

# **PLASMA-DERIVED VS RECOMBINANT FVIII PRODUCTS AND INHIBITORS IN PUPs**

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# CONFLICTS OF INTEREST

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- **Consultant and speaker at scientific meetings organized by producers of plasma-derived coagulation factor concentrates (Kedrion, Grifols, Biotest), as well as by manufacturers of recombinant factors (Bayer, Baxter, Novo Nordisk, Pfizer)**

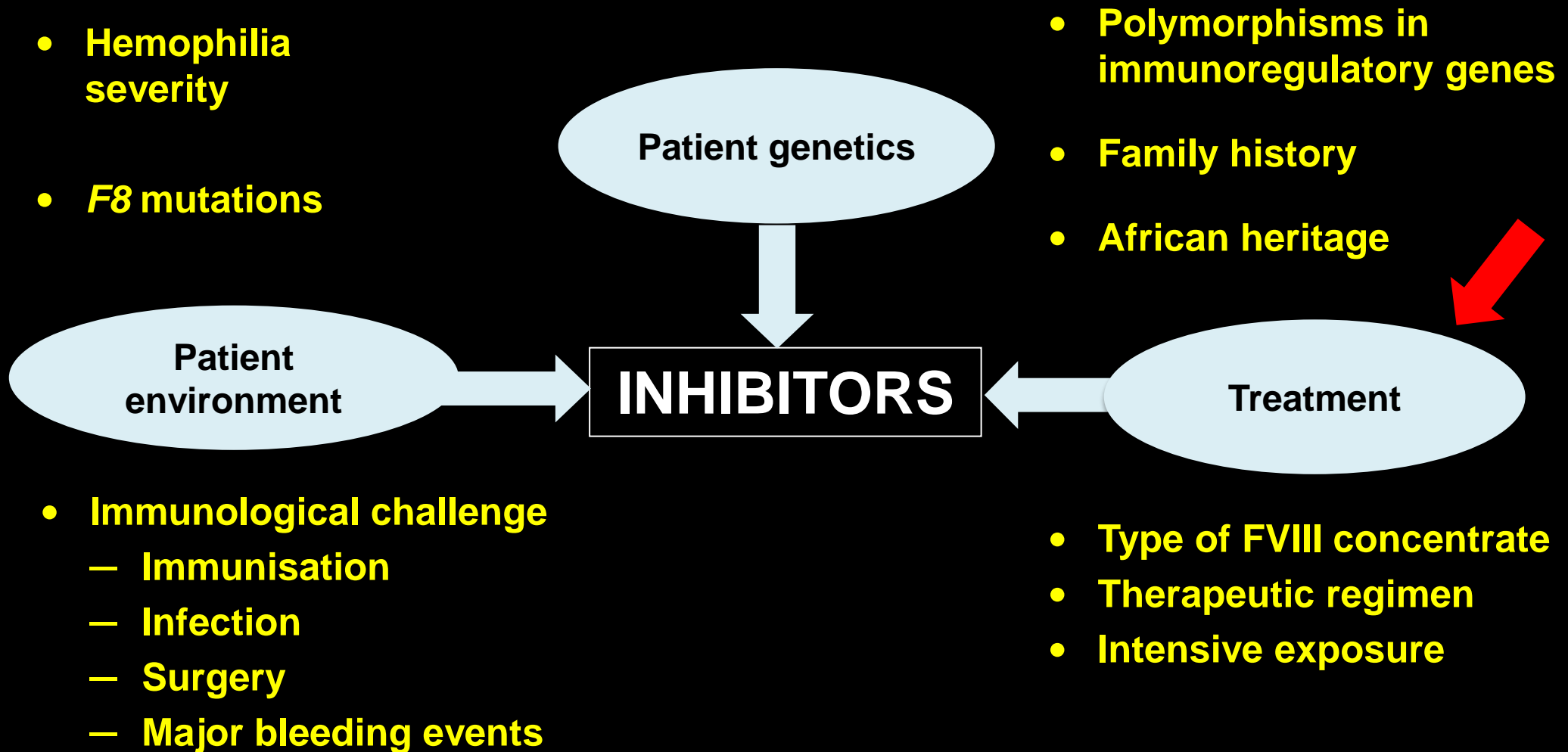
# OUTLINE

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- **Background on inhibitors in PUPs**
- **Current status of recruitment and randomization in SIPPET**
- **Overall inhibitor rate**
- **Outcome of the interim analysis**

# RISK FACTORS FOR INHIBITOR DEVELOPMENT

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# **FVIII INHIBITOR PREDICTIVE FACTORS IN PREVIOUSLY TREATED PATIENTS (PUPs)**

**POTENTIALLY MODIFIABLE**

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- 1. Source/type of factor VIII: recombinant vs plasma derived products**
- 2. Biological plausibility?**

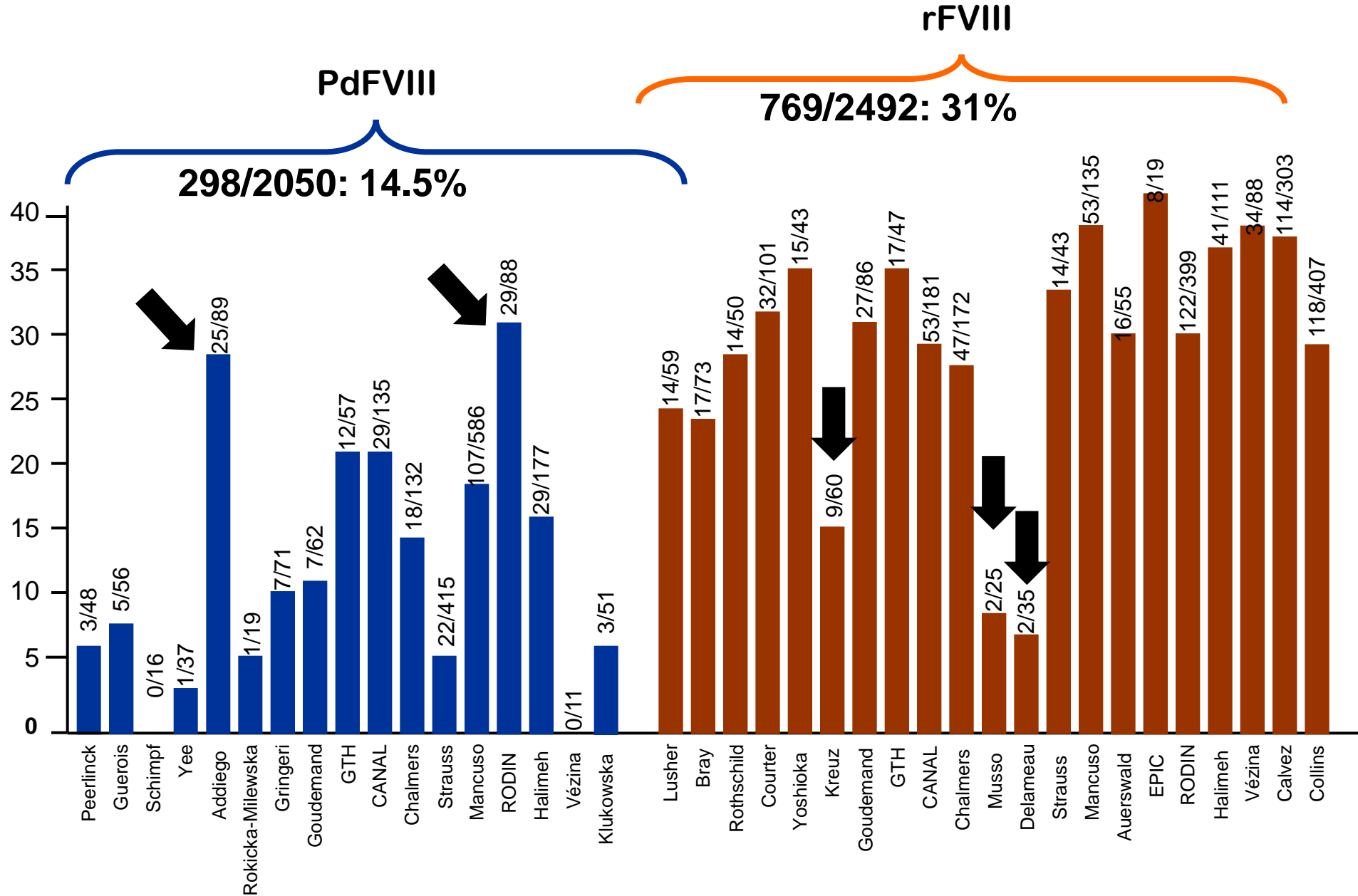
# BIOLOGICAL PLAUSIBILITY

## DIFFERENCES BETWEEN pdFVIII AND rFVIII

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- rFVIII produced from mammalian cell lines vs native FVIII from human plasma
- Post-translational modifications of rFVIII
- High VWF content in pdFVIII products (epitope masking, protection from endocytosis)
- Immunomodulatory human proteins in pdFVIII?

# Higher crude incidence of inhibitors in previously untreated children with severe hemophilia A (PUPs) treated with recombinant FVIII



# INHIBITOR INCIDENCE IN PUPs

## Limits of all available studies

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### Non-homogenous study populations

- Severity (<1/≤2%)
- mutation type
- ethnicity
- pre-treatment (previously untreated, minimally pretreated)
- therapy regimen (early vs late prophylaxis, prophylaxis vs on demand)

### Non-homogenous study designs

- frequency of inhibitor testing
- prospective/retrospective
- length of observation periods



**RODIN COHORT STUDY**  
**(Gouw et al. NEJM 2013)**  
**DESIGN**

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**Multicenter observational cohort study**  
**(mainly prospective, partially retrospective)**

**574 severe hemophilia A PUPs**  
**(29,679 exposure days)**

**177 pts (32%) developed inhibitors**

**RODIN COHORT STUDY**  
**(Gouw et al. NEJM 2013)**  
**MAIN RESULTS**

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**Risk of inhibitor development  
similar for pd FVIII and rFVIII**

**Adjusted Hazard Ratio  
0.96 (95% CI 0.62 – 1.49)**

# LIMITATIONS OF RODIN .1

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- **Lack of random assignment to FVIII products**
- **Many patients on plasmatic FVIII were treated with monoclonal FVIII, and results were conglomerated with those on VWF-rich products**
- **Smaller number of cases treated with pd FVIII (4.018 exposure days vs 25.661 for those treated with rFVIII)**

# **THERE IS STILL AN ISSUE RELATED TO FVIII INHIBITORS AND SOURCES OF FVIII?**

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- We believe that the results obtained in cohort studies are inconclusive and indicate the need for a randomized clinical trial**

# **RANDOMIZED CLINICAL TRIALS (RCTs)**

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- **Randomized clinical trials are the basis of evidence-based medicine**
- **They provide grading of evidence for therapeutic choices**

**Inhibitor Development in Previously Untreated Patients (PUPs) or Minimally Blood component-Exposed Patients (MBEPs) when Exposed to von Willebrand Factor-Containing Factor VIII Concentrates and to Recombinant Factor VIII Concentrates:  
An International, Randomised, Clinical Trial**

**Steering Committee: *P.M. Mannucci, F. Peyvandi, S. Apte, J. Aznar, H. Chambost, D. Di Michele, J. Goudemand, W. Kreuz, R. Kruse-Jarres, J. Mahlangu, E. Mancuso, C. Negrier, E. Santagostino, M. Tarantino***

**Study acronym: SIPPET  
(Sudy on Inhibitors in Plasma-Product Exposed Toddlers)**

# CHOICE OF STUDY PRODUCTS IN SIPPET

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- **SIPPET assumes that all FVIII products are equally efficacious and broadly equivalent pertaining to their capacity to control bleeding**
- **Hence, the study is based on the randomized comparison of two classes of FVIII products (plasma-derived, VWF-rich vs recombinant with no VWF) regarding inhibitor rate**

# SIPPET TREATMENT PLAN

270 PUPs or minimally treated patients with Severe HA are randomised to receive one product of 2 classes

The class of recombinant FVIII products, not containing von Willebrand factor:

- Recombinate (Baxter)
- Advate (Baxter)
- Kogenate SF (Bayer)
- Refacto AF (Pfizer)

Recombinant Arm

The class of plasma-derived FVIII products, containing von Willebrand factor:

- Alphanate (Grifols)
- Fandhi (Grifols)
- Emoclot (Kedrion)
- Factane (LFB)

Plasma-derived Arm



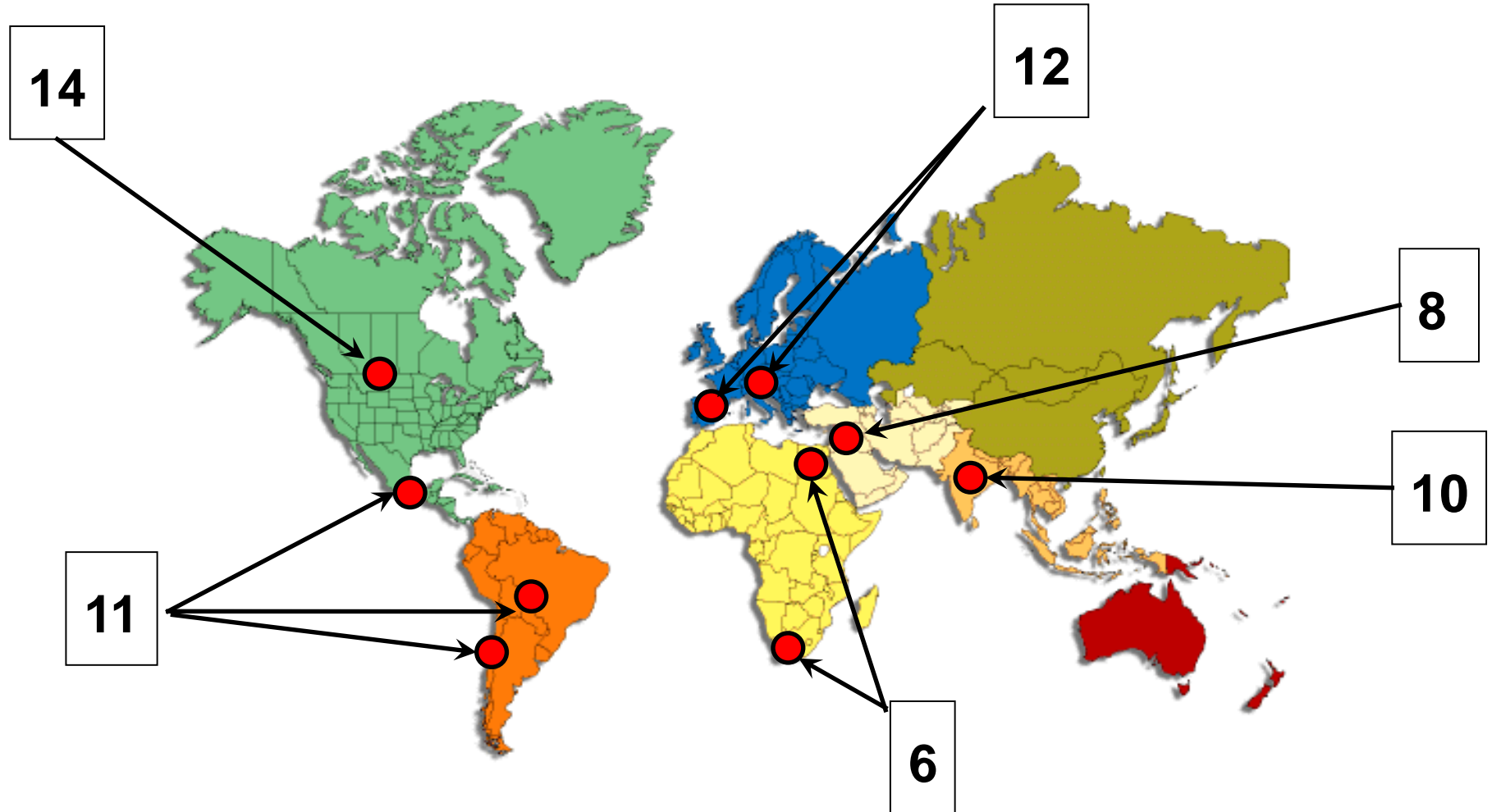
# SIPPET STUDY CHARACTERISTICS

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- **Investigator initiated study**
- **Multicentre, randomized, open label**
- **270 patients to be treated (300 recruited)**
- **Proven no inhibitor at baseline**
- **Blocked 1:1 randomization (block size 2)**
- **Main endpoint: all neutralizing antibodies (inhibitor)**
  - **Secondary: high titre inhibitors**
- **Follow-up**
  - **Inhibitors measured at frequent and established post-treatment intervals**

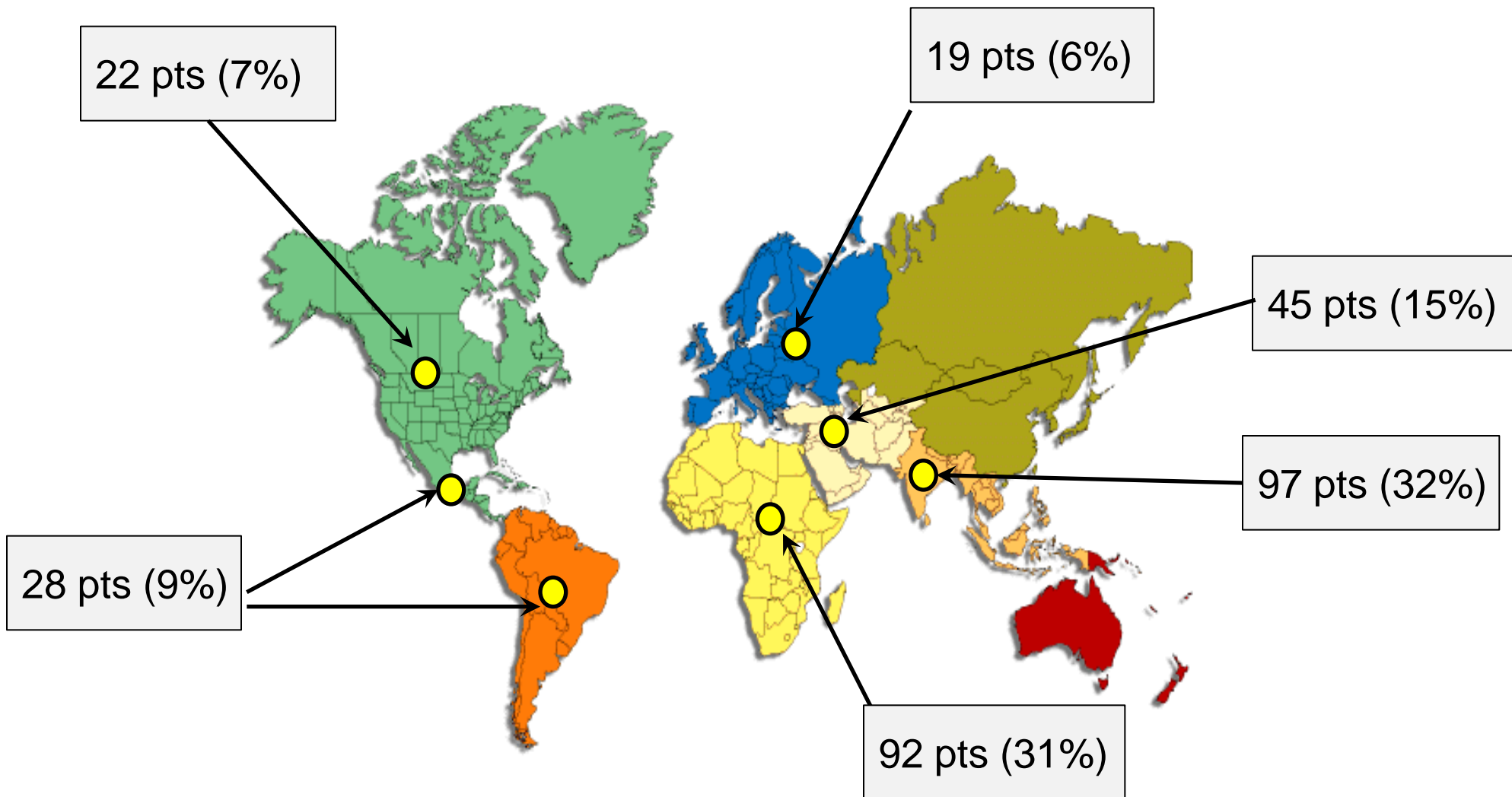
# GEOGRAPHIC DISTRIBUTION OF COUNTRIES INVOLVED IN THE SIPPET STUDY

61 centers involved

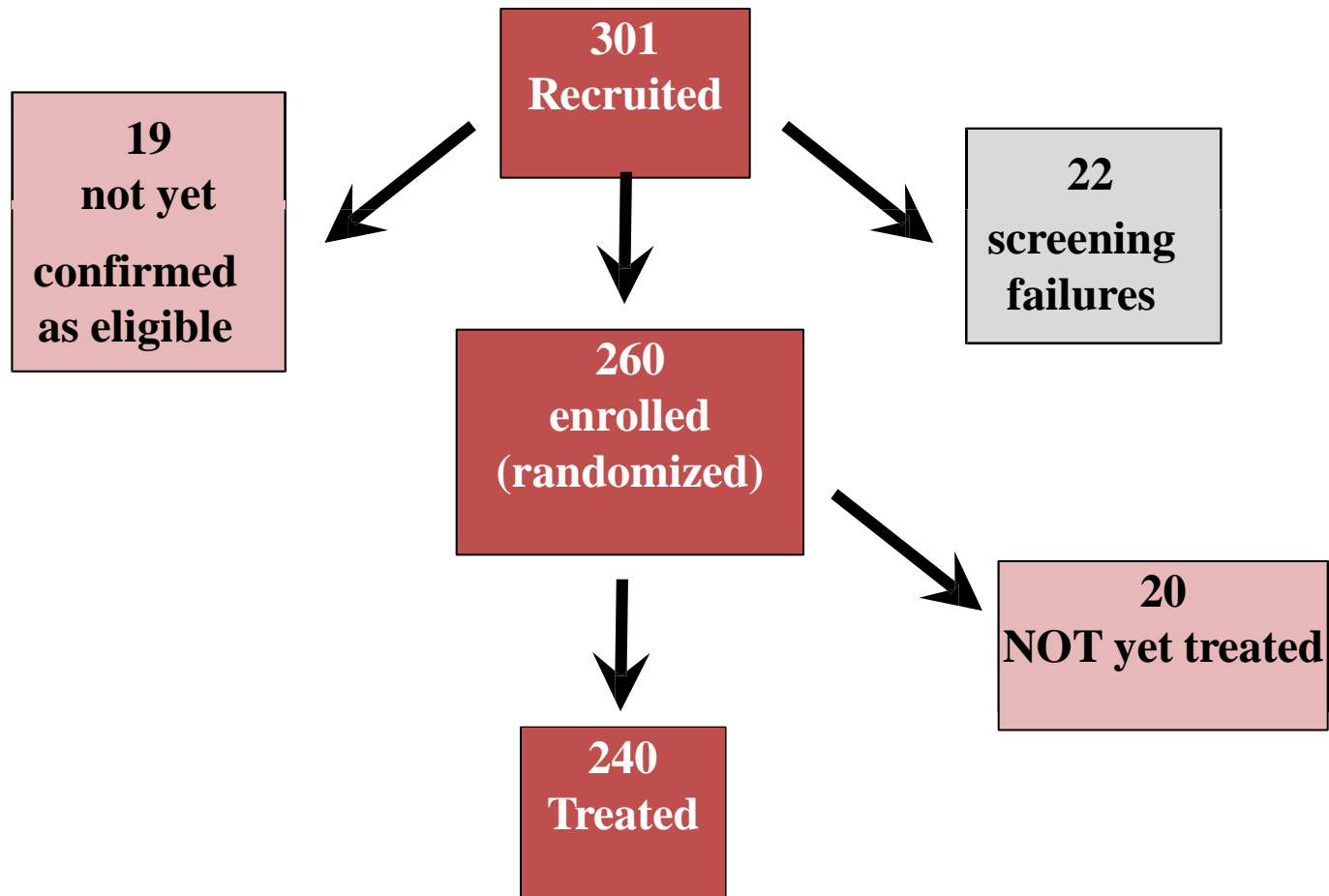


# PATIENT RECRUITMENT BY GEOGRAPHIC DISTRIBUTION

303 patients recruited

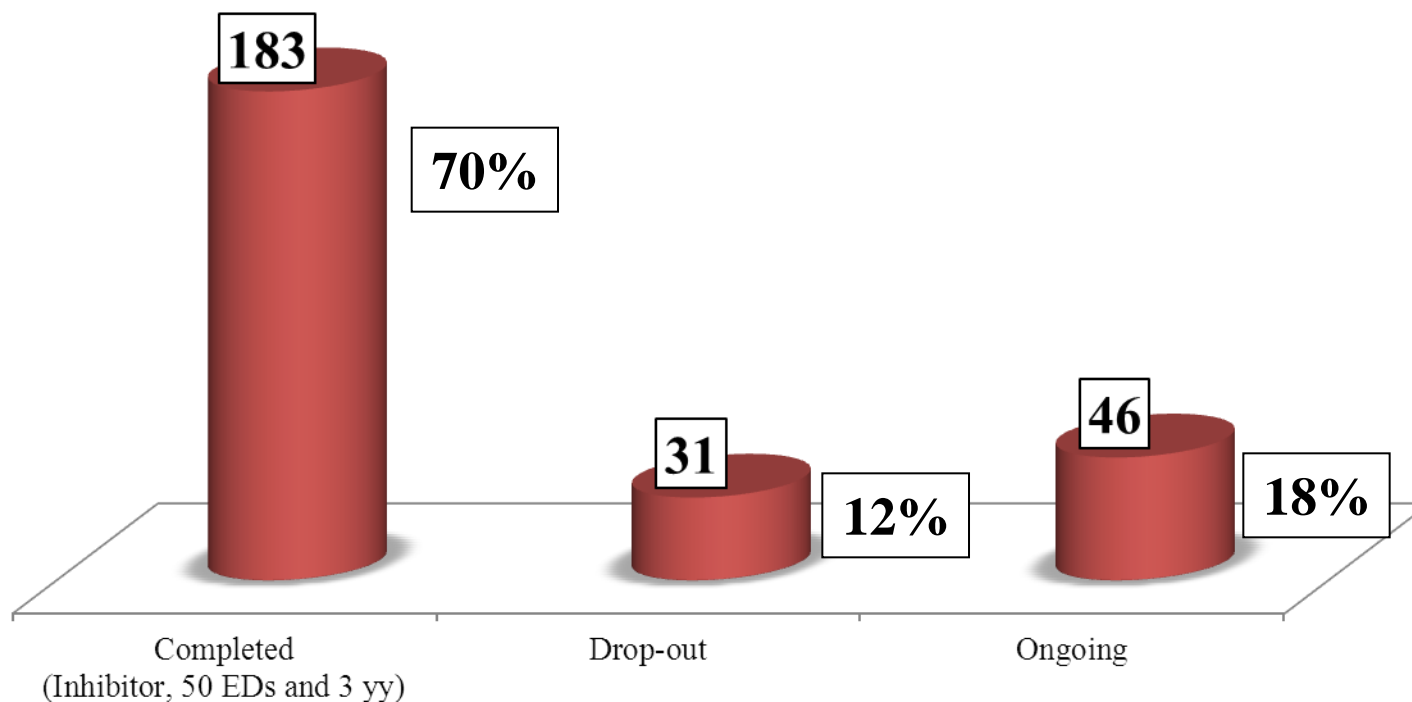


# Study Status – patients – *e-CRF update 28/01/2015*



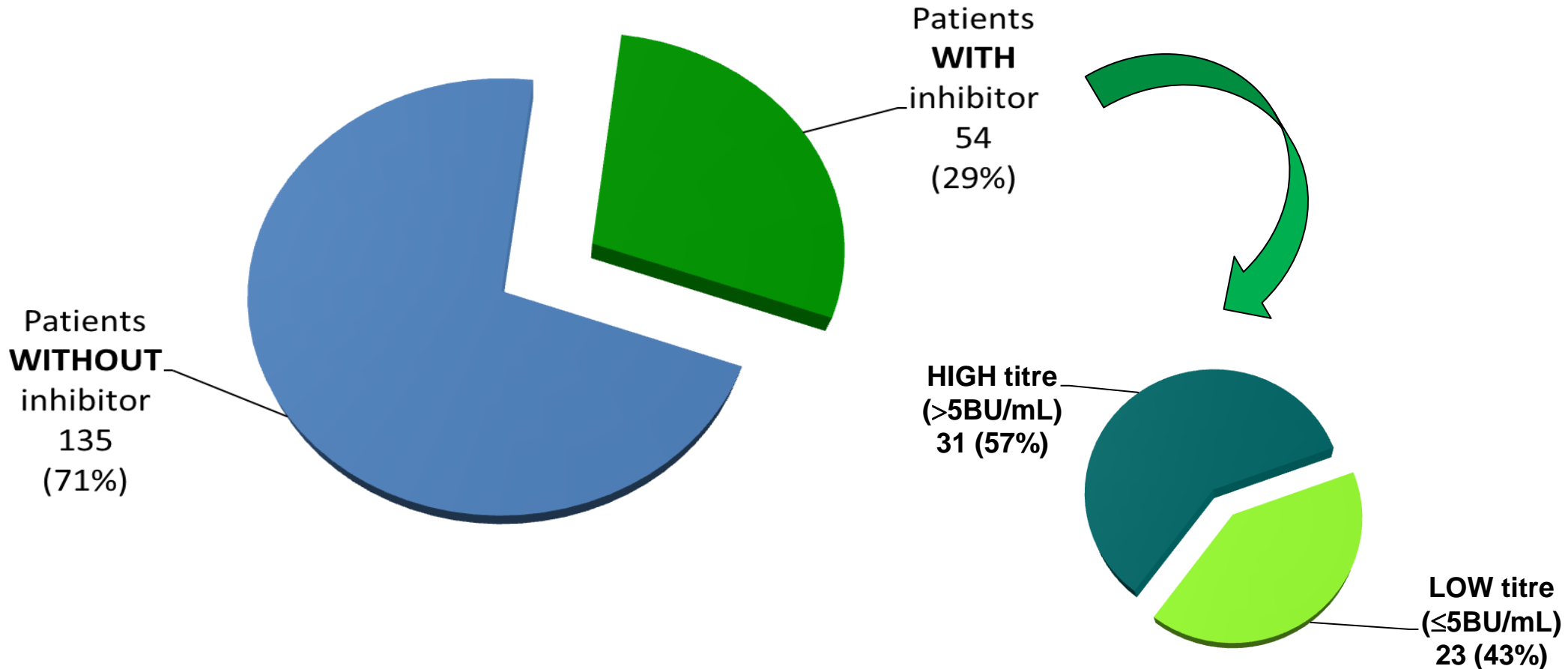
# Study Status – patients – *e-CRF update 28/01/2015*

**260 randomized patients**



# CUMULATIVE INCIDENCE OF INHIBITOR OF THE TIME OF THE INTERIM ANALYSIS

189 patients (excluding pts dropped out)



# DATA QUALITY CONTROL FOR INTERIM ANALYSIS

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- **CRO sent database to the Central Lab in Milan:**
  - **Genetic and phenotypic analysis finalization**
  - **Data quality control**
  - **Verification of exposure days (EDs) associated to inhibitor development**
- **Final database sent to F. Rosendaal at the end of September for interim analysis**

# MAIN SIPPET PARAMETERS

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- effective sample size 270 patients (2 x 135)
- Expected INH rate with pd FVIII: 12.5%
- Expected INH rate with rFVIII: 25%
- $\alpha = 0.05$ ,  $\beta = 0.20$  (power 0.80)
  
- primary endpoint: occurrence of any inhibitor (>0.4 BU/ml)
- secondary endpoint: high-titre inhibitors (>0.5 BU/ml)
  
- stratified analysis
  - age at first treatment
  - intensity of treatment
  - type of FVIII mutation
  - family history
  - ethnicity



# FORMAL ASPECTS OF THE INTERIM ANALYSIS

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- **analysis plan for interim analysis prepared by F. Rosendaal and submitted to and already approved by Steering Committee**
- **analysis in Leiden, by two people who reached consensus**
- **interim report to DMSB and Steering Committee (treatment masked)**
  - **Interim analysis**
  - **Adverse events**
- **DMSB sent advice to Steering Committee**

# SPECIFICS OF INTERIM ANALYSIS

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- When 150 patients have reached 20 ED, analysis on all those treated at least once
- superiority: on high-titre inhibitors,  $p=0.01$
- futility: on all inhibitors,  $p=0.45$  ( $z=0.7597$ )
- Cox regression, with exposure days, age, mutation, ethnicity as co-variates

# OUTCOME OF THE INTERIM ANALYSIS

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## The DSMB unanimous report:

- The study is safe to continue
- There is no futility issue to stop the study from continuing
- Going forward it is critical to maintain the data in confidence. This is key to keep the integrity of the study

Released by Louis M. Aledort, chairman of the DSMB (Aledort, Giles, Rivard)

# CONCLUSIONS

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- **In the interim analysis the absence of futility means that the original hypothesis of SIPPET of an at least 2-fold lower incidence of inhibitors with plasma-derived, VWF-containing products is still viable and valid**

# RECOMBINANT OR PLASMA-DERIVED FVIII?

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- Both sources of FVIII are needed and will be needed for many years to come
- Higher pathogen safety is the main perceived advantage of recombinant products
- Lower immunogenicity is the main perceived advantage of plasma-derived products
- There is not enough plasma FVIII to meet the current (and future) patient needs
- The long-acting products are all based on recombinant DNA technology
- The choice of fully informed patients should be respected

*Thank you for your attention!*



# RCTs IN HEMOPHILIA

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- **Hemophilia therapy is based on very few RCTs**
- **Reasons:**
  - **Excellent relationship between plasma factor levels and clinical outcome**
  - **Rarity of the disease**
  - **Ethical aspects pertaining to randomization**



# PROBLEMS OF THE SIPPET STUDY

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- **Very high cost for an investigator initiated study:**
  - **Difficulty in obtaining independent funding**
  - **CRO costs**
  - **Product costs**
  - **IRB costs**
  - **Insurance costs**
  - **Central lab and shipping costs**
- **Local and international over-regulation:**
  - **Ethical committees**
  - **Human tissue act. Sample transport regulations**

# **THE TRULY BIGGEST PROBLEM FOR SIPPET!!**

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- **Competition with trials in PUPs organized and supported by the recombinant pharma industry**
- **Much higher fees were offered than we could afford for SIPPET!**