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Human Medicines Development and Evaluation

Report of the workshop on paediatric investigation plans in type 2 diabetes mellitus

European Medicines Agency, London, 25 February 2013

Introduction

The Agency held a one-day workshop on 25 February 2013 on paediatric investigation plans for medicines to treat Type 2 Diabetes Mellitus (T2D).

European and US experts in the field of paediatric T2D (N=15), together with European drug regulators (N=10) and representatives from 13 pharmaceutical companies, discussed paediatric developments for novel glucose-lowering agents for the treatment of T2D.

The main objectives of the meeting were:

- to identify elements for agreeing Paediatric Investigation Plans in T2D in line with good clinical practice and delivering conclusive outcomes;
- to identify possible approaches to enhance feasibility of paediatric T2D trials.

The workshop was also observed by PMDA (Japan) and Health Canada via broadcasting. The FDA (USA) was not able to participate due to competing Agency work.

The morning sessions were dedicated to set the scene by clarifying current challenges for paediatric developments for novel glucose lowering agents for the treatment of T2D. Furthermore, current prevalence data of paediatric Type 2 Diabetes and therapeutic approaches in Europe and the US were presented by experts in the field. Moreover, an overview of key elements in current T2D PIP decisions was given by EMA regulators and a company perspective on trial recruitment issues was presented.

The afternoon was dedicated to discuss the answers received to the list of questions, which had been prepared and circulated to all participants in advance of the meeting. Furthermore, potential innovative clinical trial approaches were presented from industry and academic participants.

The presence of experts, industry and regulators was also used as an opportunity to further discuss the establishment of the Enpr-EMA Diabetes/Endocrinology Network.

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Problem statement

- Janina Karres (EMA)

The European Paediatric Regulation requires the agreement, with the Paediatric Committee (PDCO) of the EMA, on paediatric development via so called Paediatric Investigation Plans (PIP) before filing an adult marketing authorization application, unless a waiver is granted.

The main motivation for developing several novel T2DM drugs is the revenue expected from the adult market (due to the high prevalence of T2DM in adults). However, the paediatric T2DM patient population is currently rather limited.

PPAR-modulating agents are excluded from the obligation to conduct studies in adolescents with T2DM, since a class waiver has been adopted by the PDCO for these products.

To date 16 PIPs have been agreed for T2DM, with products mainly belonging to three classes: GLP-1 analogues, DPP-4 inhibitors ("gliptins"), or inhibitors of renal sodium-glucose co-transporter (SGLT2-inhibitors). Children older than 10 years can be included in trials.

The number of products being developed, coupled with the relative scarcity of paediatric patients, creates significant feasibility issues for the conduct of the paediatric studies. More than 23 requests for modification of the agreed PIP received to date for these T2DM products also reflects, at least in part, this issue, since requested changes of the agreed PIPs mostly concerned delay in timelines and changes to inclusion/exclusion criteria.

Current Guidelines: Treatment of T2DM in children/adolescents

- Carine de Beaufort (PDCO member; Pediatric Clinic Luxembourg)

Current Clinical Practice Consensus Guidelines were briefly summarized according to The Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence as published in 2011 and the recent Clinical Practice Guideline from the American Academy of Pediatrics (AAP) as published in 2013 (Pediatrics. 2013 Feb;131(2):364-82. doi: 10.1542/peds.2012-3494. Epub 2013 Jan 28).

Herein it is stated that initial care of type 2 diabetes will depend on the severity of symptoms at presentation. Insulin may be required for metabolic stabilization and until diagnostic classification as type 2 diabetes. Once metabolically stable, a lifestyle modification program should be initiated (including nutrition and physical activity) together with metformin treatment (first-line therapy unless insulin therapy is indicated as in the case of HbA1c > 9% or plasma BG concentrations ≥ 250 mg/dL). Self-monitoring of blood glucose should be performed at least twice per day.

The prevalence of obesity ranges from 85% amongst European and US T2DM patients to 30 to 50% amongst Asian T2DM patients.

No other therapies have been approved apart from insulin and metformin in children and greater choices are required. The TODAY study shows that still 50% of children were uncontrolled following dual therapy with Metformin and Rosiglitazone. The TODAY study also investigated CV risk factors including hypertension and dyslipidemia, publication to follow. No CV/ renal/ neurovascular/ ophthalmologic events were reported in this trial. Furthermore, it has been reported that diabetic complications such as microalbuminuria are observed after 3 years already in children.

Prevalence and treatment of T2DM in Europe

- David Dunger (University of Cambridge Metabolic Research Laboratories, UK)

Overall precise prevalence and incidence data on children/adolescents with T2DM is rather sparse throughout Europe and the quality of data is very country dependent. The most robust data presented were from Germany, Austria and the UK.

The DPV (Diabetes Patienten Verlaufsdokumentation) database captures, amongst others, the following data in German and Austrian children and young adults (0-20 years) since 1995: T2DM prevalence, patient characteristics and course of the disease and diabetes treatment. As of January 1st data from 517 patients were reported. The completeness of the data was not discussed but the number of participating centers is high (n=370). The majority of the patients were females (62%); the average age was 14.5 years at diagnosis; on average patients were obese (+ 2.4 BMI-SDS) and 33% had a migration background.

Registry data from the German regions North-Rhine Westphalia and Baden Wuerttemberg report prevalences of up to 6.5 and 2.3 respectively per 100.000 in the age group 0 to 20 years. Based on these numbers the estimated total number of paediatric T2DM patients in the whole of Germany would be between 780 and 390. The German data shows an increase in T2DM prevalence up until 2002 but no dramatic increase has been observed since then.

The currently best UK prevalence data comes from the JUMP initiative. This initiative funded by the UK MRC aims at creating a cohort of well characterized paediatric T2DM patients that could be potentially eligible for novel intervention studies to treat the disease and prevent progression to cardiovascular disease. Out of 256 children with a paediatrician diagnosis of T2DM, 175 patients were recruited into the cohort as of end January 2013 and the results from 156 children were presented. The estimated prevalence in the UK is about 250 children with T2DM and about 25,000 with T1DM; this equals a prevalence of T1DM of about 1:500 UK children and of T2DM of about 1:50,000 UK children. Again, the majority of the patients were females (70%), the median age at diagnosis was 13.4 years (range 7.9-17.5), 66% of patients had osmotic symptoms at presentation, 23% were asymptomatic and 4% had DKA. The median diabetes duration was 3.25 years. With regards to ethnic origin 42% of the patients were white UK, 15% were black and 33% South Asian. It was concluded that T2DM still only represents about 1% of childhood diabetes in the UK. White UK children are older and more obese at diagnosis than non-white children. Fasting C-peptide levels were lower in the black population. Furthermore, African-Caribbean UK children have poorer metabolic control, signs of cardiovascular dysfunction and lower fasting C-peptide levels compared to white UK and South Asian children. Only 8% of patients received diet/lifestyle intervention on its own, 55% of patients received Metformin only, 32% received Metformin and insulin. Insulin was generally used at diagnosis if osmotic symptoms were present and only used for longer duration if HbA1c values were persistently greater than 7.5% despite maximal tolerated metformin dose. Other glucose lowering agents were rarely used.

Prevalence and treatment of T2DM in the US

- William Tamborlane (Yale Centre for Clinical Investigation, USA)

The SEARCH study currently provides the best prevalence data of paediatric T2DM in the US (Pediatrics. 2006 Oct;118(4):1510-8). According to these data the prevalence amongst children and young adults below 20 years of age in 2001 was about 20.000 or cases per 10,000 US youth. Type 2 diabetes was found in all racial/ethnic groups but generally was less common than type 1, except in American Indian youth. Assuming a theoretical yearly 2.3% increase this would add up to 23.000

paediatric US patients in 2010. Estimates from paediatric T2DM Commercial and Medicaid Claims are even higher at 30-35.000 patients in 2011.

U.S. claims databases are derived from billing codes and thus may overrepresent actual diagnoses. This can be seen from the fact that only 50% of these patients were treated.

Additional glucose lowering agents are required. As the TODAY study showed, after an average of 3.86 years of follow-up 45.6% of patients failed to reach glycemic targets (HbA1c above 8%). Furthermore, the treatment options are much more limited in adolescents than adults with T2DM.

At least 16 trials in 10 medications for T2D in pediatrics are currently aiming to recruit ~2000 patients (ClinTrials.Gov website) with more products to follow. However, the disease is still not as prevalent by far as in adults and the following issues contribute to recruitment difficulties into clinical trials: about 75% of patients are from disadvantaged environments which can cause logistic recruitment problems, 2/3 of the available patients are adolescent girls and there is a general distrust into clinical studies amongst black families owing to the infamous Tuskegee study. Also, psycho-social issues (e.g. behavioral problems, depression) add to difficulties in trial recruitment and conduct. In addition, 50% of patients are controlled on metformin with an approximate additional 30% treated with insulin leaving far fewer potential subjects for clinical trials.

Suggestions for new paediatric T2DM drug developments:

Add-on efficacy studies only

The unmet need is clearly for second and third line drugs for patients with elevated A1c levels on their current treatment regimen. Metformin is well established as initial monotherapy of T2DM and insulin is recommended if patients are ketotic or in DKA, have random BG level ≥250 mg/dL or an A1c of >9.0% (AAP Consensus: Pediatrics 2013;131;364).

Experience from the TODAY study showed that out of 1000 screened paediatric patients 45% were on Metformin alone, 13% were on Insulin alone, 26% were on Insulin+metformin and only 13% of patients were not on any drug.

Therefore, new drugs for the treatment of T2D in pediatrics should be tested against placebo as add on therapy in patients with elevated A1c levels who are being treated with: metformin and/or insulin and/or any other anti-diabetic drug of a different class.

Expand the age range up to 21 years or older

Young adults behave more like adolescents than adults. Therefore, one should include also patients from 18 to 21 (or even 24) years of age into the studies.

Extrapolation and single-arm safety studies

The only qualitative difference between adults and children with T2DM is the faster pace of β-cell deterioration and progression from IGT to T2D in children. Furthermore, pediatric T2D patients are still developing (and puberty has profound effects of glycaemic control). Otherwise, presentation and pathophysiology are similar in adolescents and adults. Moreover, adolescents with T2D are of similar weight and BMI as adults with T2D. In both age groups, T2D disproportionally affects low income, Black and Hispanic patients. Therefore, partial extrapolation could be an option if PK/PD characteristics are similar in pediatric and adult T2D. In this case non-controlled safety and activity studies would be sufficient. These could be either performed through clinic-based registries or post-marketing safety studies.

Extrapolation from Adult studies

During the subsequent discussion it was pointed out that, at least according to FDA criteria, partial extrapolation is present in almost all of our T2DM PIPs (absence of two fully-powered controlled studies). The key question is rather how much extrapolation is deemed acceptable. To answer this, we must know how different T2DM is in children and whether the differences are expected to impact the efficacy of the product. The general agreement of the group was that the main difference is the more rapid progression of the disease in adolescents, which in turn seems to be caused by the higher degree of obesity in adolescents vs. adults with the disease. Furthermore, adolescents may have more rapid development of beta cell dysfunction. Currently there is few paediatric data available to know in how far the differences are expected to impact the efficacy of the product. The implication of the results of TODAY is that compared with published adult data the failure rates on metformin in children with type 2 diabetes appear to be higher.

Most PIPs contain as binding element that at least 30% of the population should be from EU countries or countries with comparable EU lifestyle and diabetes care.

Given the shortage of European patients it was pointed out that this may be very difficult to achieve. Even though it was pointed out that the ethnic differences are probably greater within rather than between European and US populations the group agreed that such a key element is an important element in the PIPs to guarantee applicability of results to European patients. European patients (average 75-80kg) do seem to be as obese as US patients (average 100kg).

Overview of PIPs for T2D

- Janina Karres (EMA)

To date 16 PIPs have been agreed, containing overall 18 pivotal and 13 separate PK/PD studies. Most of the PIPs contain one PK/PD and one Pivotal Study. However, a few PIPs contain a PK sub-study within the Pivotal Study or two Pivotal Studies.

Pivotal Studies:

Most PIPs contain either add-on to Metformin studies or studies with a mixed population (Monotherapy and Add-on to Metformin) to broaden eligibility for the studies. Only 2 pure monotherapy studies have been agreed in two of the earliest T2DM PIPs for gliptins to investigate a possible beta cell sparing effect. However, after consultation with an international expert group in 2008 the widespread initial use of metformin has been highlighted and no pure monotherapy studies have been requested by applicants or agreed by PDCO since then.

Recently the PDCO also agreed studies which contained an add-on to Insulin and add-on to Insulin and metformin population.

Most PIPs contain 2-arm studies (Placebo vs New Drug), however, a few studies have 3-arms (Placebo and New Drug and Metformin) where metformin was included for benchmarking. All studies were parallel studies which tested superiority of the new drug over placebo in mean change HbA1c levels from baseline to either 12, 16 or 26 weeks. It was emphasized that placebo controlled studies could be either add-on (majority), monotherapy or mixed-population studies, please see above.

Inclusion criteria for HbA1c values ranged from 6.5% or 7% (lower limit) up to 10 or 11% (upper limit).

Most studies allowed Insulin use for a limited duration within the 3 months prior to screening.

Most studies had a 3, 4 or 6 months placebo controlled treatment phase.

All pivotal studies contain a full year of exposure to the new drug for safety as pre-authorization obligation (mostly roll-over to an open label extension phase after the placebo controlled treatment phase).

All PIP studies:

The total minimum number of paediatric patients to be included in the studies of the agreed PIPs so far adds up to 3588. The total min. number of patients in all PK or PK/PD Studies is 504, with an average per PK or PK/PD Study of 32 (range: 12 – 100). The total minimum number of patients in all Pivotal Studies is 3196, with an average per Pivotal Study of 178 (range: 90 – 300).

In conclusion, the main differences amongst PIPs regard the patient population within studies (Mono-, Add-on, Mixed population), the duration of placebo controlled treatment phase/timepoint of primary endpoint evaluation, numbers of studies per PIP, separate PK studies vs PK sub-study integrated within the pivotal study and the use of previous glucose lowering agents.

During the discussion it was emphasized that differences in the agreed PIPs are possible, since the PDCO may accept different proposals from applicants, as long as they are suitable to determine the benefit/risk of the products in adolescents; furthermore, the differences can sometimes be explained due to the different properties of the products (e.g. expected beta cell sparing effect or not), differences in dosage forms or routes of administration (e.g. oral vs parenteral, short acting vs long acting), quality and quantity of adult data. The responses to the questionnaire which were discussed later highlighted the range of views on certain aspects.

With regards to the duration of the placebo controlled treatment phase, the FDA and EMA views are divergent. While EMA prefers 3 months, the FDA prefers 6 months in order to obtain data on the durability of the effect. There are no data currently that demonstrate that 6 months is better in terms of demonstrating durability of effect compared to 3 months. Furthermore, there were doubts among experts on whether demonstration of durability of the effect on HbA1c should be at all the aim of the marketing authorization or whether such questions should rather be addressed post-authorization.

The EMA guideline does not exclude 6 months duration of the placebo controlled treatment phase but given that studies include some highly uncontrolled patients 3 months are favoured. It was agreed that an evaluation of the outcome of shorter versus longer duration placebo data with regards to the number of rescue medications and dropout rates would be beneficial. Furthermore, the views of advocacy groups, patient organizations and Ethics Committees on the topic would be interesting to obtain. The dialogue between EMA and FDA needs to be continued either as a result of this meeting or after some of the placebo data from paediatric trials are available. However, it is likely that sufficient placebo monotherapy data will not be obtainable.

Trial recruitment issues – a company's perspective

- Philip Ambery (GlaxoSmithKline)
- Pamela Zee (Alliance AstraZeneca/Bristol-Myers Squibb)

The challenges and benefits of making novel T2DM drugs available to children were summarized again. Mainly, the rarity of the disease vs many novel T2DM drugs under development and the need for additional glucose lowering agents that do not increase weight.

The importance of an appropriate safety database and proof of a positive benefit/risk balance in adults have been emphasized in light of potential associated risks for several novel T2DM products (i.e. thyroid and pancreatic malignancies, pancreatitis).

To highlight the current trial recruitment issues, the specific example of Saxagliptin was presented. For the Monotherapy study, use of a placebo arm was a major barrier to enrollment and was turned down by many centers, ethics committees and even whole countries. For the add-on to Metformin study, the pool of eligible patients is limited as about 50% of patients achieve durable glycemic control on metformin (see TODAY study). Widespread use of concomitant insulin further challenges study feasibility. Recent PIP modifications did accommodate for additional insulin background use in the studied patient population.

Further difficulties are the strict requirement for inclusion of at least 30% of patients from EU member states or countries with ethnicities and lifestyle that are analogous to those in EU countries, the restricted age band up through age 17, existence of only a few registries to identify patients. Furthermore, there is a competitive environment of several companies seeking to currently recruit paediatric patients into their clinical trials (see also above).

For Saxagliptin, out of almost 1000 study sites approached in 20 countries for the monotherapy and add-on therapy study, approximately 40% of EU and 50% of non-EU study sites declined participation due to lack of patients. 83 (monotherapy study) and 105 (add-on study) centers accepted and after 1.5 years only 5 (monotherapy study) and 3 (add-on study) patients could be randomized.

The main reasons for pre-screening failure were as follows:

- 36% of patients used insulin within 6 months prior to screening. As the majority of responses cited only one reason for pre-screen failure, this percentage is likely an underestimation.
- 34% of patients had HbA1c levels beyond the limits of inclusion (below 7% or above 10.5%).
- 19% of patients used other anti-diabetic treatments within 2 months of screening.
- The sites/investigators reported reasons for failure on a voluntary basis; there was not 100% participation.
- The total number of reasons for pre-screening failures reported as per 4th quarter 2012 was 888.

In conclusion, new approaches are needed to provide dosing, efficacy and safety information in order to complete paediatric developments for T2DM. Possible solutions may be:

- To broaden inclusion criteria (allowing at least insulin use as background treatment, broaden HbA1c limits,…).
- To perform multi-company studies with multiple agents within the same drug class using only one control group.
- To perform single-company studies with multiple agents spanning different drug classes.
- To study the new drug in related yet more prevalent disease states (e.g. T1DM, pre-diabetes).
- Extrapolation model for efficacy based on adult data.

During the discussion it was clarified that 50% of patients on metformin have HbA1c levels at goal which would be below inclusion range for clinical trials. Those with high HbA1c levels will tend to require insulin. There is a bimodal pattern of HbA1c values observed, often either falling below or above the set HbA1c limits in PIPs. However, using the saxagliptin example, more patients fail at screening due to falling below the HbA1c limits (i.e. 4.8 – 6.9%).

With regards to the suggested multi-company studies with multiple agents it was suggested to only conduct the placebo-controlled treatment phase as a common study but separate developments again at time of the (open label) safety follow-up.

Need for paediatric friendly PK studies

- David Dunger (University of Cambridge Metabolic Research Laboratories, UK)
- Philip Ambery (GlaxoSmithKline)

A spontaneous discussion developed around the need to propose and conduct PK studies that avoid frequent sampling and the use of known sub- and supra-optimal doses as much as possible. An example from a recently agreed PIP was presented in which frequent sampling was avoided by testing only the adult therapeutic dose and taking only peak and trough PK values in a limited number of children and then construct a POP-PK analysis to bridge the missing data. This was acknowledged as a good compromise in order to get the data but avoid frequent sampling at the same time. Furthermore, the use of minimally invasive techniques to draw and analyze blood samples was raised of an important method to employ during paediatric PK studies such as use of blood spots on filter paper (only requiring small finger pricks).

A question on differences in drug tolerability in children compared to adults was raised in this regard which may necessitate different doses being tested. Experts confirmed that at least the experience from metformin shows that the drug is equally if not better tolerated in children.

However, focusing the attention on tolerability and PK may be a better strategy than proving efficacy in a drug which has already been proven to be efficacious in adults.

Conclusions of responses to preset questions to participants

- Janina Karres (EMA)
- Carine de Beaufort (PDCO member; Pediatric Clinic Luxembourg)

Question 1: Is inclusion of treatment naïve patients feasible and compatible with good clinical practice?

There was general consensus that studies should not focus on treatment-naïve patients as this is not where the unmet need is. Metformin is the recommended first line treatment (together with lifestyle management) with good safety and efficacy. Placebo controlled studies including naïve patients raise ethical concerns and are not well accepted by patients, parents and investigators. Furthermore, data suggest that treatment-naïve patients are rare (6 to 13%) and have low HbA1c levels so they are not eligible for recruitment. Inclusion of treatment-naïve patients should not be a regulatory requirement, as it is not feasible.

To date no glucose lowering drug has shown to be non-inferior to metformin with sufficiently narrow delta, let alone have they been demonstrated to be superior.

With regard to current PIPs there are only two pure monotherapy studies(old PIPs, gliptins, wanted to see if drug has beta cell sparing effects) but most other studies allow also naïve patients together with add-on to Metformin patients within one study (mixed populations to broaden spectrum of eligible patients, increase feasibility). In future, PIPs may only include add-on studies and be more accommodating for different background therapies.

Question 2 (a+b): Is inclusion of paediatric patients on stable insulin background therapy (without or with concomitant metformin) compatible with good clinical practice?

There was general consensus that inclusion of patients on stable insulin background therapy (without or with concomitant metformin) should be allowed into paediatric clinical trials. Insulin plays an important role also in T2DM in paedatric patients with DKA and high/difficult to control glycemic levels; an unmet medical need exists in these patients.

Stable and constant insulin doses seem indicated, as they do not require frequent follow-up for adjusting doses as this would add complexity and therewith create compliance issues in this already difficult population. A stable insulin dose with prespecified range of adjustment seems appropriate (with rescue criteria), maybe even a single long-acting dose. An adult study was described with a placebo-controlled add-on to long-acting insulin (without or with concomitant metformin) design with short acting meal time insulin as rescue medication and reduction of long-acting insulin in case of hypoglycemia. The endpoint was a set HbA1c value. This design provided data on time to failure, glycemic control over time, use of rescue medication and hypoglycemias. Such a study was deemed potentially interesting for paediatric patients.

It was pointed out that the treatment aims for new oral agents and parenteral agents may be different. While the use of oral agents such as gliptins and SGLT2 inhibitors may aim at the delay/avoidance of insulin therapy, a GLP-1 agonist could provide improved control or have other clinically advantageous outcomes such as reduced weight gain if introduction of insulin therapy is inevitable or weaning off insulin is desirable (i.e. insulin replacement).

Insulin weaning approaches while introducing the new study drug were deemed as being often too complex and not feasible as part of the trial protocol.

It was suggested that pure dual or triple therapy studies including insulin in children should not be mandated but it should be allowed to also include patients on insulin into the studies. Add-on to any stable therapy may be acceptable as long as it does not interfere with the drug effect or poses a specific safety concern.

Trials which include combination therapies may also consider weight neutral effects in addition to glycemic control.

Current PIPs: Up until now PDCO only allowed inclusion of patients on insulin (+/- MF) in two studies within one PIP. In the future inclusion of patients on insulin (+/- MF) should be allowed more broadly if there is no interference with the drug effect or a safety concern.

Question 3 not discussed in the interest of time.

Question 4: Which minimum and maximum HbA1c levels do you deem adequate for naïve patients and for those on metformin/insulin treatment?

The consensus for a lower HbA1c threshold was 6.5% and an upper threshold of 11%. In the US the average HbA1c in children is 9%. Most rescue criteria are triggered at 12%. Very aggressive rescue criteria can lead to inconclusive trials. Therefore, rescue criteria should be based on HbA1c levels, ketosis and other clinical symptoms (not only on glucose values).

Current PIPs: This is in compliance with most of our currently agreed PIPs.

Questions 5-6-7: How long should the duration of the placebo-controlled treatment phase of the pivotal studies be?

The great majority of participants deemed a 3 months placebo-controlled treatment phase of the pivotal studies where the agent is added too stable insulin or metformin therapy would be sufficient, followed by an open-label extension up to 12 months. The aim of the controlled period should be the demonstration of a similar size treatment effect as in adults. In the view of the clinicians, a placebo controlled phase past 3 months, may still be challenging from a feasibility (compliance) and ethical (inclusion of some highly uncontrolled patients) point of view.

A minority preferred a 6 months placebo-controlled treatment phase.

It was suggested that the decision of 3 vs 6 months could be based on the properties of the drug. For example, if a drug is expected to have a beneficial effect on weight (e.g. GLP-1 analogues), a 6 months placebo-controlled treatment phase may be chosen, given that an effect on weight after 6 months is much more predictive of the actual (12 months) effect than the effect on weight at 3 months.

With regards to the duration of the (open label) extension period it was pointed out that this should be motivated by the type of safety signals that could be expected (mainly based on adult and pre-clinical data). However, a total of one year paediatric data is desirable and this would also provide some information on potential effects on beta cell preservation and weight.

It is acknowledged that FDA has proposed a longer placebo-controlled treatment phase. As it is desirable to agree global PIPs a dialogue with FDA may be initiated again based on the expert views expressed during this meeting. Currently, there does not seem to be any data that 6 months duration provides more robust information on long-term maintenance of glucose control than 3 months. However, 3 vs 6 months do make a significant difference with regards to study feasibility and patient acceptability according to experts.

One expert challenged the need for a placebo controlled study altogether suggesting that open label studies may be sufficient. It was agreed that this is equivalent to completely extrapolating efficacy which requires that the disease behaves exactly the same way as in adults. As the disease progresses faster in children than adults this may not be the case. However, it was questioned that 3 or 6 months placebo controlled studies would be sufficient to account for this specific patho-physiologic difference. Currently paediatric T2D studies aim at demonstrating similar treatment effects (changes in HbA1c levels) as observed in adults and generating safety information on the product in the paediatric population.

Employing innovative approaches could help to reduce sample sizes and make the studies more feasible; examples such as Bayesian statistics (i.e. use of adult results as priors) or possibly allowing for greater p-values were mentioned. The importance of including the Scientific Advice Working Party/Committee for Medicinal Products for Human Use (SAWP/CHMP) in the discussions of such innovative trial approaches was emphasized.

Current PIPs: The majority of PIPs has a 3, 4 or 6 months placebo controlled treatment phase (approximately equal distribution between these 3 durations). In the future it seems important to see whether the drug is expected to have potential additional effects such as weight loss or reduction of high blood pressure. If yes, 6 months placebo controlled treatment phase may be justified, if not 3 months should be preferred for sake of feasibility.

Questions 8 and 9: What are the most appropriate primary and key secondary endpoints for paediatric pivotal T2DM studies and what is considered a minimally important clinical difference in terms of glucose lowering properties (% HbA1c lowering)?

There was a consensus that the most suitable primary endpoint for paediatric pivotal T2D studies is the mean change in HbA1c levels of active versus placebo. However, even more desirable would be a composite endpoint of HbA1c lowering and no weight gain.

Furthermore, it was agreed that mean change in FPG and weight (BMI SDS or BMI centiles) were key secondary endpoints (if not included as co-primary endpoint).

Above 0.4% HbA1c lowering was seen as minimally important clinical difference.

Current PIPs: All agreed PIPs have mean change in HbA1c levels of active versus placebo as primary endpoint for paediatric pivotal T2DM studies. A composite endpoint of HbA1c lowering together with weight (at least a neutral effect) may be a better option in the future. Otherwise, weight should be a key secondary endpoint, as currently agreed in most PIPs.

Only drugs with an expected HbA1c lowering effect of above 0.4% should be developed in children.

Question 10: If a glucose lowering agent has a potential effect on beta cell preservation, which endpoints, study duration, laboratory test parameters and patient population would you consider most appropriate?

There was a consensus that the preservation of beta-cell function should translate into clinically meaningful benefits which should be reflected in the choice of endpoints. Delay in progression to insulin use was deemed as a potentially suitable endpoint to evaluate a clinically meaningful effect on beta-cell function. The difference in c-peptide levels after MMT was regarded as most suitable laboratory parameter.

A study duration of at least one year was deemed necessary by most experts. Patients with a rather recent disease onset, ideally drug naïve, have been deemed as most adequate study population.

The feasibility of a paediatric study that should demonstrate a clear effect on beta cell function was questioned. One suggestion was the conduct of a meta-analysis of multi-company studies with the same class of drug using the same assessment technique.

Current PIPs: Only two pure monotherapy studies have been agreed for gliptins where a potential effect on beta cell preservation was expected. The placebo controlled treatment phases were 3 and 4 months respectively with an open label extension up to 1 year. Given that monotherapy studies in drug naïve patients are not recommended by experts it is questionable in how far studies can be designed to accommodate for a conclusive outcome on a potential beta cell preserving effect.

Multi arm trial designs

- James Wason (MRC Biostatistics Unit, UK)
- Jack Bowden (MRC Biostatistics Unit, UK)

Multi-arm trials are more efficient than traditional trials as they have a shared control group. Inclusion of an interim analysis would allow ineffective experimental arms to be dropped early for futility. This would be so called multi-arm multi-stage (MAMS) designs

An MAMS design was presented that assumed a family-wise error rate (FWER) of 0.05 and 80% power and an assumed treatment effect of 0.5% (assumed standard deviation = 1.2%). This scenario was shown to require far fewer patients than the current average of 178 patients per pivotal study in PIPs.

Increasing the FWER to 0.1 was shown to require even fewer patients.

A possible design for testing class effects was also presented. However, for regulatory purposes it is important that the MAMS design tests each experimental arm against the control treatment so that the efficacy of each individual drug can be established instead of testing the combined set of experimental treatments vs the control group (class effect).

Regulators would welcome such multi-drug trials. Companies were mainly concerned about the direct comparison between competitor compounds which are expected to have different safety and efficacy outcomes and the different timelines of drug developments. Because compounds used in pediatric trials will all have proven efficacy in adults, use of multi-stage elimination arms might not be viewed favorably by industry. It was pointed out that the reward for completing the PIP is not dependent on whether or not a paediatric study leads to a paediatric indication or not as long as the study was conclusive and completed as agreed in the PIP. Furthermore, whether or not a drug is inferior to another would become obvious eventually in any case.

The option of Bayesian methods with adult priors was mentioned as a means to integrate pre-existing adult data and reduce the number of patients in paediatric studies.

One way of reducing imprecision in the treatment effect estimates - due to the small number of child patients available - would be to conduct a Bayesian, as opposed to a frequentist, statistical analysis. Pre-existing knowledge about the effectiveness of each treatment in the adult population could be used to create informative priors for the treatment effect parameters. Subsequent inferences about the effect of each treatment would then be based on their posterior distribution; a weighted average of the child trial data and the adult prior information. Although the analysis will focus on each individual treatment effect estimate (via a comparison with the shared control group), common distributional assumptions about the treatment effect parameters could be employed to increase the estimate's precision further. This `random effects' analysis would be very natural if working under a Bayesian framework.

A note of caution: If the analysis were done in this way, the type-I error rate of the trial would not necessarily be controlled at the same level as the traditional frequentist analysis.

Moreover the option of further reducing the sample size in the control group or even replacing the concurrent control group with a historic control group was mentioned given that a lot of paediatric information on the use of metformin exists already.

Quantitative extrapolation via pharmacometry

- Ron Portman (Bristol-Myers Squibb)

A concept for pharmacometric approaches for extrapolation from adult to paediatric T2D was introduced using the example of a DPP-4 inhibitor. The prerequisite for extrapolation may at least be partially met considering the similarity of disease (definition according to ADA criteria in adults and children) and the potential similarity of response to treatment as described in Vaidyanathan et al. (J Pharm Sci 101:1659–1671, 2012).

Two examples suited for two different situations were presented.

Example one outlined a trial design suited for situations where efficacy can be fully extrapolated without the need for any efficacy validation, only needing PK/PD and safety data:

1-week PK/PD study vs placebo (2 doses)→ 52 week single arm add-on to metformin, for safety, efficacy as key secondary endpoint.

Example two would be suited for situations where validation of efficacy extrapolation would be required. In this scenario the sample size would be determined by clinical trial simulation:

12 or 24 week, 3-arm (2 doses vs placebo) comparative PD/efficacy study, followed by single arm up to 52 weeks total.

During the discussion it was emphasized that the decision to extrapolate from adults to children is a purely clinical one. As highlighted earlier on, the disease progresses faster in children and the insulin resistance of puberty plays a bigger role in children than adults. Furthermore, hardly any paediatric data exists to date for the novel drug classes (gliptins, GLP-1 agonists, SGLT2 inhibitors). Therefore there is still a need for clinical (efficacy) data in the paediatric population. For now, such modelling approaches are encouraged to generate hypotheses and to optimize the design however and analysis of the paediatric trials. As these medicines have already been proven efficacious in adult trials, confirmation of existing adult efficacy data is required rather than traditionally designed efficacy studies aimed at re-establishing efficacy in children. The primary data is needed to validate the extrapolation of PK, PD and/or efficacy by confirming the model-based predictions.

The paediatric developments for the individual products are staggered given the different timelines for product developments and the deferrals agreed for the PIPs. Therefore, once paediatric data for the first products from different classes becomes available the need for primary efficacy data could be re-discussed with regulatory authorities.

EnprEMA

- Peter Helms (Enpr-EMA chair; University of Aberdeen, UK)
- Irmgard Eichler (EMA)
- David Dunger (University of Cambridge Metabolic Research Laboratories, UK)

Taking advantage of the presence of key academic players and representatives of pharmaceutical companies developing in the field of diabetes mellitus, a break-out meeting was held to discuss and explore ways for establishing a paediatric clinical trial networks for diabetes and endocrinology under the umbrella of the European network of paediatric research at the EMA (Enpr-EMA). Enpr-EMA current co-chairs Peter Helms and Irmgard Eichler and Mark Turner, co-chair-elect, participated at the meeting.

David Dunger suggested that the aims of an Enpr-EMA European Children and Adolescent Diabetes and Endocrine Network could be:

- To develop research infrastructure across the EU within the field of diabetes and endocrinology.
- To work with Industry in the development and implementation of PIPs
- To work with academia to promote drug development in rare paediatric endocrine disorders
- To collaborate with the EMA PDCO in designing strategies for drug development.

The main stakeholders would be:

- Academic paediatricians
- Industry
- Patient groups
- ESPE (European Society for Paediatric Endocrinology)

- ISPAD (International Society for Pediatric and adolescent diabetes)

First steps

To secure support from relevant academic organisations (ESPE, ISPAD) and relevant European subgroup academic groups (European bone group, European DSD Consortium etc.) patient support groups and national endocrine/diabetes associations.

To establish appropriate organisational structures to enable planning and implementation of research activity with appropriate representation from stakeholders.

The proposed organisational structure would include an:

- Advisory Council
- ESPE/ISPAD Executive with a chairperson, other members and European network/ national lead sites
- International coordinating centre
- Steering committee
- National lead sites
- Individual centres.

Activities of EnprEMA networks specifically related to type 2 diabetes paediatric drug development should include:

- Collaboration with US investigators in multi-company, multi-agency academic led, pharma-funded, CRO managed trials in T2D.

- Post-marketing surveillance of all new type 2 diabetes products.

The proposals were welcomed and endorsed by the participants. Securing start-up funding for at least two years to implement basic infrastructure would be needed. Although Enpr-EMA cannot provide funding it could support the initiative by:

- sending letters to the various learned societies, national bodies as potential funding sources, support that has proved helpful in establishing networks in other therapeutic areas;
- providing access to already established networks for the sharing of expertise and practical advice;
- organisation of T-conferences;
- provision of meeting facilities at the EMA (this is however not free of charge if a registration fee is charged by organisers).

Collaboration between Academia and industry could attract funding through IMI if initiated by EFPIA.

Summary and conclusions

- Paolo Tomasi (EMA)

Main concerns:

- Feasibility and better alignment with clinical practice and medical needs:
  - Few available paediatric T2DM patients.

- Many simultaneous, competing paediatric drug developments in T2DM.
- Few consortia/networks of clinical sites/specialised centres (needed to facilitate recruitment of relevant patient population).
- 30% patients to be included from EU countries or countries with lifestyle and diabetes care similar to those of EU member states: difficult to achieve due to clustering of patients outside these areas.
- Complex PK/PD studies (many doses, many blood draws).
- Long durations of placebo controlled treatment phases of pivotal studies proposed in some studies.
- Inclusion of naïve patients/monotherapy studies.
- Widespread insulin use at onset – weaning not always possible.
- Many patients have been reported not to meet HbA1c inclusion criteria (at both ends).

Potential solutions discussed in the workshop:

- Broadened inclusion criteria:
  - For patients on background insulin treatment.
  - For wider age range (from 10 up to 20 or 24 years of age).
  - For wider HbA1c range (from 6.5% to 11%).
  - For geographical origin (non-EU)- but justify applicability of results to European patients.
- Support from studies in related diseases instead, such as pre-diabetes or T1DM.
- Staggered development of products from the same class, by means of different lengths of deferrals.
- Multi-company, multi-agent study (paediatric incentive and obligations are irrespective of outcome of studies) for products being developed concurrently: need for only one control group, with considerable reduction of total number of patients.
- Single-company, multiple-agent study: need for only one control group..
- Simplifications in PK studies (peak and trough levels, dried blood spots).
- Limit duration of placebo controlled treatment phases of pivotal studies to a minimum (i.e. 3 months).
- Potential broadened role for extrapolation (efficacy) aimed at sample size reduction:
  - Use of Bayesian methods with adult priors.
  - Pre-agreed use of lower significance levels.
  - Safety study only (pre- or post-authorization in children).
- Establishment of an Enpr-EMA diabetes/endocrinology network to facilitate access to clinical trial expertise and relevant target population.

Summary of conclusions of the meeting

- Number of patients required to complete all paediatric T2DM PIPs is high.
- Increased feasibility and acceptability of studies could be achieved in different ways as suggested above.
- Companies may consider requesting a modification of previously agreed PIPs, proposing joint innovative approaches to make the paediatric studies more feasible.
- Even though T2DM is similar in adults and children, some differences still exist which warrant the need for paediatric efficacy data.
- Once paediatric data for the first product(s) from different classes becomes available, greater extrapolation and/or reduced requirements may be acceptable.
- The Scientific Advice Working Party/Committee for Medicinal Products for Human Use (SAWP/CHMP) need to be included in the discussion around innovative trial approaches; the Extrapolation Working Group of EMA includes the chairs of SAWP and CHMP as well as PDCO members.
- The collaboration between companies to perform multi-company, multi-agent studies and thereby saving patients included in control groups is encouraged.