatory markers and others showing no significant benefit [26]. Preclinical effect sizes are often substantial but confounded by the compound's polypharmacology.

Promising potential: Limited as a clinical therapeutic owing to poor bioavailability, rapid metabolism, and polypharmacology. Extensive as a dietary supplement and research tool.

Side-effect profile: Generally well tolerated at doses of 100 to 2000 milligrams daily. Gastrointestinal symptoms (nausea, diarrhea, abdominal discomfort) are the principal adverse events at higher doses. No serious safety signals in clinical trials,

though the clinical exposure history is predominantly in supplement-grade formulations.

Overall validation: Moderate. Extensive preclinical data, inconsistent clinical data, and fundamental questions about whether SIRT1 activation is the primary mechanism of action or one of many concurrent effects.

Comparison to SRT2104: Resveratrol is approximately 1000-fold less potent than SRT2104 at SIRT1 activation and substantially less selective, with activity at numerous non-SIRT1 targets [2, 15]. SRT2104 has the advantage of target selectivity, greater potency, and a more interpretable pharmacological profile. Resveratrol has the advantage of commercial availability as a dietary supplement, extensive human exposure history, and lower cost.

12.2 SRT1720

Mechanism: First-generation synthetic STAC; selective SIRT1 activator in fluorophore-tagged assays, though the Pacholec et al. (2010) report questioned the directness of SIRT1 activation with native substrates [15]. Built on the same imidazo[2,1-b]thiazole scaffold that was later optimized to produce SRT2104.

Novelty: Low to moderate. SRT1720 was the first synthetic STAC to demonstrate in vivo efficacy in metabolic disease models. It predates SRT2104 and provided the proof-of-concept for synthetic SIRT1 activation.

Effect size: Substantial in preclinical metabolic models. SRT1720 improved insulin sensitivity, reduced body weight gain, and extended lifespan in mice fed a high-fat diet [27]. However, the compound showed significant off-target activity, with greater than 50 percent inhibition of 38 of more than 100 tested targets at 10 micromolar [15].

Promising potential: Low. SRT1720 was not advanced to clinical trials and has been superseded by SRT2104 as the clinical development candidate.

Side-effect profile: Preclinical only. No human safety data. Rodent tolerability was acceptable at studied doses, though some reports noted hepatotoxicity at high doses.

Overall validation: Moderate. Extensive preclinical pharmacology literature, but mechanism-of-action controversy and off-target activity limit confidence.

Comparison to SRT2104: SRT2104 was specifically developed to address the selectivity limitations of SRT1720. SRT2104 shows minimal activity against the same panel of targets where SRT1720 was promiscuous [2, 15]. SRT2104 has the advantage of clinical safety and pharmacokinetic data; SRT1720 has the advantage of a larger preclinical literature and lower cost as a research tool.

12.3 SRT3025

Mechanism: Second-generation synthetic STAC developed alongside SRT2104 at Sirtris, targeting SIRT1 allosteric activation through the same N-terminal binding mechanism [28]. SRT3025 has been studied primarily in oncology and cardiovascular contexts.

Novelty: Low. The mechanism is identical to SRT2104 and operates through the same allosteric activation site.

Effect size: Moderate in preclinical models. SRT3025 reduced atherosclerotic plaque in ApoE-knockout mice and improved telomere maintenance in some systems [28]. Direct comparison to SRT2104 in matched models is limited.

Promising potential: Low. SRT3025 has not been advanced to clinical trials and is less widely studied than SRT2104.

Side-effect profile: Preclinical only. No human safety data.

Overall validation: Low. Limited preclinical literature and no clinical data.

Comparison to SRT2104: SRT2104 has the decisive advantage of clinical data. SRT3025 is mechanistically indistinguishable and offers no clear pharmacological advantage. SRT2104 is the appropriate reference compound for the second-generation STAC class.

12.4 Selisistat (EX-527)

Mechanism: Selisistat is a selective SIRT1 inhibitor, not an activator [29]. It is included in this comparator panel as the mechanistic counterpart, providing the pharmacological tool for loss-of-function studies that complement SRT2104 gain-of-function experiments. Selisistat occupies the nicotinamide binding pocket of SIRT1 and competitively inhibits deacetylation.

Novelty: Moderate. Selisistat is the most selective and most widely used small-molecule SIRT1 inhibitor and has been advanced to Phase 2 clinical trials for Huntington disease [29].

Effect size: In the Huntington disease context, selisistat (SIRT1 inhibition) is mechanistically opposed to SRT2104 (SIRT1 activation), which is notable because both approaches have shown neuroprotective effects in different Huntington disease models [14, 29]. This apparent paradox reflects the complexity of SIRT1 biology in neurodegeneration.

Promising potential: Moderate. Selisistat has Phase 2 clinical data in Huntington disease and is in ongoing investigation.

Side-effect profile: Phase 1 and Phase 2 clinical data available. Generally well tolerated at studied doses [29].

Overall validation: Moderate. Clinical data exist, though the Huntington disease program did not advance to Phase 3.

Comparison to SRT2104: Selisistat is mechanistically complementary rather than competing. In a research context, SRT2104 and selisistat together provide the bidirectional pharmacological toolkit for SIRT1 gain-of-function and loss-of-function studies.

12.5 Nicotinamide riboside (NR)

Mechanism: Nicotinamide riboside is a precursor to NAD that elevates intracellular NAD levels through the nicotinamide riboside kinase pathway [30]. NAD elevation indirectly activates SIRT1 by increasing the availability of the enzymatic co-substrate. The mechanism is therefore indirect and upstream of SRT2104, which directly activates SIRT1 independently of NAD levels.

Novelty: Moderate. The NAD precursor approach to sirtuin activation is mechanistically distinct from direct allosteric activation and has generated substantial academic and commercial interest.

Effect size: Moderate in preclinical models. NR supplementation has demonstrated metabolic improvements in high-fat-diet mouse models and in some human clinical studies, though clinical effect sizes have been inconsistent [30].

Promising potential: High. NR is commercially available as a dietary supplement (Niagen and generic formulations), is in multiple ongoing clinical trials, and has substantially greater market accessibility than SRT2104.

Side-effect profile: Generally well tolerated. Gastrointestinal symptoms at high doses (1000 to 2000 milligrams daily). No serious safety signals in clinical trials.

Overall validation: Moderate to high. Substantial preclinical and emerging clinical evidence. The mechanism is less selective than direct SIRT1 activation because NAD elevation affects all seven mammalian sirtuins and numerous other NAD-dependent enzymes.

Comparison to SRT2104: NR and SRT2104 represent complementary approaches to SIRT1 activation: NR increases co-substrate availability (indirect activation of all NAD-dependent enzymes), while SRT2104 directly and selectively enhances SIRT1 catalytic efficiency. The combination is mechanistically rational and has been explored in preclinical research. NR has the advantage of commercial availability, dietary supplement status, and ongoing clinical investigation. SRT2104 has the advantage of target selectivity and direct, NAD-independent SIRT1 activation.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the SIRT1 pharmacology landscape. **Resveratrol** is the historical reference compound with extensive but promiscuous pharmacology and inconsistent clinical results. **SRT1720** is the first-generation synthetic STAC that provided proof-of-concept but was limited by off-target activity. **SRT3025** is a second-generation STAC mechanistically equivalent to SRT2104 but lacking clinical data. **Selisistat** is the mechanistic counterpart (SIRT1 inhibitor) that provides the bidirectional pharmacological toolkit. **Nicotinamide riboside** is the indirect NAD-precursor approach with broad commercial availability but non-selective sirtuin activation.

SRT2104 occupies a unique position as the most advanced clinical-stage, selective, direct SIRT1 activator. It is the only compound in this class to have completed multiple Phase 2 clinical trials, providing human pharmacokinetic, pharmacodynamic, safety, and (limited) efficacy data. Its principal limitations are the non-dose-proportional pharmacokinetics, the modest clinical efficacy signals, and the discontinuation of active development. For research applications, SRT2104 remains the standard reference direct SIRT1 activator, and its combination with NAD pre-

cursors (nicotinamide riboside, nicotinamide mononucleotide) and with the SIRT1 inhibitor selisistat provides a comprehensive pharmacological toolkit for interrogating SIRT1 biology across disease models.

13. References

1. Sirtris Pharmaceuticals. Discovery and characterization of SRT2104, a selective small molecule activator of SIRT1. Internal data referenced in: Hoffmann E, Wald J, Stehr S, et al. Pharmacokinetics and tolerability of SRT2104, a first-in-class small molecule activator of SIRT1, after single and repeated oral administration in man. *Br J Clin Pharmacol*. 2013;75(1):186-196.
2. Dai H, Kustigian L, Bhatt D, et al. SIRT1 activation by small molecules: kinetic and biophysical evidence for direct interaction of enzyme and activator. *J Biol Chem*. 2010;285(43):32695-32703.
3. Hubbard BP, Gomes AP, Dai H, et al. Evidence for a common mechanism of SIRT1 regulation by allosteric activators. *Science*. 2013;339(6124):1216-1219.
4. Haigis MC, Sinclair DA. Mammalian sirtuins: biological insights and disease relevance. *Annu Rev Pathol*. 2010;5:253-295.
5. Zhao Y, Liu Y, Chen K. Mechanisms and clinical application of SIRT1 activator SRT2104 in disease treatment. *Sci Rep*. 2024;14(1):5723.
6. Hoffmann E, Wald J, Stehr S, et al. Pharmacokinetics and tolerability of SRT2104, a first-in-class small molecule activator of SIRT1, after single and repeated oral administration in man. *Br J Clin Pharmacol*. 2013;75(1):186-196.
7. Libri V, Brown AP, Bber G, et al. A pilot randomized, placebo controlled, double blind phase I trial of the novel SIRT1 activator SRT2104 in elderly volunteers. *PLoS One*. 2012;7(12):e51395.
8. Baksi A, Kraber O, Brennan A, et al. A phase II, randomized, placebo-controlled, double-blind, multi-dose study of SRT2104, a SIRT1 activator, in subjects with type 2 diabetes. *Br J Clin Pharmacol*. 2014;78(1):69-77.
9. Venkatasubramanian S, Noh RM, Vatber S, et al. Cardiometabolic effects of a novel SIRT1 activator, SRT2104, in people with type 2 diabetes mellitus. *Open Heart*. 2017;4(2):e000647.
10. Krueger JG, Suarez-Farinas M, Cueto I, et al. A randomized, placebo-controlled study of SRT2104, a SIRT1 activator, in patients with moderate to severe psoriasis. *PLoS One*. 2015;10(11):e0142081.

11. Sands BE, Joshi S, Haddad J, et al. Assessing colonic exposure, safety, and clinical activity of SRT2104, a novel oral SIRT1 activator, in patients with mild to moderate ulcerative colitis. *Inflamm Bowel Dis*. 2016;22(3):607-614.
12. van der Meer AJ, Scicluna BP, Moerland PD, et al. The selective sirtuin 1 activator SRT2104 reduces endotoxin-induced cytokine release and coagulation activation in humans. *Crit Care Med*. 2015;43(6):e199-e202.
13. Mercken EM, Mitchell SJ, Martin-Montalvo A, et al. SRT2104 extends survival of male mice on a standard diet and preserves bone and muscle mass. *Aging Cell*. 2014;13(5):787-796.
14. Jiang M, Zheng J, Peng Q, et al. Sirtuin 1 activator SRT2104 protects Huntington's disease mice. *Ann Clin Transl Neurol*. 2014;1(12):1047-1052.
15. Pacholec M, Bleasdale JE, Chruncyk B, et al. SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. *J Biol Chem*. 2010;285(11):8340-8351.
16. Gu C, Li Y, Liu J, et al. Therapeutic effects of SRT2104 on lung injury in rats with emphysema via reduction of type II alveolar epithelial cell senescence. *COPD*. 2020;17(5):525-536.
17. Li W, Wang Y, Li S, et al. Sirtuin 1 activator alleviated lethal inflammatory injury via promotion of autophagic degradation of pyruvate kinase M2. *Front Pharmacol*. 2023;14:1092943.
18. Sirtris Pharmaceuticals. Wikipedia. Available at: en.wikipedia.org/wiki/Sirtris_Pharmaceuticals.
19. Ledford H. GSK absorbs controversial 'longevity' company. *Nature News Blog*. March 2013.
20. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. 2006;444(7117):337-342.
21. Imai S, Guarente L. NAD⁺ and sirtuins in aging and disease. *Trends Cell Biol*. 2014;24(8):464-471.
22. Yeung F, Hoberg JE, Ramsey CS, et al. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. *EMBO J*. 2004;23(12):2369-2380.

23. SRT2104 enhances dendritic outgrowth and spine formation through sirtuin 1-mediated mTORC1 signaling. Neuroscience. 2025.
 24. The SIRT1 activator SRT2104 mitigates hypoxia-induced white matter injury in neonatal mice. Brain Res. 2025.
 25. SIRT1 activation by SRT2104 enhances mitophagy and reduces senescence in auditory cells. Sci Rep. 2026.
 26. Berman AY, Motechin RA, Wiesenfeld MY, Holz MK. The therapeutic potential of resveratrol: a review of clinical trials. NPJ Precis Oncol. 2017;1:35.
 27. Minor RK, Baur JA, Gomes AP, et al. SRT1720 improves survival and healthspan of obese mice. Sci Rep. 2011;1:70.
 28. Hubbard BP, Sinclair DA. Small molecule SIRT1 activators for the treatment of aging and age-related diseases. Trends Pharmacol Sci. 2014;35(3):146-154.
 29. Sussmuth SD, Haider S, Landwehrmeyer GB, et al. An exploratory double-blind, randomised clinical trial with selisistat, a SirT1 inhibitor, in patients with Huntington's disease. Br J Clin Pharmacol. 2015;79(3):465-476.
 30. Trammell SA, Schmidt MS, Weidemann BJ, et al. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. Nat Commun. 2016;7:12948.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. SRT2104 is not approved by any regulatory authority and is not currently in active clinical development. The compound is available exclusively as a research-grade preparation; investigators should obtain analytical confirmation of identity and purity on every lot. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.