An Academic European Clinical Trial for Elderly (55y or over) Ph+ Acute Lymphoblastic Leukemia EWALL-PH-01

Ph Rousselot, WP6

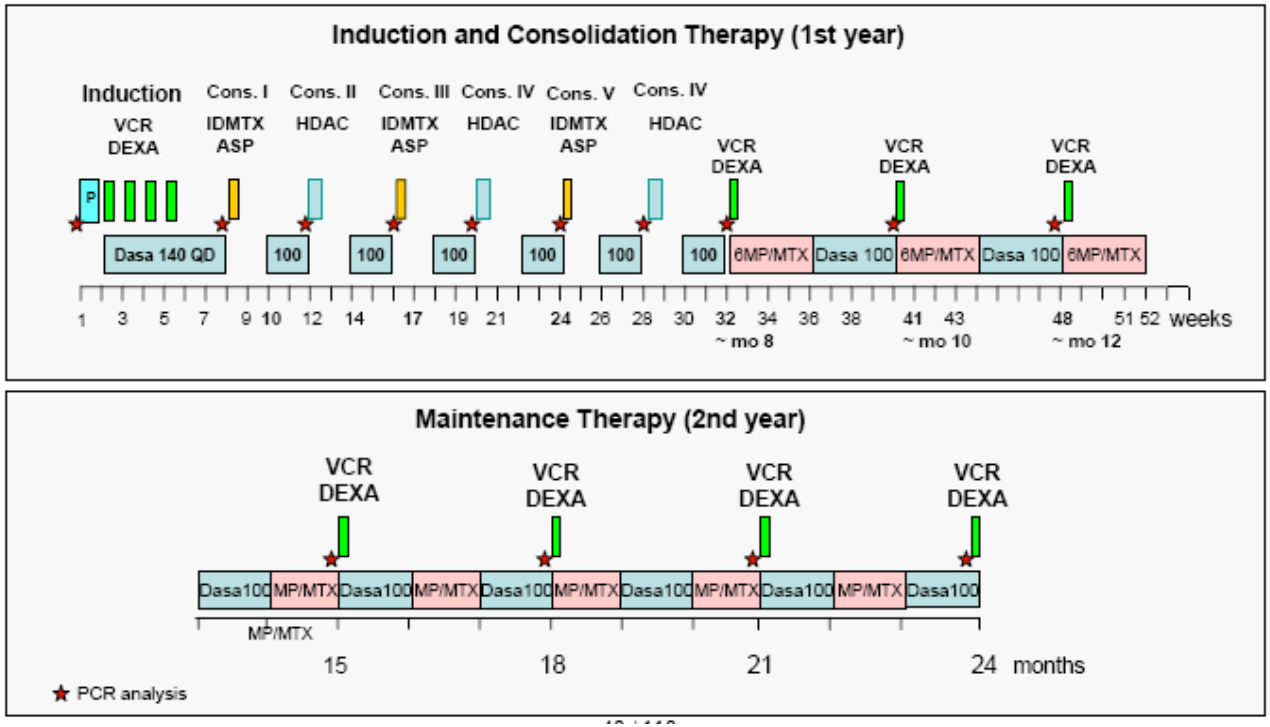
Before the draft…

- A favorable context :
  - Previous experience of each national group with Ph+ ALL treated by imatinib (IM) and chemotherapy
    - GMALL trial : IM and chemo sequentially compared with IM and chemo in combination
    - GRAALL trials : IM and chemo sequentially, IM and chemo in combination
  - A medical need :
    - Very high relapse rate in these previous studies
    - A rare disease
  - Two Mentors : Dieter Hoelzer and André Delannoy
  - Two diplomatists/writers : Oliver Ottmann and Philippe Rousselot
  - Leading countries : Germany and France

Writing the draft…

- Making the compromise : 2 years, more than 20 versions (20/11/2004 – 11/11/2006)
  - GMALL : high dose chemotherapy, standard dose Imatinib
  - GRAALL : low dose chemotherapy, high dose Imatinib
  - EWALL-PH-01
    - A non randomized trial, recruitment during max 24 months (n=55)
    - A new more potent TKI : dasatinib marketed by Bristol-Myers Squibb
    - Induction : low dose chemo, high dose dasatinib simultaneously
    - Consolidation : intermediate dose chemo, standard dose dasatinib, sequentially
    - Maintenance : low dose chemo, standard dose dasatinib, sequentially
- Protocol approved by EWALL :
  - 7th Meeting of the EWALL, November 10-11, 2006 – Frankfurt Gravenbruch

EWALL-PH-01 overview



Submitting the draft…

- December 2006 : Submission to BMS for drug support, grant and expertise in international trials
- March 2007 : protocol accepted by BMS IPRC
- April 2007 : financial support accepted by BMS Europe
- April 2007 : Submission to the Sponsor
- May 2007 : Submission to Health Authorities
  - EudraCT number
  - IRB approval : 27/05/2007
  - French National Health Agency approval : 29/06/2007

The Sponsor

- A local institution : Hôpitaux de Versailles, France
  - For :
    - Previous experience with national clinical trials
    - A confidence based relationship
    - Few persons involved in the decision process
    - A partnership with the insurance company
  - Against :
    - Lack of previous experience at the European level
    - Lack of previous knowledge of European rules

Total budget of the study

- For 4 years : 318,5 Keuros
- Including
  - Sponsor fees 20 K€
  - Central Monitoring / PV 180 K€
  - Travel / visits / local monitoring 82.5 K€
  - eCRF 12 K€
  - Drug distribution 24 K€
- Local fees
  - Submission to RA : covered
  - Local data capture : not covered
- Support : BMS, AMGEN, Institutional (France)

BMS expertise and support

- **First meeting with BMS Europe : 19/12/2006**
- **4 Key decisions :**

1. **Each country will have a Principal Investigator to which some sponsor activities/responsibilities will be delegated**
2. **The responsibilities of the PI and other investigators will be listed in a protocol appendix (i.e.: delegation agreement)**
3. **Study submission to HA / EC to be performed by the country PI**
4. **The study is off label, Commercial supply will be used, re-labeling and distribution will be outsourced (CRO)**

The contract with BMS

- Industrial property to BMS
- Intellectual property to the Sponsor/EWALL

Three key statements

1. The sponsor will delegate all trial-related tasks/duties to each principal investigator in each participating country (e.g. compiling the documents for the application to the local Ethics Committee and responsible regulatory authorities, monitoring of the trial including all responsibilities for the pharmaco-vigilance reporting system) according to Article 16 and 17 of Directive 2001/20/EC.

2. The sponsor remains ultimately responsible for ensuring that the conduct of the trial and the final data generated by those trials comply with the requirements of Directive 2001/20/EC

3. The Pharmacovigilance is delegated to a CRO

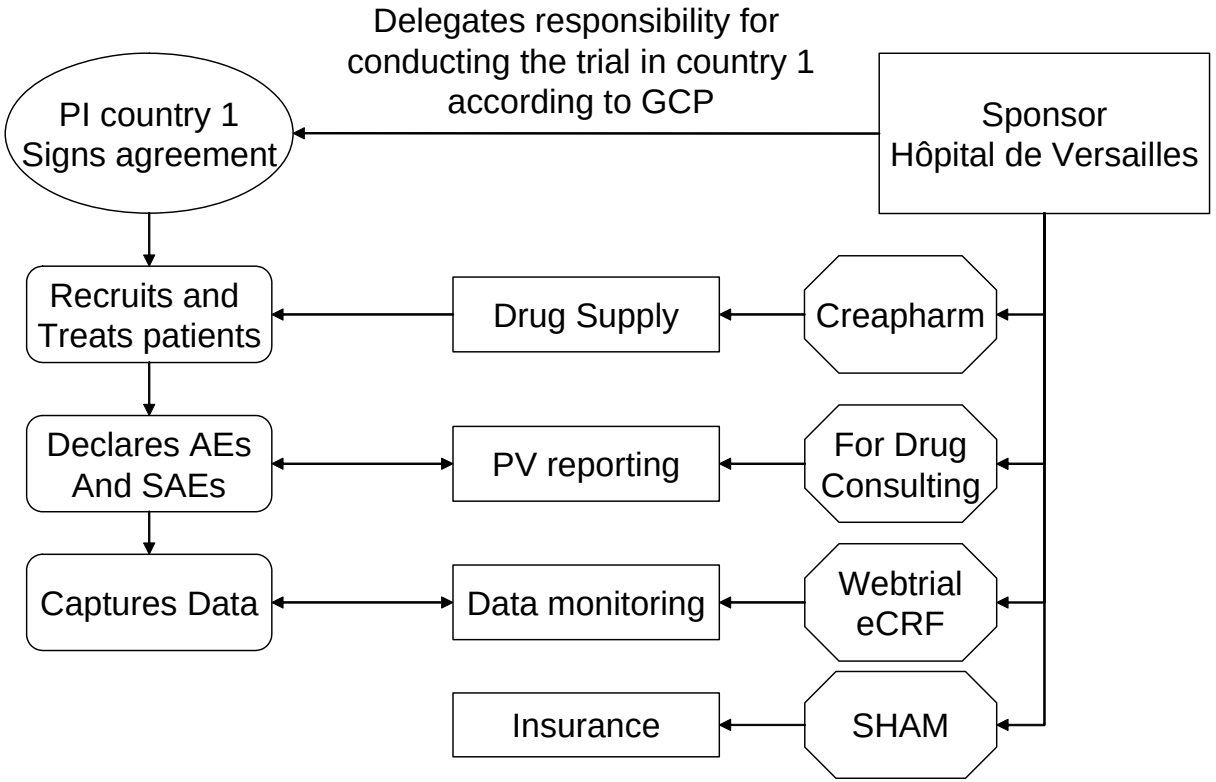
Delegation agreement with PIs

- Both parties agree to conduct the above-mentioned study in accordance with the applicable country law and regulations, the current European Standard for Good Clinical Practice, the Declaration of Helsinki and the Guideline for Good Clinical Practice as well as the protocol.

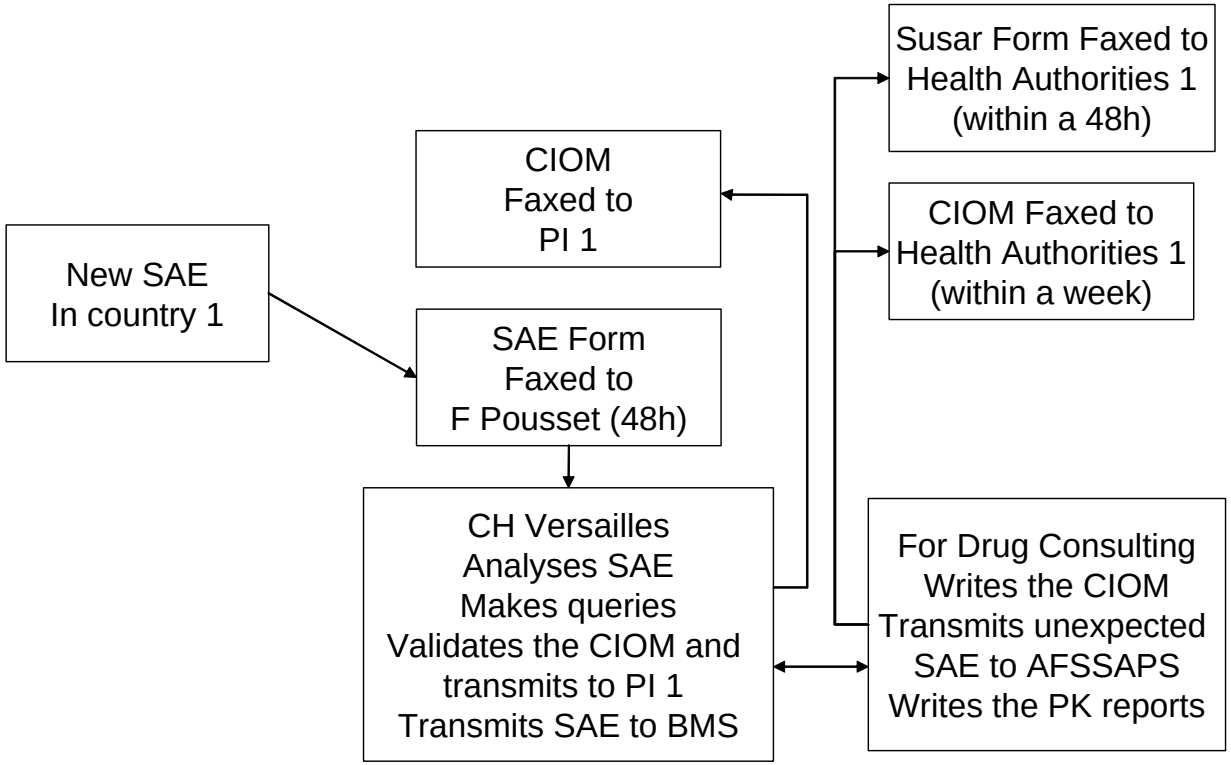
- Both parties agree that the Principal Investigator for Germany assumes sponsor responsibilities to conduct the Study in Germany according to the attached responsibility plan

- The responsibility plan lists all the sponsor´s responsibilities and the distribution of responsibilities for each country

Organization scheme



Pharmacovigilance



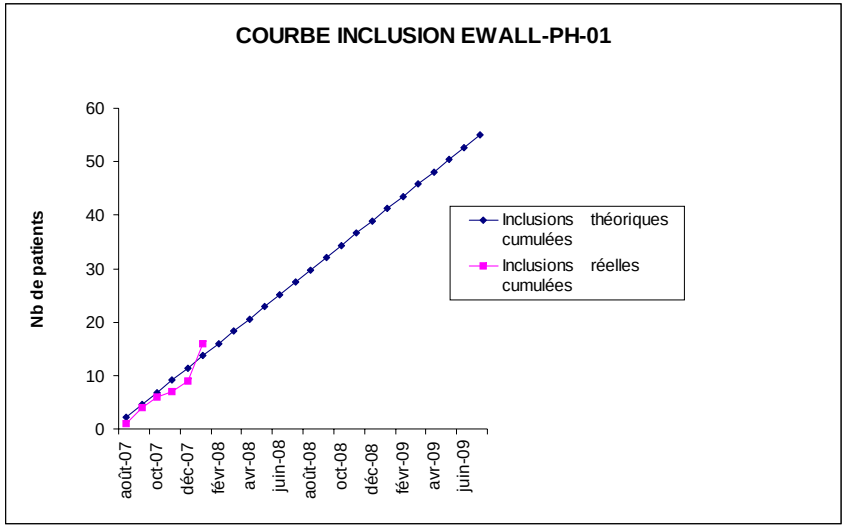
Study activation in EU

Study documents : www.leukemia-net.org

	Fra	Ger	Ital	Spain	Poland	Belg	Czech
Application to Reg Aut	x	x	x	x	x	x	x
Nat ethic Committee	x				x	x	x
Loc ethic Committees		x	x	x			
Protocol signatures	x	x	x	x	x	x	x
Delegation agreement	x	x	x	x	x	x	x
Procedures, SOPs		x					
Study Insurance	x	x	x	x	x	x	x
Patient insurance		x					
Trial med. Documents	x	x	x	x	x	x	x
CRF	x	x	x	x	x	x	x
Pharmacovigilance	x	x	x	x	x	x	x

Study Status

- Activated in France and Italy
- First patient, first visit 31/08/2007
- 16 patients included



Acknowledgments

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  - Nicola Gökbuget, Oliver G Ottmann, Dieter Hoelzer GMALL, Germany
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  - Renato Bassan NILG, Italy
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  - Jerzy Holowiecki, Sebastian Giebel PALG, Poland
  - Michael Doubek, Jiri Mayer, Czech Republic
  - Hervé Dombret, GRAALL, France
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  - F Pousset, A Chabannes
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