GAPP GAbapentin in Paediatric Pain

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

The GAPP project at the end of the FP7 funding period

Florentia Kaguelidou

Centre of Clinical Investigations, CIC1426

Robert Debré University Hospital, APHP – University Paris 7 Paris, France

Rome, 14 January 2018

Background - chronic pediatric pain

- **Chronic pain** is an area of unmet needs in children with few available properly authorized medicines
- Gabapentin was included in the priority list of medicines to evaluate in children (EMA & WHO)
  - Gabapentin is used '**off-label'** in this indication-> limited documented clinical assessment
  - Lack of **suitable oral formulation**
  - High PK variability in the younger -> **adequate dosing?**

Off label uses

Unadapted pharm. formulations

High risk of ADRs & medical errors

The GAPP project

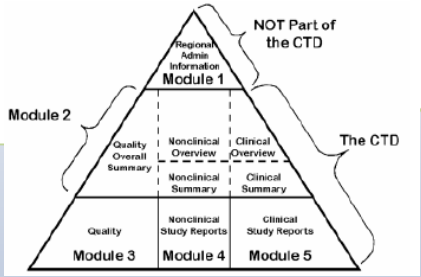
- = develop an age-appropriate oral liquid formulation for the conduct of well-designed pediatric trials for a new pediatric indication (chronic neuropathic pain) -> PUMA
  - 1) the development of a liquid oral gabapentin formulation;
  - 2) a juvenile animal toxicity study **(pre-GABA)**
  - 3) two efficacy-safety clinical trials to test gabapentin as monotherapy **(GABA-1**) and as adjuvant therapy **(GABA-2)** in children 3 months to 18 years.
  - 4) a modelling bridging study to specifically address the paucity of pharmacokinetic (PK) data in children and enhance rational dosing **(GABA-3).**

The GAPP Project procedures - regulatory requirements

FP7 application - 1° stage (2012)

FP7 application - 2° stage (2013)

SEVENTH FRAMEWORK PROGRAMME



PUMA Application

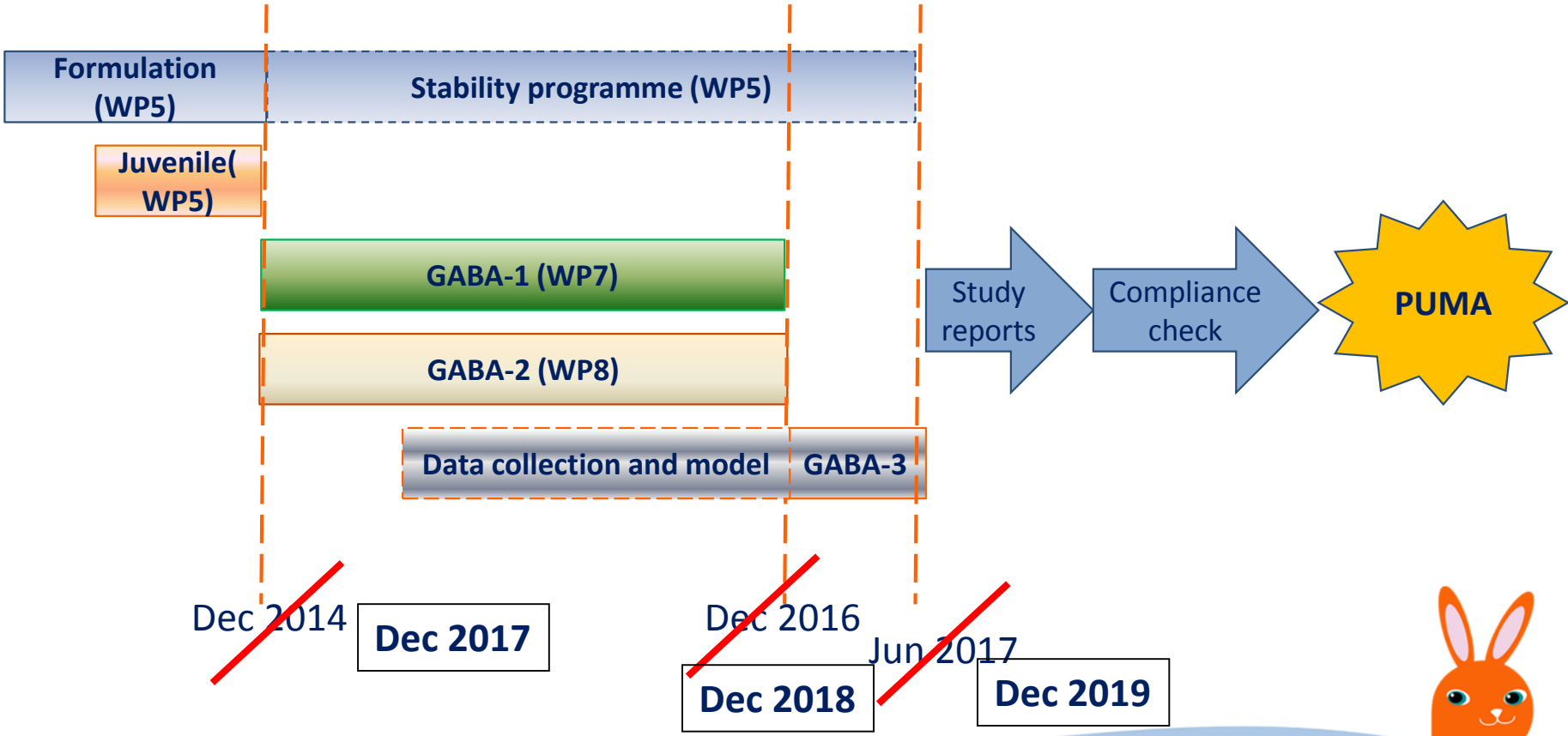
PIP application (2012-2013)

CTs Application and conduction (on-going)

Project coordinator: **CVBF**

Sponsor CT: **Pharma SRL**

The GAPP studies



WP5 - pediatric formulation

- Dompé Farmaceutici S.P.A
- New solution gabapentin: 75mg/ml (200 ml bottle)
- Masking bitter taste of gabapentin
  - ANSM: Glycamil + saccharose
- Stability + antimicrobial excipients

Component	Amount in 100 g (% w/w)
Gabapentin	6.3813 g
Kolliphor RH40	2.553 g
Methyl paraben	0.128 g
NaH2PO4 x 2H2O	0.579 g
Glycamil	0.0851 g
Sucrose	34.034 g
Cherry flavour	1.276 g
Neotame	0.0213 g
Water	up to 100 g
NaOH	up to pH 6.25

- -> 500 patient visit kits have been released since April 2017

WP6 – pre-GABA

- Dompé Farmaceutici S.P.A - > Wistar Han rats
- 1) Dose Range Finding study (DRF)
- 2) Pivotal Juvenile Study (GLP)
  - 3 doses: 500 mg/1000mg/2000mg mg/kg/d (b.i.d)
  - Mortality, vital signs, weight, functional and behavioral tests, organ histology, toxicokinetics
  - Results:
    - higher incidence of renal pelvic dilation in females at all doses and at 2000 mg/kg/bw/day in males.
    - reduction of the brain weight at the end of the treatment period in males at 1000 and 2000 mg/kg bw/day

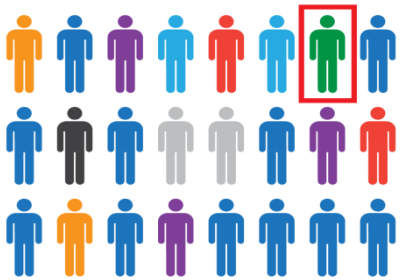
Finished since end 2014

- 3) New preclinical study requested by German CA
  - Presence of an upper limit of 0.5% lactam impurity (impurity A) -> verify neurotoxicity -> no inclusion < 3 years of age until results are available June 2018

WP7 & WP8 – clinical trials

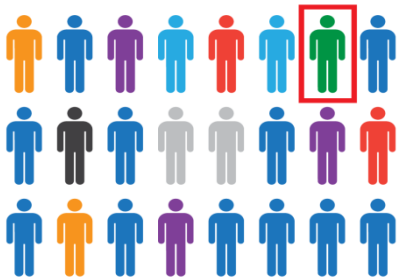
- **Challenges in clinical pain trials**
  - Absence of clinical trials in chronic pain even in adults -> no recommendations on methods
  - Differences in medical practices
  - Rare clinical condition
  - Ethical issues in 'pain management' field
  - Diagnosis of neuropathic pain in children -> inclusion criteria +++
  - Choice of adequate comparator
  - Appropriate + validated pain scales et QoL tools
  - Titration + max doses -> safety issues

CTs objectives and designs



- **GABA-1:**
  - APHP, Paris, France
  - efficacy & safety of gabapentin compared to tramadol in children 3months - 18 years with moderate to severe (≥ 4/10) chronic neuropathic or mixed pain
  - randomized, double-blind, double-dummy, active-controlled, multicenter, non-inferiority phase III study
  - 94 children + adolescents
  - 6 countries: France, Italy, the Netherlands, Germany, Albania, Greece –> 13 recruiting sites
    - Estonia initially included will not participate

CTs objectives and designs



- **GABA-2**:
  - Erasmus MC, Rotterdam, the Netherlands
  - efficacy & safety of gabapentin as add-on to morphine in children with severe pain (≥ 7/10)
  - randomized, double-blind, placebo controlled, multicenter, superiority phase II study
  - 66 children + adolescents
  - 6 countries –> 12 recruiting sites
- Both protocols are aligned in terms of assessments + endpoints

WP3 - Regulatory activities

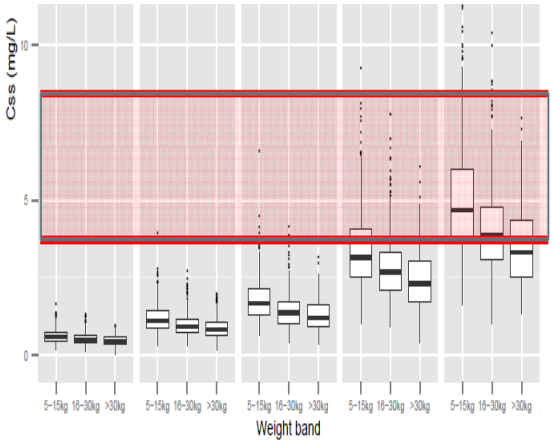
- 1) amendment of the PIP
  - Substantial modifications: sample size, inclusion criteria, design, IMP dosing, outcomes, scales etc…
  - PDCO and EMA approval end of 2015
- 2) regulatory submissions per country, GABA-1
  - Preparation of regulatory documents +++
  - Major challenges in Germany and France
- 3) Voluntary Harmonisation Procedure (VHP), GABA-2
  - Faster + less complex
- 4) composition of a common DSMC

CTs current status

- **GABA-1**
  - Approval of the amendment protocol V3.0 on-going in most countries
  - Not a EU protocol -> New Clinical Trial Agreements +++
  - SIV have been initiated in 6/12 research sites -> 1 site ready to include
  - Participation of new countries: UK, Poland, Serbia, Ukraine -> 7 sites

- **GABA-2**
  - Approval CAs in all countries since Apr. 2017 but ECs in on-going

WP9 – Bridging modelling study



- Review on PK/PD data in adults and children
- Rationale for bridging:
  - Assuming comparable etiologies and physiopathology -> doses in children that ensure systematic exposures equivalent to those observed in adults responding to gabapentin analgesic treatment
  - Simulations allow for current uncertainties in the rate of absorption and bioavailability of the new formulation.
  - Data collected in CTs to confirm dosing recommendations
- Adequate dosing of gabapentin
  - ≤15 kg of BW = 7 mg/kg/d to 63 mg/kg/D
  - >15 kg of BW = 5 mg/kg/d to 45 mg/kg/D

PK data on tramadol will be collected also in the GABA-1

WP10 – Dissemination activities

- GAPP project : promotional teaser video

- GABA-1 + GABA-2
  - Informative leaflets for CTs: 0-6 / 7-11 / 12-17 years
  - Assent forms: 7-11 / 12-17 years
  - Two animated videos

GAPP – Scientific publications

EJP European Journal of Pain

EFIC

Explore this journal >

Review Article

The research gap in chronic paediatric pain: A systematic review of randomised controlled trials

R. Boulkedid, A.Y. Abdou, E. Desselas, M. Manégat, T.G. de Leeuw, J. Avez-Couturier, S. Dugue, C. Mareau, B. Charron, C. Alberti, F. Kaguelidou ✉,
and on behalf of the GAPP Consortium

First published: 5 November 2017 Full publication history

- Systematic literature review : published
- GABA-2 study protocol : submitted Trials
- GABA-1 study protocol : in preparation
- Survey on clinical practices in chronic pain in Europe : in preparation
- Papers on PK modeling/simulations

Conclusion

- Complex project, research area with of challenges
  - Rare disease, specialized centers with expertise
  - No recommendations for care
  - Challenging adequate research methodology
  - Long administrative procedures

    -> Duration of the project was not sufficient

Clinical trials will be performed with financing from CVBF

Acknowledgements

- Laura Accame (IGG)
- Corinne Alberti (APHP)
- Marcello Allegretti (DOMPE')
- Daniel Annequin (APHP)
- Justine Avez-Couturier (APHP)
- Donjeta Bali (QSUNT)
- Corrado Battistone (DOMPE')
- Halyna Beketova (SNAPE)
- Francesca Benedetti (PENTA)
- Franca Benini (PENTA)
- Volodymyr Biliy (Acinus)
- Laura Boga (DOMPE')
- Donato Bonifazi (PHARM)
- Fedele Bonifazi (PEDIANET)
- Patty Brouwer (ICCCPO)
- Bruna Cammarata (IGG)
- Anna Cantarutti (PEDIANET)
- Adriana Ceci (CVBF)
- Giulia Chiaruttini (PHARM)
- Maria Pia Cislaghi (DOMPE')
- Francesco Craig (PB)
- Vitangelo Dattoli (PB)
- Andrea de Giacomo (PB)
- Tom de Leeuw (EMC)
- Saskia de Wildt (EMC)
- Cinzia D'Ettore (DOMPE')
- Leonard Deda (QSUNT)
- Dmytro Delva (IFRCCH)
- Oscar della Pasqua (UCL)
- Lamberto Dionigi (DOMPE')
- Antuan Divisic (PENTA)
- Maria Concetta Dragani (DOMPE')
- Sophie Dugue (APHP)
- Migen Elmazaj (QSUNT)
- Petros Eskioglou (AGIA SOPHIA)
- Katrin Faber (UKER)
- Mariagrazia Felisi (PHARM)
- Mariapaola Felisi (PHARM)
- Eleana Garini (AGIA SOPHIA)
- Marco Gentile (DOMPE')
- Bonka Georgieva (CVBF)
- Carlo Giaquinto (PENTA)
- Celine Greco (PI)
- Dan Hawcutt (AHCH)
- Paul Healy (UCL)
- Alketa Hoxha (QSUNT))
- Elisaveta Karkala (AGIA SOPHIA)
- Antonis Kattamis (AGIA SOPHIA)
- Ermira Kola (QSUNT)
- Andriy Loboda (MISSU)
- Vincenzo Lorenzelli (IGG)
- Rebecca Lundin (PENTA)
- Mariangela Lupo (PEDIANET)
- Giouli Mammi (AGIA SOPHIA)
- Cristina Manfredi (CVBF)
- Luca Manfredini (IGG)
- Cecile Mareau (APHP)
- Lucia Margari (PB)
- Maria Gabriella Marinari (IGG)
- Emilia Matera (PB)
- Alessandro Mazza (PENTA)
- Maarten Mensink (UMCU)
- Ivana Milovanovic (APHP)
- Elisa Monzani (DOMPE')
- Antje Neubert (UKER)
- Eve Oiglane-Slik (TUH)
- Virgilio Pace (DOMPE')
- Bojana Petrovacki-Dejanovic (IZZOV)
- Maria Giuseppina Petruzzelli (PB)
- Simona Ravera (PHARM)
- Pons Rose (AGIA SOPHIA)
- Pier Adelchi Ruffini (DOMPE')
- Urmas Siigur (TUH)
- Lonneke Staals (EMC)
- Anna Szumowska (CMHI)
- Luigina Tagliavacca (PHARM)
- Bianca Tempesta (CVBF)
- Airi Tenno (TUH)
- Dick Tibboel (Chair, EMC)
- Regina Trollmann (UKER)
- Tjitske van der Zanden (EMC)
- Stefan Wimmer (UKER)
- Nico Wulffraat (UMCU)
- Marcela Zubieta Acuña (ICCCPO)