Supplementary Methods

Data source: In the United Kingdom, JAK inhibitors are prescribed by specialists in secondary care. Secondary care medicines data for England are published monthly by the National Health Service (NHS) Business Services Authority (*https://opendata.nhsbsa.net/dataset/secondary-care-medicines-data-indicative-price*), with data available since January 2019. These data contain processed pharmacy stock control data from all NHS Acute, Teaching, Specialist, Mental Health and Community Hospital Trusts in England.[1] Data are aggregated across therapeutics indications for an individual medication at the Virtual Medicinal Product level (i.e. drug moiety, strength and form).[1] Aggregate monthly data are made publicly available; however, no individual-level or identifiable data are published, and separation by treatment indication is not possible within the aggregate data.

Data standardisation: We collated data on monthly quantities of tofacitinib, baricitinib, upadacitinib and filgotinib issued at all NHS Hospital Trusts in England between January 2019 and August 2023. Monthly issued drug quantities were standardised for comparison using World Health Organisation Defined Daily Doses (DDD); defined as the average maintenance dose per day for a drug used for its main indication in adults (*https://www.who.int/tools/atc-ddd-toolkit/about-ddd*). Standardised monthly quantities were converted to estimated numbers of people prescribed each medication by dividing monthly quantities by 30.4 (i.e. the mean number of days in a month, averaged across the year). Data on abrocitinib, a JAK1-selective inhibitor approved for the treatment of atopic dermatitis, were not included in these analyses, due to the small quantities dispensed.

Statistical methods. Trends in the estimated number of people prescribed JAK inhibitors over the study period were compared graphically using two-way plots. Plots are shown with and without smoothing having been applied, whereby data points represent 3-monthly averages of dispensed drug volumes. Single-group interrupted time-series analysis (ITSA) was performed to compare prescribing trends before and after sequential EMA warnings were issued in November 2019,[2] March 2021,[3] and November 2022.[4] Autocorrelation between observation periods was accounted for using Newey-West standard errors with 5 lags. All statistical analyses were conducted using Stata version 17 (StataCorp, US).

Approved therapeutic indications for JAK inhibitors in England

Dates shown represent when approval was received for a treatment indication from the National Institute for Health and Care Excellence (NICE):

***Tofacitinib*:** Rheumatoid arthritis (October 2017); Psoriatic arthritis (October 2018); Ulcerative colitis (November 2018); Juvenile idiopathic arthritis (October 2021); Ankylosing spondylitis (October 2023).

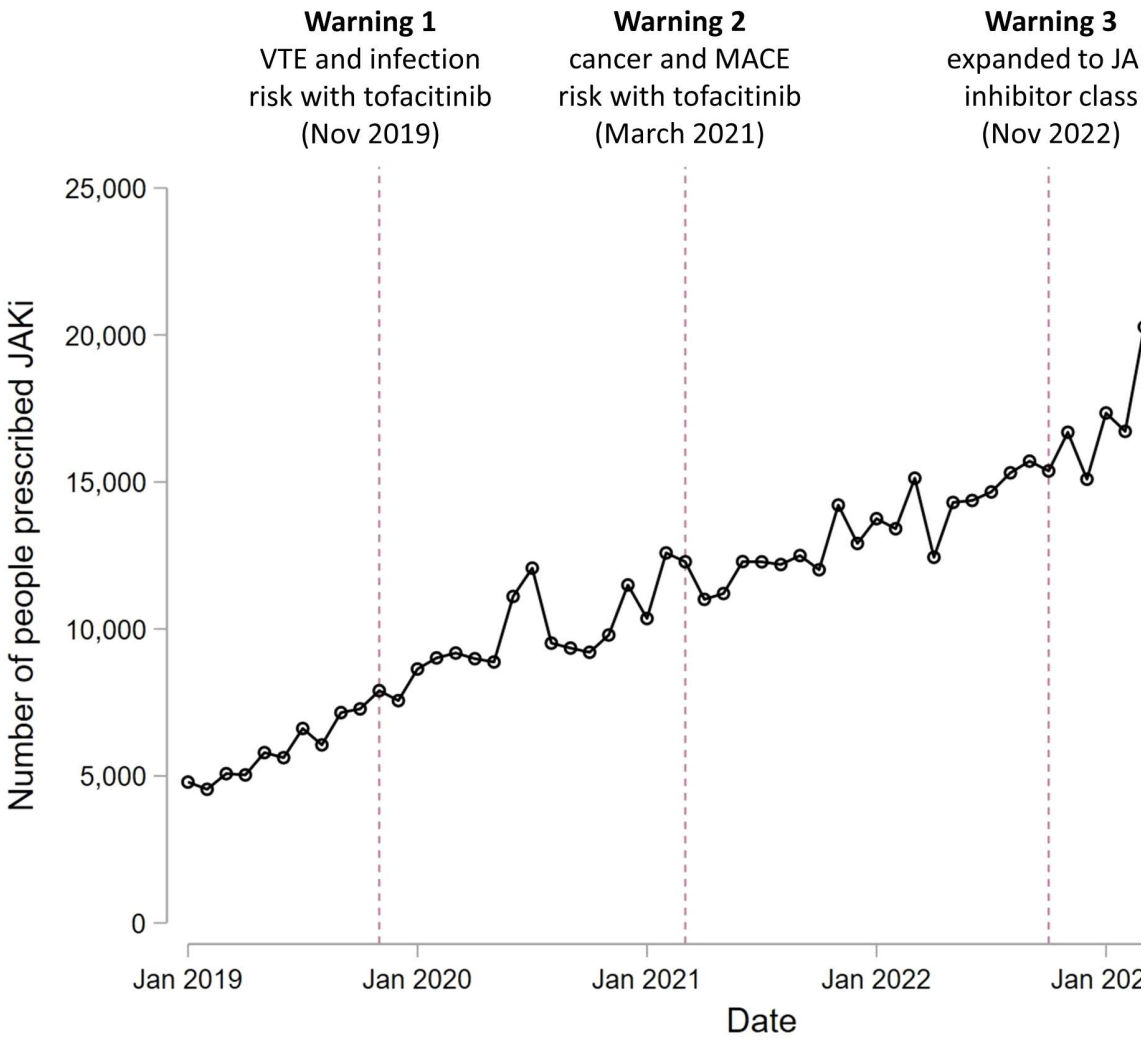
Baricitinib: Rheumatoid arthritis (August 2017); Atopic dermatitis (March 2021). Additionally, baricitinib was recommended to be made available for the treatment of hospitalised COVID-19 in May 2022; however, the request for marketing authorisation was withdrawn in February 2023.

Upadacitinib: Rheumatoid arthritis (December 2020); Psoriatic arthritis (February 2022); Atopic dermatitis (August 2022); Ankylosing spondylitis (September 2022); Ulcerative colitis (January 2023); Non-radiographic axial spondyloarthritis (February 2023); Crohn's disease (June 2023).

Filgotinib: Rheumatoid arthritis (February 2021); Ulcerative colitis (June 2022).

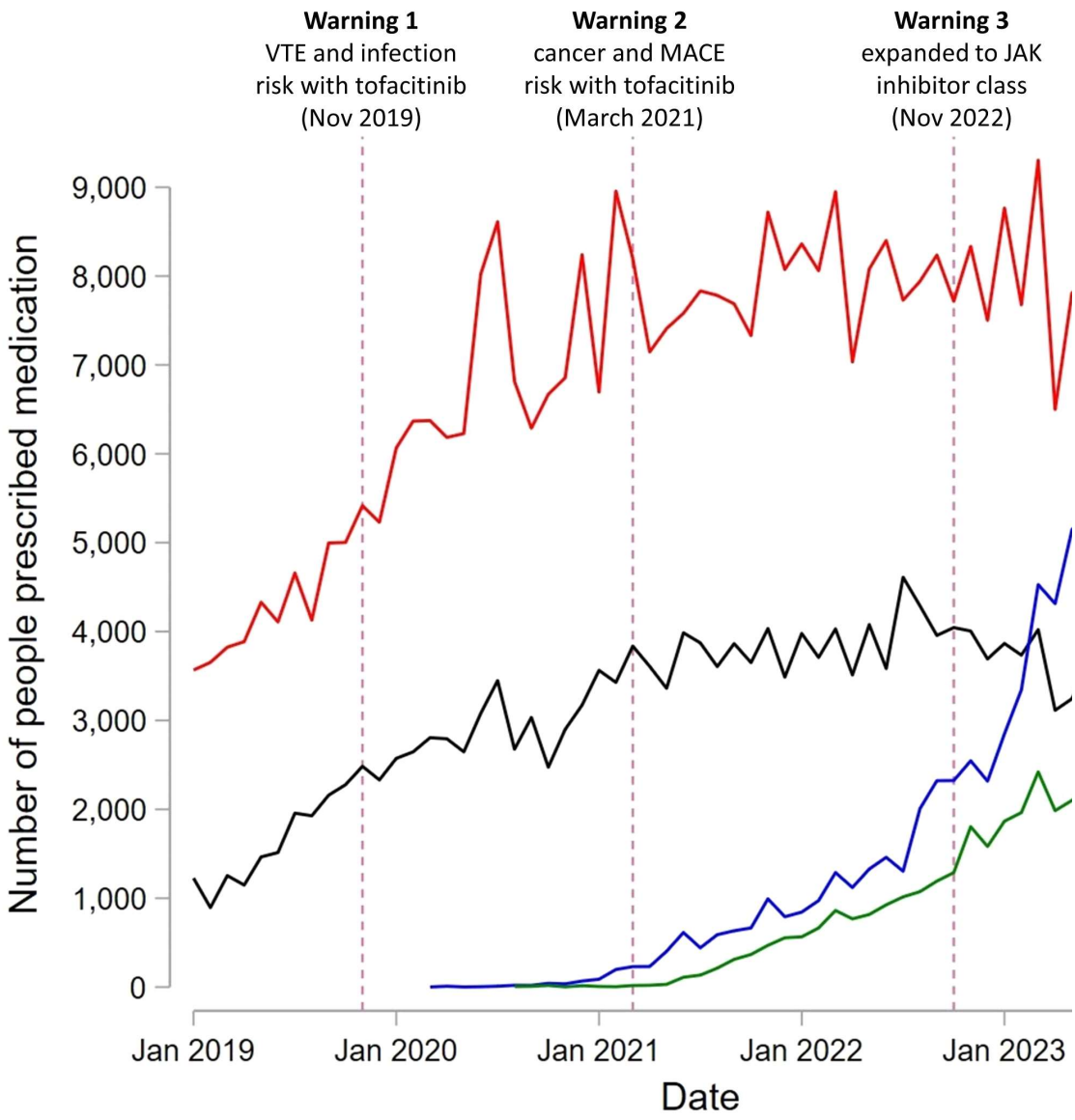
Abrocitinib: Atopic dermatitis (August 2022). Data on abrocitinib were not included in these analyses due to the small quantities dispensed.

Supplementary Figure S1. Trends in the estimated number of people prescribed JAK inhibitors in England between January 2019 and August 2023



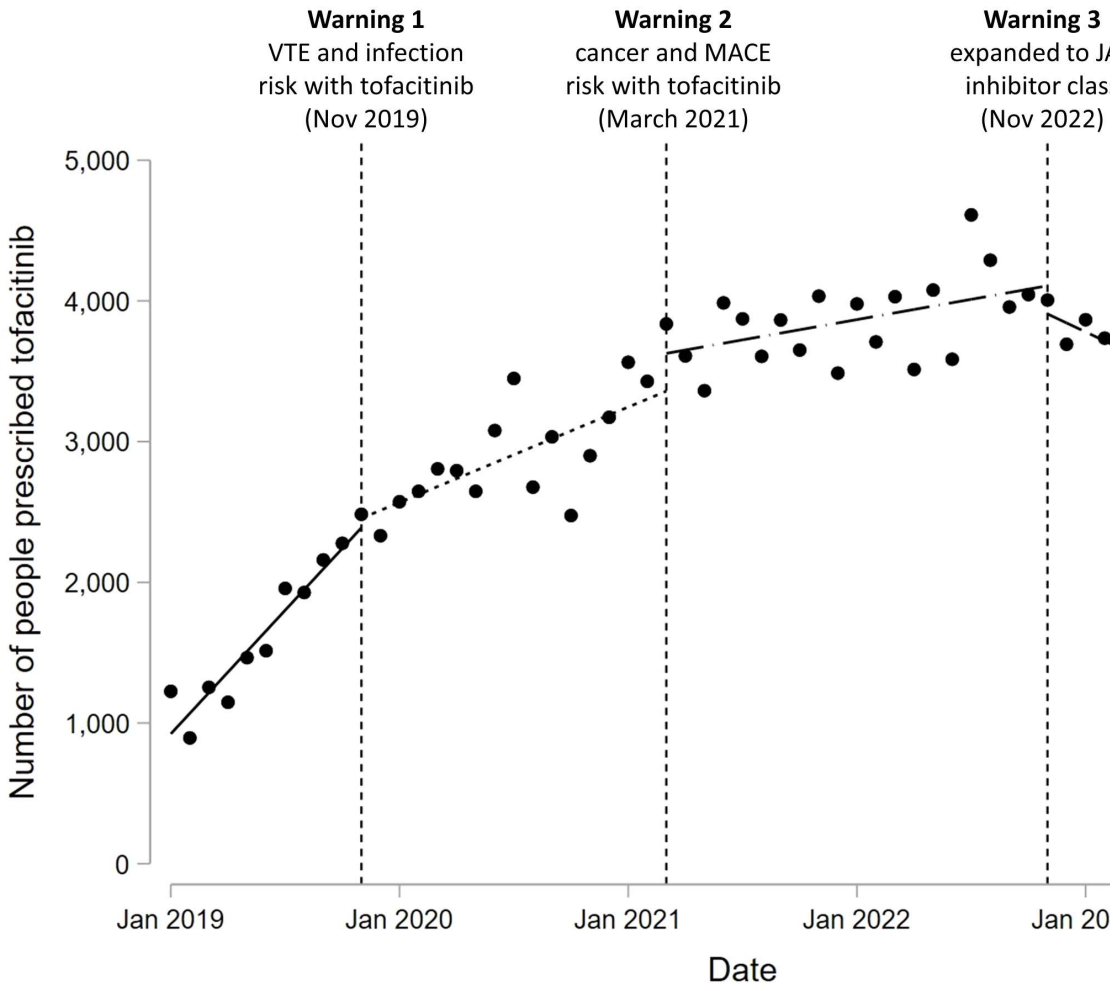
Combined monthly prescribing data are shown for tofacitinib, baricitinib, upadacitinib and filgotinib for all treatment indications in England between January 2019 and August 2023. Sequential safety warnings issued by the European Medicines Agency are denoted by vertical dashed lines. VTE: venous thromboembolism; MACE: major adverse cardiovascular events; JAKi: JAK inhibitor.

Supplementary Figure S2. Prescribing trends for individual JAK inhibitors in England between January 2019 and August 2023, without smoothing having been applied



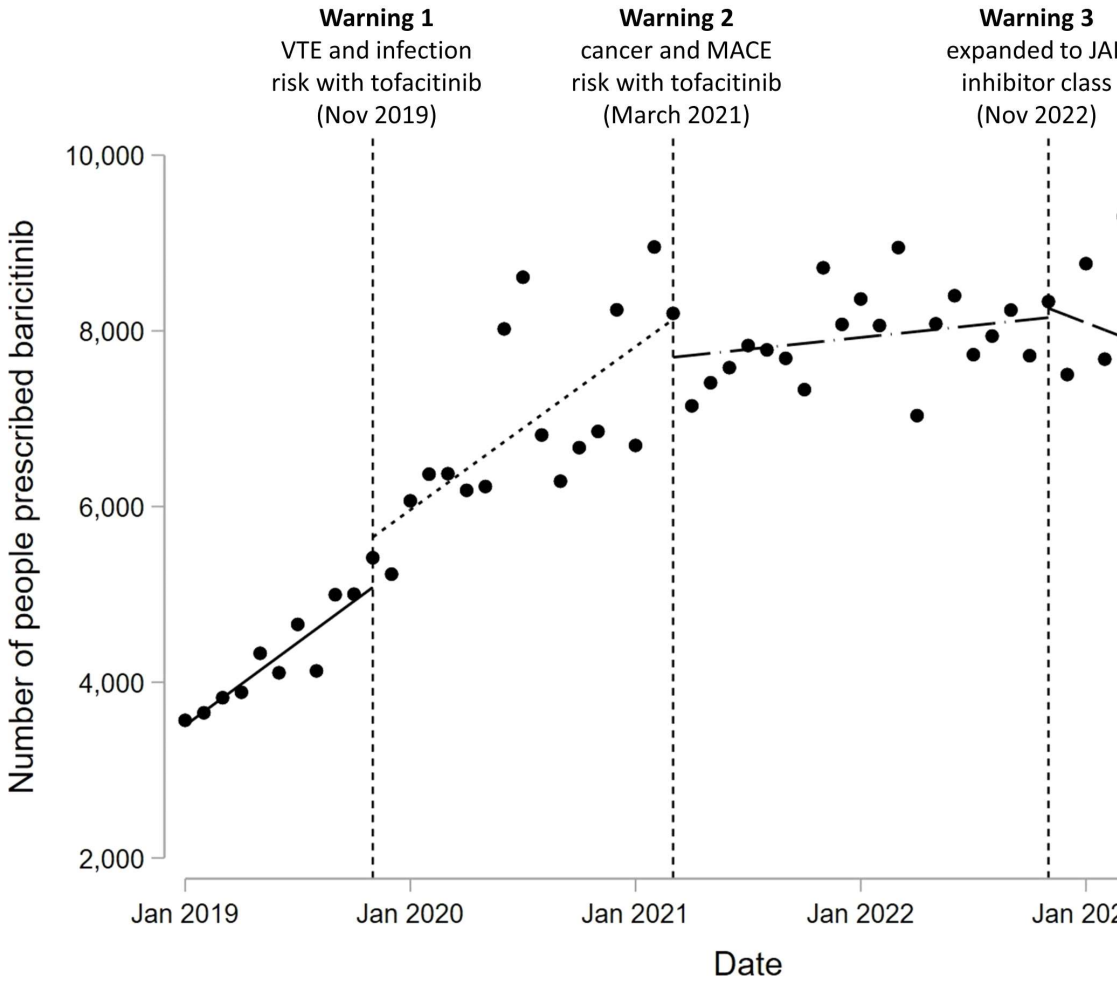
Trends in the estimated number of people prescribed tofacitinib, baricitinib, upadacitinib or filgotinib for combined treatment indications in England between January 2019 and August 2023. No smoothing has been applied to monthly dispensed volumes (see Supplementary Methods for further information). Sequential safety warnings issued by the European Medicines Agency are denoted by vertical dashed lines. VTE: venous thromboembolism; MACE: major adverse cardiovascular events.

Supplementary Figure S3. Interrupted time-series analysis of prescribing trends for tofacitinib in England between January 2019 and August 2023



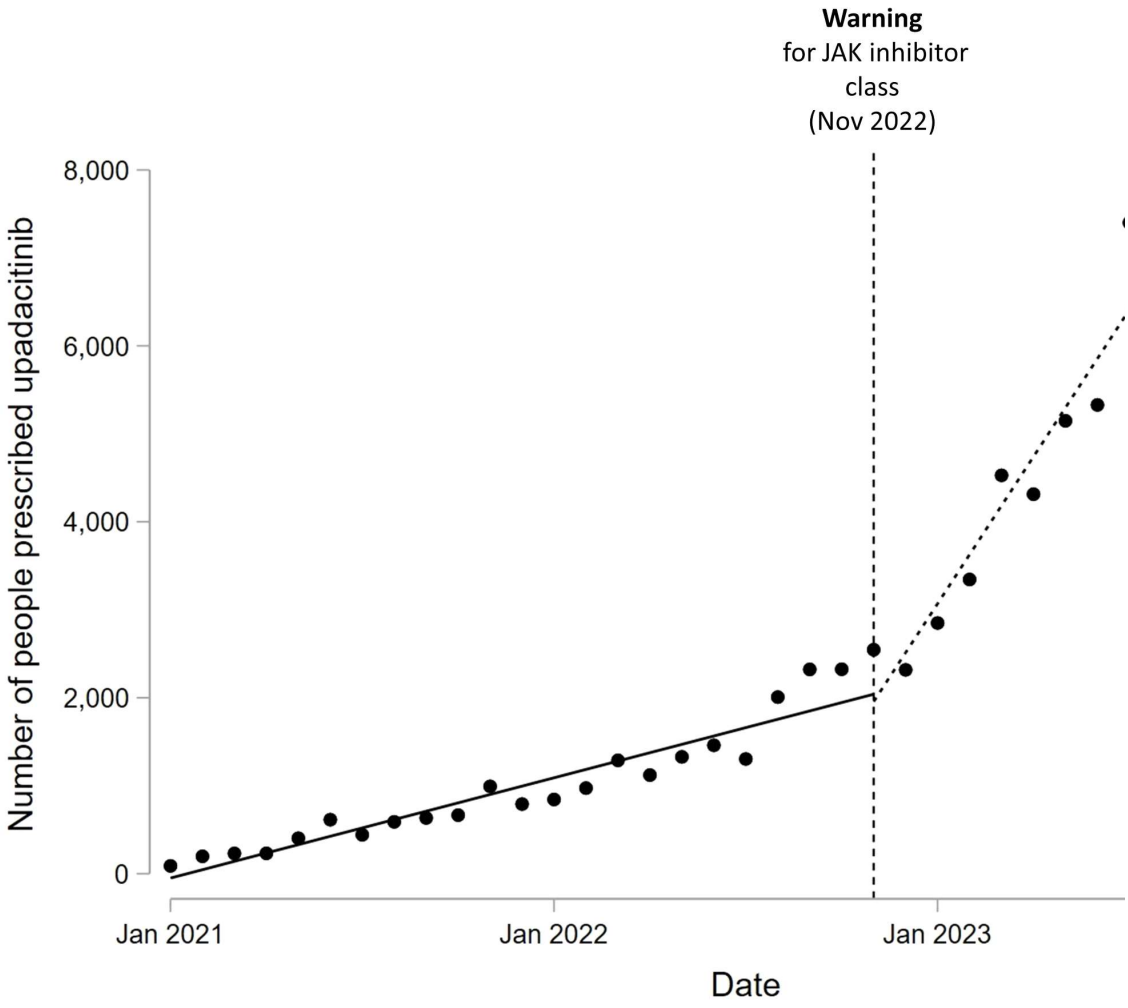
Single time points represent monthly estimates of the number of people prescribed tofacitinib in England for all treatment indications between January 2019 and August 2023. Trend lines from an interrupted time-series analysis are shown before and after sequential EMA safety warnings were issued (denoted by vertical dashed lines). VTE: venous thromboembolism; MACE: major adverse cardiovascular events.

Supplementary Figure S4. Interrupted time-series analysis of prescribing trends for baricitinib in England between January 2019 and August 2023



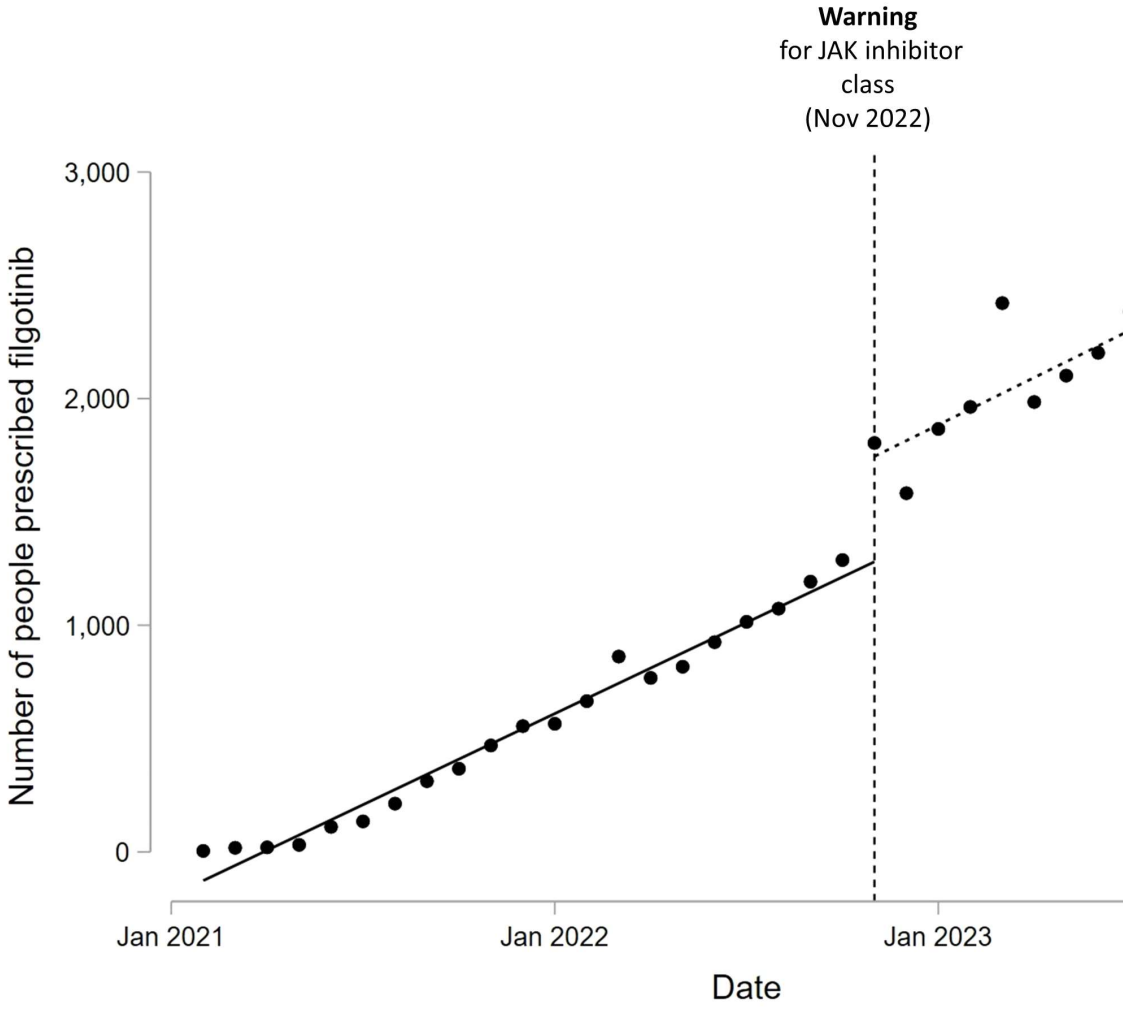
Single time points represent monthly estimates of the number of people prescribed baricitinib in England for all treatment indications between January 2019 and August 2023. Trend lines from an interrupted time-series analysis are shown before and after sequential EMA safety warnings were issued (denoted by vertical dashed lines). VTE: venous thromboembolism; MACE: major adverse cardiovascular events.

Supplementary Figure S5. Interrupted time-series analysis of prescribing trends for upadacitinib in England between January 2021 and August 2023



Single time points represent monthly estimates of the number of people prescribed upadacitinib in England for all treatment indications between January 2021 and August 2023. Upadacitinib received approval from the National Institute for Health and Care Excellence for the treatment of rheumatoid arthritis in December 2020. Trend lines from an interrupted time-series analysis are shown before and after the EMA pan-JAKi safety warning was issued in November 2022 (denoted by the vertical dashed line).

Supplementary Figure S6. Interrupted time-series analysis of prescribing trends for filgotinib in England between February 2021 and August 2023



Single time points represent monthly estimates of the number of people prescribed filgotinib in England for all treatment indications between February 2021 and August 2023. Filgotinib received approval from the National Institute for Health and Care Excellence for the treatment of rheumatoid arthritis in February 2021. Trend lines from an interrupted time-series analysis are shown before and after the EMA pan-JAKi safety warning was issued in November 2022 (denoted by the vertical dashed line).

References

1. NHS Business Services Authority. Secondary Care Medicines Data (SCMD). 2023. https://opendata.nhsbsa.net/dataset/secondary-care-medicines-data; accessed 24 October 2023.

2. European Medicines Agency. EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots. 2020. [Available from: https://www.ema.europa.eu/en/documents/referral/xeljanz-article-20-procedure-ema-confirms-xeljanz-be-used-caution-patients-high-risk-blood-clots_en.pdf; accessed 24 October 2023.

3. European Medicines Agency. Xeljanz (tofacitinib): increased risk of major adverse cardiovascular events and malignancies with use of tofacitinib relative to TNF-alpha inhibitors. 2021. https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-xeljanz-tofacitinib-increased-risk-major-adverse_en.pdf; accessed 24 October 2023.

4. European Medicines Agency. EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders. 2022. https://www.ema.europa.eu/en/news/ema-confirms-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic; accessed 24 October 2023.