









## ORIGINAL PAPER

## Haemostasis and Coagulation

# Real-world use of thrombopoietin receptor agonists for the management of immune thrombocytopenia in adult patients in the United Kingdom: Results from the TRAIT study

Nichola Cooper<sup>1</sup>  | Marie Scully<sup>2</sup>  | Charles Percy<sup>3,4</sup> | Phillip L. R. Nicolson<sup>3,5</sup> | Gillian Lowe<sup>3,4</sup> | Catherine N. Bagot<sup>6</sup>  | Jecko Thachil<sup>7</sup> | Henri Grech<sup>8</sup> | Tim Nokes<sup>9</sup> | Quentin A. Hill<sup>10</sup>  | Charlotte Bradbury<sup>11</sup> | Kate Talks<sup>12</sup> | Tina Dutt<sup>13</sup>  | Gillian Evans<sup>14</sup> | Sue Pavord<sup>15</sup>  | Sarah Wexler<sup>16</sup> | Asad Charania<sup>1</sup>  | Sarah J. Collington<sup>17</sup> | Andrew Ervin<sup>17</sup> | Nicholas Ramscar<sup>17</sup> | Drew Provan<sup>18</sup> 

**Correspondence**

Nichola Cooper, Imperial College Healthcare NHS Trust, London, UK.  
 Email: [n.cooper@imperial.ac.uk](mailto:n.cooper@imperial.ac.uk)

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**Summary**

Few studies have reported the real-world use of both romiplostim and eltrombopag in immune thrombocytopenia (ITP). TRAIT was a retrospective observational study aimed to evaluate the platelet responses and adverse effects associated with the use of these thrombopoietin receptor agonists (TPO-RAs) in adult patients with ITP in the United Kingdom. Of 267 patients (median age at diagnosis, 48 years) with ITP (primary ITP [ $n = 218$ ], secondary ITP [ $n = 49$ ]) included in the study, 112 (42%) received eltrombopag and 155 (58%) received romiplostim as the first prescribed TPO-RA. A platelet count  $\geq 30 \times 10^9/L$  was achieved in 89% of patients with the first TPO-RA treatments, while 68% achieved a platelet count  $\geq 100 \times 10^9/L$ . Treatment-free response (TFR; platelet count  $\geq 30 \times 10^9/L$ , 3 months after discontinuing treatment) was achieved by 18% of the total patients. Overall, 61 patients (23%) switched TPO-RAs, most of whom achieved platelet counts  $\geq 30 \times 10^9/L$  with the second TPO-RA (23/25 who switched from eltrombopag to romiplostim [92%]; 28/36 who switched from romiplostim to eltrombopag [78%]). TFR was associated with secondary ITP, early TPO-RA initiation after diagnosis, the presence of comorbidity and no prior splenectomy or treatment with steroids or mycophenolate mofetil. Both TPO-RAs had similar efficacy and safety profiles to those reported in clinical studies.

**KEY WORDS**

eltrombopag, immune thrombocytopenia (ITP), real-world, romiplostim, thrombopoietin receptor agonist (TPO-RA)

**INTRODUCTION**

Immune thrombocytopenia (ITP) is a rare autoimmune disorder characterised by thrombocytopenia and an increased risk of bleeding. ITP is classified as either primary, with no

known underlying cause, or secondary, which is associated with drugs, infections or other underlying diseases.<sup>1,2</sup>

Most adults (70%–90%) with newly diagnosed ITP respond to first-line treatment with corticosteroids and/or intravenous immunoglobulin (IVIg); however, only

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20%–40% achieve a sustained response off treatment. The remaining patients often require long-term treatment.<sup>1,3,4</sup> Thrombopoietin receptor agonists (TPO-RAs), eltrombopag and romiplostim, have demonstrated high sustained platelet response rates (70%–80%) in randomised clinical trials,<sup>5–7</sup> supporting TPO-RAs as a suitable second-line therapy option in primary ITP management.<sup>1–3</sup>

Eltrombopag and romiplostim have been available in the United Kingdom and European Union (EU) since 2009. These TPO-RAs are indicated for treatment of patients with primary ITP, irrespective of the time from diagnosis, who are refractory to other treatments, including corticosteroids and immunoglobulins, and are currently recommended by the National Institute for Health and Care Excellence (NICE) for treatment of ITP after 6 months.<sup>8–11</sup> Only a few studies have evaluated the platelet response outcomes achieved with TPO-RAs in real-world clinical practice, with very limited studies evaluating both eltrombopag and romiplostim in patients with ITP.<sup>12–15</sup> Clinical trials have previously used an absolute platelet count of  $>50 \times 10^9/L$  as the threshold for defining platelet response.<sup>5,7,16–20</sup> The current clinical guidelines recommend patient condition and disease phase-specific individualisation of treatment goals to maintain haemostatic platelet counts  $\geq 20 \times 10^9$  to  $\geq 30 \times 10^9/L$ .<sup>1,2,21</sup> Thus, there is a need to evaluate the efficacy and safety outcomes of TPO-RA treatment in real-world clinical practice using a broader definition of platelet response to capture clinical benefit, which may be seen with TPO-RAs at platelet response thresholds lower than those used in clinical trials. The clinical evidence reporting the use of TPO-RAs in secondary ITP is scanty.<sup>22,23</sup>

This retrospective observational study aimed to evaluate the platelet responses and adverse effects associated with the use of TPO-RAs to treat adult patients with primary and secondary ITP in the United Kingdom.

## METHODS

### Patients and data collection

This retrospective, observational, descriptive research study was conducted in 15 United Kingdom National Health Service secondary and tertiary healthcare trusts/health boards (Figure S1). Patients aged  $\geq 18$  years with a documented diagnosis of primary or secondary ITP and treated with either eltrombopag or romiplostim were eligible for inclusion. Patients receiving concomitant medications directed at improving platelet counts were not excluded. Patients were excluded if they had initiated TPO-RAs within the 4 months prior to data collection, or their hospital medical records were unavailable for retrospective review. Clinical and laboratory data were collected from paper and electronic medical records between January 2017 and April 2018. Other details of data collection are under [Supporting Information](#).

## Outcomes

The primary end-point was the proportion of patients achieving a platelet count of  $\geq 30 \times 10^9/L$  within 12 weeks of TPO-RA initiation. Secondary efficacy end-points included the proportion of patients achieving platelet count thresholds of  $\geq 50 \times 10^9/L$ ,  $\geq 100 \times 10^9/L$  (complete response) or a clinically meaningful response within 12 weeks of TPO-RA initiation; time to platelet response; duration of platelet response; and treatment-free response (TFR). A clinically meaningful response was defined as a platelet count increase from a pretreatment value  $\leq 30 \times 10^9/L$ , accompanied by documented clinical improvement in bleeding symptoms within 12 weeks of TPO-RA initiation. TFR was defined as a sustained platelet count  $\geq 30 \times 10^9/L$  for 3 months following cessation of TPO-RA treatment (i.e.  $\geq 80\%$  of recorded measurements were  $\geq 30 \times 10^9/L$  or a clinical reference to ‘stable’ as a reason for stopping TPO-RA). Complete TFR was defined as sustained platelet count  $\geq 100 \times 10^9/L$  for 3 months following cessation of TPO-RA treatment (i.e.  $\geq 80\%$  of recorded measurements were  $\geq 100 \times 10^9/L$  or a clinical reference to ‘stable’ as a reason for stopping TPO-RA). Members of the study steering committee validated the platelet response definitions used in the study.

Safety end-points included the frequency of adverse events (AEs), including bleeding episodes and infectious episodes, and hospital attendances for TPO-RA-related AEs. The AEs of special interest (AESIs), including thromboembolic events, bone marrow abnormalities, hepatic abnormalities and cataracts, as described in the TPO-RA phase 3 studies,<sup>5,19</sup> were reported in this study.

## Statistical analysis

The data were analysed using descriptive statistics with the statistical software R (version 3.4.1). All variables were reported separately and aggregately by initial TPO-RA treatment and type of ITP. Categorical variables were summarised as number (frequency), and quantitative variables were summarised as median (interquartile range [IQR]). In addition to the analysis of the overall sample, a subgroup analysis was reported based on the type of ITP (primary ITP/secondary ITP) and the first TPO-RA initiated (eltrombopag/romiplostim). Subgroup analyses of platelet response  $\geq 30 \times 10^9/L$  and TFR was also reported by disease duration  $\leq 6$  months and  $>6$  months at TPO-RA initiation.

Exploratory regression analyses evaluated the association of a range of demographic covariates, including first TPO-RA, baseline platelet counts, type of ITP, date of diagnosis, TPO-RA start date, time to TPO-RA initiation, gender, severe bleeding prior to treatment, comorbidity, prior history of treatments (corticosteroids, azathioprine, IVIg, mycophenolate mofetil [MMF], rituximab, splenectomy, other non-steroid medication), concurrent treatments (corticosteroids, azathioprine, IVIg, MMF,

rituximab, non-steroid medication) and splenectomy after TPO-RA initiation, with platelet response  $\geq 100 \times 10^9/L$  and TFR. Since these were exploratory univariate analyses with no predefined sample sizes or null hypotheses, no corrections were performed for multiple statistical testing. Where missing data could not be obtained from centres, no attempt was made to impute the missing values. No sensitivity analysis was performed.

## RESULTS

### Study cohort

Overall, 267 adult patients with ITP (primary ITP [ $n=218$ ], secondary ITP [ $n=49$ ]) were included in the study. The median (IQR) age at diagnosis was 48 years (28.0–63.8), and 52% were female. Of the 267 patients, 112 (42%) received

eltrombopag, and 155 (58%) received romiplostim as the first prescribed TPO-RA (Table 1; Figure S1). The median (IQR) study observation period, from date of diagnosis of ITP to date of data collection, was 7.5 years (3.7–15.5).

### Treatment exposure

The median (IQR) time from diagnosis of ITP to TPO-RA initiation was 3.4 years (0.7–11.5) for the overall patient population (Table 1). The duration of time with ITP prior to TPO-RA decreased over the 5 years of the study ( $p < 0.001$ ), with the average duration of disease decreasing by 6 months for each year (Figure 1). The details of treatment exposure in patients diagnosed with ITP after 2009 are summarised under Supporting Information.

Patients received a median (IQR) of 3.0 (2.0–4.0) prior treatments before TPO-RA initiation (Figure S2). Among

**TABLE 1** Patient demographics and baseline characteristics.

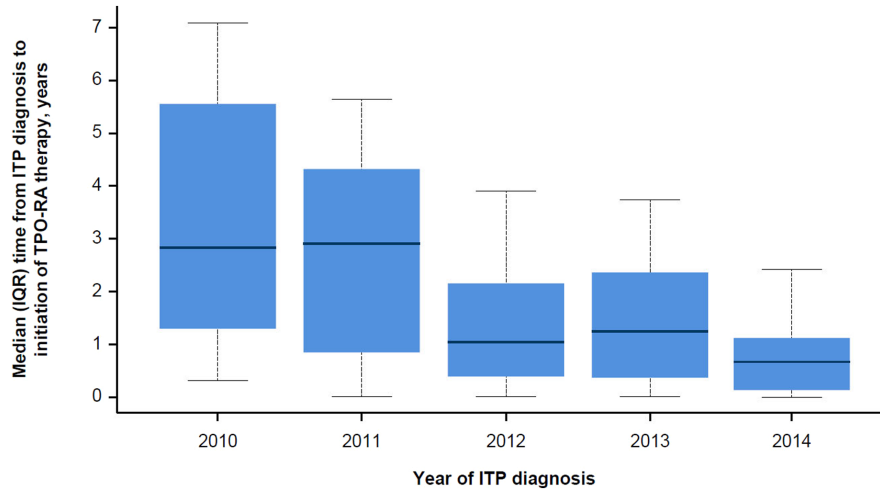
Characteristics	Initial TPO-RA		
	Eltrombopag <i>n</i> = 112	Romiplostim <i>n</i> = 155	Any TPO-RA <i>n</i> = 267
Age at TPO-RA initiation (median), years (IQR)	54.5 (38.0–65.2)	57.0 (43.0–72.0)	56.0 (40.5–69.5)
Time between diagnosis of ITP to TPO-RA initiation (median), years (IQR)	2.9 (0.7–9.6)	4.9 (0.7–13.1)	3.4 (0.7–11.5)
Female, <i>n</i> (%)	62 (55)	77 (50)	139 (52)
ITP type, <i>n</i> (%)			
Primary ITP	95 (85)	123 (79)	218 (82)
Secondary ITP	17 (15)	32 (21)	49 (18)
Causes of secondary ITP, <i>n</i> (%)	<i>n</i> = 16	<i>n</i> = 27	<i>n</i> = 46
Drug induced	3 (19)	5 (19)	8 (17)
Postrenal transplant	5 (31)	1 (4)	6 (13)
Postliver transplant	1 (6)	2 (7)	3 (7)
Lupus (systemic lupus erythematosus)	1 (6)	2 (7)	3 (7)
Human immunodeficiency virus	1 (6)	1 (4)	2 (4)
Bleeding disorders <sup>a</sup>	0	2 (7)	2 (4)
Other conditions <sup>b</sup>	5 (31)	14 (52)	19 (41)
Baseline platelet count $>30 \times 10^9/L$	42 (38)	37 (24)	79 (30)
Platelet count ( $\times 10^9/L$ ), median (IQR)	21.5 (11.2–40.0)	14.0 (5.0–29.2)	17.0 (7.2–34.0)
Presentation with severe bleeding, <i>n</i> (%)	22 (20)	13 (8)	35 (13)
Number of prior therapies, median (IQR)	2.0 (1.0–3.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Splenectomy prior to TPO-RA initiation, <i>n</i> (%)	13 (12)	33 (21)	46 (17)
With reported comorbidities, <sup>c</sup> <i>n</i> (%)	82 (73)	104 (67)	186 (70)

Abbreviations: CLL, chronic lymphocytic leukaemia; HIV, human immunodeficiency virus; Ig, immunoglobulin; IQR, interquartile range; ITP, immune thrombocytopenia; MDS, myelodysplastic syndromes; MGUS, monoclonal gammopathy of undetermined significance; TPO-RA, thrombopoietin receptor agonists.

<sup>a</sup>Bleeding disorders may mean inherited thrombocytopenia and were reported as per clinical judgement and as recorded in their clinical notes.

<sup>b</sup>Other secondary conditions included anti-phospholipid syndrome, B-cell CLL, donor lymphocyte infusion, glioblastoma treated with temozolomide and radiotherapy, IgA deficiency, IgM paraprotein/MGUS, liver disease, MDS, pancytopenia, previous alemtuzumab, post-bone marrow transplant, postchemotherapy for CLL, severe gastric haemorrhage secondary to ulceration, Sjogren's syndrome and other autoimmune conditions.

<sup>c</sup>Reported comorbidities included bleeding disorder, coeliac disease, type 1 diabetes, drug-induced ITP, hepatitis C, HIV, systemic lupus erythematosus, mixed connective tissue disorder, post-bone marrow transplant, postrenal transplant, rheumatoid arthritis, Sjogren's syndrome, thyroid disorder, vitiligo, other autoimmune disease and other comorbid conditions as specified by patients.



**FIGURE 1** Median (IQR) time from diagnosis of ITP to TPO-RA initiation by year (2010–2014). The statistical model included 96 patients diagnosed between 2010 and the end of 2014. Patients diagnosed prior to 2010 (i.e. prior to the availability of TPO-RAs) and patients diagnosed between 2014 and 2017 (i.e. closer to the end of study recruitment for some sites) were excluded to remove the upper censoring effect. IQR, interquartile range; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

**TABLE 2** Response to TPO-RA observed in 12 weeks after TPO-RA initiation.

Response to TPO-RA	Eltrombopag	Romiplostim	Any TPO-RA
Primary ITP	<i>n</i> = 95	<i>n</i> = 123	<i>n</i> = 218
Any platelet elevation $\geq 30$ ( $\times 10^9/L$ ), <i>n</i> (%)	84 (88)	110 (89)	194 (89)
$\geq 100$	66 (69)	80 (65)	146 (67)
$\geq 50$ to $< 100$	12 (13)	25 (20)	37 (17)
$\geq 30$ to $< 50$	6 (6)	5 (4)	11 (5)
No response, <i>n</i> (%)	5 (5)	8 (7)	13 (6)
Missing, <i>n</i> (%)	6	5	11
Any platelet elevation $\geq 30$ ( $\times 10^9/L$ ) by ITP duration at TPO-RA initiation, <i>n</i> (%)			
$\leq 6$ months	<i>n</i> = 18	<i>n</i> = 17	<i>n</i> = 35
$\geq 100$	17 (94)	17 (100)	34 (97)
$> 6$ months	<i>n</i> = 71	<i>n</i> = 101	<i>n</i> = 172
$\geq 100$	67 (94)	93 (92)	160 (93)
Secondary ITP	<i>n</i> = 17	<i>n</i> = 32	<i>n</i> = 49
Any platelet elevation $\geq 30$ ( $\times 10^9/L$ ), <i>n</i> (%)	15 (88)	28 (88)	43 (88)
$\geq 100$	13 (77)	23 (72)	36 (73)
$\geq 50$ to $< 100$	2 (12)	3 (9)	5 (10)
$\geq 30$ to $< 50$	0	2 (6)	2 (4)
No response, <i>n</i> (%)	2 (12)	3 (9)	5 (10)
Missing, <i>n</i> (%)	0	1	1
Any platelet elevation $\geq 30$ ( $\times 10^9/L$ ) by ITP duration at TPO-RA initiation, <i>n</i> (%)			
$\leq 6$ months	<i>n</i> = 7	<i>n</i> = 12	<i>n</i> = 19
$\geq 100$	6 (86)	12 (100)	18 (95)
$> 6$ months	<i>n</i> = 10	<i>n</i> = 18	<i>n</i> = 28
$\geq 100$	9 (90)	15 (83)	24 (96)
Missing	0	1	1

Abbreviations: ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonists.

222 patients who received  $\geq 1$  treatment immediately before initiation of the TPO-RA, the treatments prescribed included IVIg (69 [31%]), rituximab (42 [19%]), MMF (37 [17%]), corticosteroids (36 [16%]) and azathioprine (19 [9%]) (Table S1).

At the time of first clinical response, the median dose of eltrombopag was 50.0 mg/day and that of romiplostim was 2.9  $\mu\text{g}/\text{kg}/\text{week}$  (1.3–3.3). Overall, 80/112 patients (71%) continued to receive eltrombopag, and 89/155 (57%) continued to receive romiplostim at the end of the data collection period. For patients with primary ITP, the median (IQR) TPO-RA treatment duration at the time of data collection (note that treatment was ongoing for many patients at this stage) was 1.8 years (0.6–2.8) for patients initiating eltrombopag and 2.8 years (1.0–5.4) for romiplostim. For patients with secondary ITP, the median treatment duration at the time of data collection was 0.7 years (0.4–1.5) for eltrombopag and 1.6 years (0.6–2.7) for romiplostim. Among patients who discontinued within the observation period, 12/112 (11%) received eltrombopag, and 36/155 (23%) received romiplostim for  $>1$  year during the observation period.

Seventy-eight patients (36%) with primary ITP and 21 patients (43%) with secondary ITP required rescue therapies while receiving TPO-RA treatments. The mean (SD) number of rescue treatments required per patient following TPO-RA initiation was 0.7 (1.3) for eltrombopag and 1.2 (2.2) for romiplostim. Of the total rescue therapies received ( $n = 333$ ), the most frequent rescue treatments included IVIg (132 [40%]), corticosteroids (112 [34%]) and platelet infusion (31 [9%]). At the time of initiation of the first TPO-RA, almost half of the patients (122 [46%]) were receiving  $\geq 1$  ongoing concomitant medications, including corticosteroids (70 [57%]), MMF (49 [40%]), IVIg (29 [24%]), rituximab (13 [11%]) and azathioprine (11 [9%]).

## Platelet response

Most of the patients (237/267, 89%) achieved the primary end-point that is a platelet count of  $\geq 30 \times 10^9/\text{L}$  within 12 weeks of TPO-RA initiation and 182/267 patients (68%) achieved a platelet count of  $\geq 100 \times 10^9/\text{L}$  (complete response) within 12 weeks of TPO-RA initiation. Of the 54 patients with a duration of ITP  $\leq 6$  months, 52 (96%) achieved platelet counts  $\geq 30 \times 10^9/\text{L}$ , while 184/200 patients (92%) with a duration of ITP  $>6$  months achieved platelet counts  $\geq 30 \times 10^9/\text{L}$  (Table 2).

In patients with primary ITP, the median (IQR) time to achieve platelet counts of  $\geq 30 \times 10^9/\text{L}$  with eltrombopag was 1.6 weeks (1.0–2.7) and with romiplostim was 1.0 week (1.0–2.0), while in patients with secondary ITP, it was 0.6 week (0.1–1.4) and 1.0 week (1.0–2.9) respectively.

Among patients with primary and secondary ITP, 5/95 patients (5%) and 2/17 patients (12%) receiving eltrombopag, and 7/123 patients (6%) and 1/32 patients (3%) receiving romiplostim, respectively, failed to achieve the study-defined

platelet response within 12 weeks of initiation of TPO-RA treatment.

## Treatment-free response

More than one-third of patients (overall: 95/267 [36%]; primary ITP: 69/218 [32%]; secondary ITP: 26/49 [53%]) discontinued TPO-RA treatment, with the most frequent reasons ( $>15\%$  in overall population) being physician request, including improvement/stabilisation of platelet counts, remission, pregnancy, splenectomy, excessive response (primary ITP: 20/69 [29%]; secondary ITP: 16/26 [62%]) and loss of platelet response or treatment failure (primary ITP: 15/69 [22%]; secondary ITP: 2/26 [8%]).

Overall, TFR and complete TFR were achieved in 48/267 (18%) and 15/267 (6%) patients respectively (Figure 2A). Nineteen of 56 patients (34%) with a duration of ITP  $\leq 6$  months achieved TFR, while 28 of 210 patients (13%) with a duration of ITP  $>6$  months achieved TFR,  $p < 0.001$  (Figure 2B). Details for time to achieve TFR and the duration of TFR are presented in Table 3.

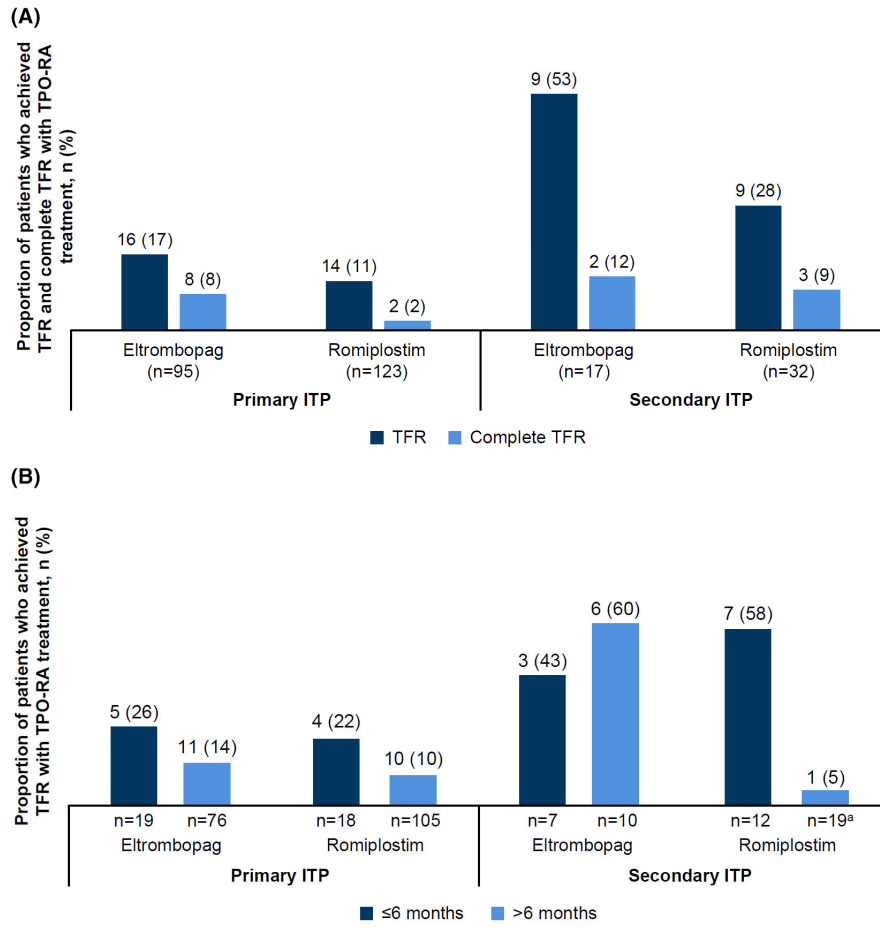
## Platelet responses in patients switching TPO-RAs

Overall, 61 patients (23%) switched TPO-RAs (eltrombopag to romiplostim [ $n = 25$ ], romiplostim to eltrombopag [ $n = 36$ ]). The most common reasons for switching were loss of response/treatment failure (28 [46%]) and AEs (13 [21%]). Most patients who switched from initial eltrombopag to romiplostim (23/25 [92%]) and from initial romiplostim to eltrombopag (28/36 [78%]) achieved platelet counts  $\geq 30 \times 10^9/\text{L}$  after TPO-RA switch (Figure 3; Table S2).

## Predictors of responses to TPO-RA treatment

In univariate logistic regression analysis, the likelihood of achieving a platelet count of  $\geq 100 \times 10^9/\text{L}$  (complete response) was significantly higher for patients who initiated TPO-RA early after diagnosis (odds ratio [OR], 0.89), those who had a prior splenectomy (OR, 2.88) or received prior treatment with rituximab (OR, 2.07) and without concomitant steroid use (OR, 0.40),  $p < 0.05$  for each (Figure 4A). The likelihood of achieving TFR was significantly higher in patients who initiated TPO-RA early after diagnosis (OR, 0.94), those with secondary ITP (OR, 3.64) or the presence of  $\geq 1$  comorbidity (OR, 2.50), no prior history of splenectomy (OR, 0.28) and no prior treatment with steroids (OR, 0.48) or MMF (OR, 0.16),  $p < 0.05$  for each (Figure 4B). The likelihood of achieving complete TFR was significantly higher in patients who started TPO-RA treatment recently (OR, 1.42),  $p < 0.05$  (Figure 4C).

Exploratory regression analysis showed that patients receiving TPO-RAs within 6 months of diagnosis of ITP



**FIGURE 2** (A) TFR and complete TFR with TPO-RA treatment. (B) TFR with TPO-RA treatment by duration of ITP ( $\leq 6$  months vs.  $> 6$  months). <sup>a</sup>Duration of ITP is missing in one patient. TFR was defined as a sustained platelet count  $\geq 30 \times 10^9/L$  for 3 months following cessation of TPO-RA treatment (i.e.  $\geq 80\%$  of recorded measurements were  $\geq 30 \times 10^9/L$  or a clinical reference to 'stable' as a reason for stopping TPO-RA). Complete TFR was defined as sustained platelet count  $\geq 100 \times 10^9/L$  for 3 months following cessation of TPO-RA treatment (i.e.  $\geq 80\%$  of recorded measurements were  $\geq 100 \times 10^9/L$  or a clinical reference to 'stable' as a reason for stopping TPO-RA). ITP, immune thrombocytopenia; TFR, treatment-free response; TPO-RA, thrombopoietin receptor agonist.

**TABLE 3** Achievement of TFR and complete TFR after TPO-RA initiation.

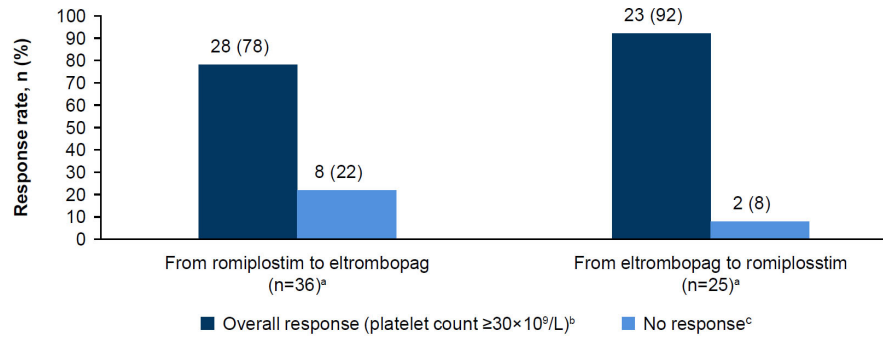
Weeks, median (IQR)	Primary ITP		Secondary ITP	
	Eltrombopag	Romiplostim	Eltrombopag	Romiplostim
Patients who achieved TFR	n = 16	n = 14	n = 9	n = 9
Duration of treatment with TPO-RA	6.6 (3.4–8.4)	8.9 (7.4–10.3)	6.6 (4.8–8.6)	4.7 (2.3–7.6)
Duration of TFR	77.8 (44.5–121.0)	133.9 (80.1–187.6)	105.4 (52.9–149.1)	88.8 (57.3–112.3)
Patients who achieved complete TFR	n = 8	n = 2	n = 2	n = 3
Duration of treatment with TPO-RA	7.3 (5.5–9.2)	8.9 (7.4–10.3)	4.8 (4.7–4.8)	6.7 (4.7–8.6)
Duration of complete TFR	77.8 (55.0–137.6)	133.9 (80.1–187.6)	111.7 (88.3–135.1)	68.3 (46.2–88.8)

Note: TFR was defined as a sustained platelet count  $\geq 30 \times 10^9/L$  for 3 months following cessation of TPO-RA treatment (i.e.  $\geq 80\%$  of recorded measurements were  $\geq 30 \times 10^9/L$  or a clinical reference to 'stable' as a reason for stopping TPO-RA). Complete TFR was defined as sustained platelet count  $\geq 100 \times 10^9/L$  for 3 months following cessation of TPO-RA treatment (i.e.  $\geq 80\%$  of recorded measurements were  $\geq 100 \times 10^9/L$  or a clinical reference to 'stable' as a reason for stopping TPO-RA).

Abbreviations: ITP, immune thrombocytopenia; TFR, treatment-free response; TPO-RA, thrombopoietin receptor agonist.

( $n = 56$ ) had higher rates of achieving platelet counts above the  $100 \times 10^9/L$  threshold when compared to those with  $> 6$  months since diagnosis of ITP (80.4% vs. 64.8%;  $p = 0.05$ ).

TFR was highly associated with receiving TPO-RAs within 6 months of diagnosis (33.9% vs. 13.3%;  $p < 0.001$ ). Significantly fewer splenectomies were observed in patients



**FIGURE 3** Treatment responses of patients after switching TPO-RAs. <sup>a</sup>Three patients (two switched from initial romiplostim to eltrombopag and one switched from initial eltrombopag to romiplostim) had missing platelet count records during the first 12 weeks of their first TPO-RA treatment, but had more records after their switch to second TPO-RA. <sup>b</sup>Overall response was defined as a platelet count increased to  $\geq 30 \times 10^9/L$  within 12 weeks of TPO-RA initiation. See [Table S2](#) for reasons for switch between the two TPO-RAs. <sup>c</sup>Patients who did not achieve or maintain a platelet count  $\geq 30 \times 10^9/L$  within 12 weeks of TPO-RA initiation, irrespective of the reasons for switch, were included under no response category; treatment failure was the reason for switch from romiplostim to eltrombopag in four patients and for switch from eltrombopag to romiplostim in two patients. TPO-RA, thrombopoietin receptor agonist.

diagnosed with ITP after 2009 versus patients diagnosed before 2009 ( $p < 0.001$ ).

## Safety

### Adverse events

Overall, 208 patients (78%) experienced AEs while receiving TPO-RA treatment as indicated by clinicians (eltrombopag: 120/148 [81%]; romiplostim: 135/180 [75%]; inclusive of treatment switching). Of these, AEs reported in 111/267 patients (42%) were considered related to treatment (eltrombopag: 69/148 [47%]; romiplostim: 69/180 [38%]; inclusive of treatment switching) ([Table 4](#)). Bleeding episodes were reported in 45 patients (30%), while receiving eltrombopag and in 75 patients (42%), while receiving romiplostim (as indicated by clinicians reviewing the notes). Infectious episodes were reported in 20 patients (14%), while receiving eltrombopag and in 43 patients (24%), while receiving romiplostim.

Among secondary ITP patients, 41/49 patients (84%) experienced AEs, while receiving TPO-RA treatment as indicated by clinicians (eltrombopag: 18/23 [78%]; romiplostim: 30/35 [86%]; inclusive of treatment switching). Of these, AEs reported in 19/49 patients (39%) were considered related to treatment by reviewing clinicians (eltrombopag: 9/23 [39%]; romiplostim: 13/35 [37%]; inclusive of treatment switching) ([Table S3](#)).

### AEs of special interest

Adverse events of special interest reported in patients receiving eltrombopag included hepatic function abnormality ( $n = 6$ ), venous thromboembolism ( $n = 5$ ) and cataracts ( $n = 2$ ). AESIs reported in patients receiving romiplostim included bone marrow disorder ( $n = 2$ ) and venous thromboembolism ( $n = 8$ ; 12 episodes).

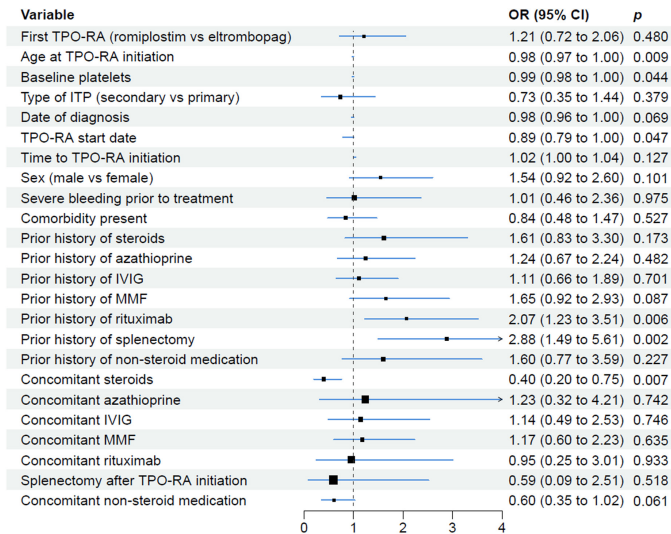
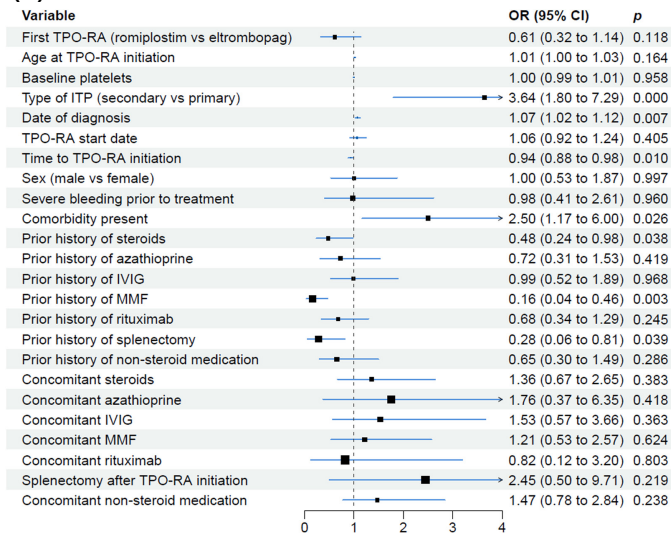
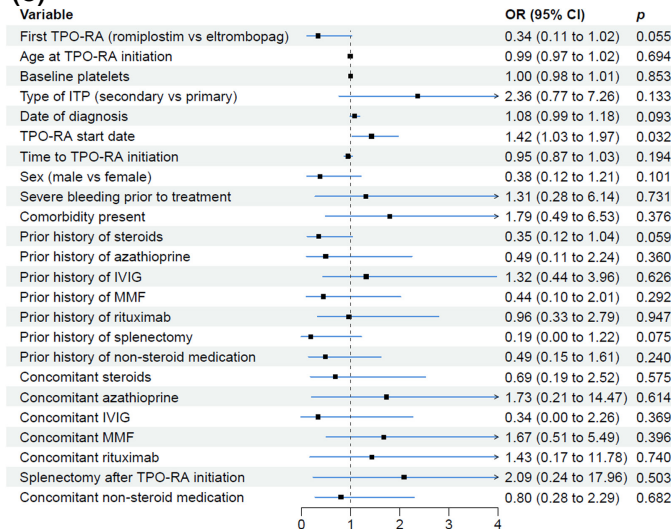
## Deaths

Overall, 20 patients (7%) were recorded as deceased. Of these, nine patients died while receiving TPO-RA (romiplostim [primary ITP:  $n = 5$ ; secondary ITP:  $n = 3$ ]; eltrombopag [primary ITP:  $n = 1$ ]), 10 deaths were reported off treatment (primary ITP:  $n = 8$ ; secondary ITP:  $n = 2$ ) and treatment status was uncertain in one death of a secondary ITP patient. The causes of on-treatment deaths with romiplostim included ischaemic cardiomyopathy, loss of response, renal failure, small bowel obstruction and infectious episode, bone marrow failure and bleeding episode, reported in one patient each and unknown cause ( $n = 3$ ). The cause for on-treatment death with eltrombopag was unknown.

Additional data on recovery status, hospitalisation/accident and emergency attendance are captured under [Supporting Information](#).

## DISCUSSION

This observational study provides real-world evidence on the efficacy and safety of eltrombopag and romiplostim in adult patients with primary and secondary ITP in UK clinical settings. While the influence of concomitant therapies for underlying diseases in this study cannot be ruled out, the observations on treatment responses of patients with secondary ITP are of interest considering the paucity of clinical trial data on secondary ITP. Similar to clinical trials<sup>5,19</sup> and other real-world studies,<sup>24,25</sup> most patients (89%) in this study achieved a platelet count of  $\geq 30 \times 10^9/L$  within 12 weeks of TPO-RA initiation. Most patients who did not respond to the initial TPO-RA treatment (80%) demonstrated a better response upon switching to the other TPO-RA. These response rates are also in line with the published real-world reports.<sup>13,26–29</sup> Despite similar response rates, individual centres across United Kingdom showed no consistency in preference to either eltrombopag or romiplostim ([Figure S1](#)).

**(A)****(B)****(C)**

**FIGURE 4** Forest plots from univariate logistic regressions of (A) platelet count of  $\geq 100 \times 10^9/L$  (complete response), (B) TFR and (C) complete TFR. ORs increase as the probability of the event increases or vice versa. If an OR = 1 ( $p > 0.05$ ), there is no association between the outcome (e.g. platelet response) and the covariate (e.g. first TPO-RA romiplostim versus eltrombopag). If OR < 1 (and  $p < 0.05$ ), there is an association, and the probability decreases while the covariate increases (or change category). If OR > 1 (and  $p < 0.05$ ), there is an association, and the probability increases along with the covariate increase (or change category). ORs are provided with their confidence intervals (if this interval does not contain 1 then it is significant: equivalent to  $p < 0.05$ ). CI, confidence interval; OR, odds ratio; TFR, treatment-free response; TPO-RA, thrombopoietin receptor agonists.

**TABLE 4** Most common ( $\geq 2\%$  of patients in any TPO-RA treatment group) adverse events related (or possibly related) to TPO-RAs in all patients.

Adverse events, n (%)	Eltrombopag only (n = 152)	Romiplostim only (n = 185)	Any TPO-RA (n = 342) <sup>a</sup>
Loss of response	29 (19)	23 (12)	53 (16)
Headache	0 (0)	26 (14)	27 (8)
Insomnia	0 (0)	14 (8)	15 (4)
Nausea	4 (3)	7 (4)	11 (3)
Diarrhoea	9 (6)	1 (1)	10 (3)
Fatigue	0 (0)	9 (5)	9 (3)
Musculoskeletal pain	9 (6)	0 (0)	9 (3)
Alopecia	3 (2)	3 (2)	7 (2)
Rash	3 (2)	4 (2)	7 (2)
Migraine	3 (2)	3 (2)	6 (2)
Others	47 (31)	27 (15)	75 (22)

Abbreviation: AE, adverse event; TPO-RA, thrombopoietin receptor agonist.

<sup>a</sup>As a result of patients switching between the TPO-RAs or taking both TPO-RAs concurrently, the number of patients experiencing an AE while on 'any TPO-RA' is not equal to the sum of the number of patients experiencing AEs on romiplostim and eltrombopag separately.

The analysis identified initiation of TPO-RA early after diagnosis, prior splenectomy, prior treatment with rituximab and absence of concomitant corticosteroid use as significant predictors of an increased platelet count of  $\geq 100 \times 10^9/L$ . In this study, the association with splenectomy may be partly confounded by the more heavily pretreated refractory patients diagnosed prior to 2009. Recent ITP treatment algorithms reserve splenectomy for treatment-resistant patients with ITP and deferred for at least a year to allow time for remission.<sup>2,3</sup> In other real-world studies, early initiation of TPO-RAs reduced the use of corticosteroids and improved bleeding outcomes in patients with ITP.<sup>30</sup> Similarly, this study highlights that the use of TPO-RAs within 6 months of ITP diagnosis results in good response rates and TFR.

Growing evidence suggests that optimised tapering and discontinuation of TPO-RAs can achieve TFR in 10%–30% of patients.<sup>2,4</sup> The TRAIT study findings demonstrated TFR in 10%–20% of patients with primary ITP, and 30%–50% of those with secondary ITP who received TPO-RAs. It is probable that even more patients could have reduced medications, given the number who continued treatment with complete platelet responses. Secondary ITP, recent diagnosis, early initiation of TPO-RA after diagnosis, presence of

$\geq 1$  comorbidity, no prior history of splenectomy and the absence of prior treatment with corticosteroids or MMF were identified as significant predictors of TFR. However, complete TFR is only associated with the recent TPO-RA start date, implying better response rates if TPO-RAs are used earlier in the disease course.

In this observational study, the median doses of eltrombopag (50 mg/day) and romiplostim ( $\sim 3 \mu\text{g}/\text{kg}/\text{week}$ ) that resulted in a platelet response were within the standard recommended dose ranges<sup>8,9</sup>; and were similar to those identified in the prospective clinical trials of TPO-RAs for patients with ITP.<sup>5,19</sup> The patient population predominantly had chronic ITP within  $\sim 3$  years from diagnosis of ITP to TPO-RA initiation. A decrease in the average duration of ITP prior to TPO-RA treatment by 6 months for each year of diagnosis reflects the increasing ease of access to TPO-RAs during this period. Before TPO-RA initiation, patients received an average of three types of ITP treatments, reflecting the relapsing or refractory nature of this cohort of chronic ITP patients.

Both TPO-RAs appeared to be tolerable with an expected safety profile.<sup>5,7</sup> Loss of response was the most reported AE related to both TPO-RAs, while other common AEs, including headache, insomnia and fatigue, were considered related to romiplostim alone, and diarrhoea and musculoskeletal pain were considered related to eltrombopag alone.

The limitations of this retrospective observational study are as expected for real-world studies that are susceptible to multiple sources of bias, including selection bias, missing data and confounding factors. Despite these limitations, these outcomes are interpretable and generalisable to the ITP population in the United Kingdom and could be of value while framing patient-tailored treatment decisions in clinical practice. The platelet responses to TPO-RAs in the management of patients with ITP in routine clinical practice in the United Kingdom remain broadly consistent with clinical trial data. It is worth considering that the patient population accrued in clinical trials are subjected to screening with defined criteria, and hence the data may not always be extrapolated to real-world outcomes.

Further data from prospective studies with larger samples of patients, specifically for secondary ITP with TFR data outcomes and for patients who have initiated TPO-RAs early in the disease course, would be needed to confirm the true response rates and the associated predictors. Further research may also be needed to ascertain how treatment goals and factors, including bleeding episodes and health-related quality of life, are being used in the management of ITP in real-world settings.

## AUTHOR CONTRIBUTIONS

All authors contributed to data interpretation, reviewed and provided their comments on this manuscript, and approved the final version of the manuscript.

## AFFILIATIONS

- <sup>1</sup>Imperial College Healthcare NHS Trust, London, UK
- <sup>2</sup>Haematology Programme, NIHR UCLH/UCL BRC, London, UK
- <sup>3</sup>University Hospital Birmingham NHS Foundation Trust, Birmingham, UK
- <sup>4</sup>Queen Elizabeth Hospital, Birmingham, UK
- <sup>5</sup>HaemSTAR, Torquay, UK
- <sup>6</sup>Glasgow Royal Infirmary, NHS Greater Glasgow and Clyde NHS Board, Glasgow, UK
- <sup>7</sup>Manchester University Hospital NHS Foundation Trust, Manchester, UK
- <sup>8</sup>Royal Berkshire Hospital NHS Foundation Trust, Reading, UK
- <sup>9</sup>University Hospitals Plymouth NHS Trust, Plymouth, UK
- <sup>10</sup>Leeds Teaching Hospitals NHS Trust, Leeds, UK
- <sup>11</sup>University Hospitals Bristol NHS Foundation Trust, Bristol, UK
- <sup>12</sup>Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
- <sup>13</sup>Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
- <sup>14</sup>East Kent Hospitals University NHS Foundation Trust, Kent and Canterbury Hospital, Kent, UK
- <sup>15</sup>Oxford University Hospitals NHS Trust, Churchill Hospital, Oxford, UK
- <sup>16</sup>Royal United Hospitals Bath NHS Foundation Trust, Bath, UK
- <sup>17</sup>Novartis Pharmaceuticals UK Limited, London, UK
- <sup>18</sup>Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

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## CONFLICT OF INTEREST STATEMENT

Nichola Cooper reports research grants and personal fees from Novartis, Amgen, Rigol, Grifols and UCB. Marie Scully reports grants and personal fees from Novartis. Phillip L. R. Nicolson reports research grants from Novartis, Rigol, Astra Zeneca, Principia Biopharma and Sanofi, as well as personal speaker fees from Bayer, Grifols and Takeda. Jecko Thachil reports honoraria from Novartis and Amgen. Henri Grech was affiliated with NHS at the time of the study but retired since 2019, and reports personal fees from Novartis. Tim Nokes has nothing to disclose. Quentin A. Hill reports personal fees from Amgen, Argenx, Gliknik, Incyte, Immunovant, Janssen, Novartis, ReAlta, Sanofi and Sobi and speaker honoraria from Grifols and Novartis. Charlotte Bradbury reports speaker honoraria from Amgen, Novartis, BMS Pfizer, Sanofi, Bayer, Eli Lilly and Janssen, advisory for Amgen, Novartis, BMS, Pfizer, Portola and Ablynx, received support to attend conferences from Amgen, Novartis and Sanofi, and received research support from Amgen. Kate Talks has nothing to disclose. Tina Dutt reports speaker

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## ETHICS STATEMENT

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by independent ethics committees at participating sites.


## PATIENT CONSENT STATEMENT

Patients provided written informed consent for a researcher to access their medical records for data collection and analysis.

## DATA AVAILABILITY STATEMENT

Key data generated or analysed during this study are included in this published article and its supporting information files. Any additional datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

## ORCID

Nichola Cooper  <https://orcid.org/0000-0002-9845-8292>  
 Marie Scully  <https://orcid.org/0000-0002-2443-6517>  
 Catherine N. Bagot  <https://orcid.org/0000-0002-6439-9706>  
 Quentin A. Hill  <https://orcid.org/0000-0002-0627-4358>  
 Tina Dutt  <https://orcid.org/0000-0003-3049-2395>  
 Sue Pavord  <https://orcid.org/0000-0002-0840-5614>  
 Asad Charania  <https://orcid.org/0000-0001-8908-4535>  
 Drew Provan  <https://orcid.org/0000-0002-5110-8455>

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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