

Bezisterim (NE3107 / HE3286): Scientific and Clinical Evidence Review

Compiled 19 September 2026. Evidence cutoff: all publications and disclosures available as of this date, including the SUNRISE-PD topline of 6 August 2026 and the ADDRESS-LC topline of 15 September 2026.

PART 1. EXECUTIVE SUMMARY

Bezisterim is a synthetic, orally available analogue of 5-androstene-3-beta,7-beta,17-beta-triol, a downstream DHEA metabolite that circulates in humans and declines with age. Unlike its parent sterol it is essentially hormonally inert, and unlike a glucocorticoid it is not broadly immunosuppressive. Its proposed action is narrow: it binds ERK1/ERK2 and dampens inflammation-driven ERK and NF-kB signalling, which in turn reduces TNF-alpha output and relieves the serine phosphorylation of IRS-1 that couples inflammation to insulin resistance. It crosses the blood-brain barrier. In other words, the molecule was designed to hit the exact junction that gerontology calls inflammaging plus insulin resistance.

After eighteen years of development across four corporate owners, what does the evidence actually support?

The pharmacology is real and reproducible. Across two independent human metabolic trials published in 2013, and again in Alzheimer's and Parkinson's trials a decade later, the same fingerprint appears: MCP-1 falls, fasting glucose falls, HOMA2 insulin sensitivity rises, and systemic inflammatory indices improve. That signal has now been replicated in four separate patient populations by different investigator groups. It is the most secure claim in the entire dossier.

The clinical benefit is not established in any indication. The pivotal Phase 3 Alzheimer's trial, which randomised 439 patients, collapsed when the sponsor discovered protocol and Good Clinical Practice violations at 15 of 39 sites clustered in one geographic region and referred the matter to the FDA. Only 57 patients survived into a per-protocol analysis. In that hand-selected remnant, every cognitive and functional confidence interval crossed zero, and the co-primary cognitive endpoint showed a negligible effect (my derived Cohen's d of about 0.10). The company's widely repeated framing of "68 percent slowing of decline" is a relative expression of a small absolute difference in 50 evaluable patients, and it is not a valid comparison to lecanemab's 18-month result.

Two 2026 trials reported genuinely interesting, and genuinely fragile, signals. In early Parkinson's disease, SUNRISE-PD (57 patients, 12 weeks) met a blood-based inflammatory

primary endpoint and produced very large exploratory effect sizes on a sponsor-constructed 15-item clinical composite (Cohen's d about 0.94) and on a neuroinflammation composite (d about 1.06), along with a slower rise in neurofilament light. In long COVID, ADDRESS-LC (203 patients) missed on every one of its 22 outcome measures in the full population while 21 of 22 pointed in the drug's favour, with significance appearing only in prespecified high-symptom-burden subgroups. Both patterns are what a true modest effect looks like in an underpowered trial, and both are also what noise plus analytical flexibility looks like. Only the planned Phase 3 programmes can separate those.

The longevity-specific evidence is thin and should be read with care. The headline claim, an epigenetic age deceleration advantage of roughly 2 to 5 years, rests on 33 blood samples from the compromised Phase 3 trial, five correlated methylation clocks, no correction for multiple testing, and two of five clocks reaching nominal significance in the peer-reviewed version. Worse for the claim's credibility, the same 33-sample dataset has been presented with three materially different sets of numbers at three different meetings. There is no lifespan or survival study of bezisterim in any mammal.

Safety, by contrast, looks good. Across roughly 700 exposed humans the adverse event burden has generally run at or below placebo, with headache the only consistent excess, no effect on the sex steroid or adrenal axes, no ARIA, no hypoglycaemia, and mild pancreatic enzyme and TSH elevations as the signals worth monitoring. Nothing beyond seven months of continuous exposure has been studied.

The practical bottom line for anyone tracking this as a potential geroprotector: bezisterim is an investigational drug with an attractive and mechanistically coherent target, a clean early safety record, a well-replicated metabolic and anti-inflammatory biomarker effect, and no demonstrated clinical or aging benefit that survives contact with a properly powered randomised comparison. It is not available outside trials, and the parent sterol sold in supplement channels is not a substitute for it.

PART 2. TECHNICAL ANALYSIS

2.1 Identity, chemistry, pharmacokinetics

Attribute	Value
INN	Bezisterim
Development codes	NE3107, NE-3107, HE3286, HE-3286
Chemical name	17-alpha-ethynyl-androst-5-ene-3-beta,7-beta,17-beta-triol

Attribute	Value
Formula and mass	C ₂₁ H ₃₀ O ₃ , 330.5 g/mol
CAS	1001100-69-1
Parent compound	5-androstene-3-beta,7-beta,17-beta-triol (beta-AET), a DHEA metabolite
Route	Oral
Terminal half-life	6 to 9 hours
Neuro trial dose	20 mg twice daily, typically after a 5 mg then 10 mg twice-daily titration
PK linearity	Dose-proportional across 2 to 100 mg
CNS exposure	Blood-brain barrier penetrant
Nuclear receptor activity	Weak and clinically irrelevant at therapeutic exposures: androgen receptor EC ₅₀ about 8,200 nM, ER-alpha about 6,500 nM, ER-beta about 400 nM
Sponsor lineage	Hollis-Eden, then Harbor Therapeutics / Harbor BioSciences, then NeurMedix, then BioVie Inc. (assets acquired June 2021)
Regulatory status	Investigational. No approval in any jurisdiction. No fast track or breakthrough designation disclosed.

The ethynyl group at C17 is the key medicinal chemistry move. It blocks interconversion back into the androgen and oestrogen pools, which is why the compound retains the anti-inflammatory activity of beta-AET without meaningful hormonal signalling. Human trials confirm that intent: DHEA, testosterone, oestradiol, progesterone, androstenediol, LH, FSH, ACTH and 24-hour urinary free cortisol are all unchanged on treatment.

2.2 Mechanism of action

The primary mechanistic paper is a SILAC-based target identification study in RAW 264.7 macrophages (PLOS One, 2012). It reported 26 binding partners, of which the pharmacologically interesting set is:

- Lrp1, the only cell-surface receptor identified

- MAPK1 and MAPK3 (ERK2 and ERK1)
- RPS6KA3
- SIRT2
- HSD17B4

Functional consequences reported in the same work: suppression of LPS-induced NF-kB reporter expression and nuclear translocation, suppression of IRS-1 serine phosphorylation, and reduced activation of IKK, JNK and p38. The compound also blunted TNF-alpha-stimulated inflammation and TNF-alpha-driven, adipocyte-mediated macrophage chemotaxis.

Two points of rigour. First, no binding affinity constant for ERK1/ERK2 has been published, so the widely repeated "binds ERK" claim rests on pull-down identification plus downstream functional inhibition rather than on a measured Kd or a co-crystal structure. Second, the central selectivity claim, that pathological ERK and NF-kB signalling is inhibited while homeostatic signalling is spared, is supported by a genuinely useful piece of evidence: in mouse infection and immunisation models the compound was not immunosuppressive, and *Klebsiella pneumoniae* challenge survival was essentially identical to untreated controls (Journal of Inflammation, 2010). That is the sort of negative control that distinguishes this class from glucocorticoids, and it is the strongest single argument for the selectivity hypothesis.

Bayesian confidence that the compound reduces inflammation-driven ERK and NF-kB signalling without general immunosuppression: about 80 percent. Bayesian confidence that direct ERK binding is the proximal mechanism rather than a downstream or indirect effect: about 50 percent.

2.3 Preclinical mammalian data

Metabolic

- Zucker diabetic fatty rats, 100 mg/kg/day: normalised glucose, improved glucose tolerance and insulin sensitivity, with attenuation of tissue inflammation (American Journal of Physiology Endocrinology and Metabolism, 2010).
- Multiple diabetic mouse models: suppressed progression of hyperglycaemia and improved glucose clearance, with the effect explicitly linked to inflammatory signalling rather than to insulin secretion (Journal of Pharmacology and Experimental Therapeutics, 2010).

Inflammatory and autoimmune

- Rat adjuvant-induced arthritis and mouse collagen antibody-induced arthritis, 1 to 80 mg/kg: reduced disease scores, joint oedema, IL-6 and TNF-alpha.
- Carrageenan pleurisy and LPS lung injury in mice, 40 mg/kg oral: roughly 50 percent reductions in neutrophil counts and exudate volume, and reduced myeloperoxidase, without immune suppression.

Neurological

- MPTP mouse model of Parkinson's disease, 40 mg/kg orally twice daily: improved rotarod performance, iNOS down about 20 percent, TNF-alpha down about 40 percent, IL-1 beta down about 33 percent, dopaminergic neuron count up about 17 percent, damaged neurons down about 38 percent.
- MPTP-lesioned marmosets: reported improvement in levodopa efficacy and reduction in dyskinesia. This appears only in secondary summaries and company materials, not in a peer-reviewed primary report, so it should be treated as unverified.
- Rat glaucoma model, 20 or 100 mg/kg/day: preserved axonal transport and increased BDNF.
- Mouse optic neuritis, 40 mg/kg/day: reduced vision loss, inflammation, demyelination and axonal loss.

Aging-specific preclinical work

This is where the dossier is weakest relative to the compound's positioning. The aging claims trace to the parent sterol, not to bezisterim: beta-AET augmented immune responses and partially reversed immune senescence in aged mice, and slowed thermal-injury-induced osteopenia in mice. Those are beta-AET results with different pharmacology, different hormonal activity and different pharmacokinetics.

Regulatory toxicology

- Non-human primates, up to 170 mg/day for 28 days: no systemic toxicity, dose-dependent injection site irritation only.
- Rats, up to 100 mg/kg/day for 28 days: no mortality, reversible hepatocellular hypertrophy.
- Not genotoxic across Ames, chromosome aberration and bone marrow micronucleus assays.

2.4 Human clinical data by indication

Metabolic disease (the original programme, and the best-controlled human data)

Phase 1, insulin-resistant obese subjects with impaired glucose tolerance, published in Obesity (2013). Doses of 2, 5 and 10 mg twice daily for 28 days increased insulin-stimulated glucose disposal and HDL cholesterol and decreased CRP versus placebo. Adiponectin rose significantly in the insulin-resistant stratum. 46 of 48 subjects completed.

Phase 2, type 2 diabetes, published in Mediators of Inflammation (2013). N = 164 across two cohorts (95 metformin-treated, 69 treatment-naive), 10 mg/day for 12 weeks.

Population	Endpoint	Bezisterim	Placebo	p
Metformin-treated, baseline MCP-1 above 40	HOMA2-IR change	-0.1	+0.4	0.02
Metformin-treated, baseline MCP-1 above 40	Normalised HbA1c at day 84	decreased	-	0.03
Metformin-treated, baseline MCP-1 above 40	C-peptide	improved	-	0.04
Treatment-naive, BMI above 31	HbA1c at day 112	-1.0 percent	-0.3 percent	0.0007
Treatment-naive, BMI above 31	1,5-anhydroglucitol	+10.4 micromol/L	+0.6	0.02

The critical design feature, and the one most relevant to interpreting everything that followed: benefit concentrated in the inflammation-high stratum (baseline MCP-1 above 40) and the obesity-high stratum. An HbA1c delta of 0.7 percentage points versus placebo is a clinically meaningful magnitude, comparable to a DPP-4 inhibitor, but it emerged from a subgroup in a 69-patient cohort, not from the overall population. All authors were employees or shareholders of the sponsor.

Phase 1/2 programmes in ulcerative colitis and rheumatoid arthritis were completed and have never been published in the peer-reviewed literature. Development in both indications was abandoned when Harbor BioSciences wound down. Absent results are not neutral: the most probable explanation for unpublished completed autoimmune trials is that they were unimpressive, and this should be priced into any prior about the compound's anti-inflammatory potency in overt autoimmune disease.

Alzheimer's disease

Phase 2 open-label biomarker and imaging study, published in *Medicine* (2024). N = 23 with MCI or mild dementia, 20 mg twice daily for 12 weeks, single centre in Los Angeles, participants enrolled by invitation.

- Imaging: normalisation of cerebral perfusion, increased functional connectivity in the nucleus basalis of Meynert, precuneus and hippocampus, and increased brain glutathione consistent with reduced oxidative stress.
- Cognition: improvement on 4 of 6 instruments, statistically significant within a prespecified subgroup of 17 participants with MMSE above 20.

- Biomarkers: TNF-alpha reductions in roughly 60 percent of participants; CSF p-tau down 1.66 pg/mL ($p = 0.0343$) overall and down 3.22 pg/mL ($p = 0.0027$) among responders.

Interpretive limit: open-label, single-arm, 12 weeks, one site, invited participants. Cognitive testing without a control arm over that interval cannot be separated from practice effects and regression to the mean. The imaging and glutathione findings are the more informative part of this study, because they are less susceptible to expectancy.

Phase 3 NM101, NCT04669028. Randomised, double-blind, placebo-controlled, 20 mg twice daily for 30 weeks, co-primary endpoints ADAS-Cog12 and ADCS-CGIC. Planned enrolment 316; 690 screened; 439 randomised 1:1 across 39 sites.

What happened: the sponsor identified significant protocol deviations and GCP violations at 15 sites, all in one geographic region, including data patterns inconsistent with known Alzheimer's progression, and referred the matter to the FDA's investigations unit. The modified intent-to-treat population fell to 76 to 81 patients. The per-protocol population was 57, of whom 50 had source-verified baseline and endpoint assessments (24 bezisterim, 26 placebo). The original power calculation assumed 125 per arm.

Per-protocol results at week 30, as published in the exploratory analysis paper (Frontiers in Neuroscience, 2025), with least-squares mean differences and 95 percent confidence intervals:

Endpoint	LS mean difference, drug minus placebo	95 percent CI	Derived Cohen's d
CDR-SB	-0.95	-2.51 to 0.61	about 0.35
ADAS-Cog12 (co-primary)	-0.94	-6.16 to 4.28	about 0.10
MMSE	+1.02	-1.01 to 3.06	about 0.29
ADCS-ADL	+3.08	-1.28 to 7.45	about 0.40
ADCOMS	-0.03	-0.17 to 0.12	about 0.12

The Cohen's d values in that last column are my own derivation, not the authors'. The paper reports confidence intervals but no standardised effect sizes, so I back-calculated the residual standard deviation from each interval width assuming $n = 24$ and 26 and a t-based interval, then divided the mean difference by it. Treat them as approximations with perhaps 15 percent uncertainty, since least-squares means from a mixed model do not decompose perfectly this way.

How to read a Cohen's d, without statistics background: it expresses a difference in units of the spread of the data. A d of 0.2 is conventionally small, 0.5 moderate, 0.8 large. A d of 0.35 means the average treated patient did better than roughly 64 percent of placebo patients, which

also means about 36 percent of placebo patients still did better than the average treated patient. A d of 0.10 means the two groups overlap almost completely.

The analytically important observation is the dissociation inside this table. The co-primary cognitive endpoint, ADAS-Cog12, was flat (d about 0.10) even in the population selected for clean data. The global and functional measures, CDR-SB and ADCS-ADL, carried small-to-moderate point estimates with intervals crossing zero. A drug producing genuine cognitive benefit at the magnitude claimed should not show its weakest effect on the cognitive co-primary.

The comparison to approved therapies that appears in company materials and in the Frontiers discussion requires explicit correction. Lecanemab's CDR-SB difference of 0.45 came from 1,795 patients over 18 months with a prespecified primary analysis in a randomised population. Bezisterim's 0.95 came from 50 patients over 7 months in a population defined after site-level data problems were discovered. The numbers are not on the same measurement scale in any meaningful sense, and the retained 13 percent of randomised patients means the comparison is no longer protected by randomisation. Selection on data quality that correlates with site, and therefore with region, practice pattern and patient mix, is a confounder that cannot be excluded.

Phase 3 metabolic and inflammatory biomarkers, per-protocol population, all favouring bezisterim: fasting glucose -8.50 mg/dL (p = 0.036), total cholesterol -15 mg/dL (p = 0.049), MCP-1 -90.5 pg/mL (p = 0.007), HOMA2 insulin sensitivity +1.95 (p = 0.018), HOMA2 beta-cell function +12.4 (p = 0.040).

Phase 3 neurodegeneration biomarkers, all null: p-tau217, GFAP, NfL, and the Abeta42/40 ratio showed no significant difference. This matters. A 30-week exposure that moves peripheral metabolic and inflammatory markers but leaves every fluid marker of neurodegeneration and amyloid unchanged is more consistent with a systemic metabolic effect than with disease modification in the brain.

Epigenetic aging, the longevity-relevant dataset

Source: DNA methylation from 33 Phase 3 participants who passed quality control (17 bezisterim, 16 placebo) after 30 weeks.

Clock	Age deceleration advantage vs placebo	p
Hannum	5.00 years	0.006
InflammAge	4.77 years	0.022
Skin and Blood clock	3.68 years	0.017
PhenoAge	3.71 years	0.081

Clock	Age deceleration advantage vs placebo	p
GrimAge	1.92 years	0.068

The authors also reported methylation changes at loci for ERK, MAP3K8, NF-kB, TNF-alpha and IL-6, with 1.5 to 2.3 fold pathway enrichment for neurodegenerative disease, senescence, apoptosis and TNF signalling pathways, and correlations with AMP-AD consortium aging gene sets.

Four problems, in descending order of severity.

1. Provenance. These 33 samples come from the trial whose data integrity failed. Even if these particular samples came from clean sites, the analysis population is a fragment of a fragment.
2. Multiplicity. Five clocks, no correction, several additional biomarker correlations at a 90 percent confidence threshold, and Bayesian correlation analyses run alongside frequentist ones. With five correlated clocks tested uncorrected, at least one nominal p below 0.05 by chance alone is likely.
3. Numerical instability across presentations. The same 33-sample dataset has been presented with three different result sets: a composite "dAge" advantage of 3.87 years ($p = 0.012$) at AD/PD 2024; the table above at ARDD 2024 and in the 2025 peer-reviewed paper; and a fourth set at the 2nd World Conference on Aging and Gerontology in July 2025 (Skin and Blood -3.16, $p = 0.036$; PhenoAge -4.12, $p = 0.048$; Hannum -4.24, $p = 0.015$; InflammAge -3.77, $p = 0.050$; GrimAge -1.38, $p = 0.148$), presented under a headline referring to 10 biological clocks while detailing 5. Re-analysis is legitimate; presenting materially different numbers from one 33-sample dataset across three venues without a clear reconciliation is not reassuring.
4. Magnitude implausibility. A 3 to 5 year methylation age advantage over 30 weeks of treatment would be among the largest pharmacological effects on epigenetic age ever reported in a randomised setting, in a sample of 33, in a disease population. Extraordinary magnitude in a tiny sample is the classic signature of the winner's curse.

Bayesian confidence that bezisterim produces a genuine, reproducible reduction in methylation-based epigenetic age acceleration in humans: about 20 to 25 percent. Bayesian confidence that some genuine effect on inflammation-associated methylation exists, given the reproducible MCP-1 and insulin sensitivity changes: about 50 percent. These are different claims and should not be conflated.

Parkinson's disease

Phase 1/2, NCT05083260. N = 45 (40 on dopamine replacement therapy), 20 mg twice daily for 28 days, 16 US sites. The registered primary objective was the drug-drug interaction with levodopa, so all clinical findings are exploratory. Reported: about 3 points greater improvement in UPDRS Part 3 at the 2 and 3 hour marks versus levodopa alone; about 6 points in patients

under 70 years, roughly half the cohort; 88.9 percent versus 63.6 percent achieving greater than 30 percent UPDRS improvement. Never published in a peer-reviewed journal.

SUNRISE-PD, Phase 2b, NCT06757010, topline 6 August 2026. N = 57 randomised 1:1, levodopa-naïve early Parkinson's disease, 20 mg twice daily, 12-week treatment period within a 20-week study, hybrid decentralised design.

Endpoint	Bezisterim	Placebo	Cohen's d	p
EPNIC-15 clinical composite	-0.04	+0.18	-0.94	0.0006
Neuroinflammation composite (CCL2, CHI3L1, VGF)	-0.28	+0.19	-1.06	0.0018
NfL slope, log2 per week	-0.0148	+0.0095	-0.746	0.008
Neuronal injury composite	-0.09	+0.06	-0.57	0.043
Abeta42	-	-	-	0.0877
p-tau217	-	-	-	0.1272

Additional findings: the primary endpoint was a set of haematologic inflammatory indices (MLR, SIRI, NLR, SII, PLR, AISI), which improved significantly; MDS-UPDRS Parts I, II and III all improved significantly versus placebo; IL-6, TNF-alpha, IFN-gamma and IL-17A improved; proteome-wide analysis showed 283 of 380 proteins shifting toward lower inflammatory burden (binomial $p = 3.2 \times 10^{-22}$); and a prespecified enrichment subgroup with baseline platelet count above 230×10^3 per microlitre, about half the cohort, showed the strongest effects. Adverse events 39.3 percent versus 51.7 percent on placebo.

Critical reading. Effect sizes of $d = 0.94$ and 1.06 are very large for a 12-week neurological trial. Three cautions apply. First, the primary endpoint was a blood index, not a clinical outcome, so the statement that the trial met its primary endpoint carries no information about clinical benefit. Second, EPNIC-15 is a sponsor-constructed composite of 15 motor and non-motor measures; composites built by the sponsor and analysed as exploratory endpoints allow substantial analytical latitude, and no prespecification document is public. Third, in $n = 57$ the sampling distribution of d is wide, so 0.94 should be read as an upper bound on a true effect that is probably considerably smaller. The NfL slope result is the most interesting item in the table, because NfL is an objective, assay-based measure of axonal injury that is harder to influence

through analytical choices, and because it is the one place where a neurodegeneration biomarker moved in the expected direction. Note also that it contradicts the null NfL result in the Alzheimer's Phase 3, though the populations and durations differ.

Next step as of September 2026: BioVie has requested an End-of-Phase 2 meeting, expects written FDA feedback before the end of 2026, and proposes a roughly 175-patient Phase 3 with MDS-UPDRS Part III as primary, MDS-UPDRS Part I as co-primary or secondary, and inflammatory enrichment by platelet count.

Long COVID

ADDRESS-LC, Phase 2, NCT06847191, triple-blind, randomised, placebo-controlled, N = 203, 20 mg twice daily. Protocol published in BMJ Open (2026); topline 15 September 2026. The design deliberately used 22 outcome measures with no single designated primary endpoint, covering global clinical benefit, subjective and objective cognition, fatigue, sleep, quality of life and post-exertional malaise.

Results: 21 of 22 endpoints trended in favour of bezisterim; none reached p below 0.05 in the full intent-to-treat population. Prespecified high-symptom-burden subgroups, which together contained about 78 percent of participants, showed statistically significant improvements: 5 endpoints in the high-fatigue subgroup, significant improvements across malaise, fatigue and objective cognition in the high post-exertional malaise subgroup, and 4 objective cognitive endpoints in the high cognitive impairment subgroup. Effect sizes reportedly more than doubled in the subgroups. Safety: treatment-emergent adverse events in 41.6 percent on drug versus 55.9 percent on placebo, headache 4 percent versus 4.9 percent, zero serious adverse events on drug versus one on placebo.

Critical reading. A 21 of 22 directional pattern with zero significant results is exactly what a small true effect looks like in a trial powered for exploration rather than confirmation, and the coherence of the pattern is a point in the drug's favour, since noise does not usually align across 22 measures. The subgroup findings are the weaker part: effect sizes that double in a subgroup half the size are often an artefact of reduced sample and of selecting on baseline severity, where regression to the mean is strongest in the most severely affected. A confirmatory trial with one prespecified primary endpoint in an enriched population is the correct next step, and the sponsor says it is planned.

2.5 Safety synthesis

Cumulative enrolment across the disclosed programme is close to 1,000 participants (48 in the Phase 1 metabolic study, 164 in the Phase 2 diabetes study, 23 in the open-label Alzheimer's study, 439 in the Phase 3, 45 in the Phase 1/2 Parkinson's study, 57 in SUNRISE-PD, 203 in ADDRESS-LC, plus unpublished ulcerative colitis and rheumatoid arthritis cohorts), of whom roughly half received active drug. The longest continuous exposure studied is 30 weeks.

What is reassuring: adverse event rates at or below placebo in the two largest recent trials; no serious adverse events attributed to the drug in the Phase 2 Parkinson's and long COVID trials; no ARIA; no hypoglycaemia despite an insulin-sensitising mechanism; no measurable effect on the gonadal or adrenal axes; no genotoxicity; discontinuation for adverse events at 2.3 percent in the Phase 3.

What to watch: headache is the one consistent excess, at 9.5 percent versus 0 percent in Phase 3 and about 4 percent in long COVID. Asymptomatic amylase and lipase elevations appeared in the metabolic programme, including one serious, transient, asymptomatic amylase elevation that resolved on study. TSH elevation appeared in 7.1 percent versus 2.9 percent in Phase 3, which is a small signal but worth tracking given the compound's steroid scaffold and the length of exposure any geroprotective use would require. Reversible hepatocellular hypertrophy in rats at 100 mg/kg/day argues for liver enzyme monitoring in longer trials.

What is unknown: anything beyond seven months. For a molecule whose thesis is chronic suppression of inflammatory signalling in aging humans, the absence of multi-year safety data is the single largest gap, and chronic partial suppression of TNF-alpha and NF-kB signalling carries theoretical infection and malignancy surveillance questions that the non-immunosuppression preclinical data mitigate but do not resolve.

Bayesian confidence in acceptable short-term (up to 6 months) tolerability: about 90 percent.
Bayesian confidence in acceptable multi-year safety: not estimable from current data.

2.6 Evidence quality audit

Journal context for the primary sources, verified by search:

- Frontiers in Neuroscience, which published the 2025 exploratory Phase 3 analysis, carries an impact factor of 3.19 (2023, Q2), which places it in the mid-tier of neuroscience journals and well below the specialty leaders in the field.
- Medicine (Baltimore), which published the 2024 Phase 2 open-label Alzheimer's study, carries an impact factor of 2.0 (2025 citation data, Q2), which places it in the lower-mid tier of general medical journals; the journal is broad-scope and has issued multiple retractions for integrity failures in recent years.
- Obesity, which published the 2013 Phase 1 metabolic trial, carries an impact factor of 4.7 (2025, Q1), which places it among the leading specialty journals in obesity and metabolism.
- Mediators of Inflammation, which published the 2013 Phase 2 diabetes trial, is a gold open access Hindawi title indexed in SCIE with a CiteScore of 8 and Q2 standing in cell biology and immunology, which places it in the mid-tier of inflammation journals.
- PLOS One, which published the 2012 target identification study, carries an impact factor of 2.8 (2025), which places it in the lower-mid tier as a broad-scope megajournal without field-specific selectivity.

- BMJ Open, which published the ADDRESS-LC protocol, carries an impact factor of 2.4 (2023, Q2), which places it in the lower-mid tier of general medical journals and reflects its role as a protocol and methods venue rather than a high-selectivity outlet.
- Journal of Pharmacology and Experimental Therapeutics, source of the 2010 glucose intolerance work, carries an impact factor of 3.8 (2025, Q2), which places it in the solid middle tier of pharmacology journals.

No result from any bezisterim trial has been published in a high-impact clinical journal. The Phase 3 primary endpoint analysis has never appeared as a standalone peer-reviewed publication; it exists as a conference poster and inside an exploratory biomarker paper. The two 2026 trials exist only as press releases and an SEC filing, which means no methods section, no prespecification document, no full adverse event tables and no independent peer review.

Structural issues to weigh:

1. Sponsor entanglement. Authorship on the key papers is dominated by sponsor employees and shareholders, including the 2013 metabolic papers under Harbor Therapeutics and the 2025 Frontiers paper under BioVie. Academic collaborators on the 2025 paper include Harvard T.H. Chan School of Public Health biostatistics, Brigham and Women's Hospital endocrinology, and the Epigenetic Clock Development Foundation, which strengthens the methylation analysis pipeline but does not make the analysis independent.
2. Data integrity precedent. The 2024 disclosure of GCP violations at 15 of 39 Phase 3 sites, referral to the FDA, and the securities class actions filed in the aftermath are not evidence about the molecule's pharmacology, but they are highly relevant to how much weight sponsor-reported, non-peer-reviewed numbers should carry. This is the main reason to discount press-release effect sizes rather than to take them at face value.
3. Publication asymmetry. The positive metabolic, Alzheimer's biomarker and epigenetic analyses are published or presented repeatedly. The ulcerative colitis and rheumatoid arthritis trials, the Phase 1/2 Parkinson's trial and the Phase 3 primary endpoint analysis are not published at all. The pattern is consistent with selective dissemination.
4. Reproducible core. Against all of the above, one signal has now replicated across four populations, two decades, two sponsors and both peer-reviewed and non-peer-reviewed reporting: reduced MCP-1 and inflammatory indices, improved HOMA2 insulin sensitivity, and lower fasting glucose. Replication across independent datasets is the strongest form of evidence in this dossier, and it is the part that should be believed.

2.7 Confidence summary

Claim	Confidence	Basis
Reduces inflammatory signalling and improves	about 85 percent	Replicated across 4 populations, 2013 to 2026,

Claim	Confidence	Basis
insulin sensitivity biomarkers in humans at 10 to 40 mg/day		including 2 peer-reviewed RCTs
Not broadly immunosuppressive at therapeutic doses	about 75 percent	Mouse infection and immunisation models, plus human adverse event profile at or below placebo
Acceptable tolerability up to 6 months	about 90 percent	Roughly 700 exposed humans, 2.3 percent adverse event discontinuation in Phase 3
Clinically meaningful disease modification in Alzheimer's disease	about 15 percent	Phase 3 failed; per-protocol remnant showed d about 0.10 on the cognitive co-primary; all fluid neurodegeneration markers null
Clinically meaningful benefit in early Parkinson's disease	about 30 to 35 percent	Large exploratory effect sizes in n = 57 with an objective NfL signal, but non-clinical primary endpoint and sponsor-built composite
Clinically meaningful benefit in long COVID high-burden subgroups	about 30 percent	Coherent 21 of 22 directional pattern, all subgroup-dependent, no peer review
Reduces methylation-based epigenetic age acceleration in humans	about 20 to 25 percent	n = 33, 5 uncorrected clocks, compromised parent trial, three inconsistent published number sets
Extends healthspan or lifespan in any mammal	not estimable	No study has ever been conducted

2.8 Explicit N/A declarations

- Lifespan and survival data in mammals: not applicable, because no lifespan, survival or healthspan study of bezisterim has been conducted in any species. The compound's

aging claims rest entirely on 30-week methylation clock analyses in 33 human blood samples.

- Pabis et al. 2023 short-lived control audit (the 900-day rule): not applicable, because there is no rodent lifespan study to audit. If a lifespan study is ever run, the parent sterol's immune-senescence work in aged mice offers no usable control survival data either, since those studies did not follow cohorts to natural death.
- Head-to-head comparison against approved agents: not applicable. No trial has compared bezisterim against an active comparator in any indication. The lecanemab and donanemab comparisons in company materials are cross-trial and should be disregarded.
- Dose-response in neurological indications: not applicable. Every neurological trial used a single 20 mg twice-daily dose, so no dose-response or exposure-response relationship can be assessed for CNS endpoints.
- Formal Cohen's d for Alzheimer's Phase 3 endpoints: not reported by the authors. The values in section 2.4 are my derivation from published confidence intervals and are labelled as such.
- Effect sizes for ADDRESS-LC: not applicable at present. The sponsor states that Cohen's d values were positive across nearly all measures and more than doubled in subgroups, but no numerical values have been released.
- Drug interaction data relevant to a supplement or drug stack: largely not applicable. The only formal interaction studies are with levodopa and carbidopa, where no clinically meaningful pharmacokinetic interference was found, and with methotrexate, whose results were never published.

2.9 Mechanistic overlap with intervention classes you already track

This section is hypothesis-level only. There are no interaction or combination data for any of these pairings, and bezisterim is not obtainable outside trials, so nothing here is actionable.

- Insulin-sensitising and metabolic agents (metformin, GLP-1 receptor agonists): bezisterim's human effect is on the inflammation-to-IRS-1 axis rather than on hepatic gluconeogenesis or incretin signalling, so the mechanisms are complementary rather than redundant. Note that the 2013 metabolic benefit was observed on top of background metformin, which is the only combination evidence that exists.
- TNF-alpha and NF-kB directed interventions: mechanistically redundant. If bezisterim's effect is genuine, additive benefit with a TNF-alpha inhibitor should not be assumed, and the theoretical infection risk of combined suppression is the relevant concern.
- Inflammaging biomarker targets you follow (IL-6, hs-CRP, GDF-15): CRP fell in the Phase 1 metabolic trial and IL-6 fell in SUNRISE-PD. MCP-1 is the most consistently moved marker across the whole programme and is the one to watch if this compound is ever independently tested. GDF-15 has never been measured in any bezisterim trial.

- cGAS-STING pathway interventions: no overlap has been studied. ERK and NF- κ B are downstream convergence points for STING signalling, so a mechanistic relationship is plausible in principle, but no bezisterim study has measured STING pathway activity.
- Epigenetic clocks (DunedinPACE, proteomic clocks): the bezisterim methylation analysis used Hannum, PhenoAge, GrimAge, Skin and Blood, and InflammAge. DunedinPACE, which measures pace of aging rather than cumulative age, was not included, and neither were proteomic clocks. Its absence is notable given that DunedinPACE is generally the more responsive measure in short intervention windows.

2.10 What would change this assessment

In ascending order of how much each would move the estimates:

1. Peer-reviewed publication of the SUNRISE-PD and ADDRESS-LC results with full methods, prespecification documents and adverse event tables. This alone would materially firm up the Parkinson's estimate.
2. An independent, non-sponsor replication of the epigenetic age finding, in a larger sample, with multiplicity correction and DunedinPACE included.
3. A positive, adequately powered Phase 3 in Parkinson's disease with MDS-UPDRS Part III as a prespecified primary endpoint. Given the enrichment strategy and the 175-patient plan, this is the single most informative readout coming.
4. Any mammalian healthspan or lifespan study. Its complete absence after eighteen years of development is the most conspicuous gap between how the compound is positioned in longevity circles and what has actually been tested.

Sources

Peer-reviewed literature

- [Molecular targets for 17-alpha-ethynyl-5-androstene-3-beta,7-beta,17-beta-triol, an anti-inflammatory agent derived from the human metabolome \(PLOS One, 2012\)](#)
- [An exploratory analysis of bezisterim treatment associated with decreased biological age acceleration, and improved clinical measure and biomarker changes in mild-to-moderate probable Alzheimer's disease \(Frontiers in Neuroscience, 2025\)](#)
- [A phase 2, open-label study of anti-inflammatory NE3107 in patients with dementias \(Medicine, 2024\)](#)
- [HE3286 Phase 2 trial in type 2 diabetes \(Mediators of Inflammation, 2013\)](#)
- [A synthetic anti-inflammatory sterol improves insulin sensitivity in insulin-resistant obese impaired glucose tolerance subjects \(Obesity, 2013\)](#)
- [Amelioration of glucose intolerance by the synthetic androstene HE3286: link to inflammatory pathways \(JPET, 2010\)](#)

- [A new antidiabetic compound attenuates inflammation and insulin resistance in Zucker diabetic fatty rats \(Am J Physiol Endocrinol Metab, 2010\)](#)
- [HE3286, an oral synthetic steroid, treats lung inflammation in mice without immune suppression \(Journal of Inflammation, 2010\)](#)
- [HE3286: A novel synthetic steroid as an oral treatment for autoimmune disease \(Annals of the NY Academy of Sciences, 2009\)](#)
- [ADDRESS-LC study protocol \(BMJ Open, 2026\)](#)
- [NM101 Phase III study of NE3107 in Alzheimer's disease: rationale and design \(Neurodegenerative Disease Management, 2021\)](#)
- [Pharmacology and immune modulating properties of 5-androstene-3-beta,7-beta,17-beta-triol \(2011\)](#)

Independent appraisals and reference profiles

- [Bezisterim therapeutics profile, ALZFORUM](#)
- [NE3107 \(HE3286\) drug review, Alzheimer's Drug Discovery Foundation Cognitive Vitality](#)
- [NE3107 update, Alzheimer's Drug Discovery Foundation Cognitive Vitality, January 2024](#)
- [Bezisterim, Wikipedia](#)

Trial reports, sponsor disclosures and journalism

- [SUNRISE-PD Phase 2 topline results, SEC Form 8-K exhibit, 6 August 2026](#)
- [ADDRESS-LC Phase 2 topline results, 15 September 2026](#)
- [ADDRESS-LC topline, BioSpace](#)
- [Parkinson's Phase 3 development programme update, 8 September 2026](#)
- [Phase 3 Alzheimer's clinical outcomes poster, AD/PD 2024](#)
- [Epigenetic and biological aging data presented at ARDD 2024](#)
- [Biological clock data presented at the 2nd World Conference on Aging and Gerontology, July 2025](#)
- [Phase 3 Alzheimer's results presented at WCAG 2025](#)
- [BioVie blames protocol errors at trial sites for Phase 3 Alzheimer's failure \(Fierce Biotech\)](#)
- [Securities class action following the Phase 3 disclosure](#)
- [Bezisterim programme overview, BioVie](#)
- [Independent patient-community analysis of the ADDRESS-LC results](#)

Journal metrics verification

- [Obesity impact factor](#)
- [Medicine impact factor](#)
- [Frontiers in Neuroscience impact factor](#)
- [Mediators of Inflammation indexing and quartile](#)
- [PLOS One impact factor](#)
- [BMJ Open impact factor](#)

- [JPET impact factor](#)