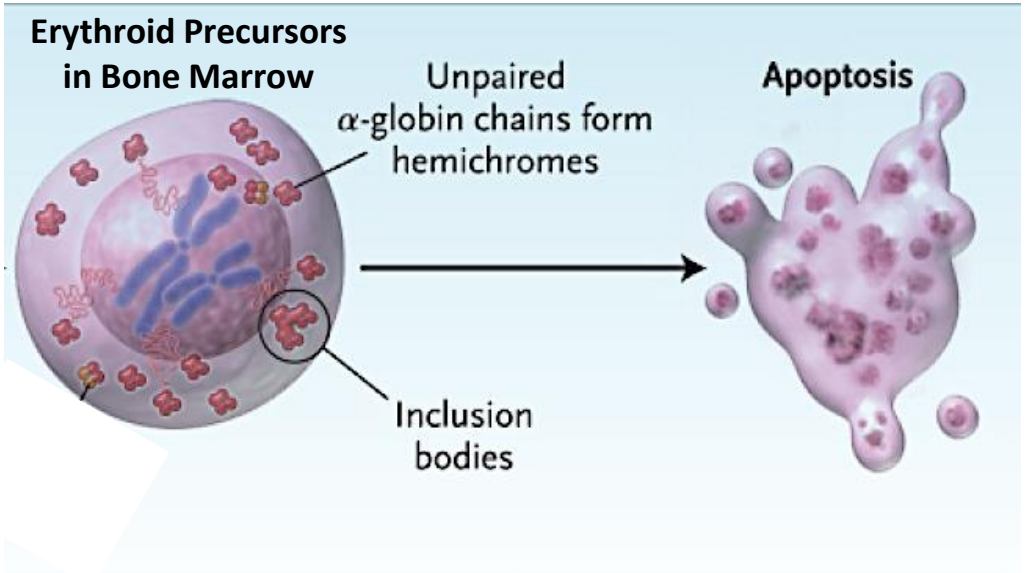
Luspatercept Decreases Transfusion Burden and Liver Iron Concentration in Regularly Transfused Adults with Beta-Thalassemia

Antonio G. Piga, MD[1], Silverio Perrotta, MD[2], Angela Melpignano, MD[3], Caterina Borgna-Pignatti, MD[4], M. Rita Gamberini, MD[4], Ersi Voskaridou, MD[5], Vincenzo Caruso, MD[6], Paolo Ricchi, MD[7], Antonello Pietrangelo, MD[8] , Xiaosha Zhang[9], Dawn M. Wilson[9], Ashley Bellevue[9], Abderrahmane Laadem, MD[10], Matthew L. Sherman, MD[9] and Kenneth M. Attie, MD[9]

[1]Turin University, Turin, [2]Second University of Naples, Naples, [3]Ospedale "A. Perrino", Brindisi, [4]Arcispedale S.Anna, Cona, Ferrara, Italy; [5]Laiko General Hospital, Athens, Greece; [6]ARNAS Garibaldi, Catania, [7]AORN "A. Cardarelli", Naples, Italy; [8]CEMEF, Medicina 2, Modena, Italy; [9]Acceleron Pharma, Cambridge, MA, USA; [10]Celgene Corporation, Summit, NJ, USA.

β-Thalassemia

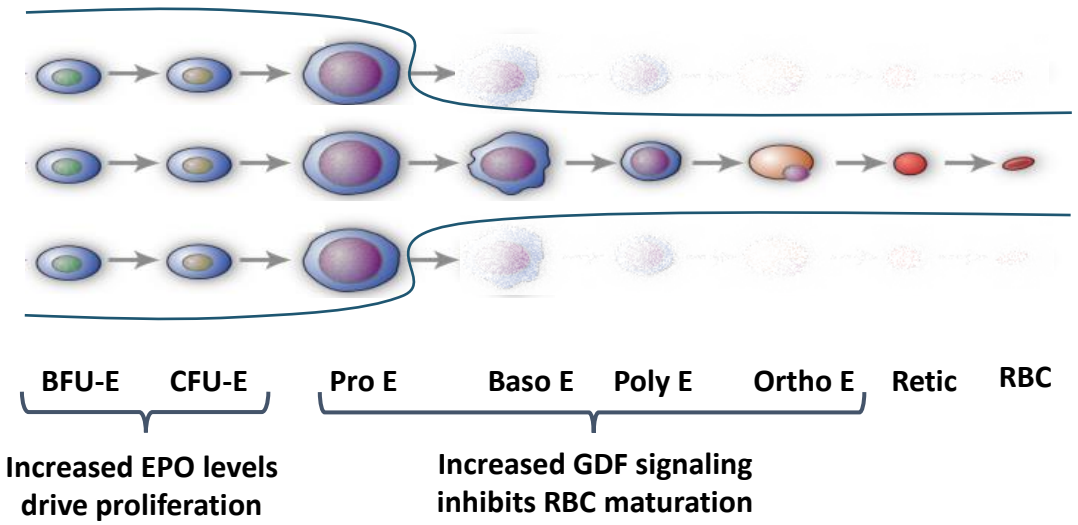
- β-thalassemia is an inherited anemia due to defective synthesis of β-globin
  - Excess unpaired α-globin chains lead to **ineffective erythropoiesis,** characterized by apoptosis of maturing erythroblasts in the bone marrow



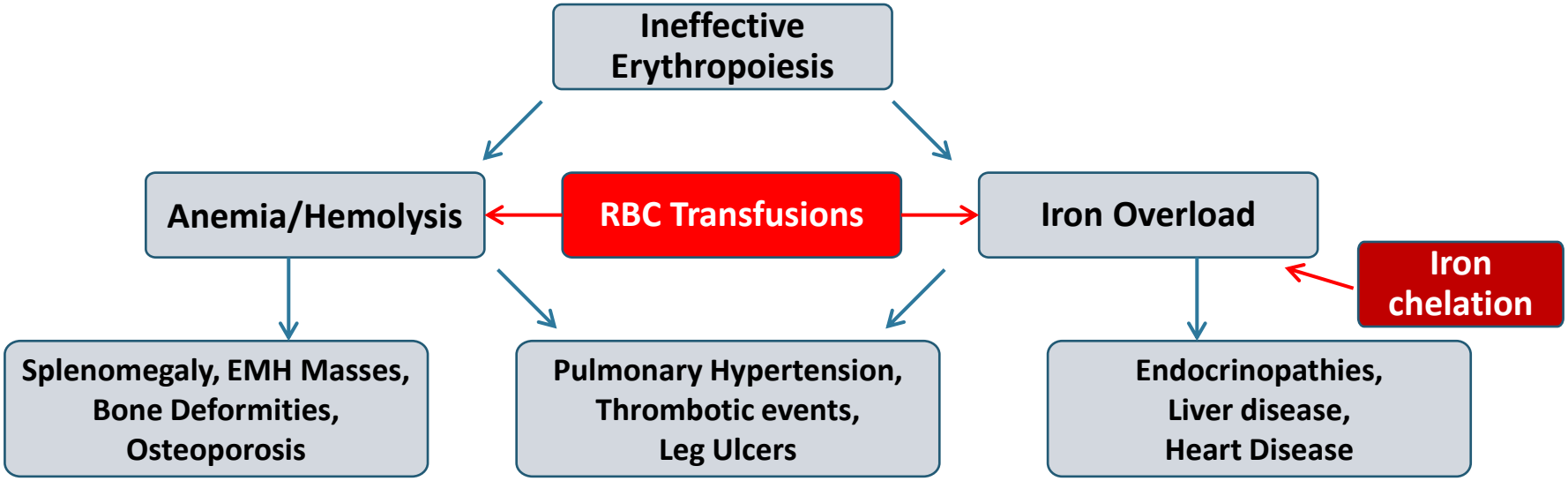
Rund D, Rachmilewitz E, NEJM 2005

β-Thalassemia

- β-thalassemia is an inherited anemia due to defective synthesis of β-globin
  - Excess unpaired α-globin chains lead to **ineffective erythropoiesis,** characterized by apoptosis of maturing erythroblasts in the bone marrow
- **Excess GDF**11 and other TGF-β superfamily **ligands** increase Smad 2/3 signaling and block RBC maturation, resulting in erythroid hyperplasia in the bone marrow



Ineffective Erythropoiesis Drives β-Thalassemia Complications



No approved drug therapy for anemia due to β-thalassemia

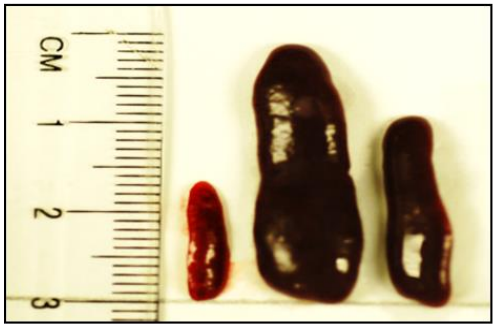
Luspatercept Reduces Promotes Late-Stage Erythropoiesis and Reduces Disease Burden in Mouse Model of β-Thalassemia

Modified ECD of ActRIIB receptor

Fc domain of human IgG_1

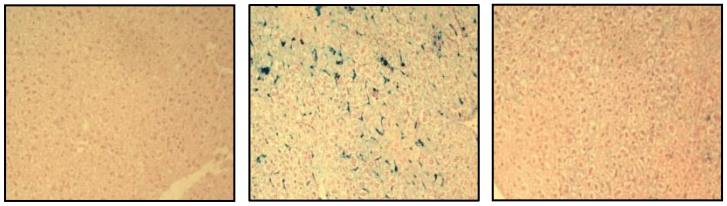
- Luspatercept is an investigational drug that is a recombinant fusion protein containing a modified extracellular domain (ECD) of the activin receptor type IIB (ActRIIB)
  - Binds to GDF11 and other ligands, inhibits Smad 2/3 signaling, and promotes late-stage erythropoiesis
  - RAP-536 (murine luspatercept) reduced disease burden in mouse model of β-thalassemia
  - Increased hemoglobin levels in healthy volunteers and patients with myelodysplastic syndromes

Spleen



WT *th1/th1* *th1/th1* + RAP-536

Liver Iron



WT *th1/th1* *th1/th1* + RAP-536

Bone

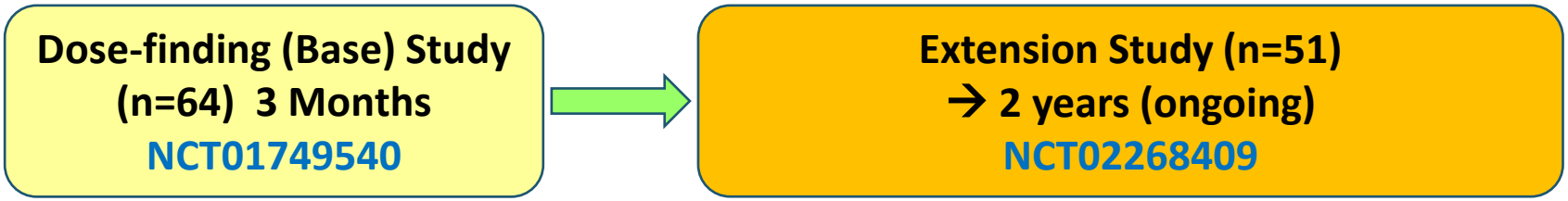
WT *th1/th1* *th1/th1* + RAP-536

Suragani R et al., Nature Med, 2014
Suragani R et al., Blood, 2014
Attie, K et al., Am J Hematol, 2014
Platzbecker U et al., EHA 2016, S131

Luspatercept β-Thalassemia Phase 2 Clinical Trials – Overview

- A phase 2, multicenter, open-label, study in adults with β-thalassemia
  - **Non-transfusion dependent (NTD):** < 4 units/8 wk and Hb < 10 g/dL
  - **Transfusion dependent (TD):** ≥ 4 units/8 wk
- **Primary efficacy endpoints** (over 8 or 12 wk)
  - TD: Transfusion burden decrease ≥ 20% or ≥ 50%
  - NTD: Hemoglobin increase ≥ 1.0 or ≥1.5 g/dL
- **Secondary endpoints** include:
  - Safety
  - Liver iron concentration (by MRI)
  - Health-related Quality of Life (FACT-An)
  - Biomarkers of erythropoiesis

Luspatercept Phase 2 Clinical Trials: Design



TD: n=30

NTD: n=34

TD: n=24

NTD: n=27

Dose levels (administered SC q3 weeks)

- Base study dose escalation phase (n=35): 0.2, 0.4, 0.6, 0.8, 1.0, and 1.25 mg/kg and expansion cohort (n=29): starting dose 0.8 mg/kg, titration up to 1.25 mg/kg (total n=64)
- Extension study (n=51): 0.8-1.25 mg/kg

Follow-up

- All patients are followed for 2 months post-treatment completion or early discontinuation

Baseline Characteristics of Transfusion Dependent Patients

Parameter	Baseline Characteristics	
	Base Study N=30	Extension Study N=24
Age, yr, median (range)	37.5 (21-54)	37.5 (22-55)
Sex, male, n (%)	12 (40%)	12 (50%)
Splenectomy, n (%)	20 (67%)	16 (67%)
RBC Units/12 weeks, median (range)	8 (4-18)	8 (4-15)
Liver iron concentration (LIC), mg/g dry wt, mean ± SD	4.9 ± 5.4 (n=29)	5.1 ± 5.3
Duration of treatment, weeks (range)	--	6-71 (ongoing)

Data as of 11 Mar 2016

Reduction in Transfusion Burden

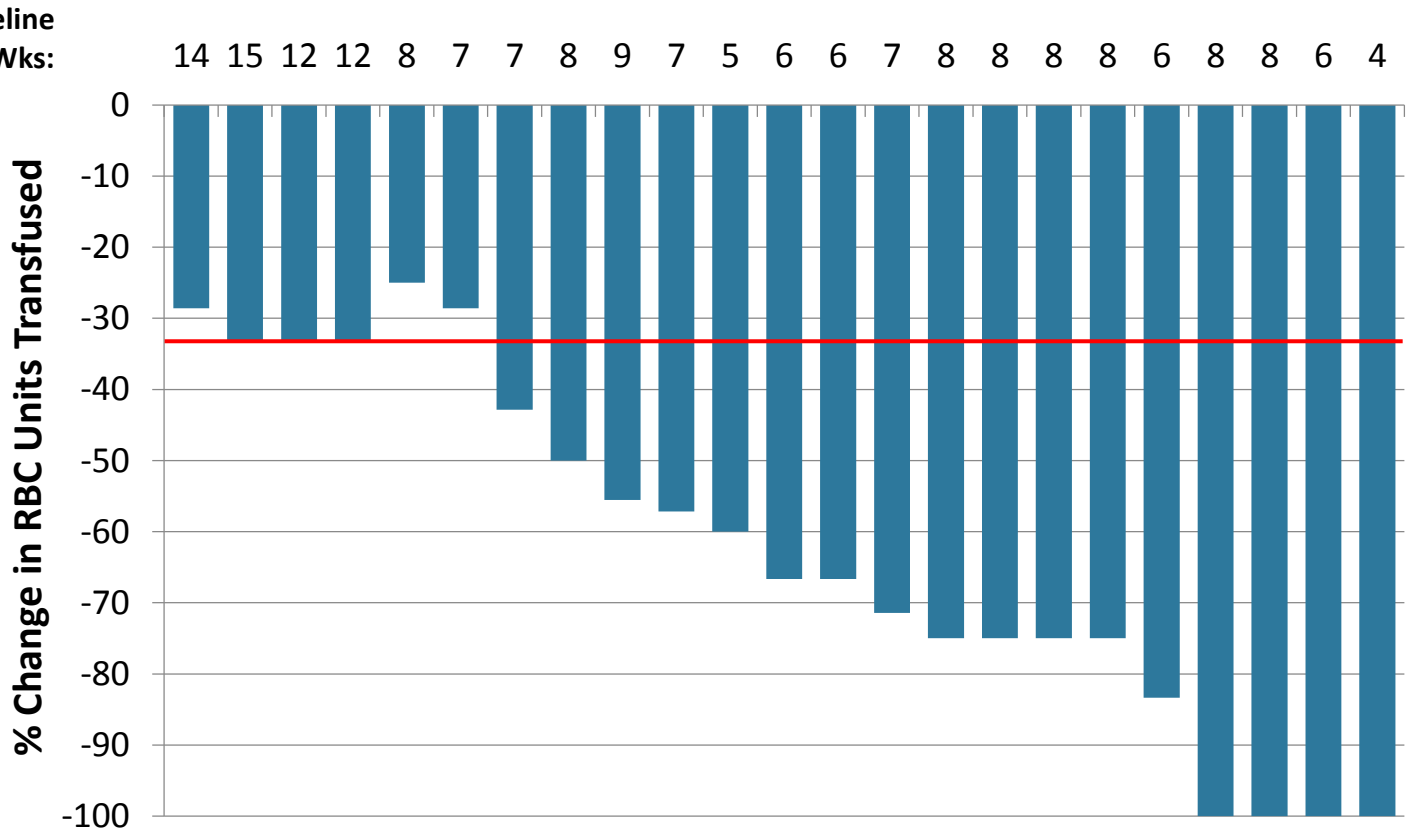
- Transfusion reduction from 12 weeks pre-treatment to any 12-wk period on treatment

% Reduction in RBC Units Transfused	Patients with Reduction in Transfusion Burden, n (%)	
	Base Study N=30	Extension Study N=24
20% reduction	24 (80%)	23 (96%)
33% reduction	20 (67%)	20 (83%)
50% reduction	16 (53%)	16 (67%)

Data as of 11 Mar 2016

Reduction in Transfusion Burden in Patients in Extension Study

- Transfusion reduction from 12 weeks pre-treatment to any 12-wk period on treatment
- Duration of ≥ 33% reduction ranged from 12 to 48+ weeks



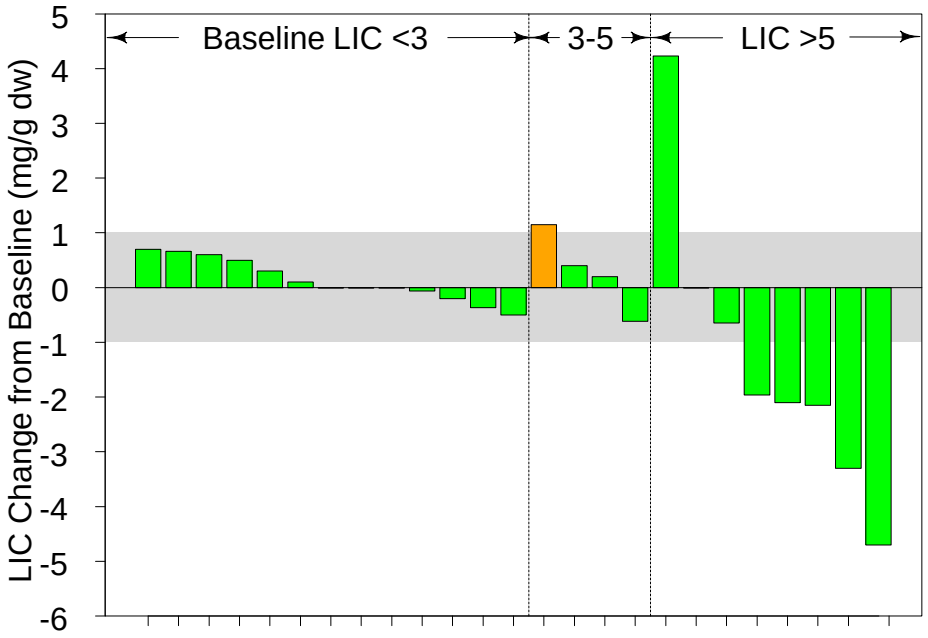
* 1 subject discontinued before completing 12 weeks, not shown

Data as of 11 Mar 2016

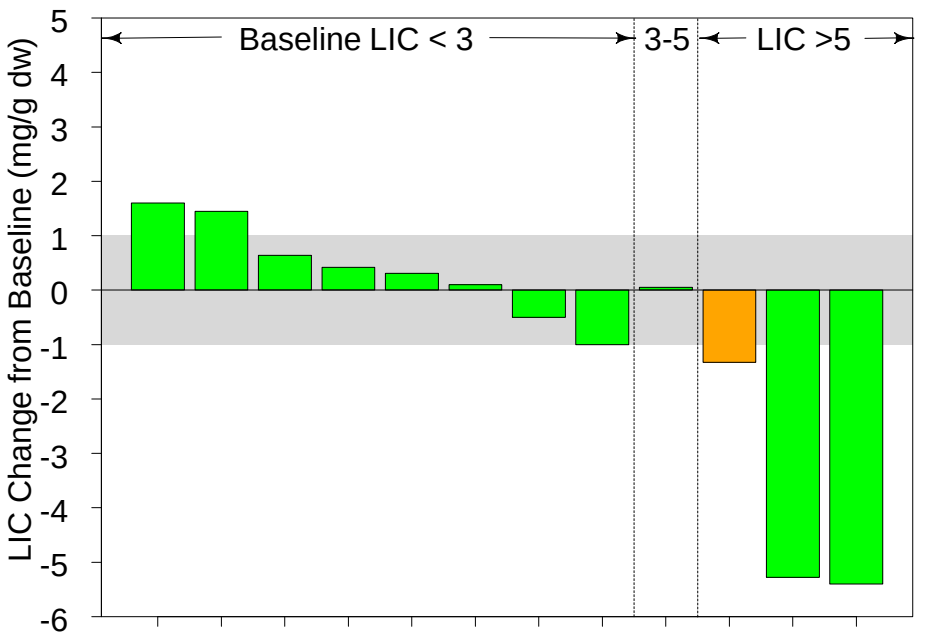
Change in Liver Iron Concentration (MRI) in TD Patients

- ~50% patients with baseline LIC ≥ 5 mg/g dw achieved ≥ 2mg/g dw

Baseline → 4 Months



Baseline → ≥ 6 Months



No Iron Chelator
Iron Chelator

Data as of 11 Mar 2016

Safety Summary – Adverse Events in TD Patients

- No related serious adverse events
- Related grade 3 adverse events included: bone pain (n=2 base, n=1 extension), asthenia (n=2 base) and myalgia (n=1 extension)
- Favorable safety profile for luspatercept in patients with β-thalassemia was maintained in long-term extension study

Preferred Term	Related AEs (all grades) in >10% TD Patients, n (%)	
	Base Study N=30	Extension Study N=24
Bone pain	15 (50%)	5 (21%)
Myalgia	8 (27%)	2 (8%)
Arthralgia	6 (20%)	2 (8%)
Headache	6 (20%)	3 (13%)
Asthenia	5 (17%)	0
Musculoskeletal pain	4 (13%)	2 (8%)

TD: Transfusion dependent patients (≥ 4 Units/8 wk)

Data as of 11 Mar 2016

Luspatercept in Transfusion-Dependent β-Thalassemia

- Luspatercept was generally safe and well-tolerated with no related serious adverse events
- Reduced transfusion burden was observed in the majority of TD patients
- Reductions in liver iron concentration (LIC) were also observed in patients on iron chelators with elevated LIC at baseline
- These results supported the initiation of a Phase 3 study of luspatercept in TD patients with β-thalassemia (The **BELIEVE** Study, NCT02604433)

The BELIEVE Study

Phase 3 Study of Luspatercept in β-thalassemia: NOW ENROLLING

Patient Population / Study Design	Randomized, double-blind, placebo-controlled study in adult β-thalassemia patients (including HbE/β-thal) 300 patients, randomized 2:1; luspatercept 1 mg/kg SC every 3 weeks, titration up to 1.25 mg/kg possible
Key Eligibility Criteria	Patients who receive 6-20 units of RBCs over past 24 weeks and no transfusion-free period ≥ 35 days (regularly transfused patients) No ESA or hydroxyurea
Primary Efficacy Endpoint	Proportion of patients with ≥ 33% reduction in transfusion burden from weeks 13-24 compared to the 12 weeks preceding treatment

Sponsored by Celgene in collaboration with Acceleron

NCT02604433

Luspatercept β-Thalassemia Phase 2 Study: Acknowledgments

- **Investigators:** A Piga, A Melpignano, S Perrotta, C Borgna-Pignatti, MR Gamberini, V Caruso, E Voskaridou, A Filosa, P Ricci, A Pietrangelo
- **Sub-investigators:** I Alasia, M Limone, E Longoni, F Della Rocca, U Pugliese, I Tartaglione, L Manfredini, A Quarta, G Abbate, S Anastasi, R Lisi, M Casale, P Cinque, S Costantini, M Marsella, P Ricchi, A Spasiano
- **Acceleron:** K Attie, M Sherman, D Wilson, A Bellevue, C Rovaldi, B O'Hare, T Akers, X Zhang, J Desiderio, S Ertel, T Sacco
- **Celgene:** A Laadem, S Ritland, J Zou, N Chen
- **Chiltern:** C Lanza, F Van der Schueren, M Belfiore
- **Central Labs:** CRL, ICON, ILS
- **Independent Safety Reviewer:** E Neufeld

Sponsored by Acceleron Pharma and Celgene