European CRO Federation

“Ethical considerations for paediatric trials - how can Ethics Committees in the European Member States and the Paediatric Committee at the European Medicines Agency work together?”
“Industry experience with ethical review of paediatric trials”
Result of survey by EUCROF

29-30 November 2011, EMA, London

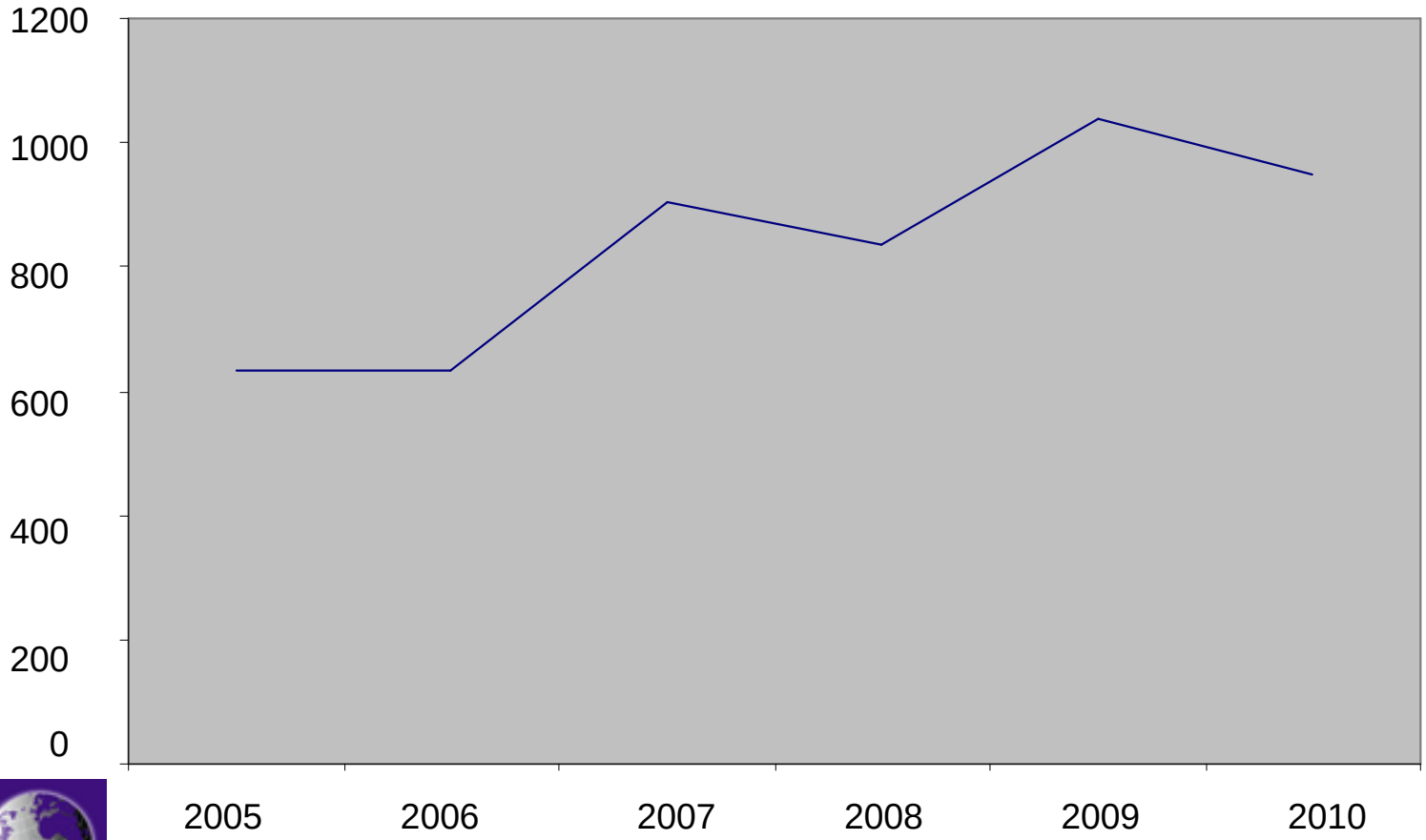
Dr. Martine Dehlinger-Kremer
Vice President Global Regulatory Affairs, RPS Inc.
Lead of Paediatric Working Group of EUCROF

Agenda

- Introduction and Background Information
- Experience with Ethical Review of Paediatric Trials; EUCROF Survey
  - Survey results
  - Individual Cases Studies
- Conclusion

Number of Paediatric Studies in EEA

Number of paediatric studies have increased from 2005 to 2010
>600 studies in 2005 to 949 studies in 2010



Source: Paolo Tomasi, Head of Paediatric Medicines, European Medicines Agency, March 2011

EUCROF SURVEY

"Industry experience with ethical review of paediatric trials" – EUCROF Survey Results

- **Data collected**
  - Collected between September - October 2011
  - Were consulted
    - All European countries through EUCROF (11 CRO Associations, approx. 300 CROs)
    - 3 Peadiatric Networks (France and Germany)
- **Data received**
  - 15 Responses: Case Studies, from CROs only

"Industry experience with ethical review of paediatric trials" – EUCROF Survey Results

- **Countries involved in the studies**
  - Austria, Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden & UK

- **Studies overview**
  - Studies performed between 2008 and 2011: 2008 (1), 2009 (5), 2010 (5), 2011 (4)
  - 14 multinational studies, 1 national study
  - 1 phase I, 5 phase II, 9 phase III

Case studies - Concerns from Ethic Committees

Concerns from the Ethic Committees	Concerns nature
• In 14 out of 15 studies	• Child protection • Study procedure • Study design • Others

Concerns from Ethic Committees

- **Child protection**
  - Request change to ICF & provide assent per age group (8/15)
  - Burden for participants, impact schooling (1/15)
  - Exclusion of mentally disabled minors (1/15)
  - Contraception (2/15)
- **Study procedure**
  - Blood volume collection, Number of Vena punctures (3/15)
  - Invasive procedures (2/15)

Concerns from Ethic Committees

- **Study design**
  - Benefit of study to paediatric subject (2/15)
  - Product already approved in adolescent (1/15)
  - Clarifications on the sample size calculation (1/15)
  - Inclusion new groups in extension study (1/15)
  - Evaluation strategy, subgroup analysis (1/15)
  - Use of placebo questioned (1/15)
- **Others**
  - Qualification of investigator & paediatric experience (1/15)
  - Insurance coverage (1/15)
- **EC with no concern**
  - 1/15

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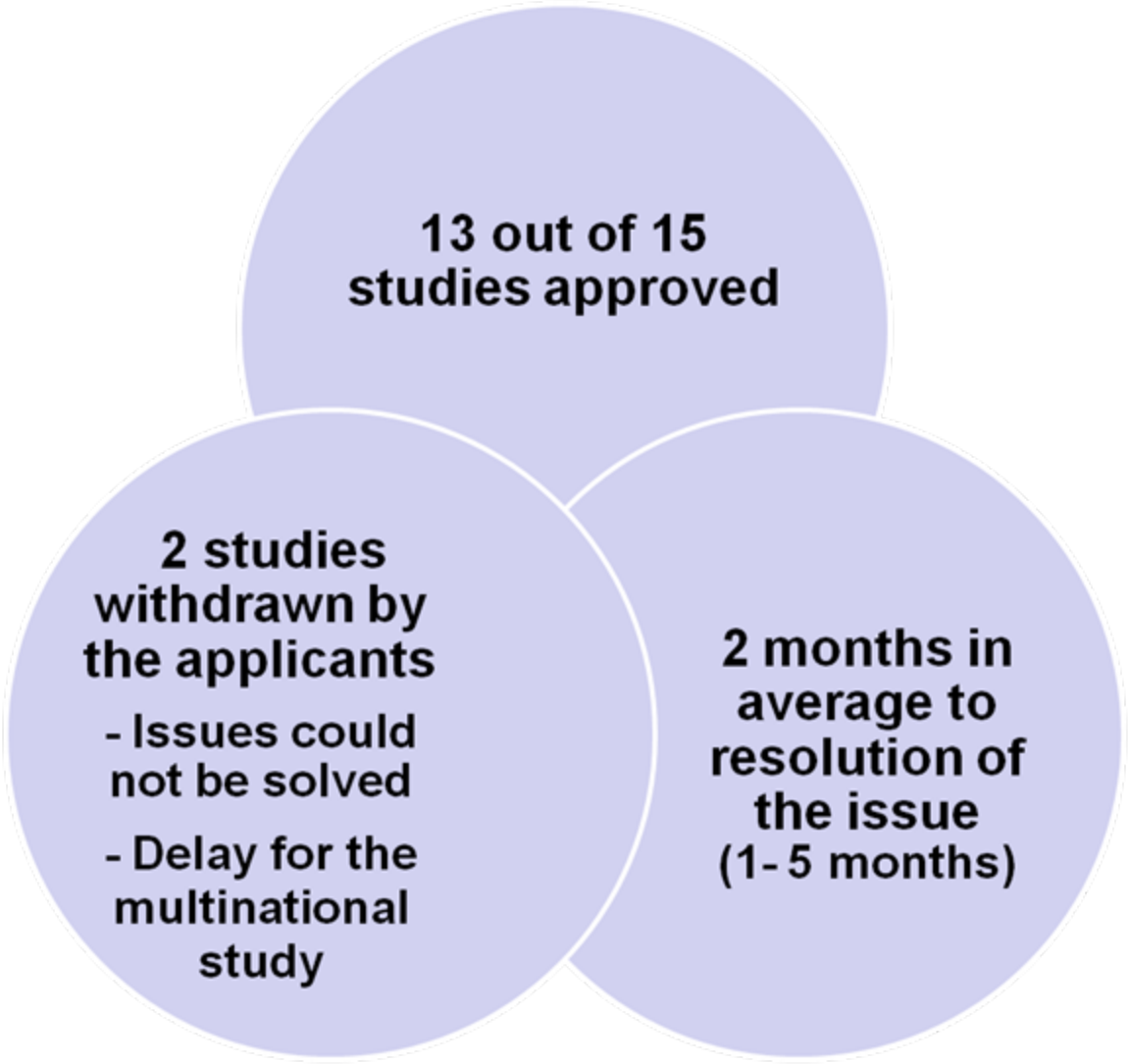
Outcome from the EC reviews

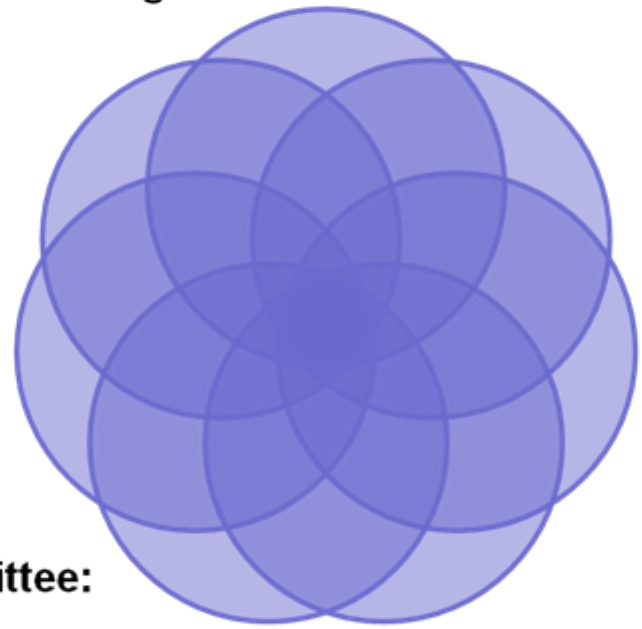


INDIVIDUAL CASE STUDIES

A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel Group Study to Evaluate the Efficacy of XX 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents - QUESTION

Phase III Study , Multinational, 2011, Neurology / Migraine

Children 11-17 years old

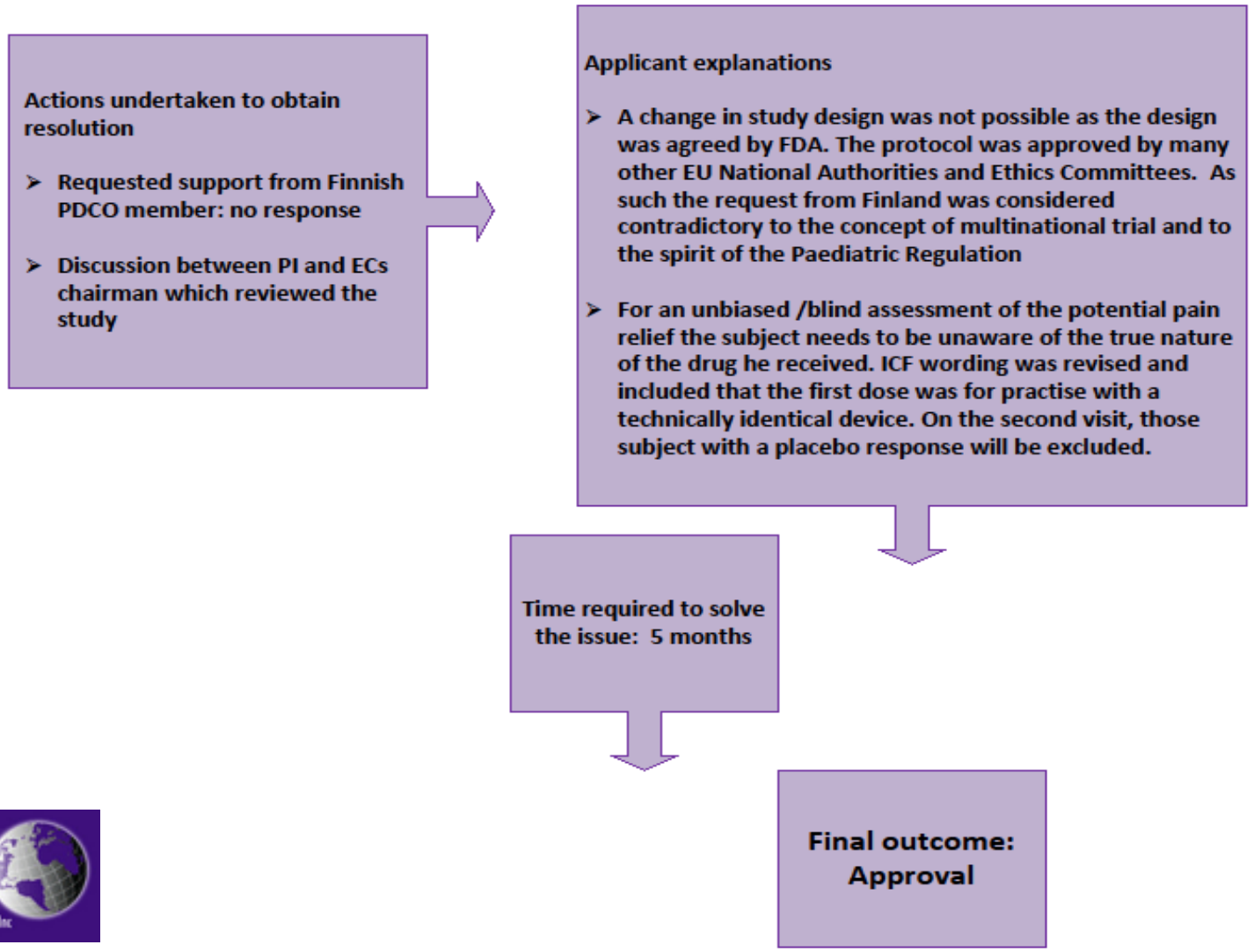


Ethic Committee: Finland . Submission early March 2011

Concerns expressed by the Ethic Committee

- Use of placebo
- As per the EC the placebo effect can be assessed by treating two attacks, in which case every subject can receive placebo and active medication, instead using placebo during the screening period and in the placebo-controlled 4-armed parallel group
- The ICF remains vague on the use of placebo in part I

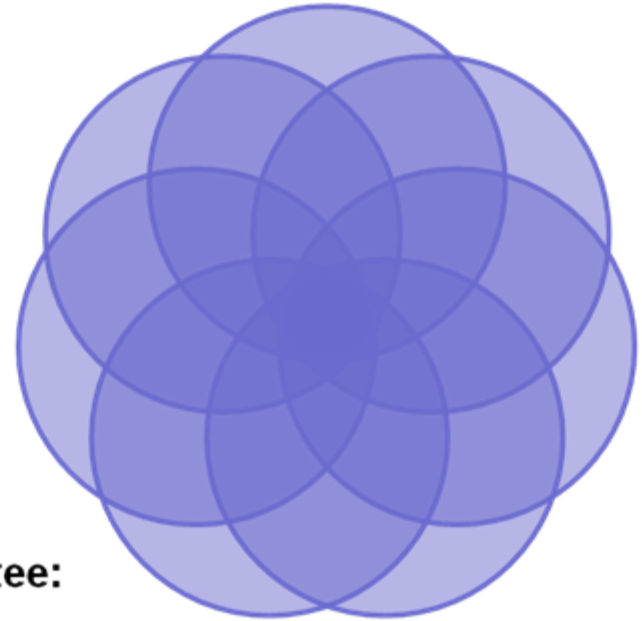
A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel Group Study to Evaluate the Efficacy of XX 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents - RESOLUTION



A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel Group Study to Evaluate the Efficacy of XX 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents

Phase III Study , Multinational, 2011, Neurology / Migraine

Children 11-17 years old

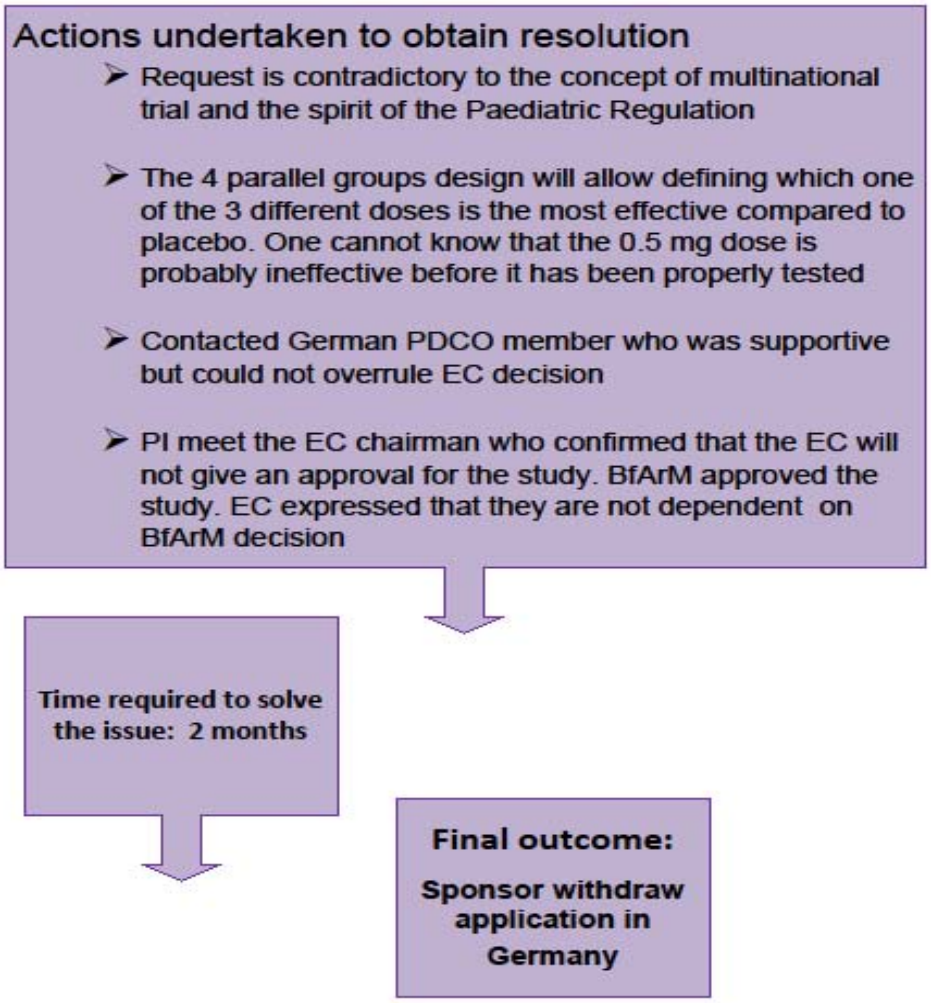


Ethic Committee: Germany. Submission March 2011

Concerns expressed by the Ethic Committee

- **EC rejected the study on the ground that XX is already approved at a dosage of 5 mg for the treatment of adolescents**

A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel Group Study to Evaluate the Efficacy of XX 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents - RESOLUTION



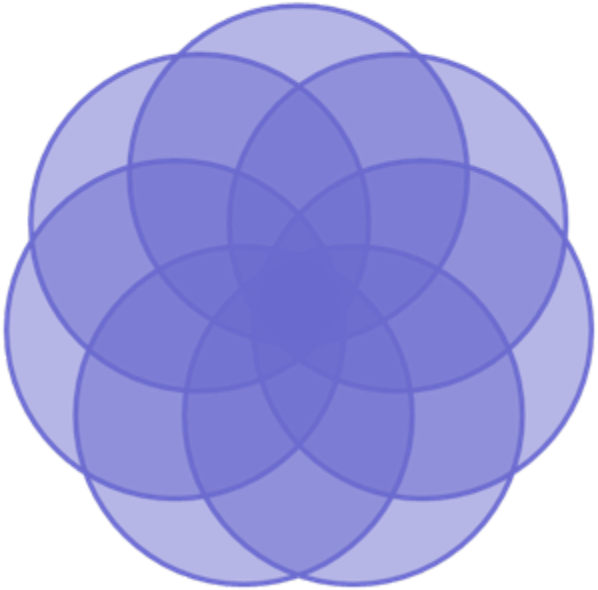
A Multicenter, Double-Blind, Parallel-group Study to Evaluate Short-Term Safety and Efficacy and Long-Term Maintenance of Two Dose Levels of Rabeprazole Sodium Delayed-Release Pediatric Bead Formulation in 1-to-11-Year-Old Paediatric Subjects With Endoscopically Proven GERD

EUCROF

Phase III Study , Multinational, 2009, Gastro- enterology

Children 1- 11 years old

Ethic Committee: Bulgaria. Submission December 2009



Concerns expressed by the Ethic Committee

- Negative opinion from EC
- Multiple invasive procedures, in total 3 EGD with biopsies, which is considered unjustified with respect to subject safety
- The EC considered there is inappropriate decision and confusion between standard of care and study requirement
- Lack of specialization of the proposed Principal Investigators in paediatric gastroenterology

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Short-Term Safety and Efficacy and Long-Term Maintenance of Two Dose Levels of Rabeprazole Sodium Delayed-Release Pediatric Bead Formulation in 1-to-11-Year-Old Pediatric Subjects With Endoscopically Proven GERD. RESOLUTION

Actions undertaken to obtain resolution

- Applicant decided not to Appeal decision of Central Ethics Committee due to the delay it would have created to have this country included in multinational study
- Amend the Protocols as per EC request was not acceptable for a multinational trial, which had been approved in all other countries and by those ECs
- The PI lack of specialization in pediatric gastroenterology could have been endorsed, although the most important was experience in performing EGD & biopsies
- Time required to solve the issue: NA

Outcome:

Bulgaria did not participate in the study

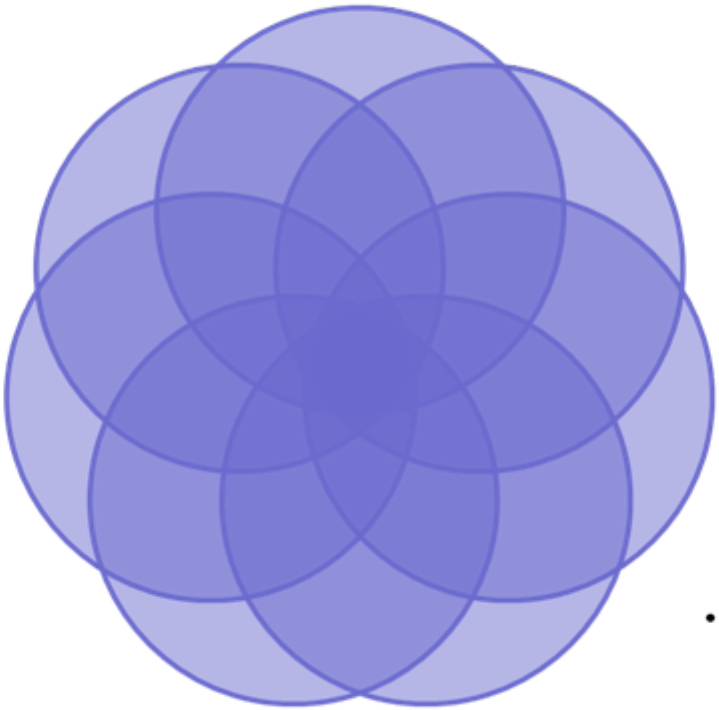
Allergy – Allergic Rhinitis & Chronic Urticaria

Phase II (PK) Study, Multinational, 2009, Allergy

Children 2 to less 12 years

Ethic Committees

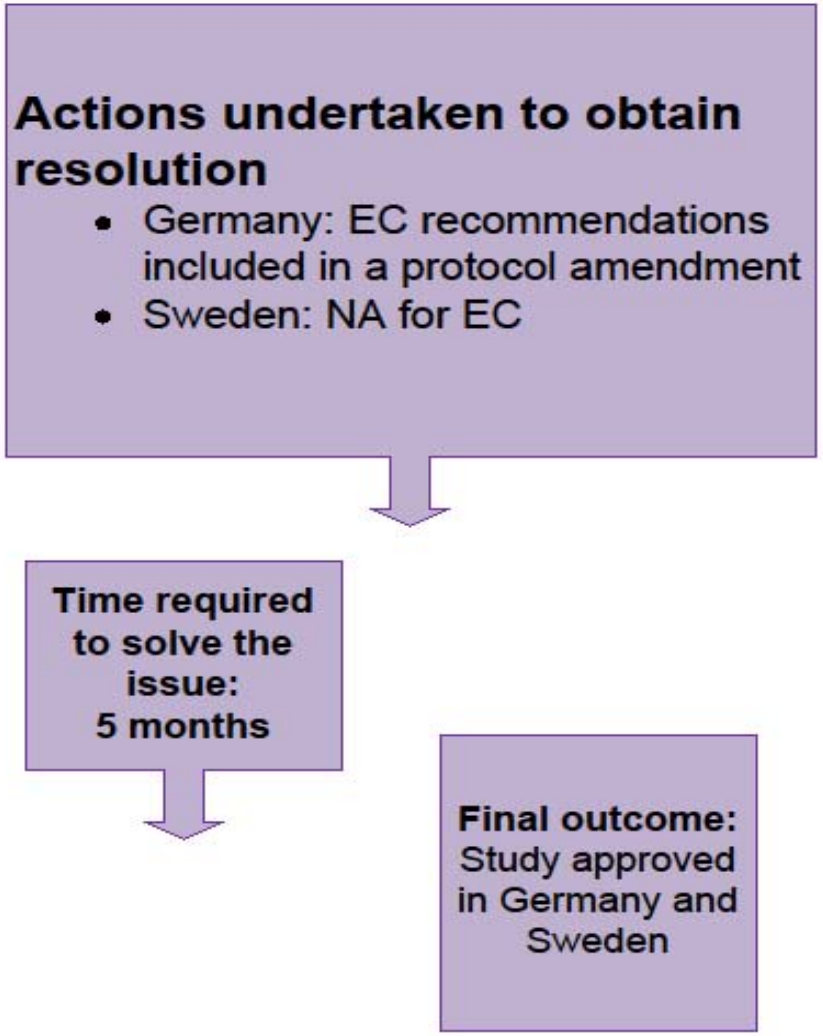
- Germany. Submission July 2009
- Sweden. Submission August 2009



Concerns expressed by the Ethic Committees

- Germany: Add to Exclusion Criteria
  - Minors who explicitly refuse to take part in the study
  - Mentally disabled minors or Minors who by official order have been institutionalised (e.g. in orphanages etc.)
  - any clinical conditions or circumstances that in the opinion of the investigator would make the subject unsuitable for the study (e.g. hepatic impairment, renal impairment, mental impairment, cardiac disease, etc)
- Sweden: No concern

Allergy – Allergic Rhinitis & Chronic Urticaria



Conclusion

Application outcome

- 80% of the studies were approved after clarification of the ECs concerns

Different standards among the ECs

- Same study was approved in Finland and had to be withdrawn in Germany
- Same study was approved in Sweden and EC Germany had further requests

Reasonable timeframe to solve the issue

- Average of 2 months
- Not much delay in the study start

Conclusion

Limited number of cases received

- Reflects a yet limited experience in Paediatric Clinical Studies performed under a PIP, at least as conducted by CROs

No cases from Paediatric Networks

Acknowledgments

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Dr. Martine Dehlinger-Kremer

Vice President, Global Regulatory Affairs, RPS Inc.
Lead Paediatric Working Group EUCROF

Eucrof email: martine.dehlinger@eucrof.eu
Web: www.eucrof.eu
RPS email: mdehlingerkremer@rpsweb.com
Web: http://www.rpsweb.com

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