SOLIRIS CASE

PNH INDICATION UPDATE BASED ON DATA FROM GLOBAL REGISTRY

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Global Regulatory Affairs

ALEXION

I. BACKGROUND

BACKGROUND - SOLIRIS

- **Soliris (eculizumab) : C5 inhibitor**
  - approved in June 2007 for PNH and November 2011 for aHUS

SmPC : section 4.1 Therapeutic Indication

Soliris is indicated in adults and children for the treatment of patients with

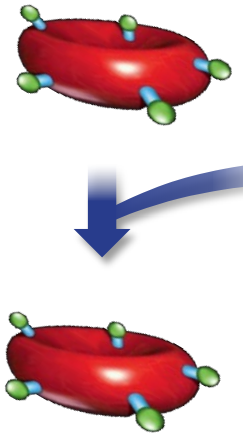
- **Paroxysmal Nocturnal Haemoglobinuria (PNH).**

> Evidence of clinical benefit of Soliris in the treatment of patients with PNH is limited to patients with history of transfusions.

- Atypical haemolytic uremic syndrome (aHUS) (see section 5.1).

CHRONIC HAEMOLYSIS IS THE UNDERLYING CAUSE OF PROGRESSIVE MORBIDITIES AND MORTALITY IN PNH

Normal RBCs are protected from complement attack by a shield of terminal complement inhibitors[1]



Intact RBC

Complement activation[1]

Without this protective complement inhibitor shield, RBCs in PNH are destroyed[1]

Haemolysis[2]

Free Hb/Elevated LDH

Decreased NO

- Thrombosis[1]
- Renal failure[3]
- Pulmonary hypertension[2]
- Abdominal pain[4]
- Dyspnoea[5]

Significant Impact on Survival

- Dysphagia[6]
- Fatigue[6]
- Haemoglobinuria[6]
- Erectile dysfunction[6]

Significant Impact on Morbidity

Hb, haemoglobin; LDH, lactate dehydrogenase; NO, nitric oxide.

1. Brodsky RA. *Hematology - Basic Principles and Practices*. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:419-427.
2. Rother RP, et al. *JAMA*. 2005;293(13):1653-1662. 3. Hillmen P, et al. *Am J Hematol*. 2010;85(8):553-559. 4. Lee JW, et al. *Haematologica*. 2010;95(suppl 2):Abstract 506.
5. Hill A, et al. *Br J Haematol*. 2010;149(3):414-425. 6. Hill A, et al. *Br J Haematol*. 2007;137(3):181-192.

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BACKGROUND – PNH REGISTRY

- **PNH REGISTRY M07-001**
  - Agreed with CHMP in a Follow-Up Measure and as additional pharmacovigilance activity in the RMP
  - Annual reports submitted to EMA/PRAC with PSUR submissions

- **Objectives**
  - **Primary:**
    - The PNH Registry will collect data to evaluate safety data specific to the use of Soliris
    - The PNH Registry will **collect data to characterize the progression of PNH as well as clinical outcomes, mortality and morbidity in Soliris and non-Soliris treated patients**
  - **Secondary:** Raising PNH awareness in the medical community and subject/potential subject

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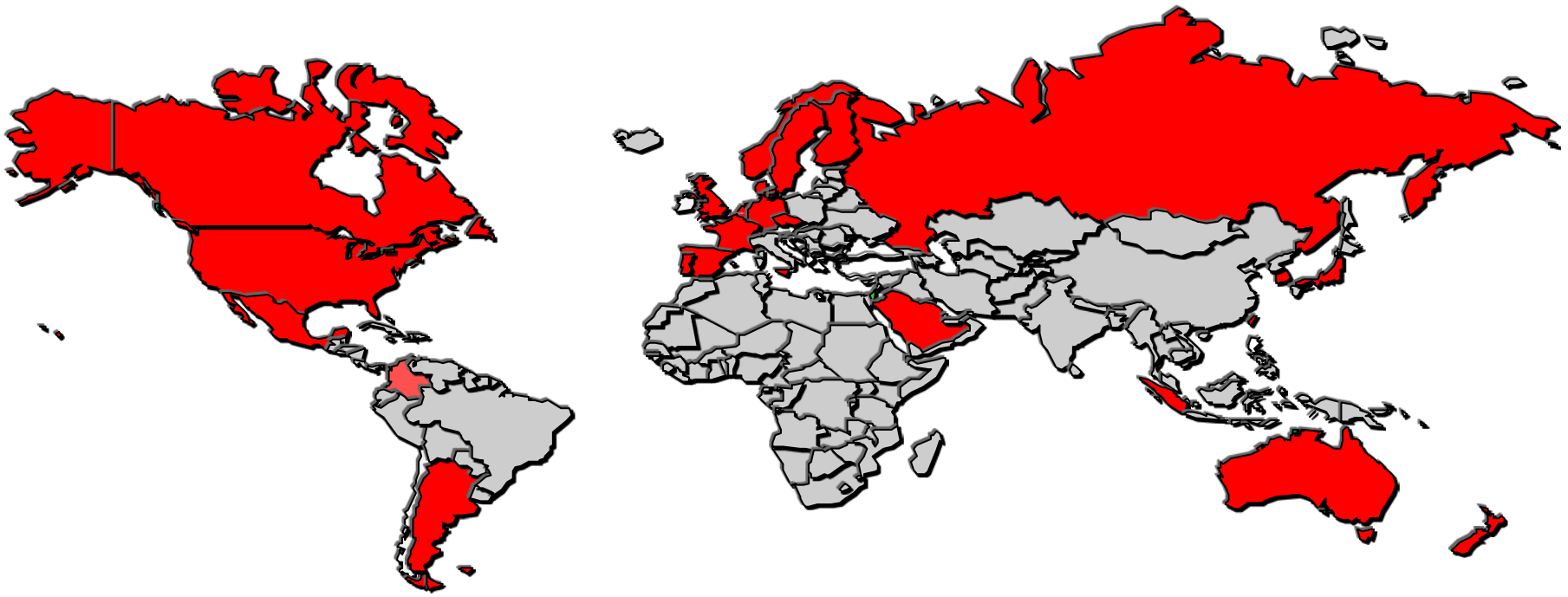
PNH REGISTRY: GLOBAL PRESENCE



The PNH Registry is a comprehensive database on PNH

End 2012, approximately **2000 patients**, 284 of 2410 discontinued

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II. REGULATORY DIALOGUE

BACKGROUND - SOLIRIS

Initial approved indication : Paroxysmal nocturnal haemoglobinuria (PNH).

Evidence of clinical benefit of Soliris in the treatment of patients with PNH is limited to patients with history of transfusions*.

** Based on the inclusion criteria[1] in :*

- *pivotal study : PNH patients with at least 4 transfusions in the prior 12 months*
- *supportive study : PNH patients with at least 1 transfusion in the prior 24 months*

[1] inclusion criteria based on the knowledge of the PNH disease in 2004 (initiation of clinical development)

Real world data show that transfusion is not an adequate criteria to define disease severity in PNH

APPROACHS TO REVISE THE INDICATION

- **Conduct a prospective randomized controlled study**
  - Required a non-treatment control group (patients not treated may present symptoms of serious intravascular haemolysis)
  - Evaluate burden of disease in PNH patients and the serious nature of the disease regardless of history of transfusion
  - Limited number of patients available for inclusion in such a study

- **Use data from PNH registry**
  - Included patients with no history of transfusion who have received eculizumab;
  - Largest prospective data collection study in patients with PNH in the real world setting (also evaluates patient outcomes, including the long-term safety of eculizumab)
  - Important source for documenting the burden of disease including morbidity and mortality, clinical outcomes and progression of PNH in treated and non treated patients regardless of transfusion history.
  - Clinical and laboratory data provide the basis for the assessment of key efficacy parameters such as degree of haemolysis and quality of life.

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SCIENTIFIC ADVICE / PROTOCOL ASSISTANCE

- **Final advice letter confirmed that using data from Registry is adequate (Oct 2012):**

*« The CHMP agrees that the **PNH registry could serve to document the burden of disease in PNH patients and the serious nature of the disease regardless of a history of transfusion.***

The CHMP agrees that whether or not a patient with PNH is considered to require transfusion is likely based on local practice and clinical opinion and therefore transfusion per se cannot be regarded as a wholly reliable marker of severity of PNH.

It appears that the registry already includes a number of patients who have received eculizumab even though they had no history of transfusion. Depending on the eventual numbers enrolled without a transfusion history who are/are not treated with eculizumab the registry may allow for some assessment of the benefit of treatment in this patient population. »

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RATIONALE FOR TYPE II VARIATION

- **Benefit to patients:**
  - The devastating nature of PNH demands early diagnosis and intervention
  - PNH Registry data highlight the unmet medical need in patients with PNH and confirms that the clinical benefit of Soliris®— control of the underlying haemolytic process in PNH — is independent of transfusion history and thus can benefit a broader patient population
  - Clinical trials and PNH Registry data (M07-001), in addition to the medical and scientific literature, show that chronic complement-mediated haemolysis (LDH ≥1.5x ULN) is the underlying cause of progressive morbidities and mortality in PNH
  - In the presence of haemolysis, even symptoms that are usually considered less severe necessitate attention and warrant intervention
  - All patients with PNH, independent of transfusion history, are at risk for the devastating consequences of PNH and should benefit from Soliris®

III. CLINICAL VARIATION

APPROACH TO CLINICAL VARIATION

- An Analysis Plan was designed to demonstrate the broad and diverse symptomatology observed among patients with PNH enrolled in the Registry and provided:
  - A longitudinal, descriptive analysis documented the burden of disease among eculizumab-treated patients, regardless of RBC transfusion history and describe biologic and clinical changes that occur over time
  - A comparative analysis between patients without a recent history of transfusion for 6 or more months prior to initiating eculizumab therapy, and those patients who were never treated with eculizumab and are also without a recent history of transfusion
  - Safety events of interest in eculizumab-treated and never treated patients
- **Primary endpoint:**
  - Change in LDH from baseline to 6 months between eculizumab treated with no history of transfusion and never treated patients with no history of transfusion reported as absolute changes in LDH values from baseline to 6-month and LDH values at 6-month
- **Secondary endpoints:**
  - Fatigue was assessed using the FACIT fatigue instrument and the fatigue component of the EORTC QLQ-C30 questionnaire
- **Exploratory endpoints**
  - Quality of life was assessed using the EORTC QLQ-C30 questionnaire as well as physician reported symptoms

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CLINICAL VARIATION

- **Analysis included all patients enrolled in the PNH Registry who meet the following criteria:**
  - Enrolled in the PNH Registry on or before April 30, 2012
    - Follow-up assessments are requested every six months
  - Initiated treatment with eculizumab after Registry enrolment or never treated with eculizumab
  - Had reported values for enrolment dates, date of birth, sex, date of first eculizumab treatment (for eculizumab-treated patients)
  - Had at minimum a follow-up assessment recorded in the study database
  - Had a granulocyte clone size of ≥1%
  - Had a baseline LDH of ≥ 1.5 over the upper limit of normal (ULN)

In addition patients were asked to complete PRO questionnaires, which included the FACIT-Fatigue and EORTC QLQ-C30, at enrolment and during routine office visits. These quality of life instruments are validated and were previously used in the original PNH submission

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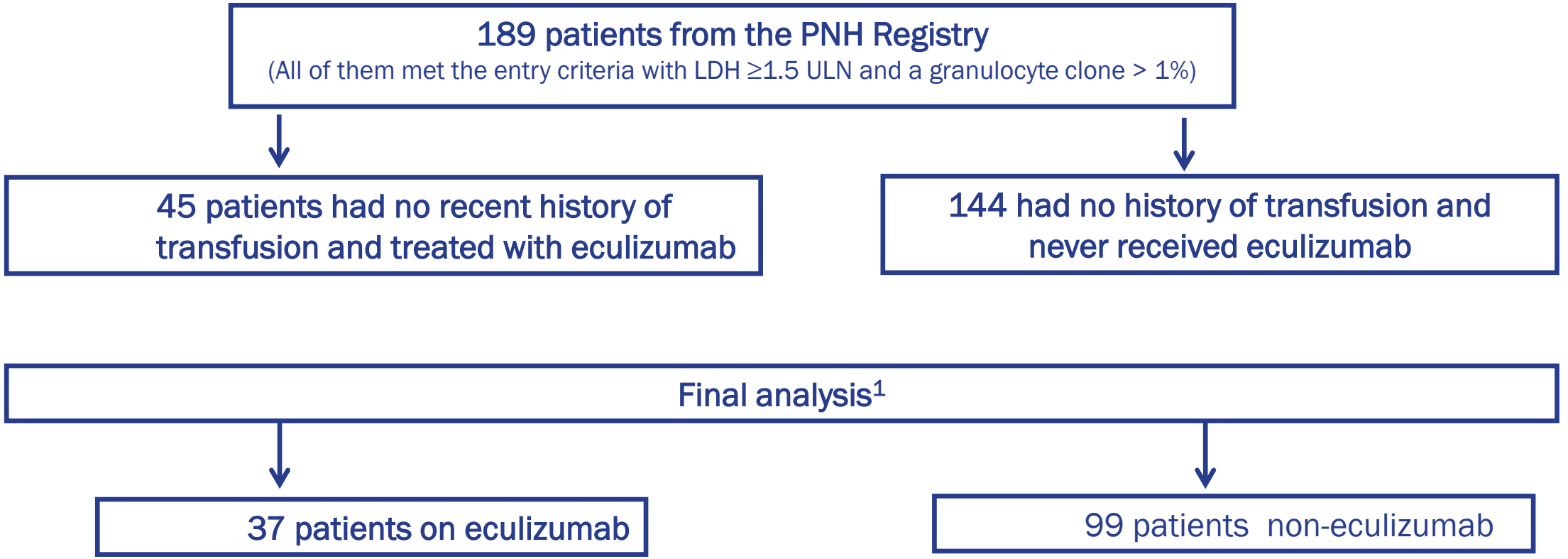
CLINICAL VARIATION: NUMBERS

Patients without a History of Transfusion in the PNH Registry



1. A substantial number of patients were excluded from this analysis
(8 patients (18%) in eculizumab group and 45 patients (35%) in non-eculizumab group) given that no LDH values at 6-month were available.

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SMPC SECTION 5.1 HIGH DISEASE ACTIVITY

- The PNH registry (M07-001) was used to evaluate the **efficacy of Soliris in PNH patients with no history of RBC transfusion**. These patients **had disease burden as defined by elevated haemolysis (LDH ≥1.5x ULN) and the presence of related clinical symptom(s): fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin <100 g/L), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction.**

- High Disease Activity

  = elevated haemolysis (LDH ≥1.5 x ULN)

  + the presence of one or more related clinical symptom(s) :

LDH ≥1.5 x ULN

+

One or more of the related clinical symptom(s):

- Fatigue
- Haemoglobinuria
- Abdominal pain
- Shortness of breath (dyspnoea)
- Anaemia (Hb <100 g/L)
- Major adverse vascular event (incl. thrombosis)
- Dysphagia
- Erectile dysfunction

CLINICAL VARIATION

- ***Changes in LDH***
  - Treatment with eculizumab was followed by a clinically relevant change in LDH values from baseline to 6-month, with most patients showing normal or near normal values
    LDH values remained almost unchanged in the no-eculizumab treatment arm

Change in LDH (U/L) at 6-Month - Patients without a History of Transfusion

	PNH Registry Eculizumab - No Transfusion (N = 37)	PNH Registry Non Eculizumab - No Transfusion (N = 99)
Baseline (median, min-max)	1431 (301, 4661)	1096 (360, 4893)
Absolute change (U/L)		
Median (min-max)	-1042 (-4215, 597)	-29 (-1128, 1320)
Percent change from baseline (%)		
Median (min-max)	-78 (-92, 66)	-3.5(-71, 200)

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SPC SECTION 5.1 M07-001 DATA

- In the PNH Registry, patients treated with Soliris were observed to have a reduction in haemolysis and associated symptoms
- At 6 months, patients treated with Soliris with no history of RBC transfusion had significantly ($p<0.001$) reduced LDH levels (median LDH of 305 U/L; Table 4) vs. Soliris non-treated patients. Furthermore, 74% of the patients treated with Soliris experienced clinically meaningful improvements in FACIT-Fatigue score (i.e., increase by 4 points or more) and 84% in EORTC fatigue score (i.e., decrease by 10 points or more)

Table 4: Efficacy Outcomes (LDH level and FACIT-Fatigue) in Patients with PNH with No History of Transfusion in M07-001

Parameter	Soliris No Transfusion
LDH level at baseline *(median, U/L)*	N=43 1447
LDH level at 6 months *(median, U/L)*	N=36 305
FACIT-Fatigue score at baseline *(median)*	N=25 32
FACIT-Fatigue score at last available assessment *(median)*	N=31 44

The hemolytic nature of PNH is reinforced by clinical benefits of Soliris® demonstrated in patients with high disease activity and independent of transfusion history

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IV. REGULATORY OUTCOME AND LESSONS LEARNT

CLINICAL VARIATION - INDICATION

Initial Indication:

Soliris® is indicated in adults and children for the treatment of patients with Paroxysmal nocturnal haemoglobinuria (PNH).

Evidence of clinical benefit **of Soliris in the treatment of patients with PNH is limited to patients with history of transfusions.**

Indication submitted :

Soliris® is indicated in adults and children for the treatment of patients with Paroxysmal nocturnal haemoglobinuria (PNH).

Approved revised indication :

Soliris is indicated in adults and children for the treatment of patients with Paroxysmal nocturnal haemoglobinuria (PNH).

Evidence of clinical benefit **is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1).**

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REGULATORY ASSESSMENT

Discussion on clinical efficacy (EPAR)

- The PNH Registry served as an important data source for documenting the burden of disease including morbidities and mortality, clinical outcomes and progression of PNH in eculizumab- and non–eculizumab-treated patients, irrespective of transfusion history
- Such a large database also provided an opportunity to investigate specific populations
- Clinical and laboratory data also provide the basis for the assessment of key efficacy parameters such as degree of haemolysis and quality of life
- Based on the known risk of significant morbidities and premature mortality in PNH and the benefit of treatment with eculizumab in patients with PNH, such a database cannot be replicated in a prospective randomized study which would require a no-treatment control group
- Despite the pre-specified statistical analysis plan and the planned assessments every 6-month, there were a number of missing evaluations
- In addition, assessment was not blinded, which might have biased evaluation of subjective endpoints such that fatigue, dyspnoea, QoL, other related symptoms

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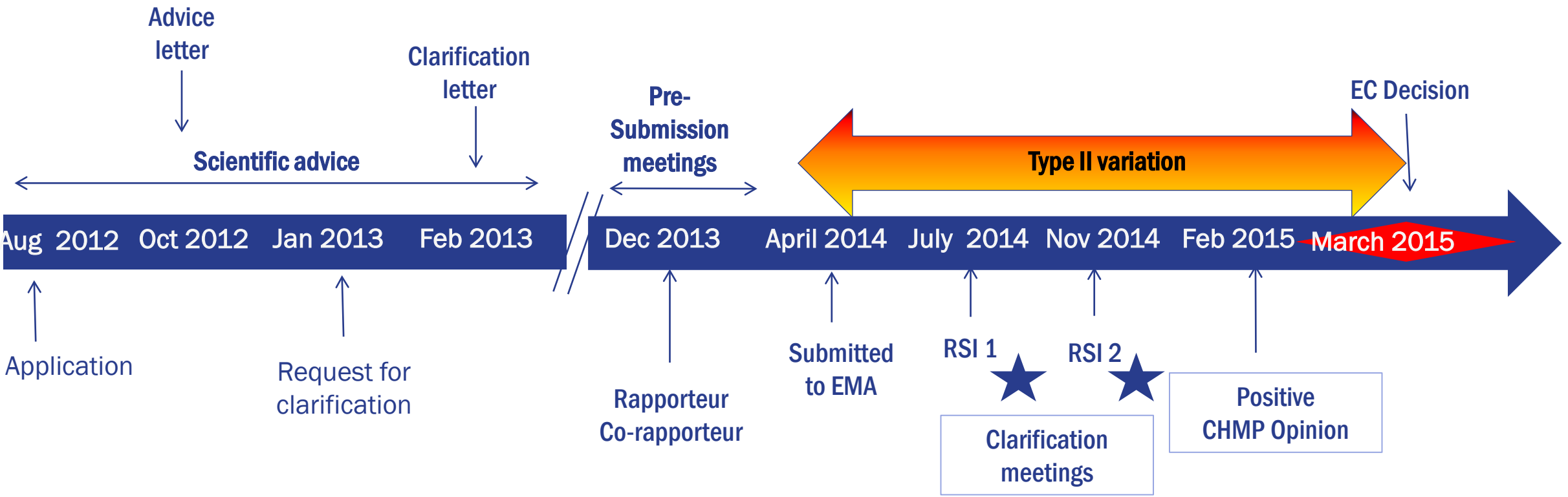
TIMELINES


Advice letter
Clarification letter
Pre-Submission meetings
EC Decision
Scientific advice
Type II variation
Aug 2012
Oct 2012
Jan 2013
Feb 2013
Dec 2013
April 2014
July 2014
Nov 2014
Feb 2015
March 2015
Application
Request for clarification
Rapporteur Co-rapporteur
Submitted to EMA
RSI 1
RSI 2
Clarification meetings
Positive CHMP Opinion

LESSONS LEARNED

- Data from registry can be used to support revision of approved Labels
- QOL data have been a key element of the data package

- A registry is a good alternative when a prospective randomized study is not possible (when a no-treatment control group is considered impossible or unethical)

- Limitations
  - The number of patients for whom data are available decreases dramatically over time
  - Data are not blinded (potential biased evaluation of subjective endpoints such that fatigue, dyspnoea, QoL, other related symptoms)

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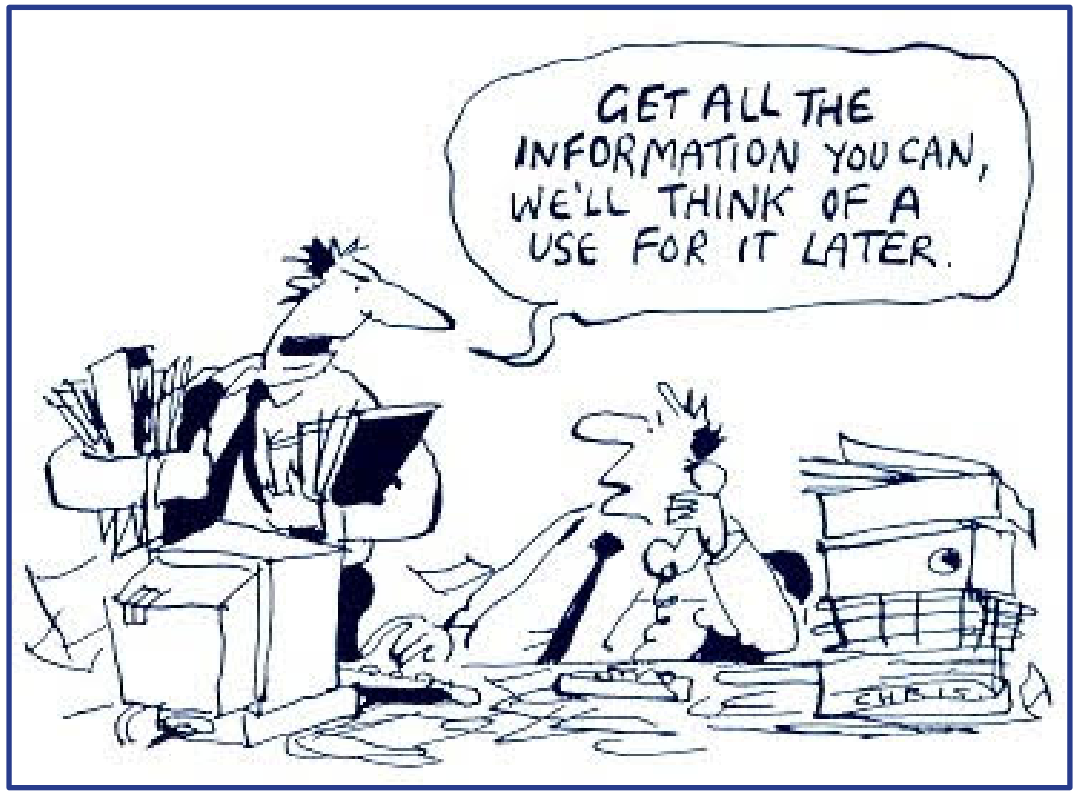
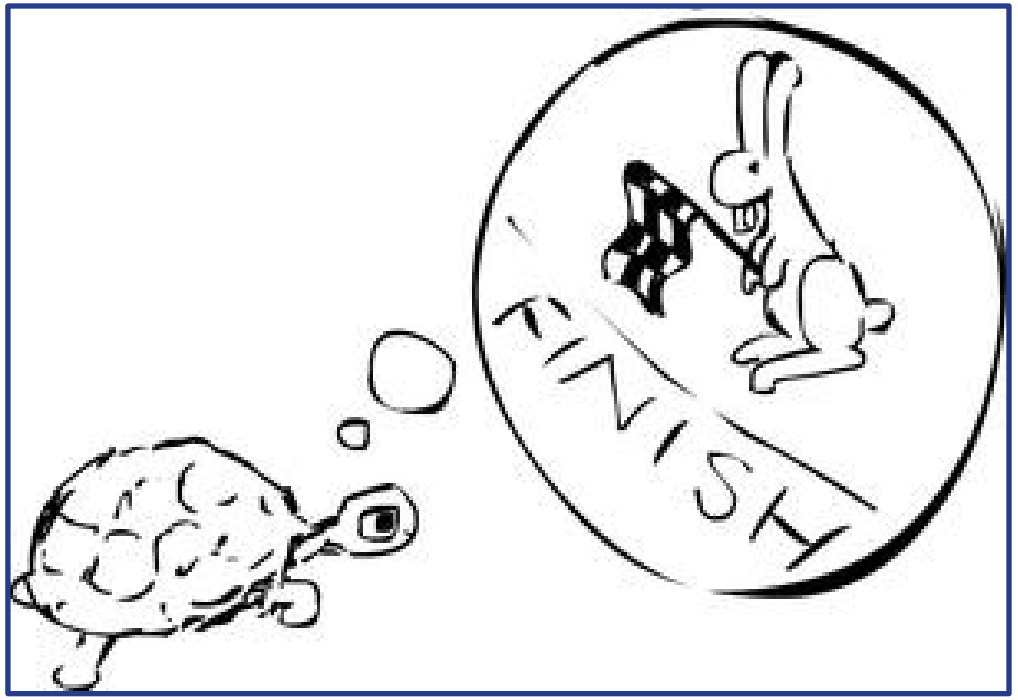
CONCLUSION





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TRANSFORMING THE LIVES OF PATIENTS

Alexion is focused on developing life-transforming treatments for patients with devastating and rare diseases

QUESTIONS ?