

# Prospective studies in ET management in the last 10 years Where are we now?

# Conflict of interest

- SHIRE
- VIFOR PHARMA

# EXELS

## EXELS STEERING COMMITTEE



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EXELS is a post authorisation study sponsored by Shire

# Publications from the EXELS so far:

- 1/ Besses C *et al.* *Leuk Res.* 2012; 37:162-8
- 2/ Kiladjian JJ, *et al.* *Clin Drug Invest.* 2013;33:55-63
- 3/ Gugliotta L, *et al.* *Haematologica.* 2014;99:679-87
- 4/ Harrison C.N. *et al.* *N Engl J Med.* 2005;353:33-45
- 5/ Gisslinger H. *et al.* *Blood.* 2013;121:1720-28

Abstract: Birgegård G, *et al.* 56<sup>th</sup> ASH meeting 2014. Abstract no. 1846

Reference: Shire DoF SPD422-024

# Study design

EXELS is an observational (non-interventional) study

## **Study population:**

3,649 high-risk ET subjects in 13 European countries

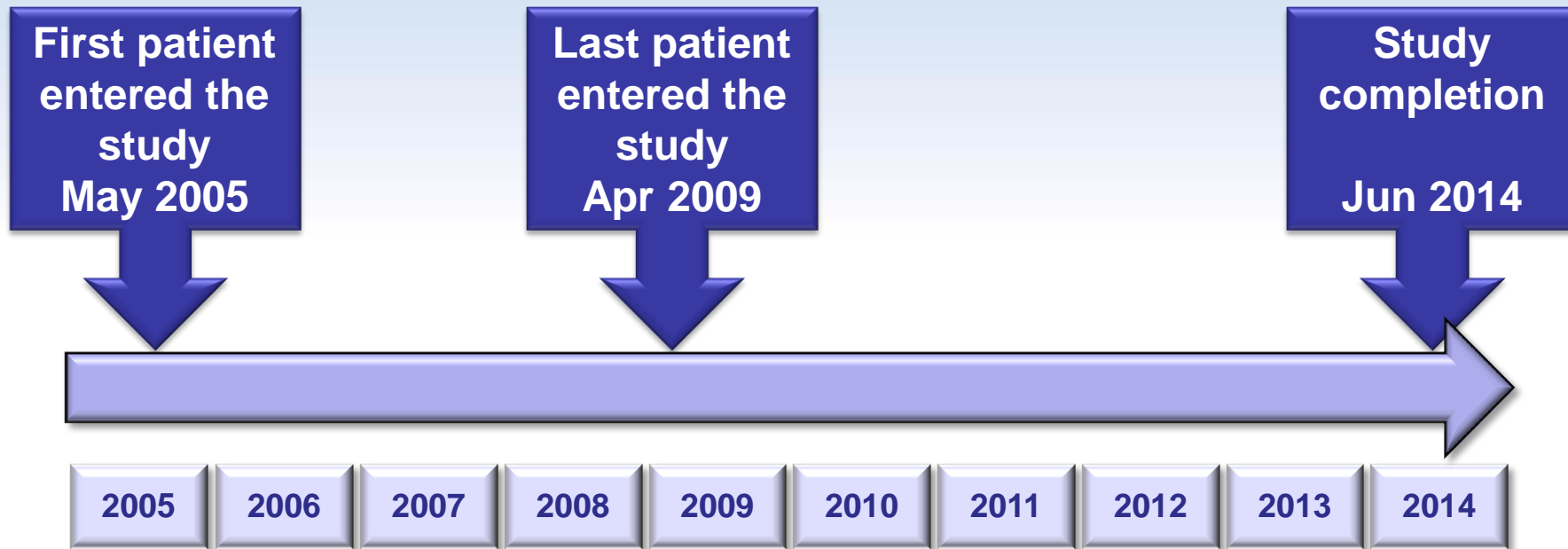
## **Primary objective:**

Safety and pregnancy outcomes

## **Secondary objective:**

- Efficacy
- Drug utilisation

# Study timeline



# Data collection

## *Data collected*

- at registration
- every 6 months for 5 years
- for cause (pre-defined or drug-related Serious Adverse Events, withdrawal and death)

# Predefined events

## Disease complications

- Thromboembolic events (arterial or venous)
  - Angina
  - Myocardial infarction
  - TIA
  - Stroke
  - DVT
  - Pulmonary embolus
- Major hemorrhagic events
- Transformation to MF, MDS or AL

## Other

- ✓ Non-hematologic malignancy
- ✓ Pregnancy
- ✓ Death from other cause than ET

## Possible toxicity

- Mucocutaneous lesions
- Congestive heart failure
- Cardiomyopathy
- Other cardiovasc. symptoms
- Pulmonary hypertension
- Pulmonary Fibrosis / Interstitial pneumonia
- Pancreatitis
- Rhabdomyolysis/ myalgia



# Baseline demographics

	<b>ANA (n=804)</b>	<b>Other CRT (n=2666)</b>
Male	303 (38)	1032 (39)
Female	501 (62)	1632 (61)
Age, median (range)	56 (18-89)	70 (17-95)
Anti-aggregatory therapy at registration, n (%)	460 (57)	1972 (74)
ANA – anagrelide, CRT – cytoreductive therapy		

# Main focus for analysis

- Thrombohemorrhagic events

- Thrombotic

- Arterial thrombosis
    - Venous thrombosis

- Hemorrhagic

Efficacy

- Transformation

- To myelofibrosis
  - To acute leukemia

Safety

EXELS is a non-randomised, observational study. Direct statistical comparison between groups using p values can not be made.

Results are presented as event rates (events per 100 patient years)

# Thrombohemorrhagic events

	ANA (n=1127)		Other CRT (n=2909)	
	Patients (events)	Event rate	Patients (events)	Event rate
Total thrombohemorrhagic events	92 (113)	2.75	270 (326)	2.60
Major thrombotic events	66 (78)	1.96	228 (267)	2.18
Arterial thrombotic events	55 (65)	1.63	171 (200)	1.62
Venous thrombotic events	12 (13)	0.35	61 (67)	0.57
Major hemorrhagic events	30 (35)	0.87	53 (59)	0.49

# Transformations

Transformation to:	ANA (n=1127)		Other CRT (n=2909)	
	Patients (events)	Event rate	Patients (events)	Event rate
Myelofibrosis	45 (45)	1.31	35 (35)	0.32
Acute leukemia	6 (6)	0.17	36 (36)	0.33
Myelodysplasia	1 (1)	0.03	14 (14)	0.13

All patients in the ANA group who transformed to AL had previous treatment with HC

# Non-haematological malignancies

	ANA (n=1127)		Other CRT (n=2909)	
	Patients (events)	Event rate	Patients (events)	Event rate
Non-haematological malignancy	17 (18)	0.49	143 (161)	1.35

Is this difference due to the age difference only or is it real?

# EXELS conclusions

- The total thrombohemorrhagic and total thrombotic event rates were similar between the ANA and other CRT group, despite the observed age difference between the ANA and other CRT group in this study.
- The venous thrombotic event rate was lower in the ANA vs other CRT group.
- The arterial event rates were similar except in patients with anti-aggregatory therapy, where the event rate was lower in the other CRT group

# EXELS conclusions, cont'd

- Transformation to MF was more frequent in the ANA vs HC group.
- Conversely, transformation to AL was more frequent in the HC group.
- Non-hematological malignancies were more common in the other CRT vs ANA group.  
(Further analysis of the influence of age and other risk factors for malignancy as confounding factors is ongoing)



# After 10 years – Where are we now?

Consistent findings with EXELS: + / Inconsistent findings with EXELS: -

	<b>PT1</b> <i>HU + ASS vs ANA + ASS</i>	<b>Anahydrat</b> <i>HU vs ANA</i>
Total thrombo-hemorrhagic events	-	+
Total thrombosis	-	+
Arterial	-	+
Venous	+	-
Hemorrhage	+	-
Transform. MF	+	-
Diagnosis	+	-

The studies mentioned on this slide have different study designs and patient populations