Treatment of essential thrombocythemia in Europe: a prospective long-term observational study of 3649 high-risk patients in the Evaluation of Anagrelide Efficacy and Long-term Safety study

Gunnar Birgegård,[1] Carlos Besses,[2] Martin Griesshammer,[3] Luigi Gugliotta,[4] Claire N. Harrison,[5] Mohamed Hamdani,[6] Jingyang Wu,[6] Heinrich Achenbach[7] and Jean-Jacques Kiladjian[8]

[1]Department of Haematology, Institute for Medical Sciences, Uppsala University, Sweden; [2]Department of Hematology, Hospital del Mar-IMIM, Barcelona, Spain; [3]Hematology and Oncology, Johannes Wesling Medical Center, Minden, Germany; [4]Department of Haematology, 'L e A Seragnoli', Sant'Orsola-Malpighi Hospital, Bologna, Italy; [5]Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, London, UK; [6]Global Biometrics, Shire Pharmaceuticals, Lexington, MA, USA; [7]Research & Development, Shire GmbH, Zug, Switzerland and [8]APHP, Hopital Saint-Louis, Paris, France

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Correspondence: gunnar.birgegard@medsci.uu.se

Supplementary Data - Treatment of essential thrombocythemia in Europe: a prospective long-term observational study of 3649 high-risk patients in the EXELS study

Gunnar Birgegård, Carlos Besses, Martin Griesshammer, Luigi Gugliotta, Claire N. Harrison, Mohamed Hamdani, Jackie Wu, Henri Achenbach and Jean-Jacques Kiladjian

Supplementary Table 1. Cumulative event rates of thrombohemorrhagic events by overall-treatment analysis population.

Treatment at time of event	**Anagrelide N=1127**		**Other CRT N=2909**		**Anagrelide + other CRT N=451**	
Predefined event	Patients (events) n	Event rate	Patients (events) n	Event rate	Patients (events) n	Event rate
Major thrombotic events	66 (78)	1.96	228 (267)	2.18	20 (22)	2.37
With A-A	44 (51)	2.23	160 (184)	1.99	10 (11)	1.66
Without A-A	25 (27)	1.78	71 (83)	2.84	11 (11)	4.48
Arterial thrombotic events	55 (65)	1.63	171 (200)	1.62	19 (21)	2.25
With A-A	38 (45)	1.93	124 (145)	1.54	10 (11)	1.66
Without A-A	18 (20)	1.28	50 (55)	1.98	10 (10)	4.08
Venous thrombotic events	12 (13)	0.35	61 (67)	0.57	1 (1)	0.11
With A-A	6 (6)	0.29	38 (39)	0.46	0	0
Without A-A	7 (7)	0.49	23 (28)	0.9	1 (1)	0.39
Major hemorrhagic events	30 (35)	0.87	53 (59)	0.49	6 (7)	0.69
With A-A	25 (28)	1.24	34 (38)	0.41	3 (3)	0.49
Without A-A	7 (7)	0.49	19 (21)	0.75	3 (4)	1.2
Total thrombohemorrhagic events	92 (113)	2.75	270 (326)	2.6	24 (29)	2.86
With A-A	65 (79)	3.33	187 (222)	2.34	12 (14)	1.99
Without A-A	32 (34)	2.29	89 (104)	3.58	13 (15)	5.4

A-A, anti-aggregatory; CRT, cytoreductive therapy.

Supplementary Table 2. Cumulative event rates of other predefined events by overall-treatment analysis population.

Treatment at time of event	**Anagrelide N=1127**		**Other CRT N=2909**		**Anagrelide + other CRT N=451**	
Predefined event	Patients (events) n	Event rate	Patients (events) n	Event rate	Patients (events) n	Event rate
Any predefined event	262 (469)		739 (1332)		75 (137)	
Congestive heart failure	21 (24)	0.61	41 (48)	0.38	3 (3)	0.34
Cardiomyopathy	5 (5)	0.14	9 (9)	0.08	0	0
Atrial fibrillation	10 (11)	0.3	35 (43)	0.33	4 (4)	0.47
Other cardiovascular symptoms	63 (79)	1.89	100 (134)	0.94	24 (26)	2.83
Severe mucocutaneous disorders	7 (8)	0.2	68 (74)	0.63	6 (7)	0.69
Pulmonary hypertension	5 (5)	0.14	7 (7)	0.06	0	0
Pulmonary fibrosis/interstitial pneumonia	2 (2)	0.06	9 (10)	0.08	0	0
Pancreatitis	0	0	4 (4)	0.04	0	0
Rhabdomyolysis/myalgia	3 (3)	0.09	3 (4)	0.03	0	0
Non-hematological malignancy	17 (18)	0.49	143 (161)	1.35	4 (5)	0.46

CRT, cytoreductive therapy; PDE, predefined event.

*Nine pregnancies in seven subjects were reported in the no treatment group (data not shown).

Supplementary Table 3. Most common cardiovascular predefined events by overall treatment population.

Treatment at time of event	**Anagrelide N=1127**		**Other CRT N=2909**		**Anagrelide + other CRT N=451**	
Predefined event	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Palpitations	19 (1.69)	21	6 (0.21)	6	8 (1.77)	8
Tachycardia	23 (2.04)	26	4 (0.14)	5	6 (1.33)	6
Arrhythmias (excluding tachycardia)	16 (1.42)	17	46 (1.65)	56	5 (1.11)	5

CRT, cytoreductive therapy.

Supplementary Table 4. Cumulative event rates of suspected serious adverse reactions by overall-treatment analysis population and organ class, in the overall treatment safety population.

SSAR system organ class	Anagrelide N=1127			Other CRT N=2909			Total N=451		
	Patients (events) n	Patient-years exposure*	Event rate**	Patients (events) n	Patient-years exposure*	Event rate**	Patients (events) n	Patient-years exposure*	Event rate**
Any SSAR	37 (49)	4 303.2	0.86	70 (77)	11 608.5	0.6	101 (118)	14 994.9	0.67
Blood and lymphatic system disorders	2 (2)	4 332.2	0.05	13 (16)	11 697.7	0.11	13 (16)	15 158.8	0.09
Cardiac disorders	17 (22)	4 327.4	0.39	5 (5)	11 710.2	0.04	21 (26)	15 143.6	0.14
Gastrointestinal disorders	6 (6)	4 330.2	0.14	6 (6)	11 708.4	0.05	11 (11)	15 159.1	0.07
General disorders and administration site conditions	1 (1)	4 334.4	0.02	1 (1)	11 718.6	<0.01	2 (2)	15 170.0	0.01
Immune system disorders	0	4 334.6	0	1 (1)	11 714.8	<0.01	1 (1)	15 174.9	<0.01
Infections and infestations	1 (1)	4 333.2	0.02	3 (3)	11 714.4	0.03	4 (4)	15 172.2	0.03
Injury, poisoning, and procedural complications	1 (1)	4 332.1	0.02	2 (2)	11 714.2	0.02	3 (3)	15 172.4	0.02
Investigations	0	4 334.6	0	1 (1)	11 718.6	<0.01	1 (1)	15 179.8	<0.01
Musculoskeletal and connective tissue disorders	1 (1)	4 334.4	0.02	0	11 718.6	0	1 (1)	15 175.2	<0.01
Neoplasm benign, malignant, and unspecified (including cysts and polyps)	2 (2)	4 334.4	0.05	18 (19)	11 701.6	0.15	19 (20)	15 161.1	0.13
Nervous system disorders	2 (2)	4 331.7	0.05	10 (10)	11 697.6	0.09	11 (11)	15 155.9	0.07
Psychiatric disorders	1 (1)	4 334.6	0.02	1 (1)	11 718.6	<0.01	1 (1)	15 179.8	<0.01
Reproductive system and breast disorders	0	4 334.6	0	1 (1)	11 718.6	<0.01	1 (1)	15 179.8	<0.01
Respiratory thoracic, and mediastinal disorders	7 (9)	4 327.9	0.16	4 (4)	11 709.5	0.03	10 (12)	15 157.9	0.07
Skin and subcutaneous disorders	0	4 334.6	0	6 (6)	11 708.5	0.05	6 (6)	15 168.0	0.04
Vascular disorders	1 (1)	4 330.7	0.02	1 (1)	11 718.0	<0.01	2 (2)	15 175.3	0.01

CRT, cytoreductive therapy; SSAR, suspected serious adverse reactions.

*Exposure is calculated at the time of each event, or up to the end of the study for patients who did not experience an event.

**The event rate is calculated as the number of patients with events/100 patient-years exposure.
Patients who received ‘anagrelide + other’ are included in both the ‘anagrelide’ and ‘other treatment’ groups for analysis of SSARs.
Events are excluded if the start date was on or after the date of first treatment change (or date of first treatment change plus 28 days if followed by a no-treatment period).
Since subjects were allowed to switch treatments during the study, they could be counted in more than one treatment group in the overall-treatment analysis.

Supplementary Table 5. Baseline characteristics considered in the multivariate analysis.

Baseline characteristics
ET diagnosis* (WHO, PVSG, other)
Age* (<65 years, ≥65 years)
Sex*
Time since diagnosis*
(0 – <1 years, 1 – <5 years, 5 – <10 years, ≥10 years)
Cardiovascular risk factors*
Normal cardiac function*
Aspirin at registration**
Hemorrhagic or vascular events*
Initial platelet count ≥1000x10^9/L*
Blood pressure
Body mass index
Hypercholesterolemia*
Diabetes*
Smoking*
Hypertension*

ET, essential thrombocythemia; PVSG, Polycythemia Vera Study Group; WHO, World Health Organization.
*Indicates baseline characteristics included in the Cox regression model to account for imbalance between 'anagrelide' vs 'anagrelide + anti-aggregatory therapy' at registration.
**The variable 'aspirin at registration' was used for the multivariate analysis in the overall population to identify risk factors. The variable 'anti-aggregatory therapy at registration' was used for the multivariate analysis in the first-treatment population.

Supplementary Figure 1. EXELS study design.

*Includes all patients who received at least one dose of CRT. Seventy-two patients were excluded from the safety population as they did not receive CRT post-registration.
**Other CRT group includes patients who received: hydroxycarbamide, busulphan, interferon-α, pegylated interferon, pipobroman, sodium phosphate P32, thromboreductin (anagrelide).
***Includes patients who did not receive CRT within 10 days of study registration, but subsequently initiated CRT, or patients for whom no CRT information was available.