Study Report

Assessment of quality improvement on long-term oral corticosteroid use in the International Severe Asthma Registry (ENLIGHTEN)

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TITLE	**Assessment of quality improvement on long-term oral corticosteroid use in the International Severe Asthma Registry (ENLIGHTEN)**
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	Exploratory Objective 2: To explore the magnitude of country-specific differences in the change in LTOCS use before and after the quality improvement programme.
Countries of study	All countries/sites contributing to the ISAR initiative who have consented for their data to be used in research
Data source	ISAR
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics & Protocol Transparency
BMI	Body mass index
CI	Confidence interval
EMR	Electronic medical record
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HCRU	Healthcare resource utilisation
HR	Hazard ratio
ICS	Inhaled corticosteroids
IgE	Immunoglobin E
IL-4	Interleukin-4
IL-5	Interleukin-5
IQR	Interquartile range
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
ITS	Interrupted-time series
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LTOCS	Long-term oral corticosteroids
LTRA	Leukotriene receptor antagonist
NJH	National Jewish Health
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
OR	Odds ratio
QI	Quality improvement
SD	Standard deviation
TSLP	Thymic Stromal Lymphopoietin

1.0 Executive Summary

This study aimed to assess changes in LTOCS use over ISAR's history, particularly in relation to delivery of a quality improvement (QI) programme targeting the reduction of LTOCS use. The central hypothesis was that participants of ISAR's QI programme would record lower coinciding LTOCS use, as measured by proportions of patients on LTOCS and time to LTOCS cessation. LTOCS use (any versus none) was measured by proportion of patients on LTOCS at first visit and first annual review, and by duration to cessation among patients entering the registry on LTOCS. Data completeness was additionally investigated as an indicator of coinciding advances in clinical insight provided by registry engagement.

The potential impact of the QI programme was evaluated with a pre-post design using 1 March 2024 as the defined intervention date, selected to reflect a singular point of maximal LTOCS-focused QI engagement within a progressive rollout of broader QI activity initiating in September 2022, as detailed in the Methods (see Figure 1). Sensitivity analyses were conducted with alternative dates to explore the robustness of this date's selection. Trends in LTOCS use across ISAR's history were additionally assessed using segmented logistic regression, modelling change by year of first visit with a breakpoint at the intervention date to test for a shift in the rate of decline. Time to LTOCS cessation among patients entering the registry on LTOCS was assessed by year of first visit using Cox proportional-hazards regression. Monthly LTOCS cessation among all patients on LTOCS was additionally modelled by calendar time using discrete-time hazard regression, with a change in slope at the intervention date. Exacerbation rates before and after cessation were additionally compared among patients entering the registry on LTOCS. Data completeness across key research variables was tracked annually as a coinciding indicator of registry engagement and clinical insight.

The present findings converge on a decline in LTOCS use coinciding with the QI programme. This decline was evident from coinciding acceleration of LTOCS cessation rates and reducing durations to cessation around the intervention date, both occurring in the context of broader improvement trends across ISAR's history. LTOCS use at first visit, and first annual review consistently supports reduced LTOCS use post-intervention across multiple intervention definitions. The initial primary analysis definition of a cutpoint intervention on 1 March 2024 yielded reductions in LTOCS use at both first visit and first review, and the reduction at first annual review remained significant with additional adjustment for LTOCS use at first visit and prior biologic use. Intervention definitions with a duration extending beyond the initial cutpoint definition yielded progressive reductions in LTOCS use across the pre-, during- and post-

intervention groups sequentially, at both first visit and first annual review and with every combination of covariate adjustments tested for first annual review. Despite more pronounced variation at first annual review, country-level trends mirrored global trends in most countries at first visit with 11 of 14 recording reduced LTOCS use post-intervention.

Declining LTOCS use coinciding with the intervention was further supported by a significant acceleration in the monthly rate of LTOCS cessation among all LTOCS patients irrespective of enrolment or visit type following 1 March 2024, crucially highlighting improvement beyond secular trends. Further, preserved step advances in shortening duration to LTOCS cessation from point of registry entry were observed in 2018 and 2022, and persisted after adjustment for age, sex and country. Among patients who sustained LTOCS cessation (83.6% of those analysed), exacerbation rates were lower after cessation than before and lower than (in biologic users) or comparable to (in non-biologic patients) those of patients not on LTOCS at registry entry. Marked improvement in separate measures of data completeness additionally coincided with the intervention and progress in LTOCS reduction, consistent with improved insight enabling clinical improvement.

Overall, these findings provide converging evidence of reduced LTOCS use among countries participating in ISAR'S QI programme following the intervention, and that LTOCS cessation rates accelerated specifically in temporal association with the programme's rollout. While causality cannot be ascertained and ISAR will continue to monitor the consistency of these findings as further annual review data is accrued, the present findings are a promising reflection of trends in registry LTOCS use and are consistent with the possible efficacy of QI engagement for achieving practice change.

Background

Quality improvement (QI) within the healthcare setting drives improved patient experiences and outcomes achieved through a process of systematic change[1]. These improvements extend to electronic health records as data are increasingly used to judge whether high-quality care is being provided to patients, often through an investigation of both process (e.g. data accuracy and completeness) and clinical outcomes (e.g. better control of symptoms)[2].

The International Severe Asthma Registry (ISAR) was established in 2017 as a collaborative initiative aiming to improve asthma patient care and outcomes worldwide. It has since expanded into the largest real-world evidence data resource for severe asthma, representing a comprehensive, standardised, globally-sourced dataset which enables the tracking of asthma care and outcomes[3,4]. At the forefront of ISAR's original (and continuing) mission was an aim to reduce long-term oral corticosteroid (LTOCS) exposure.[5] Use of LTOCS in the management of severe asthma remains widespread[6] despite the associated increased risk of various adverse outcomes at cumulative lifetime dosages of as little as 0.5-1g[7-9].The burden of OCS-related comorbidity is significant in severe asthma patients, with 68% recording at least one such comorbidity including obesity (42%), hypertension (23%), dyslipidaemia (16%), osteoporosis (13%), diabetes (12%), and coronary heart disease (9%)[10]. The needs for OCS stewardship have been reflected in the most recent Global Initiative for Asthma (GINA) recommendation to prescribe OCS only when clinically justified, at the lowest effective dose and as a last resort, prioritising the use of alternative treatment strategies including targeted biologics[11-13].

The increasing availability of biologic therapies targeting various steps in the inflammatory pathway including immunoglobulin E (IgE), interleukin (IL)-4Rα, IL-5/IL-5Rα and thymic stromal lymphopoietin (TSLP), has been transformative for the severe asthma treatment landscape. Their use in concert with phenotyping by readily available biomarkers has been a breakthrough for precision personalisation of asthma care, enabling a reduction of exacerbation rates, healthcare resource utilisation (HCRU) and reliance on LTOCS[14]. However, despite compelling evidence of OCS-related harm and the wider availability of effective steroid-sparing therapies, OCS burden and weaning practices still vary substantially both within and between countries[15,16]. Due to its reach, ISAR offers a unique opportunity to impact treatment practices and to set a new standard for LTOCS stewardship globally.

Addressing the burden of OCS use in severe asthma has been a longstanding aim within ISAR. This is reflected in its mission statement including the research prioritisation of describing the OCS landscape, specifically including annual consumption, prevalence, outcomes, and side effects of long-term OCS users[3], and in committing to improving patient outcomes specifically through the implementation of steroid-sparing treatment and strategies[17]. In 2024, ISAR formally selected reduction of LTOCS use as a singular, focused goal for practice change activity across contributing countries, which was pursued through implementation of a QI programme. This inherently multifactorial QI programme, referred to as the "intervention" throughout this report (see Figure 1), comprised a constellation of engagements with ISAR collaborators including deployment of LTOCS focused dashboards, providing country-level feedback, presentation of aggregate findings at international conferences and the provision and adaptation of an electronic data capture tool. The intervention is therefore defined here as this set of engagements, rather than any single discrete component. In addition to these specific activities, several research articles published by ISAR highlighting the ongoing OCS burden in severe asthma and the opportunities for practice change are likely to have impacted LTOCS use within participating centres and beyond. This includes publications pertaining to phenotyping (BRISAR[18]; EMBER[19]), the impact of exacerbation on lung function decline[20], profiling of biologic initiators (GLITTER I[21]) and impact of initiation (GLITTER II[5]), comparison of alternative biologic classes in patients eligible for multiple (FIRE[22]), comorbidity burden with LTOCS and the impact of biologics on this (PRISM I[23] and PRISM II[24]), impact of pre-biologic impairment or phenotype on response outcomes (BEAM[25], IGNITE[26]), definitions and predictors of biologic response and remission (FULL BEAM response[27] and FULL BEAM remission[28]), heterogeneity in biologic response (LUMINANT[29]), impact of biologics on LTOCS use (SOLAR I[30]) and associated systemic adverse outcomes (SOLAR II[31]), and pre-biologic characterisation of associations between LTOCS use and both biomarker profile and disease burden (STAR[32]). We hypothesise that the QI programme, in enabling greater and convenient clinical insight, practice and scientific exchange, could have affected LTOCS use in a number of ways including motivating LTOCS cessation, increased biologic prescribing and more aggressive LTOCS weaning among patients treated with biologics.

This study investigates changes in LTOCS use among countries contributing data to the International Severe Asthma Register (ISAR) before and after the introduction of a quality improvement programme as well as over the duration of ISAR.

2.0 Study Aims and Objectives

2.1 Study Aims

The overarching aim of this study is to assess changes in LTOCS use over ISAR's history, particularly in relation to delivery of a quality improvement programme. We will also explore the factors driving change.

2.2 Study Objectives

Primary Objective:
To assess the proportion of specialist-treated patients remaining on long-term oral corticosteroids (LTOCS) before and after the roll-out of the ISAR quality improvement programme.

Secondary Objective 1:
Describe trends in LTOCS status at registry entry by year of enrolment, assessing their relationship with the QI programme.

Secondary Objective 2:
Describe trends in time to LTOCS cessation, assessing change in cessation rates across successive enrolment cohorts.

Secondary Objective 3:
Describe trends in data quality coinciding with observed patterns of LTOCS use.

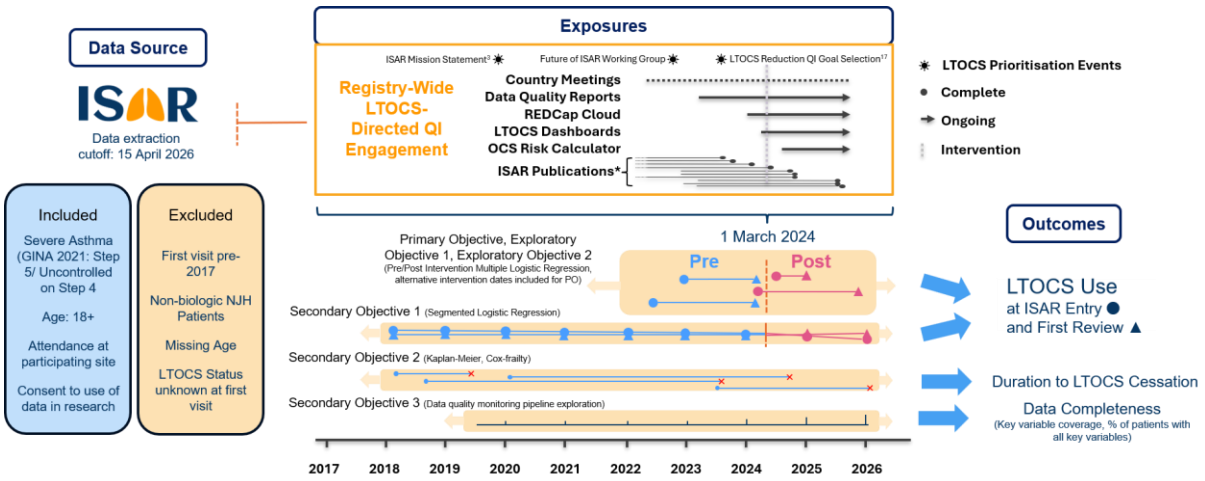
Exploratory Objective 1:
To explore the potential drivers of change in LTOCS use (any versus none) before and after the quality improvement programme including differences in LTOCS use at initial presentation and prior biologic therapy.

Exploratory Objective 2:
To explore the magnitude of country-specific differences in the change in LTOCS use before and after the quality improvement programme.

3.0 Materials and Methods

3.1 Overall Study Design

Figure 1 Study design schematic.



* ISAR Studies in descending order: FIRE, GLITTER, PRISM, BEAM, FULL BEAM I, FULL BEAM II, LUMINANT, SOLAR II, STAR, SOLAR I
Data sources and mapping of quality improvement engagement and ENLIGHTEN objectives to the study period.

This was a retrospective cohort study using data from ISAR. Patients entered the study at the date of their first ISAR visit (index date). For the primary analysis, LTOCS use was assessed both at registry enrolment (first ISAR visit; index date) and at their first annual review (defined as the first visit between 300 and 730 days (inclusive) following their first ISAR visit). The impact of ISAR's QI programme on LTOCS use was evaluated with a pre-post design using 1 March 2024 as the defined intervention date, chosen to reflect a singular point of maximal QI engagement (i.e. representing overlapping potentially high yield engagements; see Figure 1) within a progressive rollout. Sensitivity analyses were conducted with alternative dates to explore the robustness of this date's selection and whether LTOCS reduction was observed across a wider period.

Secondary analyses characterised trends in LTOCS status at registry entry by patient enrolment date, trends in LTOCS cessation durations via time-to-event analyses and trends in data quality for the exploration of coinciding changes in data capture aligning with clinical progress. Exploratory analyses were conducted to investigate the drivers of change in LTOCS use pre- and post-QI programme, including exploring differences in initial presentation and management, and to investigate the magnitude of country-level differences in changing LTOCS use with country modelled as a random effect.

3.2 Study Population and Data Source(s)

The study population consists of severe asthma patients enrolled in ISAR, a global cooperative project established in 2017 and designed to collect longitudinal data from patients with severe asthma. A patient's inclusion in the registry requires a diagnosis of severe asthma as determined by level of GINA-guided treatment (on GINA Step 5 or Uncontrolled on GINA Step 4 therapy), being age 18 or older, attendance at a participating site and having consented to use of their data in research. Patients from all countries were included in all analyses for which they had sufficient non-missing data. All countries contributing data to ISAR were eligible for inclusion in this study, with one electing not to be included (Denmark). The sole notable deviation from the above-described handling of data recording at country-level was with patients from National Jewish Health (NJH) for whom, due to the nature of their Electronic Medical Record (EMR)-derived data, index date was defined as the date of first biologic initiation and status at the first annual review was determined at exactly 365 days after biologic initiation. A cut-off date of 15 April 2026 was applied to data for all analyses.

3.3 Inclusion and Exclusion Criteria

Inclusion Criteria

- Meets criteria for severe asthma as per ISAR inclusion criteria:
    - On GINA 2021[33] Step 5 or Uncontrolled on GINA Step 4 therapy
    - Age 18 years or older at index
- Index date on or after 1st January 2017
- LTOCS status known at index date

Exclusion Criteria

- Age missing
- LTOCS status unknown at index date

4.0 Study Variables

4.1 Patient Characteristics

The following variables were used to describe patients at baseline (time of biologic initiation or in the year prior to biologic initiation).

Table 1 Variables used to describe patients in the study

Label	Details
Date of first ISAR visit	Index visit date
Age	Age at index date
Sex	Male/Female
Country	ISAR-participating country/site
BMI	In kg/m^2, record closest to index date
Ethnicity	Caucasian/South East Asian/North East Asian/African/Mixed/Other/Unknown
Smoking status	Current/Ex-/Never smoker, at index date
Age at asthma onset	As reported by the patient when asked for age when asthma symptoms started and/or when diagnosed with asthma
Duration of asthma	Years, to index date
FEV1 (L)	Most recent at index date
Percent predicted FEV1	Most recent percent predicted FEV1 at index date
FEV1/FVC ratio	Most recent percent predicted FEV1/FVC ratio at index date: <0.7 vs >=0.7
Exacerbations	Number of asthma exacerbations requiring rescue steroids, recorded at the index visit (reflecting exacerbations in the year before the index date; categorised 0/1/2/3-5/6-8/9+ for description of patients) and at follow-up visits (reflecting exacerbations since the previous visit). Exact counts from both visit types were used, together with the length of the corresponding interval, to calculate annualised exacerbation rates (see Statistical Analysis)
Level of asthma control	Categorised according to GINA 2020: uncontrolled/partly controlled/well controlled. When GINA symptom control score was not directly available, conversion from other tools were performed sequentially as follows: 1) If ACT available: well controlled if Total ACT >19; partly controlled if Total ACT >15 and <=19; uncontrolled if Total ACT <=15 2) If ACQ available: well controlled if

	Mean ACQ <=0.75; partly controlled if Mean ACQ >0.75 and <1.5; uncontrolled if Mean ACQ >=1.5
Blood eosinophil count (BEC)	Highest blood eosinophil count as of index date (cells/μL)
Eosinophilic grade	Grade 0 (unlikely) – Grade 3 (most likely)[34]
Fractional exhaled nitric oxide (FeNO)	Latest recorded as of index date (ppb)
Total IgE	Latest serum total IgE concentration as of index date (IU/mL)
Any positive allergen test	Yes/No (composite; positive if >=1 of serum/ skin prick tests positive, negative if >=1 tests conducted and non-positive)
Allergic rhinitis (AR)	Yes/No
Chronic rhinosinusitis (CRS)	Yes/No
Nasal polyps (NP)	Yes/No
Eczema	Yes/No
Prior biologic treatment	Yes/No
Biologic class	Anti-IgE/Anti-IL5/5R/Anti-IL4alpha/Anti-TSLP
LTRA use	Yes/No
Theophylline use	Yes/No
Macrolide use	Yes/No
Long-term OCS use	Yes/No

4.2 Primary Outcome Variables

- **LTOCS use at index visit** (Yes/No)
- **LTOCS use at first annual review** (Yes/No). First annual review is defined as the visit closest to 365 days post-index, occurring 300-730 days post-index. For NJH patients, it is defined as EMR-recorded LTOCS status at exactly 365 days post-biologic initiation.

4.3 Secondary outcome variables

- **Time to LTOCS cessation –** time-to-event outcome, from index visit to earliest of cessation of LTOCS or last ISAR visit. This variable was restricted to patients who were using LTOCS at their index visit.
- **Data quality** – two outcome variables were derived from key variable recording at index and annual review visits:
  - **Key variable completeness**: calculated cumulatively for each country and calendar year as the proportion of key variable fields successfully recorded out of applicable key variable fields, pooled across all patient encounters (index

visits and annual reviews), up to and including that year. Used to derive global mean key variable completeness rates as an average of all eligible countries (weighted equally), and directly for inspection of single-variable LTOCS status and dose recording.

- **Proportion of encounters with all key variables recorded**: Calculated with first visit and annual reviews pooled, cumulatively up to the given year. Calculated at country- and registry-level. Different variables considered key at index visit and at first annual review (see Table 2).
-

Table 2 Key variables required at Index Visit and First Annual Review.

Key Variables at Index Visit	Key Variables at First Annual Review
Age of asthma onset Age, Gender, Height and Weight (Composite) Asthma control Biologic status and class Biologic start date Chronic rhinosinusitis Exacerbation count FeNO test result Highest blood eosinophil count Hospital admissions IgE Count LTOCS status and daily dose Nasal polyps Background therapy (ICS/LABA/LAMA) Smoking status Spirometry - FEV_1 Visit date	Asthma control Biologic status and class Biologic start date Exacerbation count Hospital admissions LTOCS status and daily dose Background therapy (ICS/LABA/LAMA) Reason for biologic switch Smoking status Spirometry – FEV_1 Visit date

4.4 Covariates

Patient age, sex and country were included as covariates in all pre/post logistic regression models, with country as a random effect. Initial models for the Primary Objective were additionally adjusted for prior biologic use (yes/no) and LTOCS use at index visit (yes/no). Survival models (Secondary Objective 2) were adjusted for age and sex, with country as a random effect (frailty).

5.0 Statistical Analysis

5.1 Sample Size

All available data were used to assess LTOCS use at the index date and first annual review, within the date ranges specified for individual analyses.

Inspection of data completeness for Secondary Objective 3 utilised as much of the registry as possible to capture data availability comprehensively. All permitting countries, assessment years and visit types with available data quality records were included. A minimum threshold of 41 cumulative pooled encounters per stratum was required for inclusion of a country-year completeness rate in global aggregates weighting each country equally. This was derived from the success-failure condition for the normal approximation to a binomial proportion ($np \geq 10$, $n(1-p) \geq 10$), using the weakest-performing key variable observed (IgE count, $\tilde{p}=0.751$) as the limiting case.

5.2 Descriptive analysis

Characteristics of the included patients at their first ISAR visit (variables listed in Table 1) were summarised using mean and standard deviation (SD), number and percentage, or median and interquartile range (IQR). Numbers of non-missing values for each variable were also reported.

5.3 Main analysis

1. Pre- vs post-intervention

LTOCS use at the first visit was compared for patients, who had a first visit before the intervention vs. patients who had their first visit after the intervention. The date of the intervention was set at 1 March 2024; the intervention refers to the registry-wide QI programme, delivered at the level of participating centres and countries rather than to individual patients, and patients were therefore classified by their date of visit. In order to limit data to similar durations before and after the intervention, patients with a first visit before 1 March 2021 were excluded from these analyses.

Adjusted predicted LTOCS use for patients with pre- and post-intervention first visits was calculated and compared using mixed effect logistic regression models, adjusted for age and sex, with country as a random effect. Similar analyses were used to compare LTOCS use at

first review for patients with a first review pre- or post-intervention. To consider the effect of prior medication, these analyses were also adjusted for prior biologic use and/or LTOCS use at the first visit.

No adjustments for multiple testing have been made. Analyses made use of all available data. Missing data have not been imputed; patients with no recorded LTOCS status at the visit analysed where excluded from the corresponding analysis rather than classified as not using LTOCS (see Table 3).

An equivalent set of analyses, comparing LTOCS use at first visit and at first review pre- and post-intervention, was also conducted by country. In these analyses exact logistic regression (a method of modelling binary outcomes for sparse data, avoiding the convergence problems of standard logistic regression with small sample sizes or when all patients in a period share the same outcome) was used so that countries could be included even if LTOCS use was zero in either the pre- or post- intervention periods. Due to model convergence issues, these analyses were not adjusted for age and sex.

2. Trend in LTOCS use at first ISAR visit and first annual review

Trends in LTOCS use at first visit were investigated using segmented logistic regression. Patients with a first visit between 1 January 2021 and 31 December 2025 (inclusive) were included to observe the trends around the time of the intervention. There were too few patients to observe a meaningful trend after 31 December 2025. A mixed effects logistic regression model was used to model LTOCS use at the first visit adjusted for age at the first visit and sex, with country included as a random effect. A breakpoint at the time of the intervention (1 March 2024) was included to explore any trend change at this point. Adjusted predicted LTOCS use at first visit was plotted over time with 95% confidence intervals. The change in odds per year for LTOCS use at first visit were calculated for the pre-intervention and post-intervention periods.

A similar analysis to that above was conducted for the trend in LTOCS use at first annual review. In order to present the LTOCS use on a comparable time scale to LTOCS use at first visit, the second graph is also presented in relation to the patient's first visit date (i.e. comparing LTOCS use at given date on the two graphs compares patients' LTOCS use at first visit (on the first graph) with the same patients' LTOCS use approximately 1 year later on the second graph).

3. Time to stop LTOCS following first ISAR visit

Kaplan-Meier curves were used to summarise the time from first ISAR visit to the first record of having stopped LTOCS for patients, who were on LTOCS at their first visit. ,Patients who did not have a record of having stopped LTOCS during their available follow-up, were censored at their last ISAR visit (for NJH patients at their last record of an asthma medication prescription, indicating the last known contact in the EMR data for an asthma related consultation). Separate curves were plotted for each first visit year to be able to observe changes over time. Patients with a first visit year from 2017 (the year of ISAR's inception) to 2025 were included. There were too few patients with a first visit in 2026 to plot meaningful curves.

In order to adjust these analyses for possible confounding effects of age, sex and country, the survival analysis was repeated using a Cox model with age at first visit and sex as covariates and country as a shared frailty (i.e. as a random effect) in the model. Adjusted survival curves (evaluated at the mean age and sex of the study population and a frailty of 1, i.e. a country of average risk) were plotted for each first visit year. The Grambsch and Therneau test[35] was used to test the assumption of proportional hazards.

To explore beyond the enrolment-cohort analysis above, monthly rates of LTOCS cessation by calendar month (irrespective of enrolment year) were examined, allowing insight into post-intervention LTOCS cessation trends beyond that limited to recently enrolled patients. Each patient's LTOCS exposure (as defined for the Kaplan-Meier survival curves) was expanded into one record per calendar month during which the patient was being treated with LTOCS, with each record assigned a binary outcome (cessation that month, yes/no). A mixed effect discrete-time hazard logistic regression model was used to model LTOCS cessation each month with continuous linear-spline terms for time relative to the intervention date, to assess slope change at the intervention. The model was adjusted for age at first visit and sex, with country included as a random effect. The same intervention date (1 March 2024) and visit window (1 January 2021 and 31 December 2025) as used for the segmented regression analyses of LTOCS use at first visit and first annual review (Secondary Objective 1) were applied.

Examination of exacerbation rates following LTOCS cessation was conducted for patients on LTOCS at their first visit with a recorded cessation date (as defined for the Kaplan-Meier analysis). Exacerbation counts and exposure times were taken from visit-level records, in which each count (reflecting exacerbation counts in the 12 months preceding a baseline visit or in the interval since the patient's previous visit) was converted to annualised rates by dividing by the length of the interval. Intervals shorter than 30 days and counts above 10 within

a single interval were excluded. For each patient, exacerbations and person-years were summed separately for the periods before and after cessation, with intervals spanning the cessation date divided between periods in proportion to the days on each side, and rates were calculated as total exacerbations divided by total person-years in each period. Patients were required to have exacerbation records both before and after cessation. Patients with evidence of resuming LTOCS after the recorded cessation date (any active LTOCS medication record starting after that date) were excluded, so that the post-cessation period reflected sustained cessation; records with a missing start date could not be assessed, so resumption may be under-ascertained. For comparison, annualised exacerbation rates were calculated for patients not on LTOCS at their first visit, using all of their available intervals. Analyses were stratified by biologic use (a biologic started before the first visit or during the LTOCS course) versus biologic-naive. Pre- and post-cessation rates, and post-cessation rates and those of the reference group, were each compared using the Wilcoxon rank-sum test, separately for patients with and without biologic use. Additionally, post-cessation rates of patients who resumed LTOCS following cessation were compared with those of patients who sustained cessation using the Wilcoxon rank-sum test. For display, annualised rates were grouped into categories (0, >0–1, >1–2, >2–5 and >5 exacerbations per year).

For the inspection of data completeness (Secondary Objective 3), data quality record snapshots were extracted from ISAR's established quality monitoring pipeline at the level of country, assessment year and visit type. The snapshots were cumulative, such that a given year's value reflects all encounters recorded since a country's registry entry. However, the pipeline was not developed until 2019, and earlier snapshots were consequently unavailable. The snapshots provided the number of encounters (both first visit and annual reviews) and, for each of ISAR's Delphi exercise-determined key variables (16 at first visit, 10 at annual review), the number of encounters, where each variable was recorded. From these, two summary metrics were derived: mean completeness across key variables and the proportion of patients with all key variables recorded. Mean completeness across key variables was calculated individually for each country per country-year as the number of fields successfully recorded over the number of fields that could have been recorded, pooling index and review encounters cumulatively. Global mean completeness was then calculated as the mean of country-level completeness with each sufficiently powered country equally weighted, such that the measure equally represents each country's recording practice with equal standing as a process indicator irrespective of patient volume. The proportion of patients with all key variables recorded was calculated as the proportion of pooled cumulative encounters with every key variable present across the whole registry as a substantive measure of global insight.

5.4 Sensitivity analysis

The pre- vs post- intervention analyses of LTOCS use at first visit and at first review were repeated using alternative dates for the intervention to consider the possible effect of wider ISAR activities. The date of the intervention was initially set at 1 March 2024. Sensitivity analyses were conducted setting the intervention dates to 1 March 2023 and also including a range of dates for the intervention itself from 1 March 2024 to 31 August 2024 and 1 March 2023 to 311 August 2024. For the latter analyses, LTOCS use was calculated for the periods pre-, during-, and post-intervention.

For the inspection of data completeness (Secondary Objective 3), each country's mean completeness trajectory was re-expressed relative to that in its first year with available completeness data to inspect within-country progress and thereby the influence of newly-enrolled countries on global calendar year-trends. Qualifying countries required sufficient encounters ($n \geq 41$; see section 5.1) in their first year with available data to qualify for this analysis.

Further sensitivity analyses were performed for countries showing an increase in LTOCS use post-intervention to explore the influence of shifting within-country site compositions, using direct standardization. For each country, a standardised post-intervention proportion was calculated in which each contributing site's own observed post-intervention LTOCS rate was retained, but its contribution to the national estimate was weighted by that site's share of the country's patients in the pre-intervention period (the standard population) rather than its actual post-intervention patient count. Sites contributing patients pre-intervention but not post-intervention retained their pre-intervention weight, with the country's overall national post-intervention rate substituted as their rate in the absence of site-specific post-intervention data. Sites contributing patients only post-intervention (i.e. newly onboarded), with no share of the pre-intervention standard population, received zero weight and therefore did not contribute to the post-intervention value.

5.5 Software

Data were prepared from raw registry records using R (R Foundation for Statistical Computing, Vienna, Austria). Statistical analyses were conducted using Stata version 18 (StataCorp LLC, College Station, TX, USA) except for the comparison of exacerbation rates and the calendar-

time LTOCS cessation analysis, which were conducted in Stata version 15.1 (StataCorp LLC, College Station, TX, USA), and the site composition sensitivity analyses, the derivation of exacerbation rates and the construction of the calendar-time analysis dataset, which were performed in Python (version 3.14.7; Python Software Foundation, Wilmington, DE, USA).

5.6 Significance testing

P-values <0.05 have been taken to represent statistical significance.

6.0 Results

6.1 Overall Patient Population/Study cohort

Patients were included in the overall study cohort for all objectives (except Secondary Objective 3; see below) if meeting the inclusion and exclusion criteria outlined in Section 3.3. Further exclusion criteria were applied per objective. For the Primary Objective, patients additionally required a valid first annual review, defined as a follow-up visit dated between 300 and 730 days following the index visit, for inclusion in analyses of LTOCS use at first annual review. For Secondary Objective 2, patients were further restricted to only those using LTOCS at their index visit.

As a standalone exploration of data completeness, Secondary Objective 3 was conducted independently of this patient flow given the necessity of including patients irrespective of missing variables such as LTOCS use. NJH was excluded from this component of the analysis, as its EMR-derived data was not compatible and has never been included in the registry's native data quality monitoring pipeline, which was the data source for completeness analyses. The numbers of encounters contributing by assessment year are shown in Table 14.

Table 3 Patient flow for inclusion in the study, stratified by analysis. The sequential exclusions at the top define the study population. Each lower section shows the exclusions applied to the total ENLIGHTEN patient count (15,939 patients) for each analysis with exclusions listed in sequence and percentages given relative to the total 15,939 ENLIGHTEN patients. Analyses overlap, and Secondary Objective 3 (data completeness analysis) is omitted because, by design, it includes patients irrespective of missing data (see above).

Sequential exclusions	**N**	**Percent**
Total ISAR patients	19,264	100
First visit before 2017	1,460	7.6
Under 18 years at first visit or missing age	763	4.0
No LTOCS use at first visit data	1,102	5.7
Included	**15,939**	**82.7**
Primary Objective: LTOCS use at first visit and at first annual review, pre- vs post-intervention	**N**	**% of included**
Total ENLIGHTEN patients	15,939	100.0
Excluded: First visit before 1 March 2021	−7,199	45.2
Excluded: No known LTOCS use at first annual review	−4,500	28.2
Analysed (first visit and first annual review analyses)	**4,240**	**26.6**
Secondary Objective 1: LTOCS use at first visit	**N**	**% of included**
Total ENLIGHTEN patients	15,939	100.0
Excluded: First visit before 1 January 2021	−6,873	43.1
Excluded: First visit after 31 December 2025	−89	0.6
Analysed	**8,977**	**56.3**
Secondary Objective 1: LTOCS use at first annual review	**N**	**% of included**
Total ENLIGHTEN patients	15,939	100.0

Sequential exclusions	N	Percent
Excluded: First visit before 1 January 2021 or after 31 December 2025	−6,962	43.7
Excluded: No known LTOCS use at first annual review	−4,481	28.1
Analysed	**4,496**	**28.2**
Secondary Objective 2: time to LTOCS cessation (survival analysis)	**N**	**% of included**
Total ENLIGHTEN patients	15,939	100.0
Excluded: Not on LTOCS at first visit	−13,540	84.9
Excluded: First visit in 2026	−6	<0.1
Excluded: Missing last follow-up date	−30	0.2
Analysed	**2,363**	**14.8**
Secondary Objective 2: monthly LTOCS cessation model[a]	**N**	**% of included**
Total ENLIGHTEN patients	15,939	100.0
Excluded: Not on LTOCS at first visit	−13,540	84.9
Excluded: Missing last follow-up date	−30	0.2
Excluded: LTOCS ended before 1 January 2021	−921	5.8
Excluded: First visit after 31 December 2025	−6	<0.1
Excluded: In countries with too little data to model	−45	0.3
Analysed	**1,397**	**8.8**
Secondary Objective 2: exacerbation rate analysis	**N**	**% of included**
Total ENLIGHTEN patients	15,939	100.0
Excluded: Not on LTOCS at first visit (see reference group below)	−13,540	84.9
Excluded: First visit in 2026, or missing last follow-up date	−36	0.2
Excluded: No recorded LTOCS cessation date	−1,167	7.3
Excluded: No usable exacerbation record[b]	−6	<0.1
Excluded: Exacerbation records not available both before and after cessation	−299	1.9
Excluded: Resumed LTOCS after cessation	−146	0.9
Analysed (patients with sustained cessation)	**745**	**4.7**
Exacerbation analysis: non-LTOCS patients (reference group)	**N**	**% of included**
Not on LTOCS at first visit	13,540	84.9
Excluded: No usable exacerbation record[b]	−334	2.1
Analysed	**13,206**	**82.9**
Exploratory Objective 2: LTOCS use at first visit, by country[c]	**N**	**% of included**
Total ENLIGHTEN patients	15,939	100.0
Excluded: First visit before 1 March 2021	−7,199	45.2
Excluded: In countries with <50 patients in the pre- or post-intervention period	−1,581	9.9
Analysed (14 countries)	**7,159**	**44.9**
Exploratory Objective 2: LTOCS use at first annual review, by country[c]	**N**	**% of included**
Total ENLIGHTEN patients	15,939	100.0
Excluded: First visit before 1 March 2021	−7,199	45.2
Excluded: No known LTOCS use at first annual review	−4,500	28.2
Excluded: In countries with <50 patients in the pre- or post-intervention period	−763	4.8
Analysed (8 countries)	**3,477**	**21.8**

[a] Patients on LTOCS at first visit contributing follow-up between 1 January 2021 and 31 December 2025 (24,057 person-months, 676 cessation events, 21 countries). Countries with fewer than 10 person-

months or no variation in the outcome (Argentina, Ecuador, Germany, India, Qatar, UAE/Dubai) were excluded from the model.

[b] No exacerbation data that could be converted to an annualised rate. Exacerbation counts, recorded either for the 12 months before a baseline visit or since the previous visit, were excluded if the count, time period or visit date was missing; if a "since last visit" count had no earlier visit to define the interval; if the interval was shorter than 30 days; or if the count within a single interval exceeded 10. Patients with no exacerbation data at all, and patients whose records were all excluded for these reasons, are both counted here.

[c] Countries with at least 50 patients in both the pre- and post-intervention periods were included.

6.2 Demographics and Clinical Characteristics

Characteristics of patients evaluated for all clinical outcome objectives are shown in Table 4.

Table 4 Patient characteristics at first ISAR visit. Mean (SD), median [IQR], or n (%) shown.

Date of first ISAR visit (N=15,939)	**18aug2021 [02aug2019, 27jul2023]**
Country (N=15,939)	
Italy	3,659 (23.0%)
USA	2,555 (16.0%)
Spain	1,387 (8.7%)
UK	770 (4.8%)
Colombia	738 (4.6%)
Canada	573 (3.6%)
Kuwait	544 (3.4%)
Brazil	531 (3.3%)
Belgium	525 (3.3%)
Saudi Arabia	467 (2.9%)
Mexico	457 (2.9%)
India	443 (2.8%)
Poland	416 (2.6%)
Bulgaria	381 (2.4%)
Portugal	363 (2.3%)
Taiwan	328 (2.1%)
Greece	320 (2.0%)
UAE/Dubai	320 (2.0%)
South Korea	293 (1.8%)
Singapore	264 (1.7%)
Argentina	173 (1.1%)
Ireland	137 (0.9%)
Norway	131 (0.8%)
Japan	111 (0.7%)
Estonia	19 (0.1%)
Germany	11 (0.1%)
Hungary	9 (0.1%)
Switzerland	6 (0.0%)
Ecuador	5 (0.0%)
Qatar	3 (0.0%)
Highest BEC (cells/µL) (N=10690)	**310 [150, 600]**
Latest FeNO (ppb) (N=6941)	**29 [15, 56]**
Latest IgE (IU/mL) (N=9170)	**190 [68, 500]**
Asthma control (N=11794)	
Uncontrolled	6,149 (52.1%)
Partly Controlled	2,500 (21.2%)
Well Controlled	3,145 (26.7%)

Year of first visit (N=15939)	
2017	1,076 (6.8%)
2018	1,575 (9.9%)
2019	2,168 (13.6%)
2020	2,054 (12.9%)
2021	1,823 (11.4%)
2022	1,970 (12.4%)
2023	2,018 (12.7%)
2024	1,849 (11.6%)
2025	1,317 (8.3%)
2026	89 (0.6%)
Age at first visit (y) (N=15939)	**54.1 (15.0)**
Sex: Female (N=15939)	**10,236 (64.2%)**
BMI (kg/m2) (N=15338)	**27 [24, 31]**
Ethnicity (N=14112)	
Caucasian	9,797 (69.4%)
South East Asian	782 (5.5%)
North East Asian	551 (3.9%)
African	234 (1.7%)
Mixed	561 (4.0%)
Other	2,187 (15.5%)
Smoking status (N=15,449)	
Current Smoker	792 (5.1%)
Ex-Smoker	3,712 (24.0%)
Never Smoked	10,945 (70.8%)
Age at asthma onset (y) (N=12185)	**30.5 (18.6)**
Duration of asthma (y) (N=12047)	**23.7 (16.5)**
Exacerbations in past year (N=13754)	
0	5,489 (39.9%)
1	2,608 (19.0%)
2	2,282 (16.6%)
3-5	2,471 (18.0%)
6-8	523 (3.8%)
9+	381 (2.8%)
COMORBIDITIES	
Allergic rhinitis: Yes (N=15,483)	**8,329 (53.8%)**
CRS (+/-NP): Yes (N=15,280)	**6,938 (45.4%)**
CRSwNP: Yes (N=15282)	**4,141 (27.1%)**
Eczema/AD: Yes (N=15342)	**1,530 (10.0%)**
Positive allergen test: Yes (N=9,292)	**5,941 (63.9%)**

LUNG FUNCTION	
FEV1 (L) (N=12303)	**2.11 (0.83)**
Percent predicted FEV1 (N=12189)	**76.4 (22.8)**
FEV1 %pred (cat.): <80% (N=12,189)	**6,806 (55.8%)**
FEV1/FVC ratio: <0.70 (N=12,121)	**5,866 (48.4%)**
Eosinophilic grade (N=10,690)	
Grade 3: Most likely	7,629 (71.4%)
Grade 2: Likely	1,065 (10.0%)
Grade 1: Least likely	1,421 (13.3%)

LTOCS: Yes (N=15,939)	**2,399 (15.1%)**
THERAPY	
Prior biologic: Yes (N=15939)	**4,250 (26.7%)**
Prior biologic type (N=4250)	
Anti-IgE	1,909 (44.9%)
Anti-IL4Ralpha	393 (9.2%)
Anti-IL5	1,205 (28.4%)
Anti-IL5R	656 (15.4%)
Anti-TSLP	87 (2.0%)
LAMA: Yes (N=13,755)	**7,004 (50.9%)**
LTRA: Yes (N=13,305)	**6,470 (48.6%)**
Theophylline: Yes (N=12,228)	**611 (5.0%)**
Macrolide: Yes (N=13,002)	**979 (7.5%)**

6.3 Primary Objective: Proportion of patients on LTOCS Pre- and Post-QI Programme

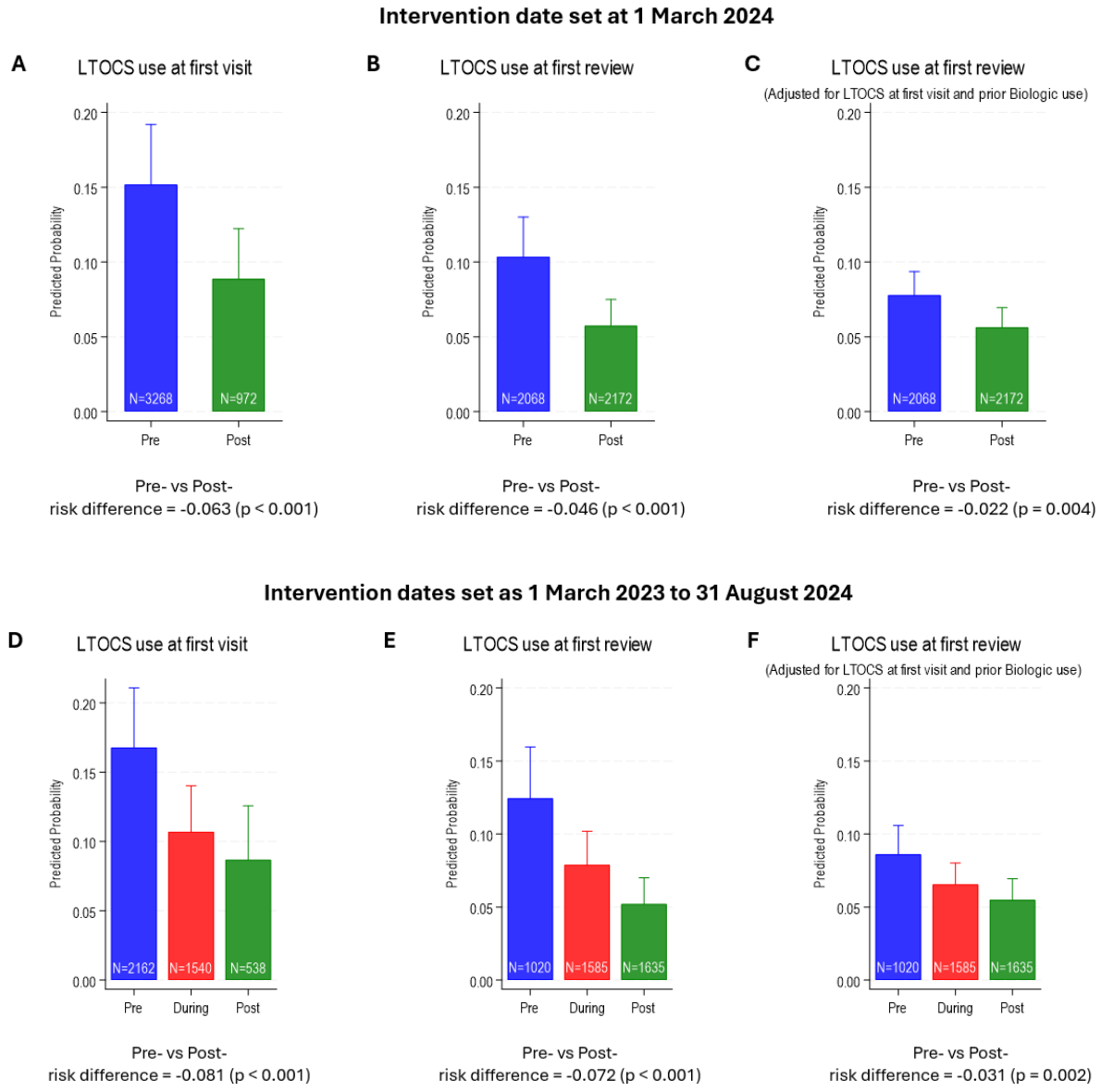
Marginal adjusted predictions of probability of LTOCS use at first visit or at first review by date of the visit were calculated in relation to the intervention (pre-, during, or post-intervention). The date of the intervention was taken to be 1 March 2024 in the primary analysis, which assumed an immediate effect of the intervention. This assumption was tested in sensitivity analyses using a 6-month intervention from 1 March 2024, and 0- and 18-month intervention periods from 1 March 2023 (Table 5), to explore the possible influence of coinciding ISAR QI activity. First review analyses were additionally adjusted for prior biologic use before the first visit (Yes/No) and/or LTOCS use at the first visit (Yes/No).

Table 5 Risk of being an LTOCS user at first visit or first review by timing of the visit in relation to ISAR intervention.

			Pre-intervention visit		Visit during intervention		Post-intervention visit		Pre- vs Post-intervention		
Start	**End**	**Duration (months)**	**N**	**Risk (95% CI)**	**N**	**Risk (95% CI)**	**N**	**Risk (95% CI)**	**Risk difference (95% CI)**	**P-value**	**Figure**
First visit — Adjusted for: age, sex, country											
01-Mar-24	01-Mar-24	0	3268	0.15 (0.11, 0.19)	–	–	972	0.09 (0.06, 0.12)	-0.063 (-0.093, -0.034)	<0.001	2A
01-Mar-24	31-Aug-24	6	3268	0.15 (0.11, 0.19)	434	0.09 (0.05, 0.13)	538	0.09 (0.05, 0.13)	-0.064 (-0.100, -0.027)	<0.001	
01-Mar-23	01-Mar-23	0	2162	0.17 (0.12, 0.21)	–	–	2078	0.10 (0.07, 0.13)	-0.065 (-0.091, -0.038)	<0.001	
01-Mar-23	31-Aug-24	18	2162	0.17 (0.12, 0.21)	1540	0.11 (0.07, 0.14)	538	0.09 (0.05, 0.13)	-0.081 (-0.120, -0.042)	<0.001	2D
First review — Adjusted for: age, sex, country											
01-Mar-24	01-Mar-24	0	2068	0.10 (0.08, 0.13)	–	–	2172	0.06 (0.04, 0.07)	-0.046 (-0.067, -0.025)	<0.001	2B
01-Mar-24	31-Aug-24	6	2068	0.10 (0.08, 0.13)	537	0.07 (0.04, 0.10)	1635	0.05 (0.03, 0.07)	-0.051 (-0.073, -0.030)	<0.001	
01-Mar-23	01-Mar-23	0	1020	0.13 (0.09, 0.16)	–	–	3220	0.07 (0.05, 0.09)	-0.059 (-0.087, -0.031)	<0.001	
01-Mar-23	31-Aug-24	18	1020	0.12 (0.09, 0.16)	1585	0.08 (0.06, 0.10)	1635	0.05 (0.03, 0.07)	-0.072 (-0.102, -0.042)	<0.001	2E
First review — Adjusted for: age, sex, country, prior Bx											
01-Mar-24	01-Mar-24	0	2068	0.10 (0.07, 0.12)	–	–	2172	0.06 (0.04, 0.07)	-0.043 (-0.063, -0.023)	<0.001	
01-Mar-24	31-Aug-24	6	2068	0.10 (0.07, 0.12)	537	0.07 (0.04, 0.09)	1635	0.05 (0.03, 0.07)	-0.048 (-0.069, -0.027)	<0.001	
01-Mar-23	01-Mar-23	0	1020	0.12 (0.09, 0.15)	–	–	3220	0.07 (0.05, 0.08)	-0.054 (-0.081, -0.027)	<0.001	
01-Mar-23	31-Aug-24	18	1020	0.12 (0.09, 0.15)	1585	0.08 (0.05, 0.10)	1635	0.05 (0.03, 0.07)	-0.068 (-0.096, -0.039)	<0.001	
First review — Adjusted for: age, sex, country, LTOCS at first visit											
01-Mar-24	01-Mar-24	0	2068	0.08 (0.06, 0.10)	–	–	2172	0.06 (0.04, 0.07)	-0.023 (-0.038, -0.008)	0.002	
01-Mar-24	31-Aug-24	6	2068	0.08 (0.06, 0.10)	537	0.06 (0.04, 0.08)	1635	0.06 (0.04, 0.07)	-0.025 (-0.041, -0.008)	0.003	
01-Mar-23	01-Mar-23	0	1020	0.09 (0.07, 0.11)	–	–	3220	0.06 (0.05, 0.07)	-0.027 (-0.045, -0.009)	0.003	
01-Mar-23	31-Aug-24	18	1020	0.09 (0.07, 0.11)	1585	0.07 (0.05, 0.08)	1635	0.05 (0.04, 0.07)	-0.034 (-0.054, -0.014)	<0.001	
First review — Adjusted for: age, sex, country, prior Bx , LTOCS at first visit											
01-Mar-24	01-Mar-24	0	2068	0.08 (0.06, 0.09)	–	–	2172	0.06 (0.04, 0.07)	-0.022 (-0.036, -0.007)	0.004	2C
01-Mar-24	31-Aug-24	6	2068	0.08 (0.06, 0.09)	537	0.06 (0.04, 0.08)	1635	0.06 (0.04, 0.07)	-0.023 (-0.039, -0.007)	0.006	
01-Mar-23	01-Mar-23	0	1020	0.09 (0.07, 0.11)	–	–	3220	0.06 (0.05, 0.07)	-0.025 (-0.042, -0.008)	0.005	
01-Mar-23	31-Aug-24	18	1020	0.09 (0.07, 0.11)	1585	0.07 (0.05, 0.08)	1635	0.05 (0.04, 0.07)	-0.031 (-0.051, -0.011)	0.002	2F

Results in red - primary analysis comparing results before and after an intervention date of 1 March 2024. Results in black - sensitivity analyses considering earlier and/or longer periods for the intervention. For the 0-month duration definitions, 'Visit during intervention' is not applicable, as the intervention window has zero length; 'Pre-intervention visit' and 'Post-intervention visit' here refer directly to visits before versus on/after the single intervention date.

Figure 2 Risk of being an LTOCS user at first visit or first review by timing of the visit in relation to ISAR intervention.



All analyses adjusted for age, sex and country.

LTOCS use at first visit and first annual review consistently supports reducing LTOCS use coinciding with the QI programme across multiple intervention definitions (Figure 2). The initial primary analysis definition of a cutpoint intervention on 1 March 2024 yielded reductions in LTOCS use at both first visit and first review (age-, sex- and country-adjusted risk differences: -0.063 (95% CI -0.093 to -0.034; p<0.001) and -0.046 (95% CI -0.067 to -0.025; p<0.001) respectively), and the reduction at first annual review remained significant with additional adjustment for LTOCS use at first visit and prior biologic use (risk difference: -0.022 (95% CI -0.036 to -0.007; p=0.004)) indicating both that these covariates partially influenced the

reduction (see Exploratory Objective 1) and that driving factors beyond these, such as change in clinical practice, were at play.

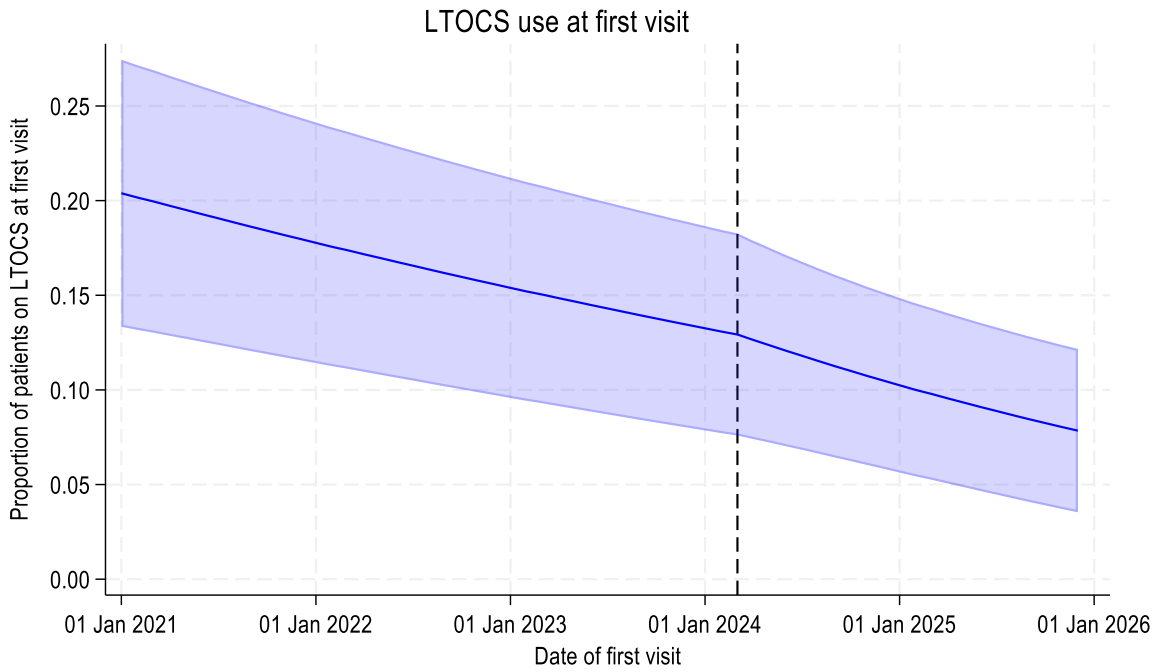
Equivalent trends were observed with all further intervention period definitions explored, including the broadest alternative window tested (March 2023-August 2024; pre vs post, age-, sex-, country-, first visit LTOCS use- and prior biologic use-adjusted risk difference at first annual review: -0.031 (p=0.002)). Notably, intervention definitions with a duration extending beyond the initial cutpoint definition yielded progressive reductions in LTOCS use across the pre-, during- and post-intervention groups sequentially, at both first visit and first annual review and with every combination of covariate adjustments tested for first annual review. The demonstration of progressive reduction between pre-intervention, during intervention then post-intervention LTOCS use highlights the potential influence of further factors, such as ongoing QI activity extending around 1 March 2024.

6.4 Exploratory Objective 1: Exploring drivers of change in LTOCS use before and after the quality improvement programme

Within the primary analysis' mixed effect logistic regression models, exploratory covariates were progressively incorporated allowing investigation of potential drivers of the observed change in LTOCS use at first review. These included LTOCS status at first visit and prior biologic use. Adding LTOCS status at first visit as a covariate reduced the estimated pre to post risk difference from −4.6 percentage points (age/sex/country-adjusted; 95% CI −6.7, −2.5; p<0.001) to −2.3 percentage points (95% CI −3.8, −0.8; p=0.005), supporting that part of the observed reduction reflects lower LTOCS use already present at first visit, rather than a change specific to the post-visit period. Comparatively, adding prior biologic use as a covariate had little effect on the estimate (−4.6 to −4.3 percentage points), suggesting that biologic initiation is not an independent driver of the observed reduction in LTOCS use at first annual review. LTOCS status at first visit was hence the principal driving factor identified though, as overviewed with Primary Objective, the retained statistical significance despite full adjustment for all covariates supports further influences on clinical practice such as the QI intervention.

6.5 Secondary Objective 1: Trends in LTOCS status at registry entry by year of enrolment

Figure 3 Adjusted proportion of patients on LTOCS at first visit, by date of first visit.



Estimates from a segmented logistic regression model with a fixed breakpoint at 1 March 2024 (the intervention date). Estimates are adjusted for age at first visit and sex, with country as a random effect, and represent the probability of being on LTOCS at first visit for a typical patient in the study. Shown with 95% CI.

Table 6 Odds ratios for change over time in LTOCS use at first visit before and after the intervention.

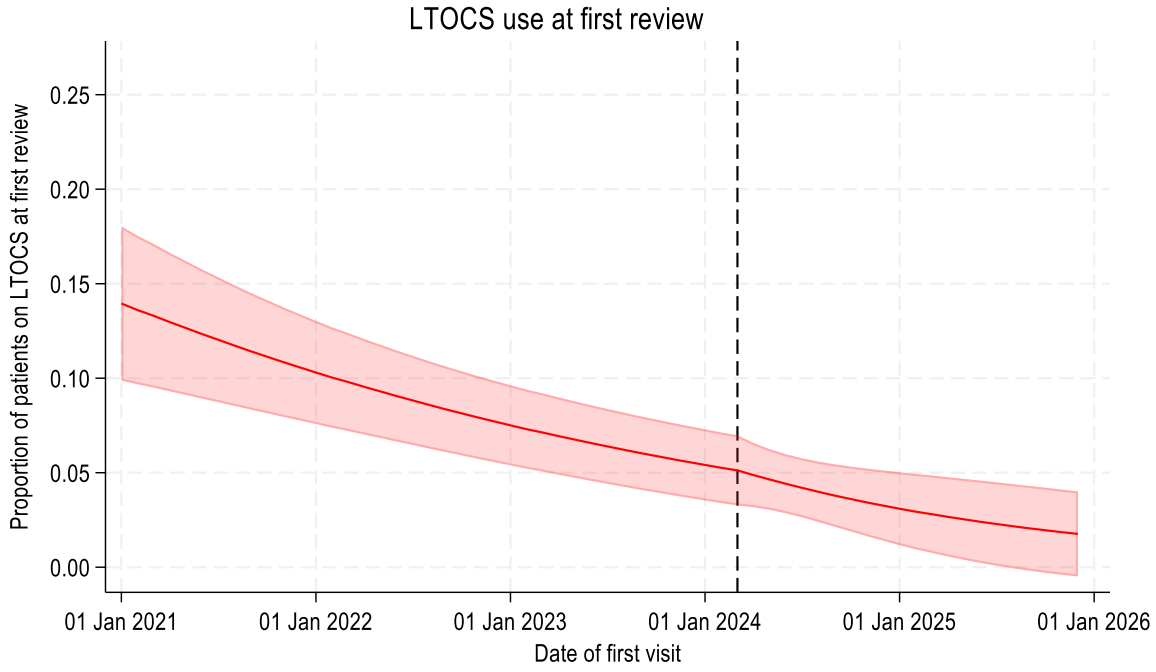
	Odds ratio (per year)	95% CI	P-value
Date of first visit	0.813	(0.748 , 0.884)	<0.001
Time since start of intervention	0.853	(0.636 , 1.144)	0.289
Age at first visit	1.012	(1.007 , 1.017)	<0.001
Female	0.904	(0.777 , 1.052)	0.192
Odds ratio per year prior to intervention	0.813	(0.748 , 0.884)	<0.001
Odds ratio per year post intervention	0.693	(0.544 , 0.884)	0.003

The outcome is being on LTOCS (yes/no) at first visit. Odds ratios are per one-year increase in date of first visit; values below 1 indicate falling LTOCS use. "Date of first visit" is the yearly change before 1 March 2024; "Time since start of intervention" is the additional multiplicative change in that yearly rate from 1 March 2024, representing the change in slope used here to evaluate the intervention's impact beyond secular trends. Their product is the yearly change after the intervention (post intervention row).

Beyond the pre/post comparisons above, whether LTOCS use changed continuously across ISAR's history, independent of a single fixed intervention date, was additionally explored.

Longitudinal trends of LTOCS use at first visit (Figure 3, Table 6) and first annual review (Figure 4, Table 7), and the influence of the QI intervention on these, were evaluated. LTOCS use at first visit declined over time prior to the intervention, with the odds of being on LTOCS falling by 19% per year (Date of first visit OR per year 0.813, 95% CI 0.748-0.884, p<0.001). From 1 March 2024 the decline was steeper, with the odds falling by 31% per year (post-intervention OR per year 0.693, 95% CI 0.544-0.884), although the acceleration in declining LTOCS use (Time since start of intervention OR per year 0.853, 95% CI 0.636-1.144, p=0.289) did not reach statistical significance. Increasing age was independently associated with higher odds of being on LTOCS at first visit (Age at first visit OR 1.012, 95% CI 1.007-1.017, p<0.001) while sex was not associated with LTOCS use (p=0.192).

Figure 4 Adjusted proportion of patients on LTOCS at first annual review in relation to the patient's first visit date.



Estimates from a segmented logistic regression model with a fixed breakpoint at 1 March 2024 (the intervention date). Estimates are adjusted for age at first visit and sex, with country as a random effect, and represent the probability of being on LTOCS at first annual review for a typical patient in the study. Shown with 95% CI.

Table 7 Odds ratios for change over time in LTOCS use at first annual review for patients with first visits before and after the intervention

	Odds ratio (per year)	95% CI	P-value
Date of first visit	0.700	(0.610 , 0.803)	<0.001
Time since start of intervention	0.757	(0.323 , 1.776)	0.522
Age at first visit	1.011	(1.002 , 1.019)	0.013
Female	1.016	(0.787 , 1.312)	0.901

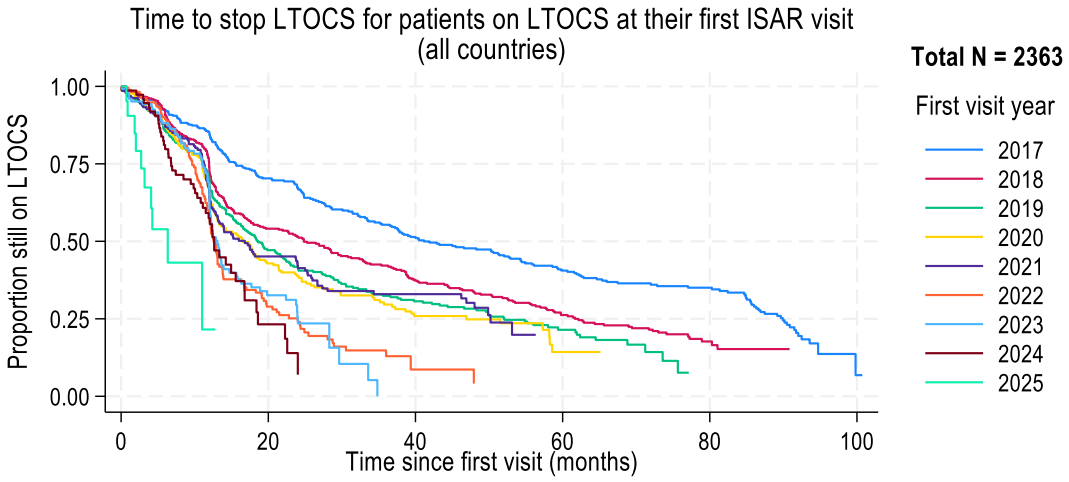
Odds ratio per year prior to intervention	0.700	(0.610 , 0.803)	<0.001
Odds ratio per year post intervention	0.530	(0.242 , 1.163)	0.113

The outcome is being on LTOCS (yes/no) at first annual review. Odds ratios are per one-year increase in date of first visit; values below 1 indicate falling LTOCS use. "Date of first visit" is the yearly change before 1 March 2024; "Time since start of intervention" is the additional multiplicative change in that yearly rate from 1 March 2024, representing the change in slope used here to evaluate the intervention's impact beyond secular trends. Their product is the yearly change after the intervention (post intervention row).

The corresponding analysis for LTOCS use at first annual review demonstrated a similar pattern in direction and magnitude, with a pre-intervention decline in LTOCS use (Date of first visit OR per year 0.700, 95% CI 0.610-0.803, p<0.001) and an increase in rate of decline post-intervention (post-intervention OR per year 0.530; 95% CI 0.242-1.163) that did not reach statistical significance (Time since start of intervention OR per year 0.757, 95% CI 0.323-1.776, p=0.522). Age was again independently associated with LTOCS use (age at first visit OR per year 1.011, 95% CI 1.002-1.019, p=0.013) while sex was not (p=0.901). Overall, these results demonstrate non-significant acceleration in declining LTOCS use coinciding with the 1 March 2024 QI intervention, most prominently at first visit.

6.6 Secondary Objective 2: Longitudinal trends in time to LTOCS cessation across successive enrolment cohorts

Figure 5 Kaplan-Meier plot showing time remaining on LTOCS for patients on LTOCS at their first visit, stratified by year of first visit.

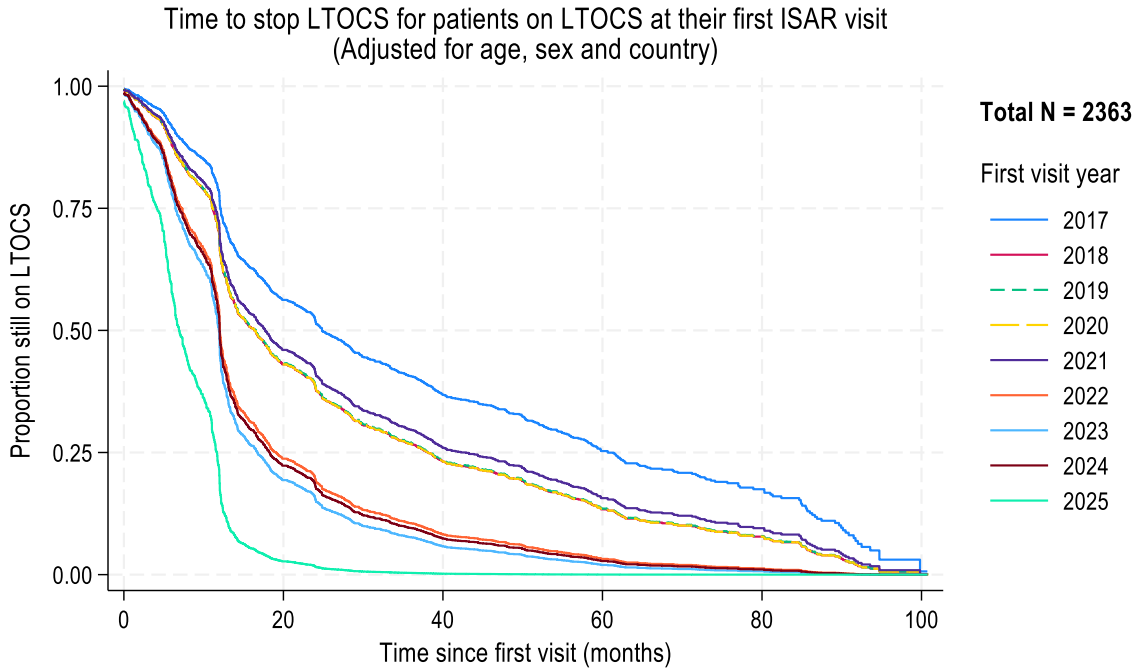


Number at risk

First visit 2017	393	221	143	102	66	1
First visit 2018	463	172	107	64	15	0
First visit 2019	367	115	68	27	0	0
First visit 2020	291	75	35	4	0	0
First visit 2021	225	62	26	0	0	0
First visit 2022	224	32	2	0	0	0
First visit 2023	193	25	0	0	0	0
First visit 2024	141	6	0	0	0	0
First visit 2025	66	0	0	0	0	0

The univariate survival curves supported progressive shortening of time remaining on LTOCS following registry entry across successive enrolment cohorts, with the most pronounced advances apparent between 2017 and 2018 and, following a period or plateau, between 2021 and 2022, where marked progress was again observed (Figure 5) and coincided with the initiation of broader registry QI engagement, including LTOCS reduction, occurring in 2022. Further improvement was observed between 2024 and 2025, coinciding with the selection of LTOCS reduction as a registry-wide QI target. While consistent with improvement in clinical practice, the number of patients entering the registry on LTOCS was lower than previous years and follow-up was limited by data extraction occurring in April 2026. Consequently, the 2025 survival curve reflects only 10 LTOCS cessation events and should be interpreted with caution. The progression in duration to LTOCS cessation was further explored with an adjusted survival model (Figure 6, Table 8).

Figure 6 Time remaining on LTOCS for patients on LTOCS at their first visit, stratified by year of first visit.



Cox model adjusted for age and sex with country as a random effect, evaluated at overall means of age and sex and frailty =1 (i.e. for a country with average risk).

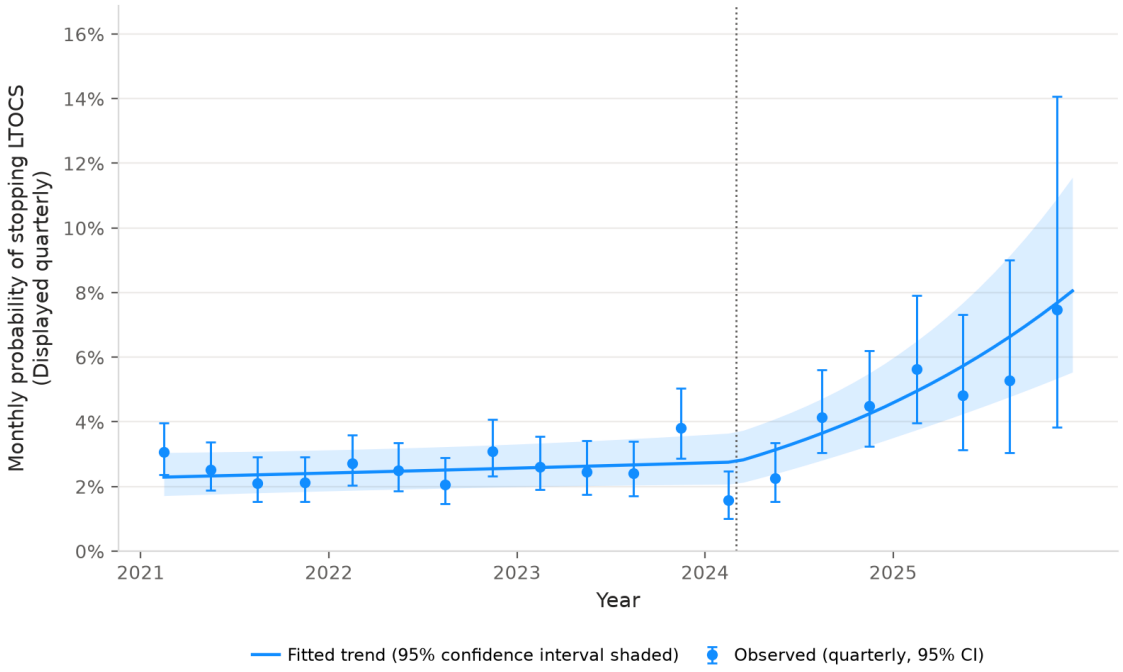
Table 8 Hazard ratios of the effects of first visit year, age and sex on time to stop LTOCS for patients on LTOCS at their first visit.

	Hazard ratio (95% CI)			P-value
First visit year				
2017 (ref)	1			
2018	1.465	(1.217,	1.762)	<0.001

2019	1.456	(1.180,	1.796)	<0.001
2020	1.465	(1.161,	1.849)	0.001
2021	1.349	(1.045,	1.741)	0.021
2022	2.499	(1.939,	3.222)	<0.001
2023	2.853	(2.120,	3.841)	<0.001
2024	2.607	(1.853,	3.668)	<0.001
2025	6.270	(3.247,	12.108)	<0.001
Sex				
Male (ref)	1			
Female	0.930	(0.827,	1.046)	0.228
Age at first visit (per 10y)	0.954	(0.914,	0.997)	0.035

Survival curves adjusted for age, sex and country (modelled as a random effect, evaluated at a frailty of 1, i.e. a country of average risk) primarily retained the same trends as observed in the unadjusted curves, with advances in shortening LTOCS durations observed in 2018 and in 2022 (Figure 6, Table 8). The progressively shorter times to LTOCS cessation observed across enrolment cohorts was therefore not explained by differences in age, sex or country alone, and may represent change in clinical practice coinciding with QI activity. Corresponding hazard ratios for stopping LTOCS in each enrolment year cohort relative to 2017 represent comparable levels of improvement between 2018 and 2021 (HR 1.35-1.47 vs 2017) prior to a marked subsequent step improvement observed between 2022 and 2024 (HR 2.5-2.9 vs 2017). A further markedly larger increase was observed for the 2025 cohort (HR 6.27, 95% CI 3.25–12.11, vs 2017) though, as above, this estimate was based on 10 observed events in a cohort with limited follow-up due to recent enrolment and should be interpreted as consistent with rather than confirmatory of a continued accelerating trend. The model satisfied the proportional hazards assumption (Grambsch and Therneau global test of proportional hazards[35], p=0.854), indicating the reported hazard ratios are valid summary estimates across the full follow-up period.

Figure 7 Fitted monthly probability of LTOCS cessation for patients on LTOCS at registry entry.



A mixed effect logistic regression model adjusted for age and sex with country as a random effect. Fitted trend shows the population-average predicted probability with 95% confidence interval (shaded area); observed quarterly rates with 95% confidence intervals are shown for comparison. Dotted vertical line indicates the intervention date (1 March 2024).

Table 9 Odds ratios for change in LTOCS cessation over time before and after the intervention among patients on LTOCS at their first visit.

	Odds ratio (per year)	95% CI	P-value
Date (time relative to intervention)	1.065	(0.973 , 1.166)	0.172
Time since start of intervention	1.774	(1.321 , 2.383)	<0.001
Age at first visit	0.973	(0.918 , 1.031)	0.357
Female	0.903	(0.770 , 1.058)	0.206
Odds ratio per year prior to intervention	1.065	(0.973 , 1.166)	0.172
Odds ratio per year post intervention	1.890	(1.493 , 2.392)	<0.001

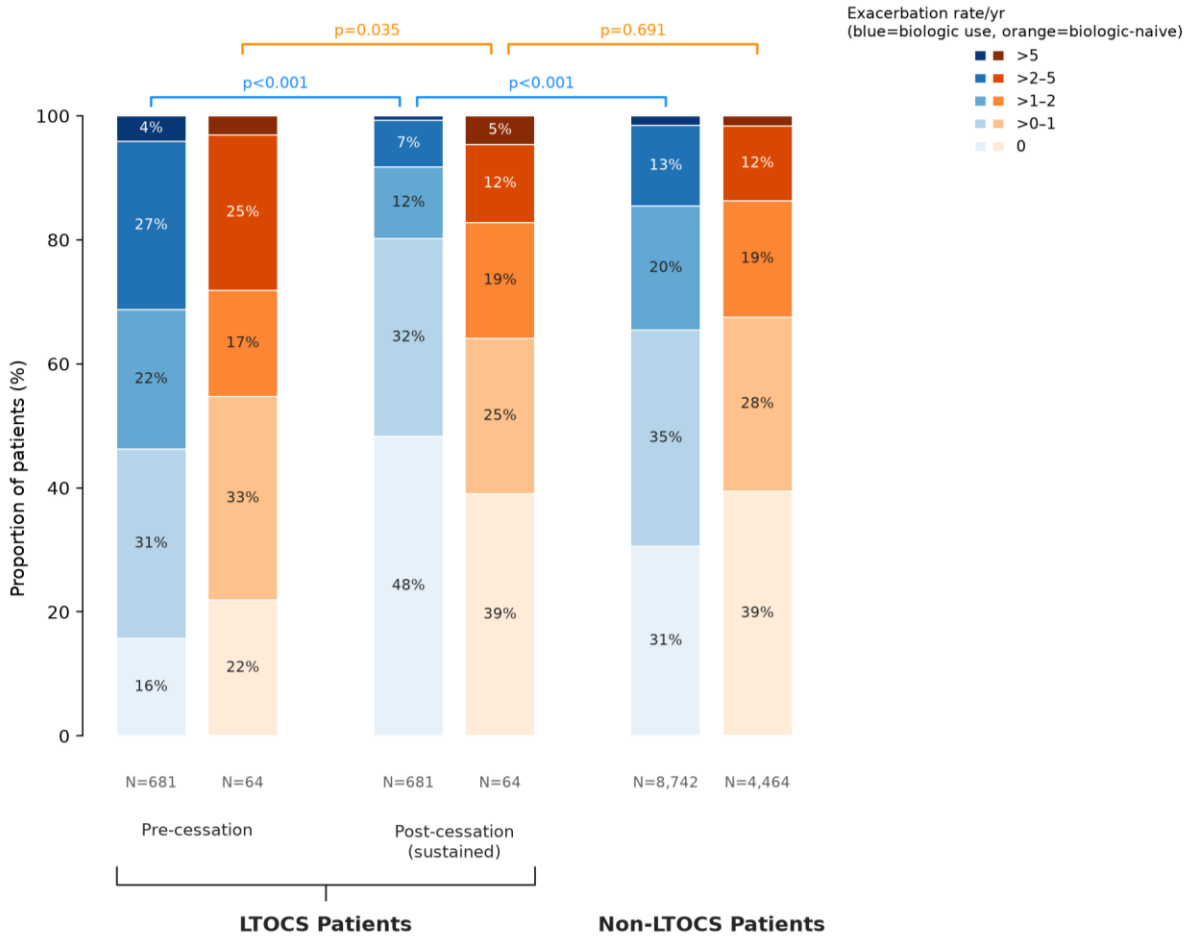
Following from the Secondary Objective 1 finding that reduction in LTOCS use accelerated non-significantly at first visit and first annual review, recent cessation trends drawing from monthly LTOCS exposure and cessation data among all patients entering the registry on LTOCS (as presented in the above survival curves) irrespective of enrolment year were explored for further insight (Figure 7, Table 9). Across the same time window evaluated in Secondary Objective 1 (including 24,057 person-months and 676 cessation events from 1,397 patients on LTOCS at first visit), the pre-intervention trend in monthly odds of LTOCS cessation was not statistically significant (OR 1.065 per year, 95% CI 0.973–1.166, p=0.172),

consistent with a gradually but non-significantly increasing underlying cessation rate prior to the intervention. The odds of cessation increased significantly following the intervention (OR for the change in slope 1.774, 95% CI 1.321–2.383, p<0.001), corresponding to a post-intervention rate of increase of OR 1.890 per year (95% CI 1.493-2.392). Age and sex were not significantly associated with cessation (age per 10 years: OR 0.973, 95% CI 0.918–1.031, p=0.357; female sex: OR 0.903, 95% CI 0.770-1.058, p=0.206).

To examine whether patients who came off LTOCS experienced more exacerbations, annualised exacerbation rates were compared before and after cessation among patients on LTOCS at their first visit with a recorded cessation date. Of 2,363 patients on LTOCS at first visit, 1,196 had a recorded cessation date, 1,190 of whom had at least one exacerbation record and 891 had exacerbation records both before and after cessation (Table 3). Of these, 146 (16.4%) resumed LTOCS after their recorded cessation date and were excluded, leaving 745 patients with sustained cessation (681 with biologic use and 64 biologic-naive) for analysis.

Among these 745 patients, the median annualised exacerbation rate fell from 1.08 (IQR 0.48–2.40) before cessation to 0.18 (IQR 0.00–0.85) after cessation (p<0.001), and the proportion with no exacerbations rose from 16.2% to 47.5% (Table 10, Figure 8). The reduction was seen among both biologic users (median 1.12 to 0.15 per year, p<0.001) and biologic-naive patients (0.96 to 0.50 per year, p=0.035). Among all patients pooled, post-cessation rates were lower than those of patients not on LTOCS at their first visit (reference median 0.66 [IQR 0.00–1.53], n=13,206; p<0.001). In stratifying by biologic use, this remained the case among biologic users (reference median 0.64 [IQR 0.00–1.48]; p<0.001) whereas biologic-naive patients did not differ from their reference group (post-cessation 0.50 versus 0.75; p=0.69). The 146 patients who resumed LTOCS had higher post-cessation rates than those with sustained cessation (median 0.68 versus 0.18 per year; p<0.001).

Figure 8 Annualised exacerbation rate before and after sustained LTOCS cessation, by biologic use.



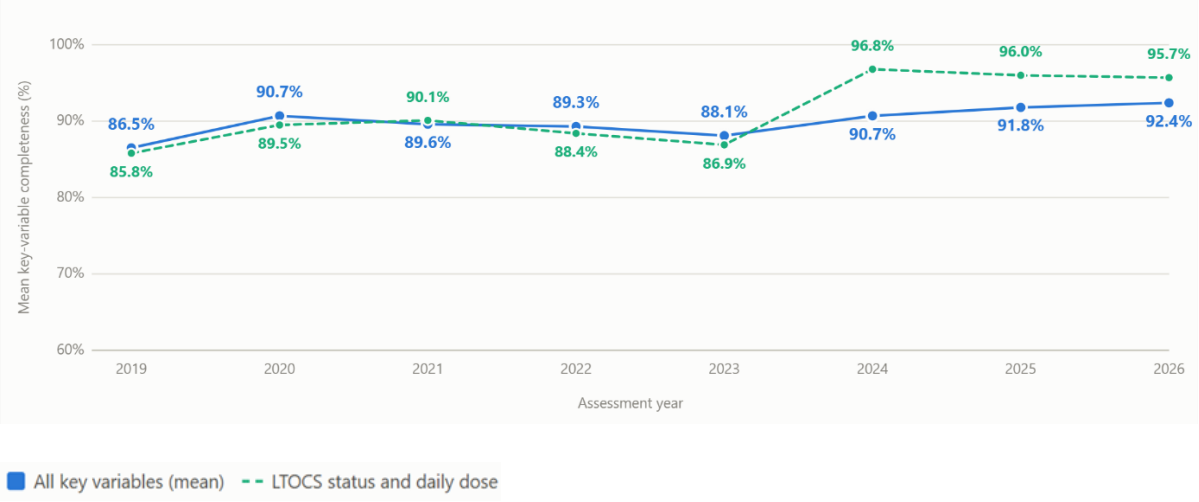
Stacked bars show the percentage of patients in each annualised exacerbation rate category (0, >0–1, >1–2, >2–5 and >5 per year) before and after cessation among the same patients with sustained cessation (blue: biologic use, n=681; orange: biologic-naive, n=64), and among patients not on LTOCS at their first visit (non-LTOCS patients; n=8,742 and n=4,464). Patients who resumed LTOCS after cessation were excluded. Rates are total exacerbations divided by total person-years in each period; intervals shorter than 30 days and counts above 10 within an interval were excluded. Brackets show Wilcoxon rank-sum tests of pre- versus post-cessation rates and of post-cessation versus non-LTOCS rates, separately for biologic use (blue) and biologic-naive (orange) patients; see Table 10.

Table 10 Annualised exacerbation rate (per year) before and after sustained LTOCS cessation, and in patients not on LTOCS at their first visit (reference). Median [IQR] shown. P-values are from Wilcoxon rank-sum tests. IQR, interquartile range.

	LTOCS Patients (Sustained Cessation)				Non-LTOCS Patients		
Group	N	**Pre-cessation**	**Post-cessation**	**P-value (Pre vs Post)**	**N**	**Median [IQR]**	**P-value (Post vs Non-LTOCS)**
All	745	1.08 [0.48, 2.40]	0.18 [0.00, 0.85]	<0.001	13,206	0.66 [0.00, 1.53]	<0.001
Biologic use	681	1.12 [0.48, 2.37]	0.15 [0.00, 0.79]	<0.001	8,742	0.64 [0.00, 1.48]	<0.001
Biologic-naive	64	0.96 [0.30, 2.57]	0.50 [0.00, 1.26]	0.035	4,464	0.75 [0.00, 2.00]	0.691

6.7 Secondary Objective 3: Trends in data quality coinciding with developing patterns of LTOCS use

Figure 9 Mean cumulative key-variable completeness across all countries by assessment year



Encounter types pooled (first visit and annual review). Cumulative data completeness per country was calculated as the proportion of all possible key variables recorded in all encounters as of each calendar year (see Table 11). Plotted global mean completeness is averaged across all countries with sufficient encounters (n ≥ 41) as of that calendar year. Blue: mean coverage of all key variables across all countries. Dashed green: mean coverage of LTOCS status and dose across all countries.

Table 11 Country-level and global mean key variable completeness, calculated as the percentage of all possible key variables successfully recorded (across all patient encounters, both first visit and annual reviews), cumulatively, up to the given year. The global mean, shown in the Total row, equally weights completeness proportions from all countries with ≥41 encounters as of the given year (cells with fewer marked × and excluded).

Country	2019		2020		2021		2022		2023		2024		2025		2026	
Italy	77%	506i+23r 6,413/8,326	92%	981i+961r 23,259/25,306	92%	981i+961r 23,259/25,306	93%	1524i+2125r 42,328/45,634	93%	2228i+5035r 79,758/85,998	93%	2228i+5035r 80,245/85,998	93%	3292i+8901r 131,326/141,682	93%	4142i+11144r 164,586/177,712
UK	87%	709i+0r 9,875/11,344	86%	709i+553r 14,532/16,874	90%	710i+994r 19,169/21,300	87%	710i+1213r 20,535/23,490	88%	714i+1857r 26,441/29,994	88%	714i+2100r 28,521/32,424	89%	914i+2822r 38,013/42,844	95%	914i+3194r 44,191/46,564
Spain	–		89%	494i+228r 9,103/10,184	93%	704i+532r 15,345/16,584	93%	704i+532r 15,472/16,584	91%	1036i+1398r 27,820/30,556	95%	1117i+1825r 34,335/36,122	93%	1528i+3308r 53,500/57,528	92%	1658i+3308r 55,031/59,608
Canada	90%	54i+0r 779/864	92%	90i+99r 2,237/2,430	91%	208i+315r 5,880/6,478	91%	297i+534r 9,153/10,092	89%	433i+795r 13,222/14,878	94%	602i+1095r 19,350/20,582	94%	605i+1206r 20,359/21,740	95%	719i+1865r 28,780/30,154
Belgium	–		–		–		–		68%	744i+1104r 15,579/22,944	83%	746i+1153r 19,374/23,466	83%	772i+1205r 20,271/24,402	85%	878i+1506r 24,832/29,108
Colombia	–		93%	222i+7r 3,356/3,622	88%	266i+112r 4,735/5,376	89%	345i+353r 8,063/9,050	89%	424i+683r 12,130/13,614	91%	550i+1027r 17,310/19,070	96%	595i+1212r 20,787/21,640	95%	835i+1344r 25,507/26,800
Mexico	–		96%	70i+51r 1,563/1,630	96%	70i+51r 1,563/1,630	93%	183i+97r 3,624/3,898	92%	208i+126r 4,233/4,588	97%	537i+608r 14,251/14,672	97%	648i+1223r 22,027/22,598	95%	698i+1223r 22,127/23,398
Kuwait	97%	103i+48r 2,059/2,128	97%	239i+338r 7,002/7,204	97%	274i+340r 7,561/7,784	97%	332i+340r 8,463/8,712	94%	456i+340r 10,023/10,696	98%	500i+340r 11,191/11,400	98%	514i+340r 11,404/11,624	97%	623i+340r 13,007/13,368
Taiwan	–		93%	211i+6r 3,201/3,436	94%	264i+69r 4,621/4,914	95%	329i+248r 7,320/7,744	92%	342i+376r 8,461/9,232	95%	348i+569r 10,730/11,258	95%	348i+569r 10,736/11,258	95%	348i+569r 10,742/11,258
Saudi Arabia	–		88%	147i+45r 2,465/2,802	89%	170i+151r 3,764/4,230	81%	299i+151r 5,082/6,294	82%	299i+151r 5,149/6,294	94%	411i+397r 9,931/10,546	95%	485i+507r 12,211/12,830	96%	573i+673r 15,217/15,898
Bulgaria	84%	140i+0r 1,873/2,240	96%	273i+125r 5,383/5,618	96%	312i+150r 6,234/6,492	96%	385i+217r 8,020/8,330	96%	390i+217r 8,098/8,410	97%	390i+234r 8,312/8,580	97%	390i+234r 8,312/8,580	97%	405i+238r 8,551/8,860
Japan	84%	58i+0r 782/928	94%	115i+88r 2,552/2,720	94%	126i+149r 3,298/3,506	93%	221i+332r 6,405/6,856	93%	243i+384r 7,157/7,728	95%	245i+417r 7,688/8,090	94%	258i+518r 8,766/9,308	95%	261i+668r 10,304/10,856
Greece	86% ×	35i+5r 524/610	95%	111i+132r 2,937/3,096	95%	147i+221r 4,327/4,562	94%	182i+266r 5,224/5,572	89%	190i+406r 6,328/7,100	95%	198i+428r 7,071/7,448	94%	208i+434r 7,226/7,668	94%	347i+575r 10,589/11,302
Poland	–		–		–		83%	205i+106r 3,617/4,340	83%	349i+215r 6,431/7,734	83%	349i+338r 7,421/8,964	89%	538i+500r 12,098/13,608	90%	538i+559r 12,749/14,198
UAE/Dubai	–		85%	130i+11r 1,854/2,190	86%	205i+99r 3,672/4,270	93%	271i+228r 6,132/6,616	93%	271i+228r 6,132/6,616	94%	311i+228r 6,820/7,256	94%	311i+228r 6,825/7,256	94%	321i+229r 6,946/7,426
India	–		74%	73i+0r 860/1,168	73%	75i+0r 874/1,200	74%	367i+3r 4,395/5,902	76%	588i+9r 7,218/9,498	76%	590i+12r 7,253/9,560	76%	590i+12r 7,253/9,560	76%	590i+12r 7,259/9,560
Brazil	–		–		–		–		–		74%	609i+50r 7,596/10,244	79%	695i+108r 9,659/12,200	86%	845i+265r 13,896/16,170
South Korea	94% ×	25i+0r 377/400	91%	123i+30r 2,062/2,268	93%	160i+58r 2,911/3,140	94%	204i+85r 3,850/4,114	92%	235i+114r 4,528/4,900	94%	270i+134r 5,317/5,660	93%	296i+156r 5,861/6,296	94%	326i+184r 6,603/7,056
Singapore	–		–		–		95%	92i+73r 2,097/2,202	96%	92i+127r 2,625/2,742	96%	179i+185r 4,539/4,714	96%	202i+256r 5,579/5,792	96%	265i+266r 6,648/6,900
Argentina	–		91%	79i+4r 1,182/1,304	92%	98i+30r 1,717/1,868	88%	214i+34r 3,308/3,764	87%	226i+34r 3,441/3,956	92%	229i+34r 3,672/4,004	91%	236i+35r 3,764/4,126	91%	243i+35r 3,876/4,238
Portugal	–		–		65%	87i+0r 907/1,392	80%	141i+43r 2,142/2,686	91%	141i+52r 2,534/2,776	92%	141i+52r 2,549/2,776	91%	220i+88r 4,021/4,400	93%	377i+129r 6,808/7,322
Norway	–		–		–		–		–		97%	97i+256r 3,996/4,112	96%	101i+277r 4,189/4,386	99%	138i+523r 7,352/7,438
Ireland (Tallaght)	–		–		–		–		–		75%	79i+13r 1,045/1,394	88%	86i+53r 1,670/1,906	92%	119i+171r 3,323/3,614
USA Michigan	–		–		–		–		–		93%	40i+36r 934/1,000	97%	45i+48r 1,161/1,200	97%	68i+137r 2,389/2,458
Ireland (Beaumont)	–		59% ×	14i+0r 132/224	62% ×	15i+0r 148/240	77%	21i+45r 602/786	77%	21i+45r 604/786	79%	21i+45r 622/786	79%	21i+45r 622/786	79%	21i+45r 622/786
Estonia	–		–		–		–		–		99%	31i+24r 725/736	99%	32i+24r 741/752	95%	39i+28r 855/904
Germany	–		–		–		–		–		–		–		90%	13i+37r 522/578
Ecuador	–		–		–		–		–		–		–		79% ×	10i+19r 275/350
USA UNC	–		–		–		–		–		–		–		89% ×	25i+0r 357/400
Netherlands	–		–		–		–		–		–		–		93% ×	18i+0r 267/288
Hungary	–		–		–		–		–		–		–		84% ×	14i+1r 197/234
Switzerland	–		–		–		–		–		–		–		96% ×	6i+6r 150/156
Qatar	–		–		–		–		–		–		–		100% ×	3i+3r 78/78
Total (unweighted, N≥41 only)	**86.5%**	n=6 (2 excl.)	**90.7%**	n=16 (1 excl.)	**89.6%**	n=17 (1 excl.)	**89.3%**	n=20 (0 excl.)	**88.1%**	n=21 (0 excl.)	**90.7%**	n=26 (0 excl.)	**91.8%**	n=26 (0 excl.)	**92.4%**	n=27 (6 excl.)

Table 12 Country-level and global mean key LTOCS status and dose completeness, calculated as the percentage of all possible records for this variable successfully completed (across all patient encounters, both first visit and annual reviews), cumulatively, up to the given year. The global mean, shown in the Total row, equally weights completeness proportions from all countries with ≥41 encounters as of the given year (cells with fewer marked × and excluded).

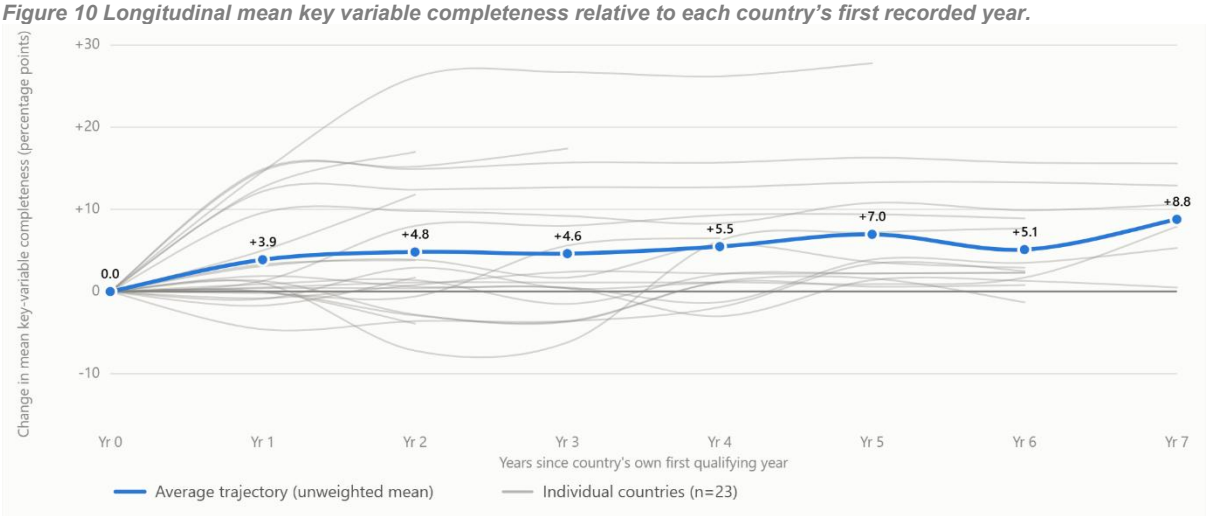
Country	2019		2020		2021		2022		2023		2024		2025		2026	
Italy	87%	506i+23r 460/529	98%	981i+961r 1,901/1,942	98%	981i+961r 1,901/1,942	97%	1524i+2125r 3,532/3,649	96%	2228i+5035r 6,976/7,263	97%	2228i+5035r 7,031/7,263	95%	3292i+8901r 11,640/12,193	96%	4142i+11144r 14,634/15,286
UK	100%	709i+0r 709/709	100%	709i+553r 1,262/1,262	100%	710i+994r 1,704/1,704	95%	710i+1213r 1,836/1,923	100%	714i+1857r 2,568/2,571	100%	714i+2100r 2,814/2,814	97%	914i+2822r 3,638/3,736	100%	914i+3194r 4,107/4,108
Spain	–		67%	494i+228r 482/722	70%	704i+532r 871/1,236	76%	704i+532r 939/1,236	68%	1036i+1398r 1,654/2,434	98%	1117i+1825r 2,880/2,942	97%	1528i+3308r 4,680/4,836	95%	1658i+3308r 4,721/4,966
Canada	89%	54i+0r 48/54	98%	90i+99r 185/189	96%	208i+315r 504/523	97%	297i+534r 809/831	95%	433i+795r 1,171/1,228	99%	602i+1095r 1,678/1,697	98%	605i+1206r 1,774/1,811	98%	719i+1865r 2,531/2,584
Belgium	–		–		–		–		96%	744i+1104r 1,766/1,848	96%	746i+1153r 1,828/1,899	96%	772i+1205r 1,890/1,977	97%	878i+1506r 2,308/2,384
Colombia	–		97%	222i+7r 222/229	72%	266i+112r 274/378	90%	345i+353r 630/698	81%	424i+683r 893/1,107	99%	550i+1027r 1,564/1,577	98%	595i+1212r 1,774/1,807	99%	835i+1344r 2,156/2,179
Mexico	–		69%	70i+51r 84/121	69%	70i+51r 84/121	67%	183i+97r 187/280	61%	208i+126r 205/334	98%	537i+608r 1,119/1,145	97%	648i+1223r 1,812/1,871	94%	698i+1223r 1,812/1,921
Kuwait	90%	103i+48r 136/151	80%	239i+338r 464/577	81%	274i+340r 499/614	83%	332i+340r 557/672	74%	456i+340r 590/796	100%	500i+340r 840/840	100%	514i+340r 854/854	97%	623i+340r 935/963
Taiwan	–		95%	211i+6r 207/217	97%	264i+69r 323/333	96%	329i+248r 552/577	88%	342i+376r 631/718	97%	348i+569r 890/917	97%	348i+569r 890/917	97%	348i+569r 890/917
Saudi Arabia	–		65%	147i+45r 125/192	79%	170i+151r 253/321	79%	299i+151r 355/450	79%	299i+151r 355/450	91%	411i+397r 739/808	91%	485i+507r 902/992	93%	573i+673r 1,154/1,246
Bulgaria	87%	140i+0r 122/140	99%	273i+125r 395/398	99%	312i+150r 457/462	99%	385i+217r 593/602	98%	390i+217r 593/607	99%	390i+234r 620/624	99%	390i+234r 620/624	99%	405i+238r 637/643
Japan	62%	58i+0r 36/58	100%	115i+88r 202/203	100%	126i+149r 274/275	98%	221i+332r 541/553	96%	243i+384r 604/627	100%	245i+417r 660/662	99%	258i+518r 766/776	98%	261i+668r 907/929
Greece	68% ×	35i+5r 27/40	95%	111i+132r 230/243	95%	147i+221r 350/368	95%	182i+266r 424/448	84%	190i+406r 500/596	99%	198i+428r 620/626	98%	208i+434r 626/642	94%	347i+575r 871/922
Poland	–		–		–		85%	205i+106r 264/311	78%	349i+215r 441/564	84%	349i+338r 577/687	87%	538i+500r 906/1,038	88%	538i+559r 967/1,097
UAE/Dubai	–		99%	130i+11r 140/141	100%	205i+99r 303/304	96%	271i+228r 481/499	96%	271i+228r 481/499	100%	311i+228r 538/539	100%	311i+228r 538/539	99%	321i+229r 545/550
India	–		85%	73i+0r 62/73	84%	75i+0r 63/75	75%	367i+3r 278/370	79%	588i+9r 470/597	79%	590i+12r 475/602	79%	590i+12r 475/602	79%	590i+12r 475/602
Brazil	–		–		–		–		–		95%	609i+50r 626/659	95%	695i+108r 761/803	97%	845i+265r 1,074/1,110
South Korea	84% ×	25i+0r 21/25	88%	123i+30r 134/153	92%	160i+58r 201/218	96%	204i+85r 278/289	94%	235i+114r 328/349	98%	270i+134r 395/404	98%	296i+156r 441/452	98%	326i+184r 498/510
Singapore	–		–		–		100%	92i+73r 165/165	100%	92i+127r 219/219	100%	179i+185r 363/364	100%	202i+256r 457/458	100%	265i+266r 530/531
Argentina	–		96%	79i+4r 80/83	98%	98i+30r 126/128	81%	214i+34r 200/248	77%	226i+34r 200/260	100%	229i+34r 262/263	97%	236i+35r 262/271	99%	243i+35r 276/278
Portugal	–		–		100%	87i+0r 87/87	70%	141i+43r 128/184	91%	141i+52r 176/193	95%	141i+52r 184/193	93%	220i+88r 286/308	95%	377i+129r 481/506
Norway	–		–		–		–		–		99%	97i+256r 351/353	96%	101i+277r 361/378	100%	138i+523r 658/661
Ireland (Tallaght)	–		–		–		–		–		100%	79i+13r 92/92	99%	86i+53r 137/139	99%	119i+171r 288/290
USA Michigan	–		–		–		–		–		100%	40i+36r 76/76	99%	45i+48r 92/93	100%	68i+137r 205/205
Ireland (Beaumont)	–		43% ×	14i+0r 6/14	47% ×	15i+0r 7/15	94%	21i+45r 62/66	94%	21i+45r 62/66	94%	21i+45r 62/66	94%	21i+45r 62/66	94%	21i+45r 62/66
Estonia	–		–		–		–		–		100%	31i+24r 55/55	100%	32i+24r 56/56	84%	39i+28r 56/67
Germany	–		–		–		–		–		–		–		96%	13i+37r 48/50
Ecuador	–		–		–		–		–		–		–		93% ×	10i+19r 27/29
USA UNC	–		–		–		–		–		–		–		96% ×	25i+0r 24/25
Netherlands	–		–		–		–		–		–		–		100% ×	18i+0r 18/18
Hungary	–		–		–		–		–		–		–		73% ×	14i+1r 11/15
Switzerland	–		–		–		–		–		–		–		100% ×	6i+6r 12/12
Qatar	–		–		–		–		–		–		–		100% ×	3i+3r 6/6
Total (unweighted, N≥41 only)	85.8%	n=6 (2 excl.)	89.5%	n=16 (1 excl.)	90.1%	n=17 (1 excl.)	88.4%	n=20 (0 excl.)	86.9%	n=21 (0 excl.)	96.8%	n=26 (0 excl.)	96.0%	n=26 (0 excl.)	95.7%	n=27 (6 excl.)

Table 13 Variable-level and overall key variable completeness, calculated as the percentage of all possible key variables successfully recorded (across all patient encounters, both first visit and annual reviews), cumulatively, up to the given year. The global mean, shown in the All Key Variables row, equally weights completeness proportions over all variables from all countries with ≥41 encounters as of the given year (cells with fewer marked × and excluded).

Key variable	2019		2020		2021		2022		2023		2024		2025		2026	
LTOCS status and daily dose	85.8%	n=6 (2 excl.)	89.5%	n=16 (1 excl.)	90.1%	n=17 (1 excl.)	88.4%	n=20 (0 excl.)	86.9%	n=21 (0 excl.)	96.8%	n=26 (0 excl.)	96.0%	n=26 (0 excl.)	95.7%	n=27 (6 excl.)
Age of asthma onset	94.3%	n=6 (2 excl.)	92.0%	n=16 (1 excl.)	87.9%	n=17 (1 excl.)	90.8%	n=20 (0 excl.)	86.7%	n=21 (0 excl.)	88.4%	n=26 (0 excl.)	91.1%	n=26 (0 excl.)	90.0%	n=27 (6 excl.)
Age, gender, height & weight	91.7%	n=6 (2 excl.)	90.8%	n=16 (1 excl.)	91.1%	n=17 (1 excl.)	94.7%	n=20 (0 excl.)	96.2%	n=21 (0 excl.)	93.3%	n=26 (0 excl.)	95.5%	n=26 (0 excl.)	95.5%	n=27 (6 excl.)
Asthma control	60.0%	n=6 (2 excl.)	81.3%	n=16 (1 excl.)	79.5%	n=17 (1 excl.)	76.1%	n=20 (0 excl.)	77.4%	n=21 (0 excl.)	82.9%	n=26 (0 excl.)	88.5%	n=26 (0 excl.)	87.2%	n=27 (6 excl.)
Biologic	88.6%	n=6 (2 excl.)	97.3%	n=16 (1 excl.)	95.9%	n=17 (1 excl.)	92.5%	n=20 (0 excl.)	88.4%	n=21 (0 excl.)	96.0%	n=26 (0 excl.)	94.3%	n=26 (0 excl.)	95.6%	n=27 (6 excl.)
Biologic start date	70.8%	n=6 (2 excl.)	92.2%	n=16 (1 excl.)	89.6%	n=17 (1 excl.)	87.5%	n=20 (0 excl.)	84.7%	n=21 (0 excl.)	95.4%	n=26 (0 excl.)	93.6%	n=26 (0 excl.)	94.3%	n=27 (6 excl.)
Chronic rhinosinusitis	88.2%	n=6 (2 excl.)	96.0%	n=16 (1 excl.)	93.9%	n=17 (1 excl.)	97.5%	n=20 (0 excl.)	93.1%	n=21 (0 excl.)	92.5%	n=26 (0 excl.)	93.6%	n=26 (0 excl.)	94.5%	n=27 (6 excl.)
Exacerbation	100.0%	n=6 (2 excl.)	100.0%	n=16 (1 excl.)	100.0%	n=17 (1 excl.)	100.0%	n=20 (0 excl.)	100.0%	n=21 (0 excl.)	96.0%	n=26 (0 excl.)	97.4%	n=26 (0 excl.)	98.1%	n=27 (6 excl.)
FeNO test result	95.0%	n=6 (2 excl.)	87.2%	n=16 (1 excl.)	88.2%	n=17 (1 excl.)	91.3%	n=20 (0 excl.)	91.4%	n=21 (0 excl.)	88.3%	n=26 (0 excl.)	90.6%	n=26 (0 excl.)	92.0%	n=27 (6 excl.)
Highest blood eosinophil count	74.0%	n=6 (2 excl.)	80.3%	n=16 (1 excl.)	81.3%	n=17 (1 excl.)	82.0%	n=20 (0 excl.)	82.3%	n=21 (0 excl.)	82.4%	n=26 (0 excl.)	83.1%	n=26 (0 excl.)	83.5%	n=27 (6 excl.)
Hospital admissions	99.0%	n=6 (2 excl.)	98.5%	n=16 (1 excl.)	98.9%	n=17 (1 excl.)	98.6%	n=20 (0 excl.)	96.8%	n=21 (0 excl.)	95.8%	n=26 (0 excl.)	97.3%	n=26 (0 excl.)	97.4%	n=27 (6 excl.)
IgE count	77.7%	n=6 (2 excl.)	72.7%	n=16 (1 excl.)	74.0%	n=17 (1 excl.)	74.6%	n=20 (0 excl.)	73.7%	n=21 (0 excl.)	75.3%	n=26 (0 excl.)	76.2%	n=26 (0 excl.)	77.8%	n=27 (6 excl.)
Nasal polyps	89.8%	n=6 (2 excl.)	95.8%	n=16 (1 excl.)	90.2%	n=17 (1 excl.)	97.0%	n=20 (0 excl.)	91.8%	n=21 (0 excl.)	92.0%	n=26 (0 excl.)	93.7%	n=26 (0 excl.)	94.5%	n=27 (6 excl.)
Background therapy (ICS/LABA/LAMA)	88.2%	n=6 (2 excl.)	96.9%	n=16 (1 excl.)	96.2%	n=17 (1 excl.)	92.0%	n=20 (0 excl.)	93.7%	n=21 (0 excl.)	96.0%	n=26 (0 excl.)	95.4%	n=26 (0 excl.)	95.7%	n=27 (6 excl.)
Reason for biologic switch	80.1%	n=2 (1 excl.)	98.3%	n=15 (0 excl.)	99.0%	n=15 (0 excl.)	91.0%	n=20 (0 excl.)	90.5%	n=21 (0 excl.)	92.1%	n=26 (0 excl.)	91.1%	n=26 (0 excl.)	95.2%	n=27 (4 excl.)
Smoking status	97.5%	n=6 (2 excl.)	95.4%	n=16 (1 excl.)	90.9%	n=17 (1 excl.)	92.2%	n=20 (0 excl.)	88.0%	n=21 (0 excl.)	92.2%	n=26 (0 excl.)	93.7%	n=26 (0 excl.)	94.4%	n=27 (6 excl.)
Spirometry – FEV1	85.5%	n=6 (2 excl.)	80.0%	n=16 (1 excl.)	77.8%	n=17 (1 excl.)	76.7%	n=20 (0 excl.)	79.4%	n=21 (0 excl.)	80.5%	n=26 (0 excl.)	82.8%	n=26 (0 excl.)	82.8%	n=27 (6 excl.)
All key variables (mean)	86.5%	n=6 (2 excl.)	90.7%	n=16 (1 excl.)	89.6%	n=17 (1 excl.)	89.3%	n=20 (0 excl.)	88.1%	n=21 (0 excl.)	90.7%	n=26 (0 excl.)	91.8%	n=26 (0 excl.)	92.4%	n=27 (6 excl.)

Key variable completeness trends spanning ISAR's wider population (thereby applying its own exclusion criteria for comprehensive capture of missing data not reflected in cohorts constructed for other objectives) were calculated as a process outcome for investigation of coincidence with QI activity and LTOCS use reduction. Country-level completeness was calculated as the proportion of all key variables across all encounters (first visits and reviews pooled) with all patients as of each calendar year. Completeness was calculated cumulatively each year, such that the value for a given year additionally reflects records from all preceding years from the date the country joined ISAR. Completeness for each year was assessed retrospectively against the registry's data quality requirements as of April 2026, at the point of data extraction. The global trend constructed by means for each year among all countries with sufficient data. Mean completion across key variables was averaged across all contributing countries (if sufficiently powered as of that year) with equal weighting, as a process indicator to explore the quality of key variable recording across the entire registry while preventing the dominating influence of larger contributors.

Figure 10 Longitudinal mean key variable completeness relative to each country's first recorded year.



Countries were included where sufficiently powered (n ≥41). As an exploration of progressive data quality relative to onboarding or earliest available data completeness recording, countries with insufficient data in their first recorded year, or only one year to contribute, were excluded.

Mean completeness across key variables, averaged equally across contributing countries, ranged between 86.5% and 90.7% between 2019 and 2024 (Figure 9, Table 11). This reflected a broadly high standard of data coverage with some minor volatility driven by the registry's onboarding of new countries (where data completeness at country-level tends to be lowest at onboarding prior to progressive improvement; Figure 10, Table 11) in addition to fluctuations in individual key variable completeness. Globally, mean completeness rose continuously from 2023, from 88.1% to 92.4% in 2026, appearing to reflect maturation of enrolled countries (Figure 10) and the improvement of variable-level coverage. This notably included LTOCS status and dose (Figure 9, Tables 12 and 13) which exhibited marked improvement (from 85.8 – 90.1% between 2019 and 2023, to 95.7 - 96.8% between 2024-2026) coinciding with QI engagement focusing on data quality and LTOCS use.

The proportion of patients with all key variables recorded was determined as a further exploration of the process outcome of data completeness. This was calculated as the proportion of encounters (first visits and reviews pooled) where every key variable was recorded, cumulatively as of each calendar year. Unlike mean completeness above, which averaged country-level rates with equal weighting to explore recording practice in different sites, this measure was calculated across the entire registry as a simple, direct reflection of the number of encounters with fully comprehensive data and therefore the substantive completeness of the registry as a whole. In-keeping with the data quality generally improving at country-level post-enrolment, the global proportion of fully comprehensive encounters was at its lowest earliest in the registry's recorded history (10.3% in 2019). A sustained step improvement was observed between 2020 and 2023 (36.5 – 39.5%), before continuous improvement progressing from 2023, with 57.2% of encounters recorded with all key variables by 2026 (Figure 11, Table 14).

Notably, the developed status of data completeness at the date of data extraction (April 2026), particularly for LTOCS recording in which 95.7% of all variables across all historical encounters were non-missing, reflects extensive insight over time and across countries which allowed for accurate analysis of LTOCS usage as reported in the other objectives.

Figure 11 Proportion of cumulative encounters (first visits and reviews pooled) with all key variables recorded over time.

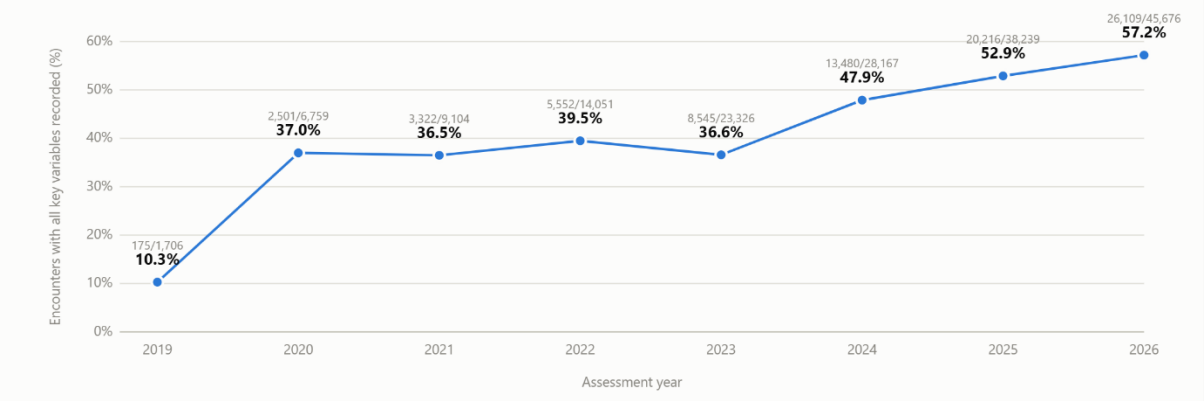


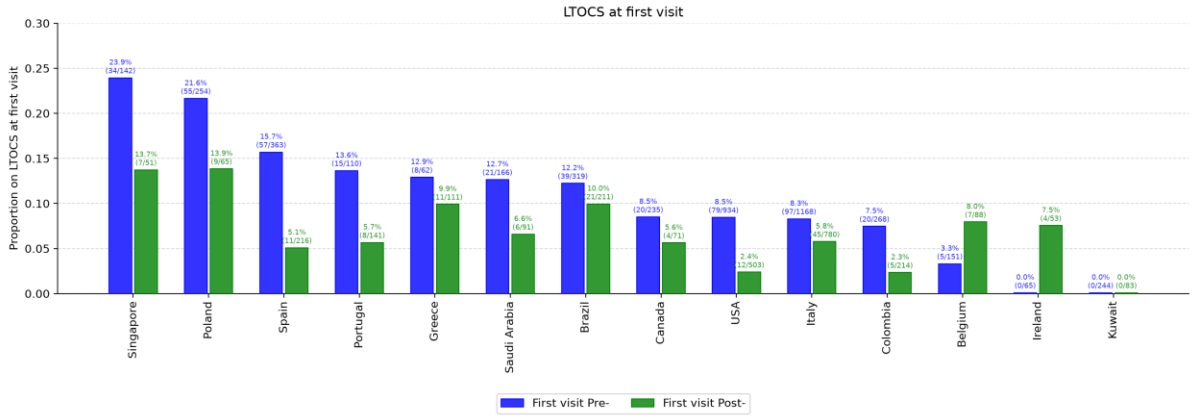
Table 14 Proportion of cumulative encounters (first visits and reviews pooled) with all key variables recorded over time at country-level.

Country	2019		2020		2021		2022		2023		2024		2025		2026	
Italy	0%	506i+23r 0/529	47%	981i+961r 904/1,942	47%	981i+961r 904/1,942	49%	1524i+2125r 1,804/3,649	52%	2228i+5035r 3,744/7,263	53%	2228i+5035r 3,831/7,263	53%	3292i+8901r 6,424/12,193	52%	4142i+11144r 8,018/15,286
UK	0%	709i+0r 0/709	0%	709i+553r 0/1,262	0%	710i+994r 0/1,704	0%	710i+1213r 0/1,923	0%	714i+1857r 0/2,571	0%	714i+2100r 0/2,814	21%	914i+2822r 777/3,736	57%	914i+3194r 2,359/4,108
Spain	–		22%	494i+228r 161/722	38%	704i+532r 468/1,236	45%	704i+532r 554/1,236	42%	1036i+1398r 1,033/2,434	61%	1117i+1825r 1,792/2,942	63%	1528i+3308r 3,038/4,836	62%	1658i+3308r 3,060/4,966
Canada	30%	54i+0r 16/54	31%	90i+99r 58/189	29%	208i+315r 151/523	30%	297i+534r 248/831	28%	433i+795r 339/1,228	53%	602i+1095r 893/1,697	53%	605i+1206r 960/1,811	64%	719i+1865r 1,657/2,584
Belgium	–		–		–		–		0%	744i+1104r 0/1,848	40%	746i+1153r 753/1,899	41%	772i+1205r 819/1,977	46%	878i+1506r 1,105/2,384
Colombia	–		36%	222i+7r 83/229	27%	266i+112r 101/378	39%	345i+353r 269/698	43%	424i+683r 477/1,107	43%	550i+1027r 683/1,577	67%	595i+1212r 1,217/1,807	60%	835i+1344r 1,316/2,179
Mexico	–		55%	70i+51r 66/121	55%	70i+51r 66/121	45%	183i+97r 125/280	39%	208i+126r 129/334	81%	537i+608r 924/1,145	86%	648i+1223r 1,615/1,871	84%	698i+1223r 1,615/1,921
Kuwait	70%	103i+48r 105/151	71%	239i+338r 407/577	71%	274i+340r 438/614	73%	332i+340r 489/672	61%	456i+340r 489/796	83%	500i+340r 698/840	82%	514i+340r 702/854	82%	623i+340r 785/963
Taiwan	–		52%	211i+6r 113/217	61%	264i+69r 204/333	66%	329i+248r 381/577	60%	342i+376r 434/718	71%	348i+569r 649/917	71%	348i+569r 649/917	71%	348i+569r 649/917
Saudi Arabia	–		39%	147i+45r 74/192	29%	170i+151r 93/321	21%	299i+151r 94/450	21%	299i+151r 95/450	79%	411i+397r 639/808	77%	485i+507r 759/992	76%	573i+673r 948/1,246
Bulgaria	11%	140i+0r 16/140	68%	273i+125r 269/398	69%	312i+150r 317/462	69%	385i+217r 416/602	69%	390i+217r 416/607	75%	390i+234r 468/624	75%	390i+234r 468/624	73%	405i+238r 468/643
Japan	36%	58i+0r 21/58	58%	115i+88r 117/203	57%	126i+149r 158/275	58%	221i+332r 318/553	57%	243i+384r 357/627	61%	245i+417r 401/662	57%	258i+518r 446/776	62%	261i+668r 575/929
Greece	18%	35i+5r 7/40	58%	111i+132r 141/243	60%	147i+221r 220/368	55%	182i+266r 248/448	45%	190i+406r 268/596	56%	198i+428r 348/626	55%	208i+434r 356/642	55%	347i+575r 507/922
Poland	–		–		–		0%	205i+106r 0/311	0%	349i+215r 0/564	9%	349i+338r 61/687	29%	538i+500r 299/1,038	35%	538i+559r 381/1,097
UAE/Dubai	–		28%	130i+11r 39/141	21%	205i+99r 63/304	48%	271i+228r 238/499	48%	271i+228r 238/499	54%	311i+228r 290/539	54%	311i+228r 290/539	53%	321i+229r 290/550
India	–		0%	73i+0r 0/73	0%	75i+0r 0/75	10%	367i+3r 38/370	11%	588i+9r 64/597	11%	590i+12r 65/602	11%	590i+12r 65/602	11%	590i+12r 65/602
Brazil	–		–		–		–		–		1%	609i+50r 9/659	19%	695i+108r 152/803	37%	845i+265r 412/1,110
South Korea	40%	25i+0r 10/25	20%	123i+30r 31/153	34%	160i+58r 75/218	40%	204i+85r 115/289	39%	235i+114r 136/349	43%	270i+134r 174/404	41%	296i+156r 184/452	44%	326i+184r 224/510
Singapore	–		–		–		48%	92i+73r 80/165	51%	92i+127r 112/219	57%	179i+185r 207/364	57%	202i+256r 263/458	58%	265i+266r 308/531
Argentina	–		45%	79i+4r 37/83	48%	98i+30r 62/128	37%	214i+34r 92/248	35%	226i+34r 92/260	47%	229i+34r 123/263	45%	236i+35r 123/271	46%	243i+35r 127/278
Portugal	–		–		0%	87i+0r 0/87	16%	141i+43r 29/184	56%	141i+52r 108/193	57%	141i+52r 110/193	45%	220i+88r 138/308	56%	377i+129r 281/506
Norway	–		–		–		–		–		76%	97i+256r 267/353	83%	101i+277r 315/378	88%	138i+523r 583/661
Ireland (Tallaght)	–		–		–		–		–		0%	79i+13r 0/92	26%	86i+53r 36/139	39%	119i+171r 113/290
USA Michigan	–		–		–		–		–		47%	40i+36r 36/76	66%	45i+48r 61/93	70%	68i+137r 144/205
Ireland (Beaumont)	–		7%	14i+0r 1/14	13%	15i+0r 2/15	21%	21i+45r 14/66	21%	21i+45r 14/66	21%	21i+45r 14/66	21%	21i+45r 14/66	21%	21i+45r 14/66
Estonia	–		–		–		–		–		82%	31i+24r 45/55	82%	32i+24r 46/56	69%	39i+28r 46/67
Germany	–		–		–		–		–		–		–		54%	13i+37r 27/50
Ecuador	–		–		–		–		–		–		–		14%	10i+19r 4/29
USA UNC	–		–		–		–		–		–		–		28%	25i+0r 7/25
Netherlands	–		–		–		–		–		–		–		39%	18i+0r 7/18
Hungary	–		–		–		–		–		–		–		13%	14i+1r 2/15
Switzerland	–		–		–		–		–		–		–		50%	6i+6r 6/12
Qatar	–		–		–		–		–		–		–		100%	3i+3r 6/6
Total (weighted, all countries)	**10.3%**	175/1,706	**37.0%**	2,501/6,759	**36.5%**	3,322/9,104	**39.5%**	5,552/14,051	**36.6%**	8,545/23,326	**47.9%**	13,480/28,167	**52.9%**	20,216/38,239	**57.2%**	26,109/45,676

6.8 Exploratory Objective 2: Exploring the magnitude of country-specific differences in the change in LTOCS use before and after the quality improvement programme

For comparison of LTOCS use at first visit, 14 countries had sufficient (≥50) patients in both the pre-and post-intervention periods (Figure 12, Table 15). LTOCS use at first visit was lower after the intervention in 11 of these 14 countries and this reached statistical significance in four: Colombia (7.5 to 2.3%, p=0.017), Italy (8.3% to 5.8%, p=0.041), Spain (15.7% to 5.1%, P<0.001), and the USA (8.5% to 2.4%, p<0.001). Two countries recorded increases (Belgium; 3.3% to 8.0%, p=0.204, and Ireland; 0% to 7.5%, P=0.076) although both were non-significant and were derived from pre-intervention proportions that were small or zero. Kuwait recorded no LTOCS use at first visit in either period (0/244 pre-intervention; 0/83 post-intervention), indicating LTOCS was unused at first visit in this country throughout the study period examined, independent of the intervention. Overall, the differences at country level are consistent with the registry-wide finding of reduced LTOCS use following the intervention (Primary Objective, Secondary Objective 1).

Figure 12 Unadjusted proportion of patients on LTOCS at first visit, before and after the ISAR quality improvement intervention (1 March 2024), by country.



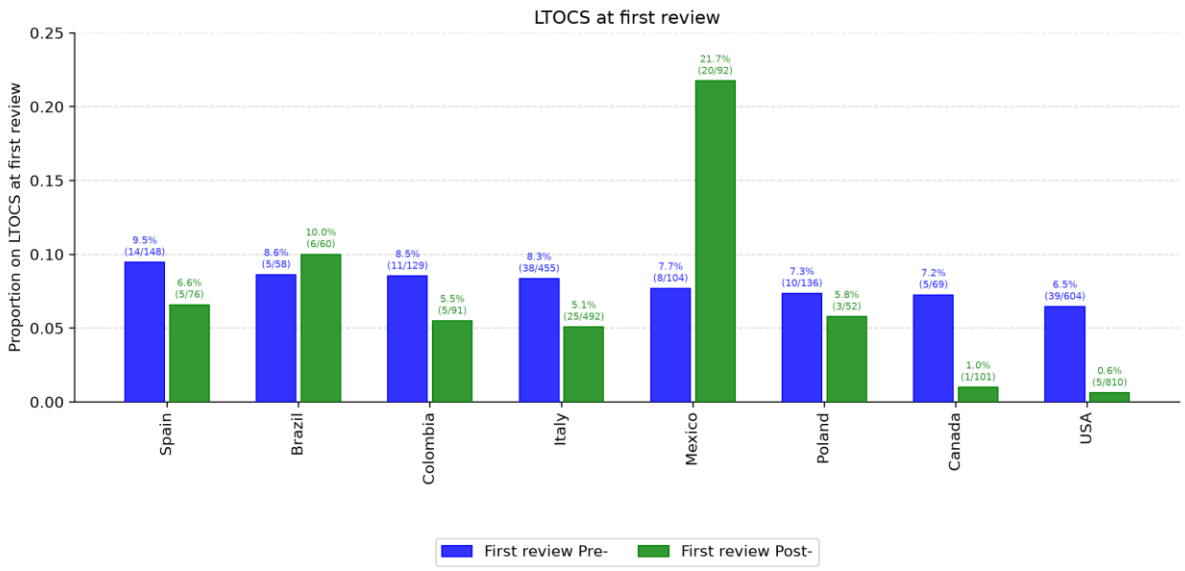
Countries are ordered by decreasing proportion on LTOCS at first visit in the pre-intervention period, and only those with 50 or more patients with a first visit in both the pre- and post-intervention periods are shown. Patients with a first visit before 1 March 2021 are excluded. See Table 15 for 95% confidence intervals. Bar annotations show the percentage on LTOCS with (number on LTOCS / number of patients) in each period.

Table 15 Unadjusted proportion of patients on LTOCS at first visit, before and after the intervention (1 March 2024), by country, with exact (Clopper-Pearson) 95% confidence intervals. Adjustment for additional covariates was not performed at country level due to the consequent exclusion of many countries with limited sample sizes; unadjusted rates are therefore presented. P-values were derived using exact logistic regression, selected for its validity in countries with zero events in either period. Patients required a first visit on or after 1 March 2021 and known LTOCS status at first visit for inclusion. nc = not calculable.

	Pre-intervention			Post-intervention			
Country	**N**	**Proportion**	**95% CI**	**N**	**Proportion**	**95% CI**	**P-value**
Belgium	151	0.033	(0.011, 0.076)	88	0.080	(0.033, 0.157)	0.204
Brazil	319	0.122	(0.088, 0.163)	211	0.100	(0.063, 0.148)	0.507
Canada	235	0.085	(0.053, 0.128)	71	0.056	(0.016, 0.138)	0.611
Colombia	268	0.075	(0.046, 0.113)	214	0.023	(0.008, 0.054)	0.017
Greece	62	0.129	(0.057, 0.239)	111	0.099	(0.051, 0.170)	0.714
Ireland	65	0.000	(0.000, 0.055)	53	0.075	(0.021, 0.182)	0.076
Italy	1168	0.083	(0.068, 0.100)	780	0.058	(0.042, 0.076)	0.041
Kuwait	244	0.000	(0.000, 0.015)	83	0.000	(0.000, 0.043)	nc
Poland	254	0.217	(0.167, 0.272)	65	0.138	(0.065, 0.247)	0.214
Portugal	110	0.136	(0.078, 0.215)	141	0.057	(0.025, 0.109)	0.052
Saudi Arabia	166	0.127	(0.080, 0.187)	91	0.066	(0.025, 0.138)	0.188
Singapore	142	0.239	(0.172, 0.318)	51	0.137	(0.057, 0.263)	0.178
Spain	363	0.157	(0.121, 0.199)	216	0.051	(0.026, 0.089)	0.0001
USA	934	0.085	(0.068, 0.104)	503	0.024	(0.012, 0.041)	<0.001

At first annual review, the trends in LTOCS use change were less consistent at country-level (Figure 13, Table 16). Of the 8 countries with sufficient patients (≥50) in both the pre- and post-intervention periods, 6 showed any reduction after the intervention, and only the USA reached statistical significance (6.5% to 0.6%, p<0.001). Two countries recorded an increase: Mexico, where the increase was substantial and statistically significant (7.7% to 21.7%, P=0.009), and Brazil (8.6% to 10.0%, p=1.000).

Figure 13 Unadjusted proportion of patients on LTOCS at first annual review, before and after the ISAR quality improvement intervention (1 March 2024), by country.



Countries are ordered by decreasing proportion on LTOCS at first annual review in the pre-intervention period, and only those with 50 or more patients with a first annual review in both the pre- and post-intervention periods are shown. Patients with a first visit before 1 March 2021 are excluded. See Table 16 for 95% confidence intervals. Bar annotations show the percentage on LTOCS with (number on LTOCS / number of patients) in each period.

Table 16 Unadjusted proportion of patients on LTOCS at first annual review, before and after the intervention (1 March 2024), by country, with exact (Clopper-Pearson) 95% confidence intervals. As with the equivalent analysis of LTOCS use at first visit (Table 15), adjustment for additional covariates was not performed at country level due to the consequent exclusion of many countries with limited sample sizes; unadjusted rates are therefore presented. P-values were derived using exact logistic regression, selected for its validity in countries with zero events in either period. Patients required a first visit on or after 1 March 2021 and known LTOCS status at first annual review for inclusion. nc = not calculable.

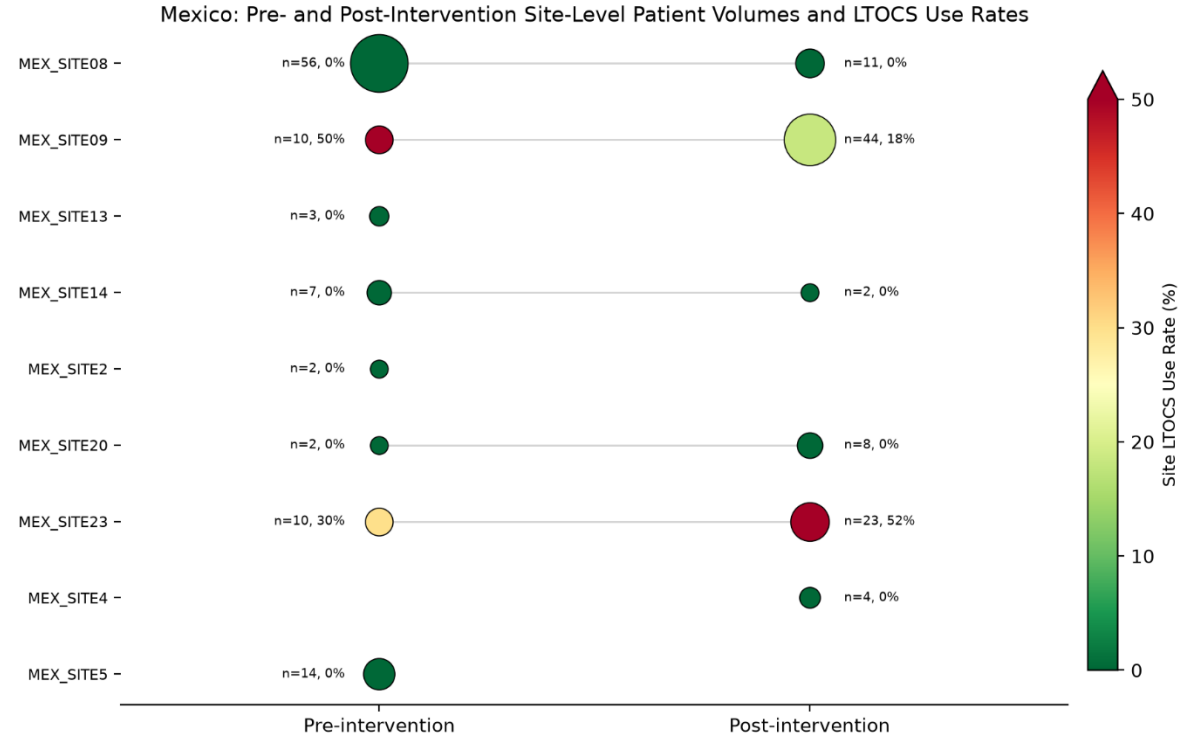
	Pre-intervention				Post-intervention				
Country	**N**	**Proportion**	**95% CI**		**N**	**Proportion**	**95% CI**		**P-value**
Brazil	58	0.086	(0.029,	0.190)	60	0.100	(0.038,	0.205)	1.000
Canada	69	0.072	(0.024,	0.161)	101	0.010	(0.000,	0.054)	0.082
Colombia	129	0.085	(0.043,	0.147)	91	0.055	(0.018,	0.124)	0.563
Italy	455	0.084	(0.060,	0.113)	492	0.051	(0.033,	0.074)	0.059
Mexico	104	0.077	(0.034,	0.146)	92	0.217	(0.138,	0.316)	0.009
Poland	136	0.074	(0.036,	0.131)	52	0.058	(0.012,	0.159)	0.986
Spain	148	0.095	(0.053,	0.154)	76	0.066	(0.022,	0.147)	0.646
USA	604	0.065	(0.046,	0.087)	810	0.006	(0.002,	0.014)	<0.001

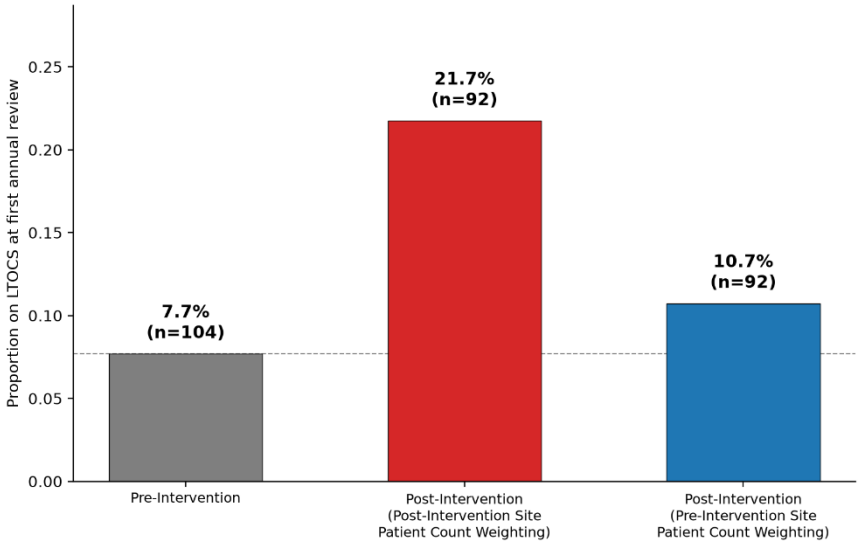
The influence of changing within-country site composition on apparently increasing post-intervention LTOCS use at first annual review, as observed in Mexico and Brazil, was explored. For this, the contributions of site-level post-intervention proportions of LTOCS use were reweighted to reflect pre-intervention patient counts by site. For Mexico, reweighting of post-intervention site contributions to reflect pre-intervention contributions markedly reduced the LTOCS usage at first annual review from 21.7% to 10.7%, a proportion more comparable to the pre-intervention rate of 7.7%. This indicates that a large component of the apparent increase in LTOCS use post-intervention could be attributed to a shift in site composition;

particularly with the declining post-intervention contribution of Site 08, reporting very low LTOCS use (56 patients with 0% on LTOCS pre-intervention; 11 patients with 0% on LTOCS post-intervention), and the increasing influence of Site 23, with high LTOCS use and a much higher patient count post-intervention (10 patients with 30% on LTOCS pre-intervention; 23 patients with 52% on LTOCS post-intervention; Figure 14A). The increase in LTOCS use post-intervention observed in Brazil, apparently driven by the increased post-intervention patient count from Site 19 (6 patients with 17% on LTOCS pre-intervention; 26 patients with 15% on LTOCS post-intervention), reversed with reweighting, now reducing to an LTOCS use rate of 8.3% (Figure 14B).

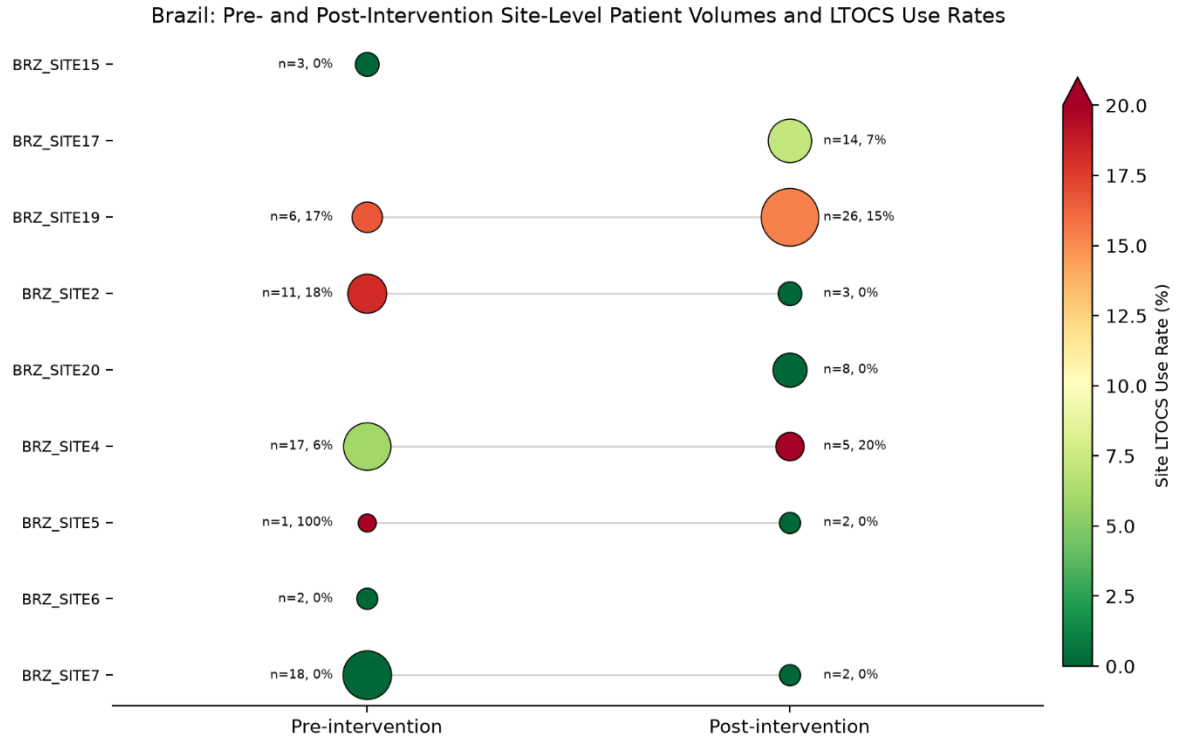
Figure 14 Site-level composition sensitivity analysis for exploration of post-intervention increases in LTOCS use observed in Mexico (A) and Brazil (B).

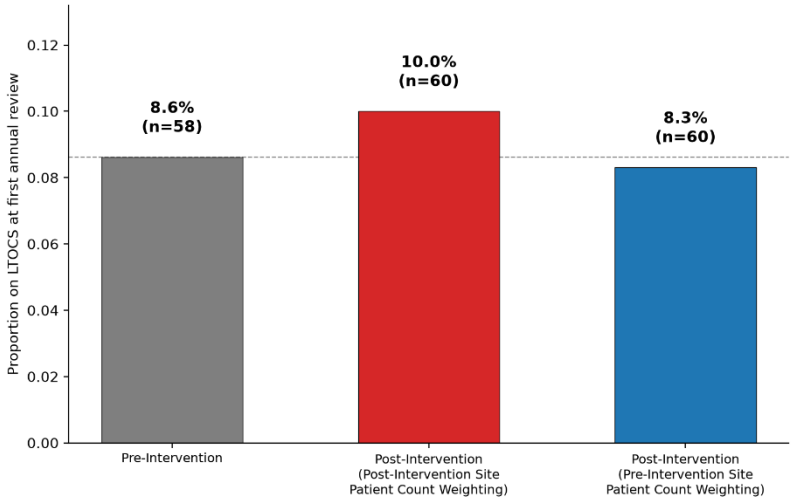
A




Proportion on LTOCS at first annual review
0.25
0.20
0.15
0.10
0.05
0.00
7.7%
(n=104)
21.7%
(n=92)
10.7%
(n=92)
Pre-Intervention
Post-Intervention
(Post-Intervention Site
Patient Count Weighting)
Post-Intervention
(Pre-Intervention Site
Patient Count Weighting)

B


Brazil: Pre- and Post-Intervention Site-Level Patient Volumes and LTOCS Use Rates
BRZ_SITE15
BRZ_SITE17
BRZ_SITE19
BRZ_SITE2
BRZ_SITE20
BRZ_SITE4
BRZ_SITE5
BRZ_SITE6
BRZ_SITE7
n=3, 0%
n=14, 7%
n=6, 17%
n=26, 15%
n=11, 18%
n=3, 0%
n=8, 0%
n=17, 6%
n=5, 20%
n=1, 100%
n=2, 0%
n=2, 0%
n=18, 0%
n=2, 0%
Pre-intervention
Post-intervention
Site LTOCS Use Rate (%)
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0



Top panels: Per-site patient volumes (bubble area) and local LTOCS use rates (colour coded; green = low, red = high) at first annual review pre- and post-intervention. Bottom panels: Comparison of observed pre-intervention LTOCS use (left), observed post-intervention LTOCS use (middle) and post-intervention LTOCS use reweighted by site-level pre-intervention patient share. Sites with patients in only one period are shown for full insight; in reweighting, a site with no post-intervention patients is assigned the country's overall post-intervention rate and a site with no pre-intervention patients receives no weight.

Summary and Discussion

The present findings converge on a decline in LTOCS use across ISAR's history with some evidence of acceleration in LTOCS cessation coinciding with the rollout of the registry's QI efforts. This was evident across multiple independent analyses, including discrete pre-/post-QI intervention comparison (the Primary Objective) of LTOCS use at first visit and first annual review, a continuous segmented regression explicitly testing for change in the rate of LTOCS cessation at the intervention date and time-to-event analyses of LTOCS cessation across successive annual enrolment cohorts (Secondary Objective 2), with further exploration elucidating driving factors and varying country-level trends.

Global reduction of LTOCS use at first visit and first annual review following the QI intervention was statistically significant and, with adjustment, was found to be only partially explained by reduced pre-existing LTOCS use recorded at first visit as adjustment for baseline LTOCS status reduced the estimated risk difference from −4.6 to −2.3 percentage points at first annual review. Interestingly, adjustment for prior biologic use had negligible additional effect. The finding that significantly reduced LTOCS use at first annual review post-intervention is not wholly accounted for by LTOCS use at first visit or prior biologic use indicates that other factors, such as changing clinical practice possibly resulting from the QI intervention, were at

play. The suitability of the primary intervention period definition of 1 March 2024 as a single cutpoint within a progressive QI rollout was explored with sensitivity analyses using earlier or longer intervention windows, which yielded equivalent or greater risk differences, with LTOCS use declining progressively through the pre-, during- and post-intervention groups across all adjustment combinations tested. While this would be consistent with longer-standing QI-related activity influencing practice more broadly or earlier than as reflected by the primary intervention definition, wider windows would also be expected to show larger differences irrespective of QI engagement in the context of a broader secular decline driven by factors external to registry influence: determination of an impact beyond secular trends would require exploration via trend analyses (see below).

Whether or not the post-intervention reduction held consistently across the registry or was concentrated in particular countries was also examined. At first visit, LTOCS use reduced post-intervention in most countries with sufficient data (11 of 14, with four reaching statistical significance), consistent with registry-wide observations. Country-level trends at first annual review were more heterogenous, with six of the eight sufficiently-powered countries showing reduction, but none significantly, and Mexico recording a large, statistically significant increase. Beyond the influence of site composition explored, increased inter-country heterogeneity at first annual review may in part reflect the influence of increased sampling noise on individual country estimates, resulting from sample sizes being limited by the 2-year time range (restricted between the intervention date and the date of data extraction). Both at country-level and globally, increased heterogeneity at first review may reflect the persisting influence of prescribing decisions made at the previous visit. Better-powered first annual review data and further analyses of subsequent visits would facilitate cleaner insight into pre-/post-QI intervention trends and may allow for adjustments to explore driving factors which could not be applied presently at country-level; these are opportunities for further insight as this data materialises in the coming years. These factors may include those explored presently, or further influences such as biologic accessibility, further patient characteristics such as phenotype, country-specific QI engagement intensity or local changes in clinical guidance.

Beyond this discrete pre-/post-intervention comparison, whether the rate of decline in LTOCS use changed specifically at the intervention date was tested directly, initially mirroring the Primary Objective's focus on LTOCS use at first visit and first annual review (Secondary Objective 1). At both visit types, LTOCS use showed a significant declining trend across ISAR's history predating the intervention (first visit OR per year 0.813, 95% CI 0.748–0.884, p<0.001; first annual review OR per year 0.700, 95% CI 0.610–0.803, p<0.001), consistent

with the pre-existing trajectory noted above. However, the additional change in this rate of decline coinciding with the intervention did not reach statistical significance at either visit type (first visit OR per year 0.853, 95% CI 0.636-1.144, p=0.289; first annual review OR per year 0.757, 95% CI 0.323-1.776, p=0.522). This called into question whether the Primary Objective's pre-/post-intervention reduction in LTOCS use reflects clinical change specifically coinciding with the QI programme or continuation of a pre-existing secular trend of decline.

To explore this further, an additional analysis reframed LTOCS cessation by calendar time rather than restricting to fixed early snapshots, generalising beyond the Primary Objective and Secondary Objective 1's focus on first visit and first annual review to all patients on LTOCS at any point during the observation window irrespective of enrolment year (Secondary Objective 2). This circumvented two limitations of the visit-snapshot framing above: the shrinking number of patients reaching a first annual review within the relatively brief post-intervention window and the restriction to only two fixed timepoints in each patient's journey. Testing explicitly for a change in the underlying monthly rate of LTOCS cessation at the pre-specified 1 March 2024 cutpoint, this analysis found no significant pre-intervention trend (OR per year 1.065, 95% CI 0.973-1.166, p=0.172), but a marked and highly significant increase in the rate of cessation post-intervention (OR Time since start of intervention 1.774, 95% CI 1.321-2.383, p<0.001; OR per year post intervention 1.890 per year). This supports that LTOCS cessation accelerated specifically around the intervention date, and therefore that coinciding clinical impact beyond broader longitudinal trends was observed.

A separate, complementary question was also addressed in exploring durations to LTOCS cessation among patients entering the registry on LTOCS, and whether this has changed across successive enrolment cohorts spanning ISAR's history. Time-to-cessation shortened progressively across enrolment years, with comparable improvement in the hazard of cessation between 2018 and 2021 (HR 1.35-1.47 vs. 2017) followed by a further, more pronounced step improvement among patients enrolling from 2022 onwards (HR 2.5-2.9 vs. 2017; Table 8), and a markedly larger further increase for the 2025 cohort (HR 6.27, 95% CI 3.25–12.11, vs. 2017); however, this last estimate rests on only 10 observed cessation events in a cohort with limited follow-up due to recent enrolment, and should be read as consistent with, rather than confirmatory of, continued improvement. The initial improvement evident by 2018 may reflect a combination of the progressive availability of pre-existing anti-IL5 biologics, the expanding regulatory approval of the first anti-IL5Rα biologic between 2017 and 2018, and/or early-registry practice and scientific exchange. The subsequent step improvement from 2022 coincides with formalisation of LTOCS reduction as a QI priority within ISAR, and with external developments in the evidence base of the associated risks[12] and steroid-sparing

strategies (PONENTE).[36] Regarding the registry's impact, the marked improvement in time-to-cessation evident from 2022 could support influence across a broader window extending earlier than the single date cutpoint definition principally used above, in-keeping with the alternative intervention definition sensitivity analyses.

Exacerbation rates were examined before and after LTOCS cessation among patients who did not resume LTOCS. Before cessation, a smaller proportion of LTOCS patients recorded zero exacerbations than patients not on LTOCS at registry entry (16.2% versus 33.6%). After cessation, exacerbation rates fell markedly with the proportion recording zero rising to 47.5%, indicating that cessation was achieved safely without deterioration in exacerbation control among patients who remained off LTOCS. Post-cessation rates were comparable to those of patients not on LTOCS at registry entry among biologic-naive patients (39.1% versus 39.5% exacerbation-free) and lower among biologic-treated patients (48.3% versus 30.6%). The minority of patients who resumed LTOCS (16.4% of patients with exacerbation records before and after cessation) recorded higher post-cessation rates, consistent with LTOCS being resumed where cessation was not tolerated. The lower post-cessation rates among biologic-treated patients relative to patients not on LTOCS at registry entry likely reflect LTOCS having been ceased preferentially in patients with fewer exacerbations, including in response to biologics, although patients not on LTOCS at registry entry will include those whose exacerbations were not sufficient to prompt its initiation. The separate contributions of biologic therapy and cessation cannot be distinguished presently. Overall, in terms of exacerbation rate the findings are consistent with LTOCS reduction having been accomplished successfully and safely in the majority of patients within the registry, particularly in the context of biologic use.

As the registry's presently-evaluated goal of LTOCS use reduction took place in the broader context of a pre-existing and ongoing QI target of increasing data completeness initiated one year prior, the potential influence of data quality on LTOCS use was considered. The observed reduction in LTOCS use does appear to coincide with concomitant progression in data quality, particularly that specifically in LTOCS data completeness. Improvement in overall data coverage as determined by mean cumulative key variable completeness exhibits a trend of gradual modest improvement over the course of ISAR's history, with the most stable improvement aligning with the registry's goal to improve data between 2023 and 2026. LTOCS data completeness' contribution to this composite measure takes shape as a marked step improvement from 86.9% to 96.8% 2024, corresponding with the point of declining LTOCS use identified in the Primary Objective and Secondary Objectives 1 and 2. As this coincidence alone cannot exclude the completeness improvement itself contributing to an apparent

reduction in LTOCS use, the proportions of known non-LTOCS users was examined: 90.7% of encounters newly capturing LTOCS status in 2024 were non-users, continuing a trend evident since 2017 (84.9% non-users among newly-recorded encounters in 2017, rising to 85.3% by 2022, 88.2% in 2023, and 94.1% by 2025). The year-on-year increase in this proportion between 2023 and 2024 (+2.5 percentage points) was no larger than changes in adjacent years (+2.9pp in 2022–2023, +3.4pp in 2024–2025), suggesting continuation of a pre-existing trend in recorded LTOCS use rather than a discrete recording or imputation artefact coincident with the intervention. The improvement in LTOCS data completeness likely reflects both the specific focus on LTOCS usage initiating this year and the preceding groundwork laid for improving general data quality in the year prior, in which the submission of high-quality data was incentivised to motivate optimal extraction from all available sources. This further supports that improved data quality may have heightened systemic clinical insight to facilitate practice change in reducing LTOCS use.

Limitation(s)

This was a single-arm, pre-post study without a contemporaneous comparator group and so, while the coincidence of the intervention with practice change is evident, changes in LTOCS use cannot be attributed specifically to the QI programme. The observed reductions occurred in the context of an established downward trend in LTOCS use and wider external developments over the study period that may also have influenced practice, including broader access to biologic therapies, updated clinical guidelines and changing referral patterns. ISAR's global reach makes identification of a truly representative comparator challenging. Consequently, the study design cannot distinguish changes attributable specifically to the QI programme from broader secular changes in OCS stewardship and severe asthma management, and the findings should be interpreted as describing change in temporal association with ISAR's QI activity rather than confirmation of its causal effect.

LTOCS use was analysed as a binary outcome (any use versus none) at first visit and first annual review, and cessation as a binary event among patients on LTOCS at registry entry. Dose reductions short of cessation, and total OCS exposure including intermittent courses for exacerbations, were therefore not captured by these analyses, and changes in practice that reduced rather than stopped LTOCS would not be detected. Reduction of dose to physiological replacement levels (e.g. for adrenal insufficiency) would have been particularly attractive and may be considered in future work. In settings where LTOCS prescribing is uncommon but intermittent OCS use is frequent, a measure restricted to LTOCS use may also under-represent the systemic steroid burden.

While global regression models were adjusted for age, sex and country (as a random effect), with additional adjustment for prior biologic use and LTOCS use at first visit in selected first annual review models, country-level analyses were unadjusted. Further, disease severity, exacerbation history, asthma phenotype, biologic class, background inhaled therapy, and changes over time in the case-mix or referral patterns of patients entering the registry, including any shift in the severity of patients referred to severe asthma centres, were not adjusted for and may be considered in continuation of this work.

As per local recording approach, LTOCS status at any given visit may reflect the prescribing decision made at the preceding visit. For example, a patient, who ceases steroids on the date of their first annual review or requires tapering from that date, may still be recorded as on LTOCS at that date. Therefore, a patient's first annual review alone may not capture whether

a new decision to stop LTOCS, prompted by the QI intervention, has been made and sustained; further follow-up beyond their first annual review would be needed to clarify this.

As the data extraction used in this study only captured around two years of follow-up post-intervention, and the recency of data varied by country, relatively few patients had reached the first annual review by the time of analysis. This may explain the lower precision of estimated change in the rate of decline in LTOCS use, and in places the lower consistency, observed at first annual review than at first visit.

The overall pre-/post-intervention reduction in LTOCS use was broadly consistent when examined by country, particularly at first visit. However, country-level results were particularly more variable at first annual review and could not be adjusted for age and sex due to limited sample sizes. Country-level estimates therefore relied on unadjusted rates, calculated using exact logistic regression to enable inclusion of countries with zero LTOCS use in either period.

The QI programme's rollout comprised several components introduced at different times variably across participating countries, and 1 March 2024 was selected as a single cutpoint intended to represent peak concentration LTOCS-focused activity. However, the intervention was not a discrete event, as may be evidenced by the presently conducted sensitivity analyses with varying intervention definitions. OCS elimination was a stated target from the formal onset of the registry's wider QI activity in September 2022, though measuring engagement prior to formal adoption of LTOCS reduction as a registry-wide QI goal is challenging. The 1 March 2024 cutpoint definition used was therefore generalised throughout further analyses for simplicity, although findings should be interpreted with the above in mind.

The data completeness analyses draw from the registry's native data quality monitoring pipeline which was developed following the registry's inception. As such, data are only available from 2019 onwards. Additionally, one US site included in the other analyses was exempt from the registry's normal data quality monitoring pipeline (due to the incompatibility of its EMR-derived data) and therefore was also excluded from the data completeness analyses.

Country-level estimates in this study pool all contributing sites within that country, and this composition is not fixed over the study period. New sites joining the registry over time may do so with substantially different LTOCS use patterns and may thereby influence country-wide trends, as appeared to be the case in the present pre-/post- analyses upon focused inspection of apparently rising LTOCS use following the intervention.

7.0 Conclusion

Overall, these findings provide converging evidence of reduced LTOCS use among countries participating in ISAR'S QI programme following the intervention, and that LTOCS cessation rates accelerated specifically in temporal association with the programme's rollout. While improvements in LTOCS cessation rates coincided with the QI programme and accelerated beyond broader trends, causality cannot be ascertained and the influence of both longer-standing scientific and practice exchange within the registry and external factors must be considered. ISAR will continue to monitor the consistency of these findings as further data is accrued, building on the findings to date which are already a promising reflection of registry trends in LTOCS use and consistent with the contribution of QI engagement in driving meaningful change in LTOCS prescribing practice.

8.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC). Other members of the committee, as listed in the following table, will form the Advisory Group.

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11.0 List of Tables