

# Use of second-line and beyond maintenance therapies in adult patients with primary immune thrombocytopenia in Europe: a parallel study of six prospective multicenter national registries

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## **SUPPLEMENTARY MATERIAL**

### **Use of second-line and beyond maintenance therapies in adult patients with primary immune thrombocytopenia in Europe: a parallel study of six prospective multicenter national registries**

*European Research Consortium on ITP (ERCI) group*

**Table S1.** Guidelines and main reimbursement restrictions in the European countries participating to this study.

**Table S2.** Patients with pITP exposed to initial and maintenance treatment by subgroups.

**Table S3.** Number of patients with pITP exposed to a first and to a second maintenance treatment by registry. Proportions are expressed relative to the total number of patients exposed to first and second maintenance treatment, respectively, in each registry.

**Table S1.** Guidelines and main reimbursement restrictions in the European countries participating to this study.

Guidelines and restrictions of use	Countries				
	United Kingdom (British guidelines 2003, then use international guidelines 2019)	France (2009, 2017)	Italy (2021)	Norway (use international guidelines, 2019)	Germany/Switzerland/Serbia (2018, 2021, 2023)
<b>National guidelines</b>					
<b>Initiation of first-line treatment</b>	Rarely indicated if platelet count > 20 x 10 <sup>9</sup> /L	Bleeding or platelet count <30 x 10 <sup>9</sup> /L	Bleeding or platelet count <30 x 10 <sup>9</sup> /L	Rarely indicated if platelet count > 20 x 10 <sup>9</sup> /L	Bleeding or platelet count < 20-30 x 10 <sup>9</sup> /L
<b>Initiation of second-line treatment</b>	Non-response to first-line or relapse	Non-response to first-line or relapse	Non-response or relapse to/after steroids	Non-response to first-line or relapse	After 2-4 weeks of non-response to steroids or side-effect of steroids or temporary response to steroids but relapse on taper, or response to steroids but relapse within 6 months
<b>Choice of second-line treatment (first maintenance therapy)</b>	Individualized Treatments are further categorized by those with robust evidence (TPO-RA, rituximab, fostamatinib) and those with less robust evidence (azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate), Splenectomy is recommended after 12-24 months from ITP diagnosis)	Danazol, dapsone, rituximab, TPO-RA, splenectomy (the latter should be considered after 1 year of ITP course)	In ITP > 6 months* TPO-RAs, rituximab, splenectomy with a suggestion for TPO-RAs > rituximab > splenectomy sequence (splenectomy after 1 year from diagnosis)	Individualized Treatments are further categorized by those with robust evidence (TPO-RA, rituximab, fostamatinib) and those with less robust evidence (azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate), Splenectomy is recommended after 12-24 months from ITP diagnosis)	TPO-RA, fostamatinib, splenectomy, off-label rituximab
<b>National reimbursement restrictions</b>	NICE restrictions: - eltrombopag and romiplostim: to chronic ITP patients refractory to	- Avatrombopag is not marketed in France. - Fostamatinib has	- Treatment of chronic ITP in adult patients who are refractory to first-line treatments such as	-	- Fostamatinib is not approved in Switzerland at the time of this study.

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<p>standard active treatments and rescue therapies, or to those with severe disease and at high risk of bleeding requiring frequent courses of rescue therapies (recommendation updated in 2018).</p> <p>- avatrombopag: recommendation for use in 2022 in line with its European label being considered an option for the treatment of primary chronic immune thrombocytopenia (ITP) refractory to other treatments (e.g., corticosteroids, immunoglobulins) in adults.</p> <p>- fostamatinib: in cases of previous exposure to (or ineligibility for) a TPO-RA.</p>	<p>been approved for reimbursement in cases of refractoriness (or contraindication) to romiplostim, eltrombopag, rituximab and splenectomy.</p>	<p>corticosteroids and IVIg and refractory to or with contraindications to at least one of TPO-RA and rituximab</p> <p>- The initial restriction of use of TPO-RA after 6 months of ITP for reimbursement is no longer applied, in line with changes in the European label.</p>
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Abbreviations: IVIg, intravenous immunoglobulin; NICE, National Institute for Health and Care Excellence; TPO-RA, thrombopoietin receptor agonist.

**Table S2.** Patients with pITP who exposed to initial and maintenance treatment by subgroups.

Characteristics	UK	France	Italy*	Norway	Germany	Switzerland-Serbia
<b>Number of patients with pITP</b>	3020	1263	n/a	172	105	25
<b>Number of patients with pITP exposed to ITP treatment, n (%)</b>						
<b>Total</b>	2467 (81.7%)	1072 (84.9%)	604 (n/a)	145 (84.3%)	65 (61.9%)	18 (72.0%)
<b>Age &lt;40 years</b>	698/863 (80.9%)	271/320 (84.7%)	164 (n/a)	51/61 (83.6%)	11/18 (61.1%)	7/8 (87.5%)
<b>Age 40-59 years</b>	653/817 (79.9%)	222/264 (84.1%)	151 (n/a)	36/47 (76.6%)	18/22 (81.8%)	5/10 (50.0%)
<b>Age 60-79 years</b>	911/1104 (82.5%)	370/444 (83.3%)	241 (n/a)	47/53 (88.7%)	23/47 (48.9%)	6/7 (85.7%)
<b>Age 80+ years</b>	205/236 (86.9%)	209/375 (55.7%)	48 (n/a)	11/11 (100%)	13/18 (72.2%)	0/0
<b>Women</b>	1308/1613 (81.1%)	573/668 (85.8%)	336 (n/a)	81/97 (83.5%)	27/43 (62.8%)	11/13 (84.6%)
<b>Men</b>	1159/1407 (82.4%)	499/595 (83.9%)	268 (n/a)	64/75 (85.3)	38/62 (61.3%)	3/12 (25.0%)
<b>2010-2016</b>	1434/1796 (79.8%)	217/263 (82.5%)	224 (n/a)	66/80 (82.5%)	0	16/23 (69.6%)
<b>2017-2022</b>	1033/1224 (84.4%)	855/1000 (85.5%)	380 (n/a)	79/92 (85.9%)	65/105 (61.9%)	2/2 (100%)
<b>Number of patients with pITP exposed to ITP maintenance treatment, n (%)</b>						
<b>Total</b>	1233 (40.5%)	576 (45.6%)	428 (n/a)	92 (53.4%)	31 (29.5%)	9/25 (36.0%)
<b>Age &lt;40 years</b>	315/863 (36.5%)	129/320 (40.3%)	107 (n/a)	31/61 (50.8%)	3/18 (16.7%)	2/8 (25.0%)
<b>Age 40-59 years</b>	339/817 (41.5%)	135/264 (51.1%)	117 (n/a)	23/47 (48.9%)	10/22 (45.5%)	3/10 (30.0%)
<b>Age 60-79 years</b>	473/1104 (42.8%)	194/444 (43.7%)	173 (n/a)	30/53 (56.7%)	14/47 (29.8%)	4/7 (57.1%)
<b>Age 80+ years</b>	96/236 (40.7%)	118/375 (50.2%)	31 (n/a)	8/11 (72.7%)	4/18 (22.2%)	0/0
<b>Women</b>	636/1308 (39.4%)	302/668 (45.2%)	247 (n/a)	43/97 (44.3%)	10/43 (23.3%)	5/13 (38.5%)
<b>Men</b>	587/1159 (41.7%)	274/595 (46.1%)	181 (n/a)	49/75 (65.3%)	21/62 (33.9%)	4/12 (33.3%)
<b>2010-2016</b>	725/1434 (40.4%)	115/263 (43.7%)	197 (n/a)	44/80 (55.0%)	0/0	9/23 (39.1%)
<b>2017-2022</b>	498/1033 (40.7%)	461/1000 (46.1%)	231 (n/a)	48/92 (52.2%)	31/105 (29.5%)	0/2

Abbreviations: n/a, not available; pITP, primary immune thrombocytopenia.

\*In the Italian registry, only patients on active treatment are included (at time of starting treatment or at first monitoring visit if already on treatment). Consequently, age at ITP diagnosis, sex and time period groups are presented only for patients on active ITP treatment.

**Table S3.** Number of patients with pITP exposed to a first and to a second maintenance treatment by registry. Proportions are expressed relative to the total number of patients exposed to first and second maintenance treatment, respectively, in each registry.

Maintenance treatments	Countries					
First maintenance treatment	UK n=1233	France n=576	Italy n=428	Norway n=92	Germany n=31	Switzerland-Serbia n=9
Eltrombopag, n (%)	262 (21.5%)	214 (37.2%)	281 (65.7%)	19 (20.7%)	20 (64.5%)	1 (11.1%)
Romiplostim, n (%)	150 (12.2%)	77 (13.4%)	56 (13.1%)	7 (7.6%)	6 (19.3%)	0
Avatrombopag, n (%)	2 (0.2%)	n/a	1 (0.2%)	8 (8.7%)	3 (9.7%)	0
Rituximab, n (%)	301 (24.4%)	85 (14.6%)	49 (11.5%)	50 (54.4%)	1 (3.2%)	1 (11.1%)
Fostamatinib, n (%)	1 (0.1%)	0	1 (0.2%)	0	0	0
Mycophenolate, n (%)	265 (21.5%)	1 (0.2%)	6 (1.4%)	0	0	0
Splenectomy, n (%)	15 (1.2%)	2 (0.4%)	9 (2.1%)	6 (6.5%)	0	0
Azathioprine, n (%)	150 (12.2%)	2 (0.4%)	32 (7.5%)	3 (3.3%)	0	6 (66.7%)
Cyclosporin, n (%)	7 (0.6%)	2 (0.4%)	11 (2.6%)	0	0	0
Cyclophosphamide, n (%)	5 (0.4%)	0	0	0	0	0
Dapsone, n (%)	5 (0.4%)	94 (16.3%)	3 (0.7%)	0	0	0
Danazol, n (%)	7 (0.6%)	10 (1.7%)	4 (0.9%)	0	0	0
Hydroxychloroquine n (%)	2 (0.2%)	76 (13.2%)	0	0	0	0
Other, n (%)	20 (1.6%)	13 (2.3%)	0	0	1 (3.2%)	1 (11.1%)
Second maintenance treatment	UK n=607	France n=272	Italy n=134	Norway n=40	Germany n=7	Switzerland-Serbia n=2
Eltrombopag, n (%)	167 (27.5%)	70 (25.7%)	38 (28.4%)	13 (32.5%)	2 (28.6%)	0
Romiplostim, n (%)	148 (24.4%)	64 (23.5%)	43 (32.1%)	10 (25.0%)	3 (42.9%)	0
Avatrombopag, n (%)	5 (0.8%)	0	1 (0.7%)	9 (22.5%)	0	0
Rituximab, n (%)	99 (16.3%)	72 (26.5%)	12 (9.0%)	3 (7.5%)	0	0
Fostamatinib, n (%)	1 (0.2%)	1 (0.4%)	2 (1.5%)	0	1 (14.3%)	0
Mycophenolate, n (%)	90 (14.8%)	0	7 (5.2%)	0	0	0
Splenectomy, n (%)	20 (3.3%)	2 (0.7%)	14 (10.5%)	4 (10.0%)	0	0
Azathioprine, n (%)	46 (7.8%)	1 (0.4%)	7 (5.2%)	1 (2.5%)	1 (14.3%)	1 (50.0%)
Cyclosporin, n (%)	7 (1.2%)	0	5 (3.7%)	0	0	0
Cyclophosphamide, n (%)	3 (0.5%)	0	1 (0.7%)	0	0	0
Dapsone, n (%)	5 (0.8%)	16 (5.9%)	1 (0.7%)	0	0	0
Danazol, n (%)	3 (0.5%)	1 (0.4%)	1 (0.7%)	0	0	0
Hydroxychloroquine, n (%)	2 (0.3%)	19 (7.0%)	0	0	0	0
Other, n (%)	11 (1.8%)	24 (8.8%)	2 (1.5%)	0	0	1 (50.0%)

Abbreviation: n/a, not available.