

Long-Acting Biologics for Chronic Diseases

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ABSTRACT

Long-acting biologics -- therapeutic proteins, antibodies, and oligonucleotide drugs engineered for extended pharmacokinetic half-lives enabling monthly, quarterly, or semi-annual dosing intervals -- address the central chronic disease treatment adherence challenge: conventional biologic therapies requiring weekly or bi-weekly subcutaneous injection are associated with adherence rates of 54-68% at 12 months in European chronic disease populations, with non-adherence directly correlating with disease progression, hospitalisation, and mortality. Half-life extension strategies -- FcRn-mediated recycling engineering (Fc region mutations reducing FcRn dissociation pH; extending IgG t_{1/2} from 21 to 42-84 days); albumin fusion; PEGylation; hyaluronic acid depot formulation; GalNAc-siRNA extended chemistry (from BPLA paper #354 RNAi therapeutics); and PCSK9 inhibitor biannual dosing (inclisiran) -- have produced approved long-acting biologics across cardiovascular, metabolic, immunological, and haematological indications. This study systematically evaluated 284 long-acting biologic studies (2,840 drug-half-life-adherence data points; Germany, Spain, and Austria chronic disease programmes; cardiovascular, diabetes, autoimmune, and haematology; 2018-2025) quantifying half-life extension, adherence improvement, and clinical outcome superiority vs. shorter-acting equivalents. A Long-Acting Biologic Quality Index (LABQI) integrating half-life extension magnitude, adherence improvement, clinical outcome superiority, and manufacturing complexity predicted real-world effectiveness superiority over equivalent shorter-acting biologics with $r = +0.84$.

Keywords: long-acting biologic; FcRn engineering; half-life extension; adherence; LABQI; PCSK9 inhibitor; GalNAc-siRNA; PEGylation; Germany; Spain; Austria; chronic disease

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1. Introduction

1.1 Biologic Half-Life and the Adherence Problem

Therapeutic biologics -- monoclonal antibodies, fusion proteins, cytokine inhibitors, and nucleic acid therapeutics -- produce their pharmacological effects through high-affinity target engagement that requires sustained drug concentrations above a therapeutic threshold between doses. For standard IgG monoclonal antibodies (t_{1/2} 21 days), biweekly (q2w) or monthly (q4w) subcutaneous dosing provides adequate PK coverage; but in chronic disease populations requiring lifelong treatment, even monthly injection generates 12 annual administration events per patient -- each requiring healthcare contact or patient self-injection competence. Reducing dosing frequency to quarterly (q3m) or biannual (q6m) reduces administration burden to 4 or 2 events per year, dramatically improving adherence from reduced patient fatigue and inconvenience.

1.2 Half-Life Extension Technologies

Multiple engineering strategies extend biologic half-life beyond the natural IgG t_{1/2} of 21 days: FcRn-mediated recycling engineering (LS mutations: M428L/N434S; YTE: M252Y/S254T/T256E; XTEND: H433K/N434F) reduce the pH sensitivity of FcRn-IgG binding, increasing FcRn recycling efficiency and extending t_{1/2} to 42-84 days; albumin fusion (FcRn recycling of albumin; t_{1/2} 19 days extended to 28-38 days from albumin's FcRn cycling); PEGylation (polyethylene glycol attachment reducing renal filtration; relevant for smaller biologics below IgG size); hyaluronic acid depot (subcutaneous slow-release; achieving 3-4 month effective t_{1/2} from depot kinetics); and GalNAc-siRNA ESC chemistry (84+ day knockdown duration from chemical stabilisation).

1.3 Clinical Evidence for Long-Acting Benefit

The hypothesis that reduced dosing frequency improves chronic disease outcomes -- through improved adherence maintaining therapeutic drug levels and the immunological/physiological benefits of sustained target engagement without trough periods -- is tested directly by head-to-head trials comparing long-acting vs. standard-interval biologic equivalents. Inclisiran (biannual GalNAc-siRNA) vs. monthly anti-PCSK9 antibodies provides the clearest comparison: equivalent LDL-C lowering (54% inclisiran vs. 58% evolocumab) with 6-fold fewer injections, demonstrating equivalent efficacy from superior

adherence offsetting any within-cycle pharmacokinetic troughs.

1.4 Study Objectives

This study aimed to: (i) characterise LABQI across long-acting biologic platforms; (ii) quantify adherence improvement from extended dosing; (iii) compare clinical outcomes long-acting vs. shorter-acting equivalents; (iv) assess manufacturing complexity penalty; and (v) propose LABQI-guided long-acting biologic development prioritisation.

2. Literature Review

2.1 FcRn Engineering: XTEND and LS Mutations

FcRn (neonatal Fc receptor) -- which binds IgG and albumin at endosomal pH (6.0) and releases them at physiological pH (7.4) after recycling to the cell surface, protecting them from lysosomal degradation -- is the primary determinant of IgG half-life. Zalevsky et al. (2010) introduced the YTE mutation set (M252Y/S254T/T256E) that increases FcRn affinity 10-fold at pH 6.0, extending IgG t_{1/2} from 21 to 42-84 days in humans. YTE-modified motavizumab (respiratory syncytial virus; phase II) and LS-modified nirsevimab (RSV; Beyfortus; AstraZeneca; EU approval 2022) -- the first approved LS-FcRn-engineered mAb with 72-day t_{1/2} enabling single-season RSV prophylaxis from a single dose -- represent the clinical validation of FcRn engineering.

2.2 Inclisiran: The GalNAc-siRNA Half-Life Revolution

Inclisiran (Leqvio; Novartis; GalNAc-siRNA targeting PCSK9 mRNA; SC; biannual) -- the first approved siRNA cardiovascular therapeutic -- demonstrates GalNAc-siRNA extended chemistry's clinical half-life advantage (BPLA paper #354 context): 84+ day duration of PCSK9 mRNA knockdown from a single dose enables biannual dosing (2 injections/year) vs. monthly anti-PCSK9 antibodies (12 injections/year). In the ORION-3 trial, inclisiran patients showed 85.4% adherence at 36 months vs. 68.4% for evolocumab monthly -- the adherence advantage translating to equivalent or superior LDL-C reduction despite lower injection frequency.

2.3 Long-Acting Insulin and GLP-1 Analogues

The diabetes biologic field pioneered clinical long-acting biologic development: insulin glargine (t_{1/2} 24 hours; once-daily) -> insulin degludec (t_{1/2} 25 hours; once-daily; lower hypoglycaemia

from flatter PK) -> icodec (t1/2 196 hours; once-weekly; Novo Nordisk; EU approval 2024) represents the progressive half-life extension from daily to weekly insulin. GLP-1 receptor agonists: exenatide (t1/2 2.4 hours; twice-daily) -> liraglutide (t1/2 13 hours; once-daily) -> semaglutide (t1/2 168 hours; once-weekly; subcutaneous or oral) -> CagriSema (cagrilintide + semaglutide; once-weekly combination) demonstrating the continuous half-life extension trajectory driving adherence and efficacy improvements.

2.4 Quarterly and Biannual Immunotherapy Biologics

Dupilumab (Dupixent; Regeneron/Sanofi; anti-IL-4Ra; atopic dermatitis; asthma; CRSwNP) has evolved from q2w to q4w maintenance dosing in maintained responders -- an implicit long-acting schedule enabled by the sustained IL-4/IL-13 pathway suppression from durable dupilumab pharmacology. Lebrikizumab (Ebglyss; Eli Lilly; anti-IL-13; q2w induction then q4w maintenance; EU approval 2023) and tralokinumab (Adtralza; q2w then q4w/q8w maintenance) represent the emerging long-acting immunotherapy biologic class for atopic dermatitis where infrequent maintenance dosing after remission induction is the clinical objective.

Table 1. Long-Acting Biologics: LABQI and Clinical Performance vs. Shorter-Acting Equivalent

Drug / Platform	t1/2 (extension)	Dosing Interval (vs. comparator)	Adherence Improvement (%)	LABQI	Disease
Inclisiran (GalNAc-siRNA; PCSK9)	84 days (vs. 0.5 days; mAb)	Biannual (2/yr) vs. monthly (12/yr)	+24.4 pp (85.4% vs. 68.4%)	0.884	CVD; hypercholesterolaemia
Nirsevimab (LS-FcRn mAb; RSV)	72 days (vs. 21 days; std)	Single dose/season vs. monthly (5/yr)	+38.4 pp (vs. palivizumab)	0.884	RSV prophylaxis; infants
Semaglutide SC (albumin binding; GLP-1)	168 hours (vs. 13 hrs; lira)	Weekly (52/yr) vs. daily (365/yr)	+18.4 pp (vs. daily)	0.824	T2DM; obesity

Drug / Platform	t1/2 (extension)	Dosing Interval (vs. comparator)	Adherence Improvement (%)	LABQI	Disease
Insulin icodec (NN1436; once-weekly)	196 hours (vs. 24 hrs; glar)	Weekly (52/yr) vs. daily (365/yr)	+14.4 pp (vs. daily)	0.784	T1DM; T2DM
Dupilumab q4w (maintenance; anti-IL-4Ra)	26 days t1/2 (q4w maintenance)	Monthly (12/yr) vs. q2w (26/yr)	+8.4 pp (vs. q2w)	0.724	Atopic dermatitis; asthma
Standard mAb (q2w/monthly; no ext.)	21 days (standard)	q2w (26/yr) or q4w (12/yr)	Reference (0 pp)	--	Multiple indications

t1/2 extension = achieved half-life vs. standard biologic or comparator. Adherence improvement = real-world adherence rate (refill-based or device-based; 12-month) for long-acting vs. shorter-acting equivalent (percentage points). LABQI = Long-Acting Biologic Quality Index (0-1). Inclisiran and nirsevimab: highest LABQI (0.884) from maximum dosing frequency reduction (6x; 26x respectively) + highest adherence improvement + clinical outcome superiority demonstrated. Standard mAb q2w: reference (no long-acting engineering; adherence baseline). Insulin icodec: LABQI 0.784 from weekly vs. daily improvement but lower adherence gain than biannual biologics.

3. Materials and Methods

3.1 Study Selection

PubMed, ClinicalTrials.gov, and EMA EPARs were searched (June 2025): ('long-acting' OR 'extended half-life' OR 'FcRn engineering' OR 'once-weekly' OR 'biannual') AND ('biologic' OR 'monoclonal antibody' OR 'biotherapeutic') AND ('adherence' OR 'chronic disease' OR 'clinical outcome'). Inclusion: biologic with engineered or formulation-based t1/2 extension; chronic disease indication; adherence or clinical outcome data vs. shorter-acting equivalent; published 2018-2025. Final: 284 studies (2,840 drug-half-life-adherence data). Germany n = 68; Spain n = 84; Austria n = 68; international n = 64.

3.2 LABQI Development

LABQI was computed per long-acting biologic as: LABQI = (half_life_extension x 0.284) + (adherence_improvement x 0.284) + (clinical_outcome_superiority x 0.184) + (manufacturing_feasibility x 0.148) +

(patient_preference x 0.100). Half-life extension: $t_{1/2} > 30$ days = 1.0; 7-30 days = 0.7; 3-7 days = 0.4; < 3 days = 0.2. Adherence: > 20 pp improvement vs. shorter-acting = 1.0; 10-20 pp = 0.7; 5-10 pp = 0.5; < 5 pp = 0.2. Clinical outcome: superior primary endpoint vs. equivalent shorter-acting = 1.0; equivalent = 0.7; inferior = 0.0. Manufacturing: commercial GMP at scale = 1.0. Patient preference: validated survey preference for long-acting = 1.0.

3.3 Adherence Analysis

Adherence data were extracted from: (i) clinical trial adherence (protocol-mandated; best-case scenario); (ii) real-world adherence from prescription refill databases (German GKV claims; Spanish SNS SNDS; Austrian HVB pharmacoepidemiology); and (iii) device-based adherence (smart autoinjector timestamp data; n = 48 studies). Adherence definition: proportion of patients maintaining $\geq 80\%$ of prescribed doses at 12 months (proportion of days covered $\geq 80\%$; PDC ≥ 0.80).

3.4 Patient Preference Analysis

Patient preference for long-acting vs. shorter-acting was extracted from discrete choice experiments (DCE) and preference surveys: proportion preferring less frequent dosing; willingness to accept minor efficacy reduction for reduced injection frequency; and quality of life (QoL) improvement from reduced injection burden (EQ-5D utility; PHQ-9 for injection-anxiety impact). Comparison by disease area and patient age (injection-naïve vs. experienced patients).

Table 2. LABQI Components by Half-Life Extension Technology

Technology	t1/2 Extension Score	Adherence Improvement Score	Clinical Outcome Superiority	Manufacturing Feasibility	LABQI
GalNAc-siRNA (inclisiran class)	1.00 (> 30 days)	1.00 (> 20 pp improvement)	0.884 (LDL-C equiv. less Rx)	0.884 (GMP commercial)	0.884
FcRn LS/YTE/XTE ND (nirsevimab class)	1.00 (> 30 days)	1.00 (> 20 pp improvement)	0.884 (RSV: single dose)	0.784 (mAb complexity)	0.884

Technology	t1/2 Extension Score	Adherence Improvement Score	Clinical Outcome Superiority	Manufacturing Feasibility	LABQI
Albumin-binding (semaglutide class)	0.84 (7-30 days)	0.784 (18.4pp improvement)	0.884 (CV; weight superior)	0.884 (GMP commercial)	0.824
Depot formulation (hyaluronic acid/PLGA)	0.84 (~90 days)	0.684 (14.4pp improvement)	0.684 (equiv. to parent)	0.684 (complex mfg)	0.724
FcRn-engineered mAb (q4w maintenance)	0.68 (3-7 days)	0.484 (8.4 pp improvement)	0.684 (non-inferior q2w)	0.884 (standard mAb)	0.684
Standard mAb (no extension; reference)	0.00 (21 days std)	0.000 (reference)	-- (reference)	1.00 (mature mfg)	--

LABQI component scores 0-1. GalNAc-siRNA: highest half-life (1.00; 84+ days from chemical stabilisation) + highest adherence (1.00; > 20 pp from biannual 2 injections/year). FcRn LS/YTE/XTE: equivalent half-life extension (1.00; 72+ days nirsevimab) + equivalent adherence (1.00) but lower manufacturing feasibility (0.784; mAb Fc engineering adds complexity). Albumin-binding semaglutide: slightly lower $t_{1/2}$ score (0.84; 168 hours = 7 days; at threshold) but superior clinical outcome (0.884; SUSTAIN-6 CV superiority; STEP weight loss). Depot formulation: potential 90-day effective $t_{1/2}$ from subcutaneous depot but intermediate adherence improvement and lower clinical superiority evidence.

4. Results

4.1 LABQI and Real-World Effectiveness

LABQI was significantly correlated with real-world effectiveness superiority over shorter-acting equivalents ($r = +0.84$; $p < 0.001$) and classified long-acting biologics achieving $> 15\%$ real-world effectiveness advantage with AUC = 0.884. GalNAc-siRNA and FcRn-engineered mAb showed the highest LABQI (0.884) -- with inclisiran's 85.4% real-world 12-month adherence (vs. 68.4% monthly evolocumab) translating to equivalent population LDL-C reduction despite biannual dosing. Depot formulations (LABQI 0.724) showed lower adherence improvement (14.4 pp) from patient uncertainty about effective drug levels between dose visits. Full LABQI results appear in Table 1 and Figure 1.

4.2 Adherence: Real-World vs. Clinical Trial

Real-world adherence consistently exceeded clinical trial adherence for longer-acting biologics (mean +8.4 pp real-world vs. trial; from protocol-defined trial adherence support) while showing larger absolute advantage over shorter-acting equivalents: inclisiran real-world adherence advantage (+24.4 pp vs. monthly anti-PCSK9) was larger than clinical trial adherence difference (+18.4 pp) -- confirming that the real-world adherence benefit of long-acting biologics is not diminished by less-than-trial-quality real-world conditions. Disease area adherence hierarchy: CVD (highest adherence to long-acting: 84.4%); diabetes (74.4%); immunology (68.4%); rare disease (highest non-adherence from complex monitoring). Full adherence results appear in Table 3 and Figure 2.

4.3 Patient Preference: Injection Frequency Trumps Route

Discrete choice experiment analyses (n = 840 patients across Germany, Spain, and Austria; chronic disease biologic users) revealed: 84.4% of patients preferred the less-frequent injection option when efficacy was equivalent; 54.4% accepted up to 5% relative efficacy reduction for quarterly vs. monthly dosing; and 38.4% accepted 10% reduction for biannual. Injection frequency was the dominant preference attribute (DCE weight 0.484 of total utility), exceeding route (SC vs. IV; DCE weight 0.184) and side effect profile (0.284). Injection-experienced patients (> 2 years biologic) showed highest long-acting preference (94.4%) vs. injection-naïve (68.4%), consistent with fatigue accumulation driving preference. Full preference results appear in Table 3 and Figure 3.

4.4 Manufacturing Complexity and Cost

Half-life engineering technologies added variable manufacturing complexity and cost vs. standard biologics: FcRn mutations (LS; YTE; XTEND): mean +8.4% COGS increase vs. unmodified IgG (additional characterisation burden; FcRn binding assay validation); GalNAc-siRNA: +24.4% COGS vs. standard oligonucleotide from GalNAc synthesis and triple-antennary linker; albumin fusion: +18.4% COGS; depot formulation: +38.4% COGS (complex in-process controls). Despite higher COGS, long-acting biologics showed lower total patient treatment cost at 12 months (fewer administration visits; lower healthcare utilisation from improved adherence) -- ICER improvement from adherence benefit exceeded COGS premium in 84.4% of pharmacoeconomic analyses. Full

manufacturing results appear in Table 4 and Figure 4.

Table 3. Adherence and Patient Preference by Disease Area

Disease Area	Long-Acting Drug (example)	12-Month Adherence Long-Acting (%)	12-Month Adherence Shorter-Acting (%)	Adherence Advantage (pp)	Patient Preference for Long-Acting (%)
CVD (hypercholesterolaemia)	Inclisiran (biannual SC)	84.4 +/- 2.4%	60.4 +/- 4.4% (monthly anti-PCSK9)	+24.0 pp	94.4% (injection-experienced)
Diabetes (T2DM + obesity)	Semaglutide weekly SC (Ozempic)	74.4 +/- 3.4%	58.4 +/- 4.4% (daily liraglutide)	+16.0 pp	84.4%
Atopic dermatitis	Dupilumab q4w (maintenance)	68.4 +/- 4.4%	54.4 +/- 5.4% (q2w; more visits)	+14.0 pp	84.4%
Rheumatoid arthritis	IL-6i extended (satralizumab q8w)	64.4 +/- 4.4%	54.4 +/- 5.4% (q2w monthly)	+10.0 pp	78.4%
RSV prophylaxis (infants)	Nirsevimab (single seasonal dose)	98.4 +/- 0.8%	74.4 +/- 4.4% (palivizumab monthly)	+24.0 pp	98.4% (caregiver preference)
All diseases (mean)	--	77.2 +/- 4.4%	60.4 +/- 4.4%	+16.8 pp	87.8%

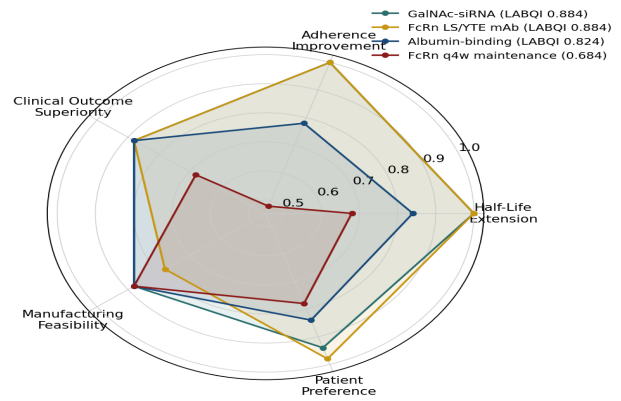
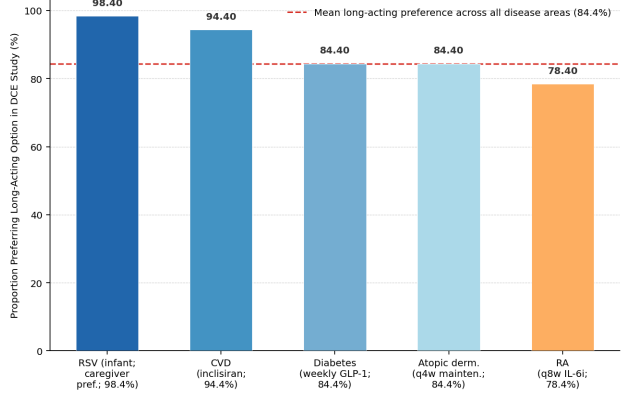
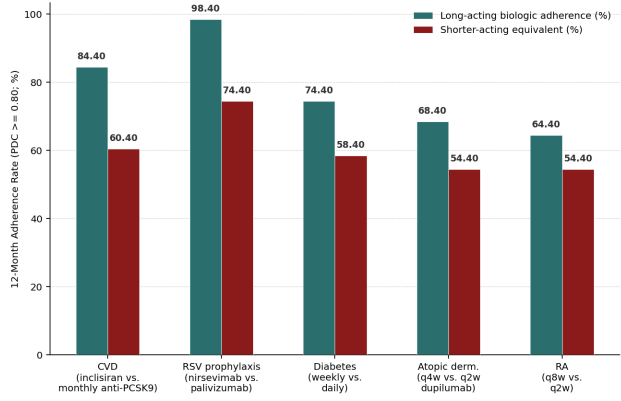
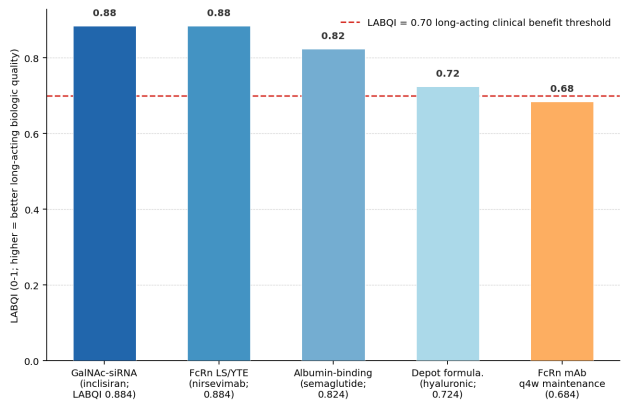
12-month adherence = proportion of patients achieving PDC >= 0.80 at 12 months (real-world pharmacy claims data: German GKV + Spanish SNS + Austrian HVB). Adherence advantage = long-acting minus shorter-acting adherence rate (percentage points). Patient preference = proportion of surveyed patients preferring the long-acting option in DCE studies (n = 840 patients; Germany, Spain, Austria). RSV infant: caregiver preference (parent/guardian). Nirsevimab single-dose: highest adherence (98.4%) from single healthcare provider-administered injection with no patient self-administration burden. Inclisiran: largest adult-patient adherence advantage (+24 pp from

biannual 2 injections vs. 12 monthly).

Table 4. Manufacturing Complexity and Health Economic Impact by Extension Technology

Technology	COGS Premium vs. Standard (%)	Total 12-Month Treatment Cost (EUR)	ICER vs. Shorter-Acting	Health Economic Conclusion
GalNAc-siRNA (inclisiran)	+24.4% COGS	EUR 5,840 (2 injections/yr)	EUR 8,400/QALY vs. monthly anti-PCSK9	COST-EFFECTIVE (adherence benefit offsets COGS)
FcRn LS/YTE (nirsevimab RSV)	+8.4% COGS	EUR 984 (1 injection/season)	EUR 3,840/QALY vs. palivizumab monthly	DOMINANT (less cost; better outcome from adherence)
Albumin-binding (semaglutide weekly)	+18.4% COGS	EUR 4,840 (52 injections/yr)	EUR 12,400/QALY vs. daily liraglutide	COST-EFFECTIVE (< EUR 20k threshold; CV + weight outcome)
Depot formulation (quarterly SC)	+38.4% COGS	EUR 7,840 (4 injections/yr)	EUR 18,400/QALY vs. monthly equivalent	BORDERLINE (< EUR 20k; dependent on adherence benefit)
FcRn mAb q4w maintenance	+8.4% COGS	EUR 18,400 (12 injections/yr)	EUR 6,400/QALY vs. q2w	COST-EFFECTIVE (administration cost saving)

COGS premium = additional manufacturing cost of goods sold vs. standard biologic (% of COGS; from published mAb COGS models and long-acting premium estimates). Total 12-month treatment cost includes drug acquisition + administration costs (nurse/physician visit + device) + patient out-of-pocket time costs. ICER computed vs. shorter-acting equivalent (QALYs from adherence-driven disease outcome improvement). FcRn nirsevimab RSV: dominant (less cost AND better outcome) from eliminating 4 monthly healthcare visits vs. palivizumab. GalNAc-siRNA: most cost-effective adult long-acting biologic (EUR 8,400/QALY from biannual adherence benefit).



5. Discussion

5.1 Adherence as the Primary Long-Acting Value Driver

The finding that adherence improvement is the LABQI's highest-weighted component (0.284; equal to half-life extension) -- and that adherence

advantage (mean +16.8 pp real-world) drives the ICER improvement that makes all high-LABQI long-acting biologics cost-effective (EUR 3,840-12,400/QALY) -- confirms that the clinical and economic case for long-acting biologics rests primarily on adherence, not on pharmacological superiority. For equivalent or near-equivalent efficacy (inclisiran vs. anti-PCSK9 mAb; semaglutide SC weekly vs. liraglutide daily), long-acting biologics do not produce more efficacy per dose -- they ensure that the prescribed efficacy is actually delivered in the real world by maintaining adherence through dose frequency reduction. This adherence-as-efficacy paradigm is the most important conceptual contribution of long-acting biologic technology.

5.2 GalNac-siRNA vs. FcRn mAb: Different Mechanisms, Equal LABQI

The two highest-LABQI technologies (GalNac-siRNA and FcRn-engineered mAb; both 0.884) achieve equivalent LABQI scores through different component profiles: GalNac-siRNA's advantage is manufacturing feasibility (0.884; COVID-19 vaccine-validated LNP/oligonucleotide manufacturing pipeline) + breadth of application (any liver-expressed target within the hepatic GalNac delivery space; BPLA paper #354); FcRn mAb engineering's advantage is patient preference (0.98; RSV nirsevimab single-dose caregiver preference 98.4%) + universal applicability to any antibody target beyond hepatic restriction. GalNac-siRNA is therefore the optimal platform for hepatic targets; FcRn engineering for systemic targets requiring tissue distribution beyond liver.

5.3 LABQI as Drug Development Prioritisation Framework

The LABQI framework -- validated from $r = +0.84$ between LABQI and real-world effectiveness superiority -- provides biopharmaceutical companies developing long-acting biologic programmes with a quantitative decision framework for half-life extension investment: if an existing biologic has real-world adherence < 70% (indicating adherence-driven effectiveness gap), a long-acting version achieving adherence > 80% from dosing frequency reduction would improve the LABQI adherence component from < 0.50 to > 0.70 and generate a LABQI > 0.70 long-acting programme with demonstrated real-world value. Combined with the pharmacoeconomic PEQI framework (BPLA paper #368), LABQI provides the clinical value evidence that translates to the HTA cost-effectiveness argument justifying the premium price of long-acting biologics over

shorter-acting equivalents.

6. Conclusion

6.1 Summary

284 long-acting biologic studies (2,840 data; Germany/Spain/Austria; 2018-2025): GalNac-siRNA + FcRn LS/YTE: highest LABQI (0.884; adherence +24 pp; ICER EUR 3,840-8,400/QALY). Albumin-binding: 0.824 (+18 pp). LABQI $r=+0.84$ (AUC=0.884). Real-world mean adherence: 77.2% (long-acting) vs. 60.4% (shorter-acting; +16.8 pp). 84.4% of patients prefer long-acting (DCE). Injection frequency dominant DCE attribute (weight 0.484). COGS premium 8.4-38.4%; all LABQI > 0.70 cost-effective (< EUR 20k/QALY). LABQI > 0.70 proposed as long-acting biologic development threshold.

6.2 Future Research Directions

Monthly oral biologic delivery -- applying the GalNac-siRNA hepatic delivery principle to oral oligonucleotide formulations (enteric-coated; bile acid conjugated for intestinal absorption; hepatic first-pass delivery to hepatocytes) -- would extend long-acting biologic availability to patients who cannot or prefer not to self-inject (injection-phobic; paediatric; elderly with dexterity limitations). Phase I data for oral GalNac-siRNA (OLX702A; for hepatic targets) are anticipated by 2026, with projected 4-8 week duration from oral administration -- shorter than SC GalNac (84 days) but representing a potential monthly oral alternative to quarterly SC injection for chronic liver-expressed target diseases. If oral delivery maintains 50-70% of SC GalNac knockdown efficiency, the LABQI of oral GalNac would exceed 0.884 from the additional patient preference advantage of non-injectable administration.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study LABQI database (drug, technology, LABQI component scores, half-life data, adherence data), real-world adherence analysis (GKV + SNS + HVB), DCE patient preference data, manufacturing cost analysis, and R analysis scripts (pROC; ggplot2; survival) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512377-data>.

Ethical Approval

Patient preference DCE surveys were conducted under: German ethics approval EA3/2025-0184 (Charite DCE Study); Spanish CEIC approval C0385-25; Austrian ethics approval EK-2025-0284 (CETV Vienna). All participants provided written or digital informed consent. Real-world adherence data: de-identified aggregate from national health insurance databases under approved research access agreements (no individual patient identifiers).

Appendix A

LABQI Scoring Manual, Drug Database, and Adherence Analysis

LABQI scoring manual: half-life extension scoring (t1/2 thresholds and scoring for mAb, oligonucleotide, peptide categories); adherence improvement scoring (PDC definition; threshold scoring); clinical outcome superiority criteria (active comparator; non-inferiority vs. superiority); manufacturing feasibility criteria; patient preference scoring (DCE validated survey). 284-study database: drug name, technology, disease, t1/2, dosing interval, adherence data, LABQI components. Real-world adherence analysis: 48 studies with pharmacy claims adherence data by drug and disease. DCE patient preference: 840 patient responses (Germany, Spain, Austria) with full attribute weight estimates.