



Metformin for treatment of polycystic ovary syndrome in children



Co-funded by
the European Union

On January 13, 2012, EMA released an updated priority list ("call") for requested Paediatric Use Marketing Authorization (PUMA) studies into off-patent medicinal products (EMA Reflection paper: formulations of choice for the paediatric population (emea/chmp/peg/194810/2005); July 28, 2006) . Metformin was specifically identified as a requested drug product for treatment of PCOS in children. The call requested data on efficacy and safety, as well as pharmacokinetic data in this indication and population. Moreover, the Committee for Medicinal Products for Human use (CHMP) of the EMA issued a reflection paper , in which soluble effervescent formulations have specifically been identified as suitable and preferred for use in paediatric populations, which is also aligned with the current FP7 call.

Currently, there are no age-appropriate dosing forms of metformin indicated for treatment of PCOS in paediatric (juvenile/adolescent) populations; METFIZZ addresses this unmet medical need.

The main goal of METFIZZ was to complete the required product development and clinical studies to establish efficacy and safety of metformin in Polycystic Ovary Syndrome (PCOS). The project plan included development of an age-appropriate innovative effervescent soluble formulation of metformin; design and conduct of a relevant clinical development trial; the manufacturing and scale up of the product; and ultimately the preparation and handling of registration aspects of this pharmaceutical development project.

Moreover, in line with the objectives of the call, it was the intention of METFIZZ to contribute to expanding the availability of medicines for children whilst ensuring that attention was given to considering the ethical aspects and particular needs of children and their families.

The METFIZZ consortium brings together an SME dedicated to improving pharmaceutical products by utilizing proprietary effervescent technology to develop products that improve efficacy, compliance and convenience of existing prescription drugs, 4 Contract Research Organisations covering the full range of competences to conduct trial trials, a dedicated FP7 project management company, and the UK National Institute for Health Research (NIHR) Medicines for Children Research Network bringing in patient advocacy groups to ensure the study is truly patient-centered:

- 1 **EffRx Pharmaceuticals S.A**
- 2 **KLIFO A/S**
- 3 **CCA Campbell Charles Associates**
- 4 **Sermes CRO**
- 5 **RCTs**
- 6 **SCIPROM Srl**
- 7 **Medicines for Children Research Network hosted at the University of Liverpool**

This collective approach comprises – apart from and beyond merely developing a new product - conducting the clinical development work necessary to establish new claims and indications as well as demonstrating the safety of a new drug product.

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Early awareness of the research project among potential investigators and patients was raised and a website was launched for the consortium in December 2013. Also, a project flyer was developed. The flyer was conceived as a publicity tool and to support patient recruitment during the clinical phase. It was approved by the consortium but approval by the ethics committee is pending before being finalized and printed.

Patient involvement - young people involved in the NIHR CRN were encouraged to raise their voice: Children afflicted with PCOS appreciated that their preferences on flavour and packaging options were considered during the pharmaceutical development project. This highlights the importance of ensuring that young people's input is genuinely taken on board.

Significant laboratory work leading to a final formulation, interim product specifications, analytical test methods, and packaging design for both Active and Placebo has been carried out.

The METFIZZ project achieved a product formulation against an organoleptic target profile, based on input from the Young Patients' Group, with the critical design criteria being:

- Colourless and essentially free from chemical or food dye colorants,
- sugar free (tooth friendly),
- sodium free or low sodium (repeated dosing can lead to increased sodium intake),
- orange flavour (resulting from the YPG involvement – up to 5 different versions were tested),
- slightly acidic, and
- a fresh mouth feel to best mask the Metformin-HCl inherent flavour characteristics.

What is PCOS ?

Polycystic ovary syndrome, or PCOS, is a health problem that can affect teenage girls and women. Having polycystic ovaries, means that small cysts or follicles may develop in your ovaries and prevent you from ovulating. If you do not ovulate, then you may not have a period.

Girls with PCOS may experience some or all of the following:

- irregular periods or no periods at all
- weight gain, obesity, or difficulty maintaining a normal weight
- excess body hair 'hirsutism'
- oily skin or acne
- darkened, thickened skin around the neck, armpits, or breasts ('acanthosis nigricans')
- high blood pressure, high cholesterol and high insulin levels

Girls who show certain signs of puberty early — such as girls who develop underarm or pubic hair before the age of 8 — may be at greater risk of having PCOS later on.

The formulation will also be fizzy for rapid dissolution and to avoid the need for stirring with a spoon (to achieve consumer convenience).

This stability study is still ongoing for the active formulation. Stability at 25°C/ 60%rh proven for up to 24 months of product shelf-life has been now been demonstrated with the outlook looking positive.

The project accomplished the necessary steps to launch the clinical phase – pre-clinical work, logistics, the study protocol, and data management support was put in a stand-by position awaiting the go-ahead from the coordinator and by the European Commission against some hurdles encountered during the formulation development phase and the assessment of the commercial viability of the project's eventual product EX404.

The various tasks of the project METFIZZ were all on track until scientific results on the product formulation in June 2014 triggered the requirement of additional CMC work to achieve the desired results. Further, a detailed assessment of the commercial viability of the eventual product EX404 suggested a critical reanalysis of the entire project. At this point in time it was agreed with the Project Officer, until a decision was taken on whether to continue with the project, work would only be carried out up to the point before clinical trial supply manufacturing was ready to commence.

As a result, the further work/completion of deliverables and milestones dependent on the final formulation report was halted. Large cost blocks such as the clinical phase (supplies manufacture, packaging, distribution, data management) were put on stand-by as well as all the documentation and registration procedures related to it.

Significant Work achieved by METFIZZ

To date, the largest part of work leading to the finalisation of the formulation of the METFIZZ product (EX404) to be clinically tested, including packaging design, has been carried out. However, the need for some additional CMC work to address critical findings on product stability and hence final formulation resulted in a considerable delay. Despite the delay, METFIZZ achieved all project deliverables and milestones along the project timelines, up to the point of formula finalisation. A placebo formulation has been developed as well. Sufficient shelf-life supporting stability data have been generated for the EX404 product formula. Throughout this process, the Consortium was made aware of the challenges faced and was kept updated along the way.

As mentioned, despite of the considerable delay, work was carried out to achieve project deliverables which included reports on the final formulation, CMC Study Documentation and the manufacturing process, the Clinical Trial Protocol, and the final label text. Moreover, the Management Guidelines, Project Flyer final draft and Project Website were also delivered.

In terms of milestones, the Constitution of the Ethics Advisory Board, Online Services including Mailing lists and Data Exchange, The Final Protocol, and eCRF were accomplished.

In the next paragraphs, the results achieved by METFIZZ are described, followed by an account of the events that eventually led to the discontinuation of the project.

Patient-Involvement

With the objective in mind to have a truly patient-centred study, METFIZZ sought input from patient focus groups (the Young Persons Group) through the efforts of the Medicines

What is metformin ?

Metformin, the drug substance used in the METFIZZ project, was identified by the European Medicines Agency (EMA) as a requested drug for treatment of PCOS in teenage girls and young women.

It is usually used to treat people with diabetes by lowering insulin levels and can be helpful for girls with PCOS too.

In girls with PCOS, metformin can help control ovulation and androgen levels. This can make a girl's menstrual cycles more regular.

Some girls and women treated with metformin have also experienced weight loss and lowering of high blood pressure.

Metformin is currently used to treat PCOS in young girls without a standard prescription, and appears to have no greater risk than

that of adults.

Tolerance to this medicine is good with limited side effects.

for Children Research Network hosted by the University of Liverpool.

METFIZZ has been hailed as the gold standard in patient involvement, linking industry to the consumers, whereby the views of consumers are taken on board right from the study design (protocol), formulation, presentation, packaging, and project flyer, all the way through to the patient information leaflets.

Further Details on Work done towards the METFIZZ Deliverables and Milestones

As mentioned, extensive laboratory work leading to a final formulation, interim product specifications, analytical test methods, and packaging design for both Active and Placebo has been carried out.

CMC documentation describing the current state of knowledge has been compiled in proper regulatory format for submission that includes formulation, analytical and stability data as well as manufacturing process descriptions, in the form of an IMPD Draft.

The compilation of the Clinical Trial Protocol based upon the study outline has been initiated and a version 1.0 has been finalized, ready to be submitted for ethics approval.

A Protocol Preparation and Review Team was established and has reviewed the Clinical Trial Protocol during several rounds. The team has likewise ensured that the Clinical Trial Protocol was compliant with the paediatric investigation plan (PIP) and Good Clinical Practices (GCPs).

A final version of the Investigator Brochure based on the PIP and protocol Version 1.0 has been issued and the study has been registered in the European Clinical Trials Database (EudraCT). Likewise, a final label text has been produced, approved and distributed for translation and local adaptation to national requirements. A packaging plan has also been drafted in order to have sufficient material available to distribute to all participating sites.

The global and country-specific templates for the Trial Master File and Investigator Site Files have been completed and distributed for implementation. Moreover, final versions of the Patient Information Leaflets incorporating feedback from the PCOS Patient Focus Group, have been prepared (for under 16 age group, over 16 age group, and parent/caregiver).

Coordinating investigators have been identified for each country and a draft monitoring plan has been drawn up.

The first version of the Electronic Case Report Form (eCRF) has been set up for the visits and the patient diary. The next version for review would include on-line controls, randomization, and treatments management. The validation of the eCRF and development of the three modules of the eCRF remained on hold.

Dissemination Efforts

Project Website

A temporary METFIZZ public website has been set up (<http://www.mETFIZZ.org/>). It contains a public section that serves as a dissemination gateway.

Project flyer

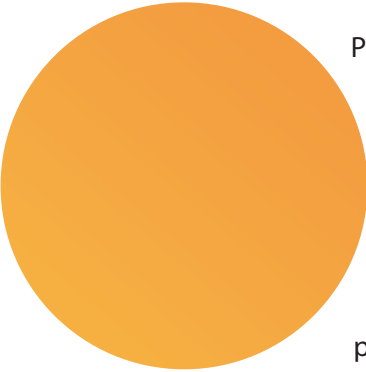
A project flyer has been conceived as a study awareness and patient recruitment tool. Its objective is to attract curiosity of potential patients and their parents, providing clear and interesting information about PCOS and the clinical trial.

Patient Advocacy

Dissemination efforts in fact, began with engaging patient-advocacy groups via the Young Persons Group led by the University of Liverpool (coordinated with EffRx and the clinical investigators), with the aim of assuring that the success of the study as a whole, and the eventual product was a meaningful result of this significant collaboration.

Project METFIZZ was identified as the 'gold standard' for the inclusion and involvement of young people in a study right from the beginning and throughout its duration: <http://www.brapp.org/images/journals/2015/PP2505sml.pdf>.

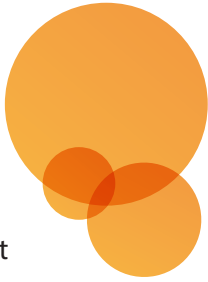
This is the first time a pharmaceutical company has formed a partnership with the NIHR CRN Children, who are part of the patient advocacy groups working with the METFIZZ




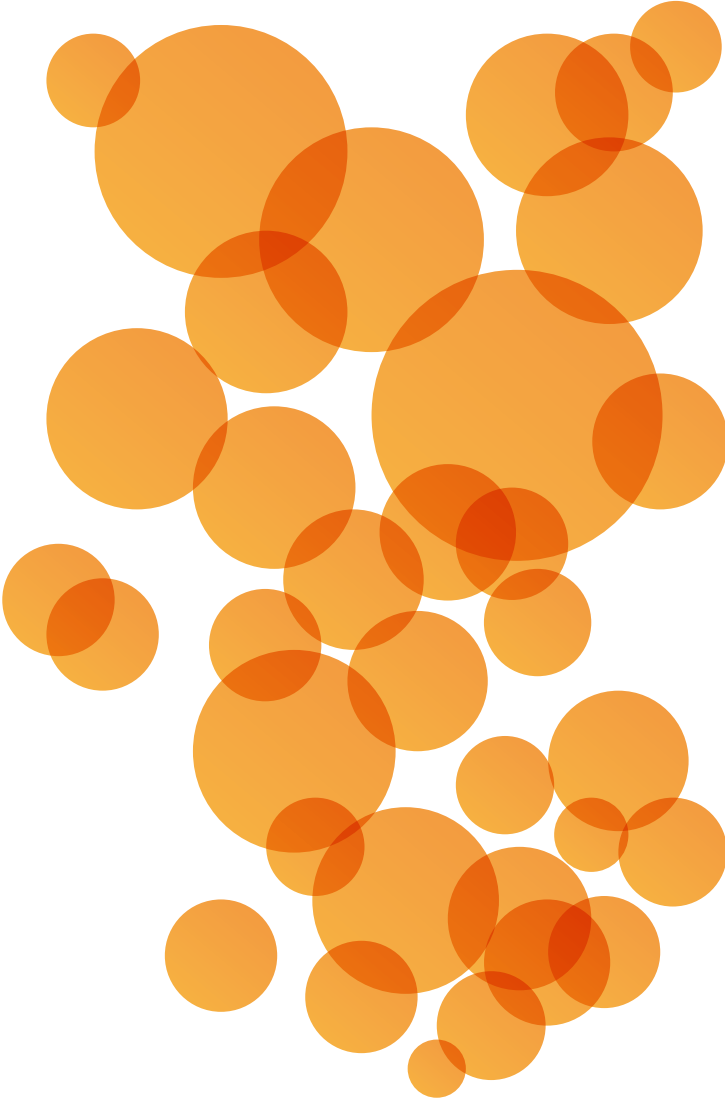
Project, to involve patients from the initial design stage right the way through to completion of the study. The overall expectation is that young people will be involved

throughout, inputting on a range of aspects over time, including the presentation and packaging of medicines, the study protocols, the outcomes to be measured in the study, as well as patient information leaflets. To date young members of the Liverpool group and a specialist PCOS group made up of young people who live with the condition have contributed to the project. So

far young people have contributed to the flavour, packaging and presentation of the new formulation, designed patient information sheets, and more importantly highlighted important outcomes that are relevant to them.



To date two groups of young people have been consulted: (i) 20 members of the NIHR Liverpool Young Person's Advisory Group (YPAG), aged eight to 18, and (ii) a group of nine young women currently being treated for PCOS, aged 13 to 18. The YPAG members initially worked together in a group to shortlist possible flavours for the medicine, such as banana, strawberry and orange, and to develop a discussion guide which could be used for consultation and involvement with the PCOS group. The PCOS group were then interviewed individually via one-to-one in-depth interviews to explore their views on the medicine (flavour, packaging and colour). This group were also given a 'sniff test' of the shortlisted flavours to choose from. The majority of young people consulted recommended that the medicine should be orange flavoured. The consortium has therefore opted for this flavour with the expectation that using a flavour that appeals to young people will help support compliance with taking the medicine during the trial.



The YPAG members also fed back their views about what the packaging should be like, and many of their suggestions were taken on board. The METFIZZ consortium felt that taking young people's views into account on the appropriate presentation and packaging of the medicine will have helped to support effective participant engagement in the study, and thereby support its overall success.

Other Dissemination activities

The study kicked off with a press release published by the project's sponsor and coordinator EffRx on the 1st of October 2013.

Several activities have since taken place during the course of this project. To list a few:

A case study was presented in an internal evaluation report produced by the National Children's Bureau as part of the NIHR Clinical Research Network (CRN): Children. This report can be accessed via the CRN NIHR website: <http://www.crn.nihr.ac.uk/resources/>.

Another case study was submitted for a book chapter entitled: "Working alongside industry: involving young people in formulation development." The chapter was part of a book called "The Patient Group Handbook, A Practical Guide for Research and Drug Development" by Anthony Hall and Nicolas Sireau – produced by Findacure (<http://www.findacure.org.uk> - a rare disease group charity).

A young person who is a member of the PCOS group was invited to co-author a book chapter with Ms. Jenny Preston who leads the Patient Advocacy tasks within the METFIZZ Project. The book chapter was entitled: Research together: the value of patient and family involvement. This was a collection of examples of how young people and families are adding value to research design and delivery and METFIZZ was used as an example of collaboration between industry and patients. The chapter will form part of a Neonatal and Paediatric Prescribing Book by Dr. Mark Turner and Professor Mike Sharland, which aims to provide a basic level of knowledge on the optimal prescribing of medicines for children, in a clinically focused handbook format. The project is being led by Dr Mark Turner and Prof Mike Sharland, and forms part of the work plan of the FP7-funded Network of Excellence,

Global Research in Paediatrics (GRiP), <http://www.grip-network.org>. The chapter was submitted on the 25 April 2015.

In December 2014 the PPI/E Manager and two young people from the Young Person's Advisory Group were invited to an Annual Meeting of the Ethical Medicines Industry Group (EMIG). EMIG is the UK research-based trade association that represents the interests of small to medium-sized Pharmaceutical, Biotech and Medtech companies (SMEs).

This meeting provided an opportunity for young people to present their views about how they want to be involved in the development of research and highlighted how young



people and families can add value to paediatric research.

This led to a publication in JOURNAL OF THE BRITISH ASSOCIATION OF PHARMACEUTICAL PHYSICIANS in March 2015 entitled: "Young people add value to research design and delivery." EMIG Annual Meeting, The Royal Society, <http://www.brapp.org/images/journals/2015/PP2505sml.pdf>, p. 8. Preston., J, Van't Hoff., W, Semple., G, Challinor., R. Young People's Voices Improving Research. Pharmaceutical Physician, Vol 25 issue 5.

A young member of the PCOS group was invited to speak at the Royal College of Paediatrics and Child Health (RCPCH) Annual Meeting on the 30th April 2015 to highlight the importance of working with young people. Presentation Title: "The role of young people developing meaningful research – The METFIZZ Study"

Exploitation activities

Since the initiation of the METFIZZ project, EffRx started an assessment of the commercial viability which became more rigorous as we learned more about the commercial realities of PUMA products in Europe.

EffRx has developed a comprehensive presentation of the targeted product presentation (EX404) encompassing among other items a Value story and a very solid Health Economic Data Generation Plan (that has been included in the design Clinical Study of EX404).

On this base EffRx has presented the product to potential external partners and consultants.

Despite the professional introduction of the EX404 opportunity, the consistent feedback, supported by work of an independent external market research institute, has been that it will be very challenging to achieve a commercially

viable product as local payers in the key-assessed EU countries would likely not grant a premium or would just recognize a marginal premium over available generic metformin for the innovative age-specific EX404 presentation.

The events which led to the discontinuation of the project

As mentioned, work on exploitation-related activities were initiated for key European countries where typically such products would be commercialized. The results of the exploitation activities were both surprising and alarming, having revealed an unfavourable commercial outlook for the METFIZZ resulting product (EX404) in the whole of Europe due to broad and cheap availability of the drug. Reimbursement investigations indicated that even if registered under a PUMA, the drug could only be marketed at a financial loss. These results of the commercial assessment caused the METFIZZ consortium to question the value of further expenditure on a project with no commercial viability (with essentially no end result benefit to the European population).

Furthermore, the investigation has indicated that obtaining a PUMA will not in itself increase the chance of obtaining a reasonable price in Europe, and in most EU countries, PUMA status will not influence payers who follow national reimbursement laws. An initial payer assessment was performed by a potential licensing and commercialization partner who then later declined to further pursue the product due to the findings in the report.

In light of the adverse commercial opportunity in Europe an assessment on regulatory approval requirements in other territories was done. In the United States, a Pre-Investigational New Drug (Pre-IND) meeting was

held with US FDA on September 30th 2014, to understand clinical requirements for approval. Initial feedback from FDA is that US approval requirements are significantly different from those documented in the Paediatric Investigation Plan or PIP in Europe. In particular, a Phase 2 dose finding study and Phase 3 studies in US patients are required. In essence, the PIP approved for the European investigation was rejected by FDA as unsuitable for a clinical development plan for a US approval.

A teleconference was held with the METFIZZ project officers to discuss the issues on delays due to required additional CMC work (WP 2), the findings on the commercial viability of EX404 based on exploitation efforts (WP 8) through METFIZZ, as well as the position of FDA on the anticipated clinical studies. In consideration of these findings, the EC Officers had requested METFIZZ to propose possible scenarios to the EC in terms of how to proceed with the project.

EffRx on behalf of the coordination team, formally communicated to the EC officers the adverse viability assessment of the project, along with 5 suggestions (options) for the path forward of METFIZZ.

The mutually favourable option put forward was to evaluate the possibility of continuing the project with a reduced scope, hence, an “enhanced project” as explained below:

‘Option 3: Continue, but reduce scope of EC project.

EC continues to support an ‘enhanced’ project mainly aimed at US registration, preferentially utilizing relevant expertise of consortium members and resources, resulting in a high quality clinical development program, which will satisfy the FP7 Call (demonstrating safety and efficacy of metformin in ado-

lescent PCOS). EffRx will not commercialize the product in Europe, but the clinical study data will be made available to the EC for its use. For example, the EC could allow data to be used to support a Compassionate Use program (not reimbursed) In Europe, provided that the EC can organize an appropriate sponsor.’

If continued EC support is provided, the sponsor and coordinator EffRx would ensure that the full clinical study data will be made directly available to the EC for its free use, provided the clinical program in the US can be initiated and successfully completed in line with US FDA guidance.

This scenario would have meant the following for METFIZZ:

- FP7 call is satisfied with respect to the clinical demonstration of safety and efficacy of metformin in adolescent PCOS, as EffRx will publish study outcomes.
- The optimal dose for the use of metformin in adolescent PCOS is established.
- Relevant METFIZZ consortium members still have the opportunity to be part of the project, even though a large part of the clinical aspects of the study will be conducted in the US. It is anticipated that the EC would only fund the tasks of the program that are relevant to the call.

The above scenario was further discussed and explored during a Face-to-Face meeting held in the EC offices attended by the METFIZZ coordination team, the project officers and head of the EMA PDCO, to discuss such way forward for the project.

During this meeting it was reiterated that EC is in favour of supporting off-patent medication for children, and, from a practical point of view, research should lead to a benefit for

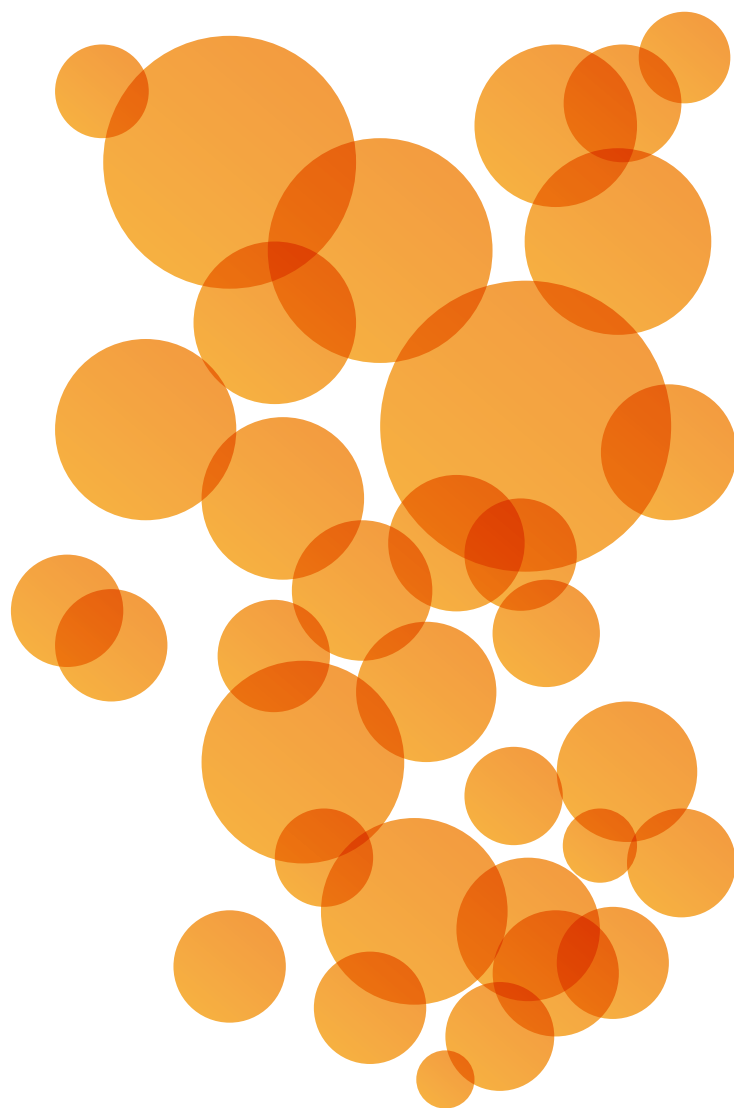
European patients, despite the mentioned shortcomings of PUMA program. While it is outside of the remit of EMA, the EMA has acknowledged that they are aware of the limited appeal of the PUMA concept due to the fact that the national health systems attribute different values and that the exclusivity incentive has little to no value due to reimbursement issues.

Moreover, the EMA-PDCO expressed that its main objective is the availability of the data and the medicinal product in Europe.

Further, it was established at this meeting that the assessment on the project METFIZZ was still ongoing, and that there was no clear indication whether to continue or not the funding of the project. It was also communicated that the clinical study would merit continuation of funding, for as long as the project is recognized as valuable by the PDCO and can show benefits to European patients by making clinical outcome data available. The EC also maintained that all work carried out until the point of being ready to manufacture clinical trial supplies will be funded and that METFIZZ was to hold off on any significant spending until a decision was taken on how to proceed.

At the conclusion of the Face-to-Face meeting, it was agreed to continue to maintain the activities on hold until further guidance from the EC officers would be received. Additionally, work on the periodic reports were continued based on the status of the project at that time.

Meanwhile, project sponsor and scientific coordinator EffRx progressed efforts to outline the US clinical protocol and opened an IND in the USA, all at its own cost. The IND, containing the revised clinical protocols, was opened and submitted to the US FDA. Concomitantly, the identical clinical protocols were also sent



to the European Commission project team and Dr. Tomasi (EMA PDCO) for review and comment.

Since informally providing the protocol to the EMA PDCO for review, the US-FDA responded with several issues that will further impact the clinical protocol and timelines.

To complete the history of events, Coordinator EffRx submitted the first periodic report in May. Upon the receipt of the formal letter by the EC dated 21st August 2015, EffRx engaged with the EC officers to clarify the situation and inquired for further guidance to address the subject of the letter.

The EC officers advised METFIZZ to contact PDCO to highlight the relevance of the proposed option to EMA PDCO. EMA PDCO has in the meantime stated that a revision of the PIP would be required. It will take a period of several months to revise the PIP, incorporating FDA requirements as well as anticipated EMA requests.

In consideration of the time needed to pursue ongoing work with regard to the revised study protocol and dialogue with both the FDA and EMA PDCO, the METFIZZ team, requested to put the project on official HOLD for at least one year from September 2015, with then a potential continuation of METFIZZ for the activities relevant to the EC under the auspices of the FP7 program. This would have given METFIZZ a chance to exhaust all possible options to keep the project relevant to Europe and obtain approval from the FDA on the planned clinical studies and alignment with EMA PDCO regarding the design and scope of these studies. During this holding time, no other activities were foreseen to be funded (apart from the ongoing stability / CMC work done on the current formulation) by the EC until such time when the project is given the go ahead to re-commence.

EffRx continued to exert efforts to find potential co-developers or commercial partners to share the costs of the US Study, but unfortunately, although there was some initial interest, it was not enough to engage potential partners and eventually continue the project.

After careful consideration of the required work and accompanying costs required to undertake the US program, and having been unsuccessful in finding an interested partner to co-develop the product and share the costs

of the US clinical program, which would then enable the project in Europe to continue, where part of the patient population would be done in Europe within the existing consortium teams, EffRx has decided not to go ahead with the program. All things considered, including the questionable commercial viability of the eventual product EX404, EffRx declared that it could no longer continue as Sponsor and Coordinator of the project.

After discussions with the Consortium, it was established that no other partner nor potential candi-date was willing and able to take the place of EffRx, as was officially communicated to the EC officers.

With the project being severely delayed, the coordinator and sponsor of the study having renounced its roles with no success in finding a replacement , and the economic prospects of commercialising the eventual product EX404 which still remains unconvincing, the EC officially communicated the termination of the grant agreement on the 5th of July 2016 in accordance to Article II.38.1 b) of the grant agreement , due to the fact that “no reparatory measures could have resulted in a viable solution for the continuation of the project.”.

As a whole, the METFIZZ team learned some valuable lessons from this project in terms of challenges one can face in such a study. Despite the decision to discontinue the project, a lasting impression was hopefully achieved, if only to raise awareness about the realities of the PUMA concept as insufficient to promote off-patent paediatric indications and the significance of having a truly patient-centred study where industry empowers patient/ consumer groups to become involved in the research agenda of drug development.