8th Annual Symposium of the European LeukemiaNet / 12th Annual Symposium of the German Competence Network "Acute and chronic Leukemias", February 1-2,

Topic: European Clinical Trials Directive: Suggestions for modification and practical approaches

Multinational Clinical trials in Europe and the Voluntary Harmonisation Procedure (VHP)

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Situation of clinical trials in Europe before the implementation of the Clinical Trials Directive in 2004

- 15 different national approaches of the Member States
- Differences between approval and notification systems
- Completely different documentation
- Different timelines
- Languages
- .....
- .....

Situation of clinical trials in Europe before CTD

Situation of clinical trials after the implementation of the Clinical Trials Directive in 2004

- 15/27 Member States working with the same english versions of documents like
  - Investigational Medicinal Product Dossier (IMPD)
  - Protocol
  - Investigators Brochure
  - SmPCs

- but

Situation of clinical trials after the implementation of the Clinical Trials Directive in 2004

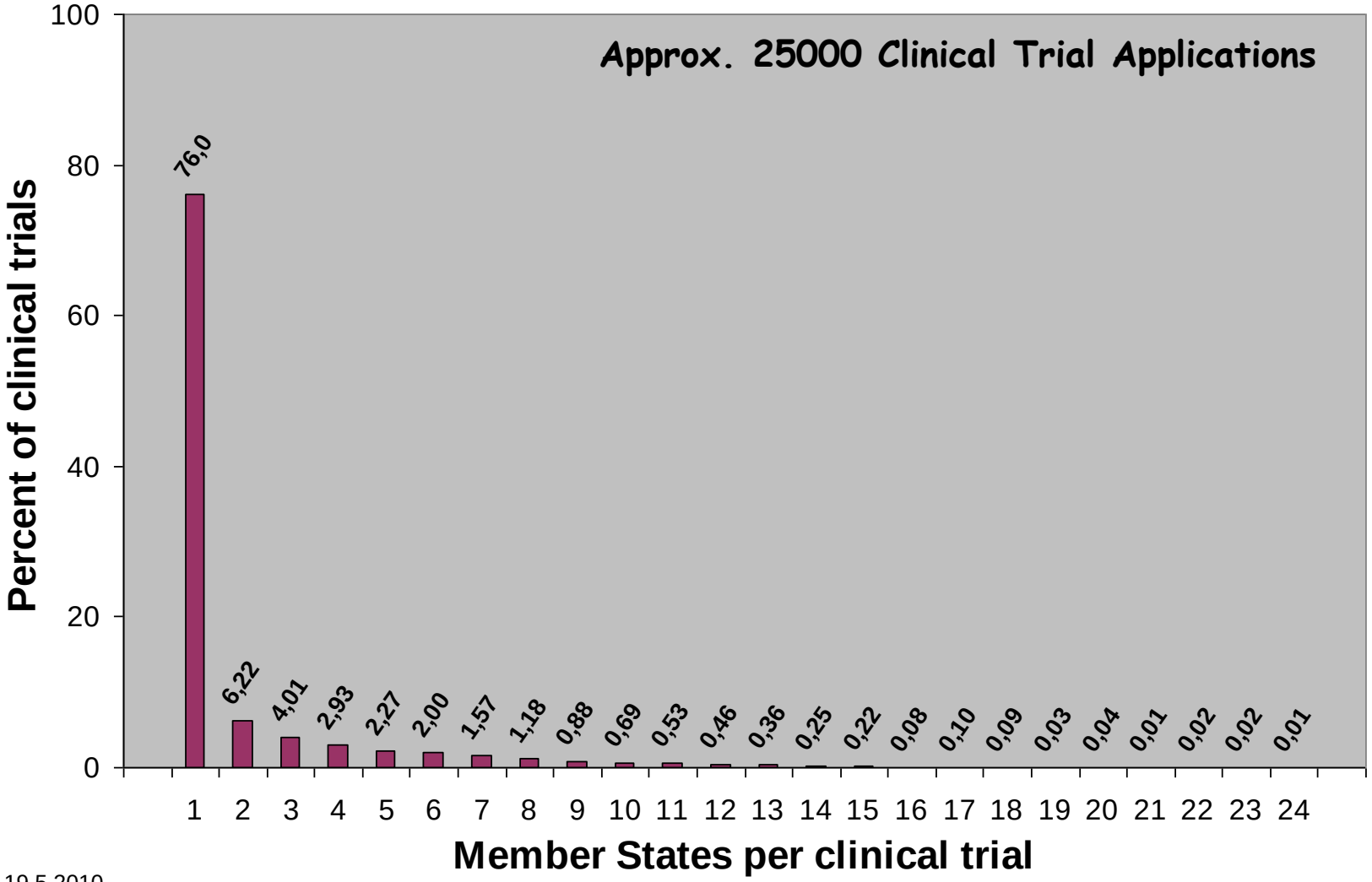
- not harmonised are
  - Assessments
  - Treatment options and standards
  - Some documents related to the clinical trial applications due to different interpretations of guidance documents
  - Application times at the national Competent Authorities

Erleichterungen für zugelassene Arzneimittel / bereits genehmigte Anträge auf klinische Prüfung gibt es schon seit Einführung der GCP-V in Deutschland

The Voluntary Harmonisation Procedure offers a solution to address these points within the existing European legal framework

Distribution of Clinical Trials in Europe

in one Member State vs multinational in percent



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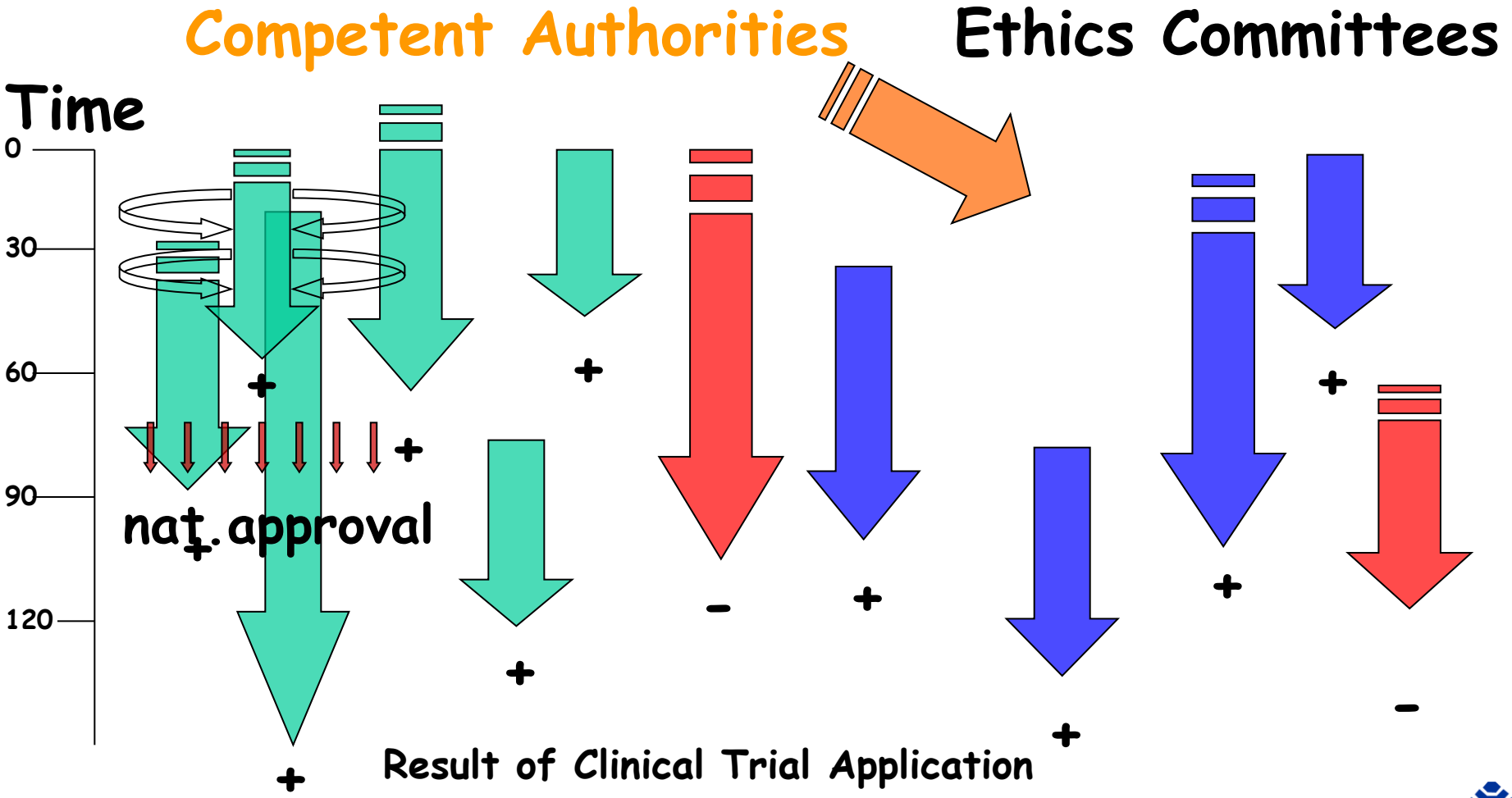
Present situation for the approval of a multinational Clinical Trial



The HMAs Clinical Trials Facilitation Group (CTFG) voluntary harmonisation procedure (VHP)

http://www.hma.eu/77.html

Contact and submissions:

VHP-CTFG@VHP-CTFG.EU

or Tel.:+ 49 6103 771811

Ideal situation of clinical trials in Europe after VHP?

Key features of the Voluntary Harmonisation Procedure

- Only electronic documents sent to one address (one stop shop)
- Only general documents required, which are part of any clinical trial application (Protocol, Investigators brochure, Investigational Med. Product Dossier)
- Reliable timelines for Sponsor and Member States
- Harmonised scientific discussion resulting in harmonised applications in the Member States
  - no tracking of Member States specific modifications necessary
  - consolidated lists of grounds for non-acceptance, if needed

The VHP consists of three phases

- VHP-Phase 1:Request for a VHP at any time
  - Request by sponsors including the identification of the participating NCAs and submission of a full dossier
  - Decision by Member States to participate in the VHP

Max. 5 Days

- VHP-Phase 2: the assessment phase
  - Review of the CTA by all the participating NCAs
  - 1st common position around D30, total period maximum 60 days
  - Administrative co-ordination by the VHP coordinator

Max. 60 Days

- VHP-Phase 3: the national Member States step
  - Formal CTA applications to NCAs.
  - CTA approval by NCAs within short timelines (after positive VHP)

10 Days

Summary of VHP-Substantial Amendments (VHP-SA)

- Offered for successful VHPs after national approval of the initial Clinical Trial Applications
- One-stop-shop for submission
- VHP-SA accepts electronic submissions only
- Approval after 20 days, if none of participating Member State raises internally GNAs
- Approval after 35 days, if GNAs are resolved after the final internal discussion
- Rejection after 35 days giving reasons for GNA to the applicant
- Resubmission after rejection in shorter time lines possible

VHP with ATMPs and GMOs

- **Points under Discussion within the Clinical Trials Facilitation Group**

  - General acceptance of VHPs with ATMPs
  - Standard timelines for ATMPs

  - Problems with GMO:
  - Additional national requirements e.g release certificates for the Release of GMO / external boards

Experience with VHP

International CTFG Workshop on the Voluntary Harmonisation Procedure (VHP) for the Assessment of Multinational Clinical Trial Applications, 30 April 2010, Bonn

http://www.bfarm.de/cln_103/EN/drugs/1_befAuth/clinTrials/meetings/meetings-node-en.html

Distribution of Sponsors of VHPs

Sponsor	No. of VHP	Country
Actelion Pharmaceuticals Ltd	5	SWITZERLAND
Agence nationale de recherche sur le sida et les hépatites virales hépatites virales (ANRS	1	FRANCE
Amgen Inc	3	United States of America
ARIAD Pharmaceuticals, Inc.	1	United States of America
Baxter Innovations GmbH	2	AUSTRIA
bioprojet	2	FRANCE
Bristol-Myers Squibb International Corporation	1	BELGIUM
Cambridge University Hospitals NHS Foundation Trust	1	UNITED KINGDOM
Centocor BV	1	NETHERLANDS
Cephalon, Inc.	2	USA
Dr. Falk Pharma GmbH	1	GERMANY
EORTC	4	BELGIUM
Excited States, LLC	1	United States of America
F.Hoffmann-La Roche	2	SWITZERLAND
Fresenius Biotech GmbH	1	GERMANY
Gilead Sciences International Ltd	1	UNITED KINGDOM
GlaxoSmithKline Biologicals	9	BELGIUM
HANNOVER CLİNICAL TRIAL CENTER GMBH	1	GERMANY
Innovacell Biotechnologie AG	1	AUSTRIA
Merck & Co., Inc.	1	United States of America
Merck KGaA	1	GERMANY
Merck Serono	2	GERMANY
MolMed S.p.a	1	ITALY
Morphotek Inc.	1	United States of America
Movetis NV	1	BELGIUM
Nycomed GmbH	1	GERMANY
Orfagen	1	FRANCE
Shire-Movetis NV	2	BELGIUM
University of Birmingham	1	UNITED KINGDOM
Wyeth Pharmaceuticals Inc	1	United States of America

Status 17.1.2011

Participating Member States in 52 VHPs

Country	Number of VHP
GERMANY	39
FRANCE	32
SPAIN	29
BELGIUM	19
UNITED KINGDOM	19
NETHERLANDS	16
HUNGARY	15
CZECH REPUBLIC	13
SWEDEN	12
AUSTRIA	12
PORTUGAL	7
DENMARK	7
ROMANIA	6
GREECE	5
FINLAND	4
IRELAND	3
ITALY	2
BULGARIA	2
NORWAY	2
LATVIA	1
ICELAND	1

Country	rejects joining VHP
Poland	

The following MS weren‘t yet selected for a VHP:

Estonia
Malta
Cyprus
Luxemburg
Slovenia
Lithuania

VHP numbers (March 2009 - 31. Jan. 2011)

- 55 applications
  - 44 standard VHP
  - 11 accelerated VHP (Pandemic Influenza Vaccines)
- 43 finished positive
  - 1 negative (GNA not addressed)
  - 3 withdrawals (before dossier subm.)
  - 8 ongoing
- Leading MS: UK;FR;DE;CZ;DK;ES

Summary results of the standard VHP

- Average time used for a VHP: 51 days (SD 8,3 days)
  (Min. 29 days; Max. 68 days)
  mean 2009: 52 days; mean 2010: 47 days
- Mean of 7 Member States per standard VHP
  - Range 2-18 Member States
- Time until national CTA by applicant: mean ~30d
  - Range 1-139 days
- Time for national approval by NCAs: mean ~19d
  - Range 0-101 days

- Commercial applicants 85%,
- Non-commercial applicants 15%

- Biologicals 43%
- Chemicals 57%

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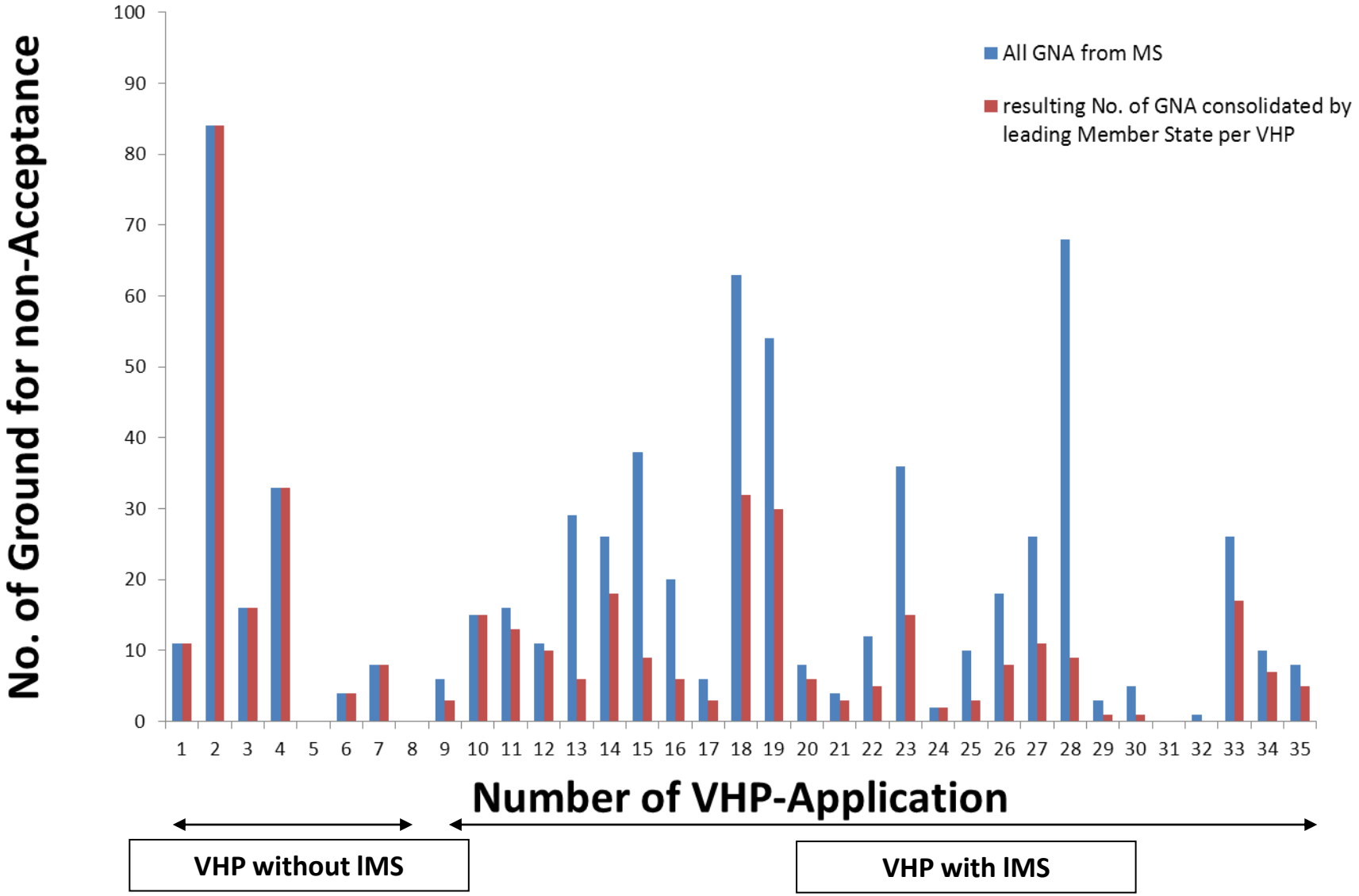
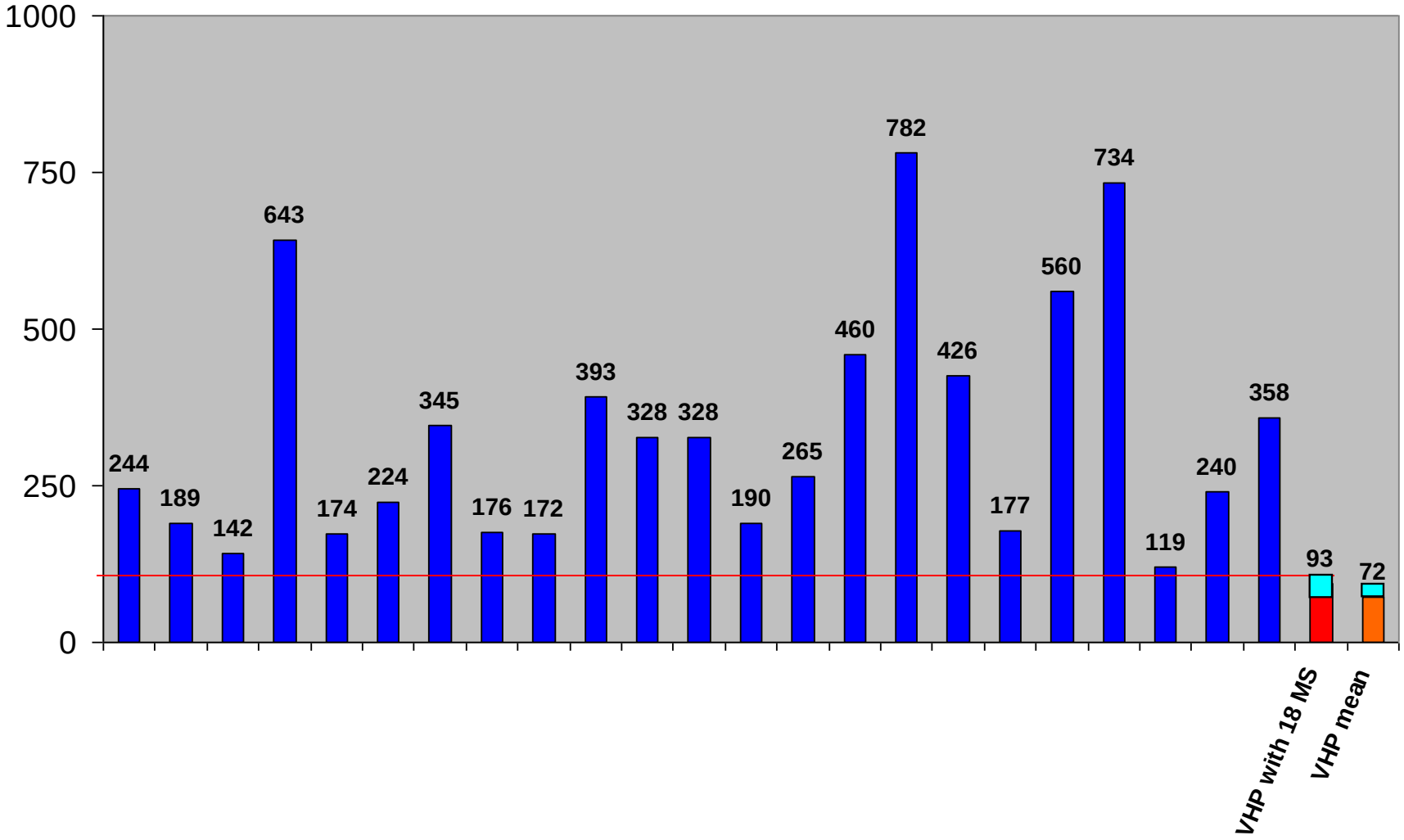
GNA with/out a leading MS in the same VHP



Comparison of approval times of 23 multinational clinical trials with 18 Member States vs VHP

from the first application date to the last approval date by the national Competent Authorities



Conclusions on VHP

- The Voluntary Harmonisation Procedure is an efficient tool to achieve harmonised and quick approvals of clinical trials in many Member States of the EU in one procedure
- VHP offers a one-stop-shop for CTAs
- VHP accepts electronic submissions only
- Time lines for applicants and Competent Authorities are reliable and are met
- Substantial Amendments are now included in the VHP

Thank you for your attention and I'm ready for discussion