29 April 2010
EMA/299447/2010
Human Medicines Development and Evaluation

Agenda, participants and minutes of the EMA workshop on paediatric diabetes, 17 April 2009

Improved treatments medication for children/adolescents with diabetes mellitus

EMA, 7 Westferry Circus, Canary Wharf, London E14 4HB

Aim: to identify the best possible research approaches for new medication in the field of diabetes in childhood and adolescence. Participants were sent the questions in advance, with a request to submit short answers in writing, to be discussed during the meeting.

Chair: Carine de Beaufort (PDCO); co-chair: Paolo Tomasi (EMA)

Introduction by C de Beaufort and P Tomasi

Type 2 diabetes:

- new products → non insulin and insulin
- Results of the premail questions
- Can we extrapolate safety / efficacy from adults? If so, what?
- Studies to evaluate new products for use in T2DM adolescents:
  - Run in period / how long with diet/lifestyle only?
  - Subject inclusion criteria (e.g.: naïve = never treated or only treated for a limited time with glucose lowering medication; if previously treated patients are included : how long should they be without medication prior to inclusion?)
  - Can add-on to metformin be acceptable to evaluate the effect of new treatments?
  - Study duration: how long should these studies be, placebo controlled, 12-16 weeks, other?
  - Outcome Parameters Primary /Secondary:

    HbA1c: what delta HbA1c could be considered significant , non inferiority compared to metformin, to insulin, superiority to placebo

    Glycaemic variability, fasting and/or post prandial to be included or not?

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Role for CGMS?

Vascular pathology: primary or secondary endpoint, renal, retinal, liver, flow mediated dilation what to include/how to evaluate, time frame to evaluate

Evaluation of beta cell preservation: what tests can be accepted

- Insulin analogs in T2DM short and basal analogs: are they indicated?

- Off-patent priority list

Type 1 diabetes:

- Extrapolation: Can we extrapolate safety / efficacy from adults? If so, what?
- Prevention:
  - study duration and primary endpoints secondary endpoints should be considered
  - remission criteria: complete, partial, HbA1c , insulin rescue medication,
  - Beta cell preservation testing
  - Auto immune modification
- Treatment
  - primary outcome: HbA1c, what delta should be considered significant in superiority /non inferiority studies to existing insulins with the rapid / intermediate/long acting profile
  - All age groups to be included? 1-<6, 6- <12, 12- <18 yrs
  - Co primary outcome: hypoglycaemia , definitions (ISPAD) in all ages ? only in the <6 yrs? How to evaluate HPGM 8 controls /24 hrs, CGMS, If CGMS : how long and how frequent should it be used
  - Glycaemic variability Primary /secondary ? How to evaluate
  - Quality of Life outcome.
  - Duration of the studies
  - Secondary outcome/long term outcome – micro- macrovascular to be included
  - Safety monitoring

Minutes

General questions

Question 1

For non-inferiority studies in paediatric diabetes, which would be considered an acceptable delta for HbA1c, vs. insulin or metformin?

The participants agreed that, if non-inferiority trials are accepted, the delta should be sufficiently low, for example 0.3%, as any decrease of HbA1c is useful.

Question 2

For new insulin analogues (prolonged or rapid action), do you think that actual data in adolescents with type 2 diabetes are not necessary, as they can be extrapolated from available data in type 2 diabetes in adults and in type 1 diabetes in adults and children? If not, what type of studies would you consider needed in T2DM in children, before marketing authorisation?

The following arguments against extrapolation were identified:

A As type II diabetes and type I diabetes in children are very different diseases, the risk of hypoglycaemia may be different.

B T2DM adolescents may be more insulin-resistant than adults with T2DM

C The proliferative effects of insulin analogues, may be different in growing tissues compared to adult tissues.

The following arguments in favor of extrapolation were mentioned:

A If efficacy and safety of insulin analogues are similar in adults with T1DM and T2DM and in children with T1DM, extrapolation might be possible (as a study in T2DM in children could be difficult to achieve).

Overall, opinions were divided in the panel. It was agreed that, adolescents with T2DM in USA have different lifestyle and ethnicity from EU patients. This necessitates either inclusion of representative number of adolescents from the EU or countries with similar lifestyle and diet, or separate studies.

The main differences between adolescents vs. adults with T2DM are the increased insulin resistance due to puberty, and the more rapid beta-cell destruction.. For these reasons, complete extrapolation from adult results in T2DM is considered non acceptable.

The panel considered that PK/PD studies may be feasible; it was discussed that efficacy studies may be unfeasible, and safety could be addressed through a RMP.

Type 1 diabetes mellitus

Question 3

Do you think that there is a need for additional long-acting insulin analogues (in addition to detemir and glargine) in the treatment of type 1 DM in children?

Most experts in the panel agreed that new analogues may improve the PK and clinical characteristics of current long-acting analogues, which may still require a twice daily administration (whereas one would be preferable). The panel agreed that the need is certainly greater for type I than for type II. However, there is still room for improvement in both conditions, and the panel overall was convinced that new analogues would be welcome, both short acting and long-acting.

Question 4

Do you think that the incidence of hypoglycaemia should be a primary endpoint, or a co-primary with HbA1c, for children younger than 6 years of age with type 1 diabetes?

The panel acknowledged that recent data in children and adolescents suggest that the association of intensive glycaemic control with more episodes of hypoglycaemia as seen in adults, may not be present in children, and actually the inverse may be true (at least in terms of severe episodes with convulsions or loss of consciousness). In a multicentre study, those centres with a lower mean HbA1c in T1DM children , also had lower frequency of hypoglycaemia. In Denmark, recent data have NOT shown an increase of hypoglycaemia in patients who are targeted at lower HbA1c levels. Current consensus among specialists is that all children, from 0 to 18 years , should be targeted at 6.5 to 7.5% HbA1c levels.

Regarding the definition of hypoglycaemia: the ISPAD definition is acceptable, as it is based on both criteria of severe with convulsion, severe without convulsion; moderate or mild hypoglycaemia is based on the glucose level or a less evident effect. It is not known whether asymptomatic hypoglycaemic events are relevant in children, and in any case they do not seem to be associated with rebound hyperglycaemia.

In conclusion, the panel was of the opinion that only severe symptomatic hypoglycaemia is of relevance in children, as even mildly symptomatic episodes are difficult to detect in children compared to adults. However, since severe symptomatic hypoglycaemia is rare, the use of all hypoglycaemia as secondary endpoint may be justified, provided that data for the severe episodes are also detailed. For these reasons, the panel considered that the incidence of hypoglycaemia cannot be the primary endpoint alone in any age subset; it could be useful as co-primary, or more likely, secondary endpoint.

Question 5

For the detection of the total number of nocturnal hypoglycaemia episodes in children, what is the best method between CGMS and repeated BG samples? (for children below the age of 6, 6 to puberty, puberty to 18).

The panel on the whole agreed that continuous glucose measurement systems (CGMS) appears to be the best method. However, data so far is lacking. From a regulatory point of view either method could be used provided that the CGMS methodology is validated and well established in all centers participating in the studies. However, since the use of this method in clinical studies still seems to be rather limited, the definition of nocturnal hypoglycemia for the CGMS may have to be established as well as the sample size needed. The decision as to which method is most adequate in different age

groups should be based on clinical experience. Also, it may be difficult to apply CGMS to adolescents, in this age group repeated BG measurements may be preferable.

Question 6

If nocturnal or 24hr CGMS sampling is performed, for how many nights/days should it be conducted, in order to be able to compare the incidence with two different treatments?

The panel unanimously agreed that CGMS is the most useful tool to evaluate glucose control (glucose variability, post-prandial glycaemia), as even 3-4 daily measurement of glycaemia are not useful for this purpose in adolescents. If used, it should be done for at least 5 days. Use of CGMS might be indicated particularly in younger children, because they sleep more and CGMS is particularly useful for evaluating sleep-time BG levels.

Between 3 and 6 am adolescents need much more insulin than an adult, so CGMS could help to demonstrate this. Also, CGMS provides a PD profile. However whether CGMS is required in regulatory studies for approval is not clear. No consensus was therefore reached on the need to require CGMS data for the regulatory studies.

Question 7

Are there enough patients with T1DM below the age of 6 (between 1 and 6) to perform efficacy or safety studies with significant endpoints?

All experts considered these studies to be feasible, if needed in multiple centers. HbA1c measurement should be centralized whenever possible.

Other issues

Extrapolation safety and efficacy for insulins or other treatments in T1DM between adults and adolescents/children:

The panel considered that this is not possible.

New therapies and immunotherapies aimed at preservation of residual beta cell function and prevention of progression of type I diabetes:

The panel considered that improvement of stimulated C-peptide level (after mixed meal) from baseline can be accepted as primary endpoint, but not alone: other co-primary endpoints is necessary, such as reduced insulin requirement accompanied by a similar magnitude of glycaemic control or reduced rate of hypoglycaemia. Specifically, a new surrogate endpoint for residual beta cell function, insulin dose adjusted HbA1c (IDAA1c, Diabetes Care 2009) is recommended. IDAA1c includes both current HbA1c (percent) and 4 times the insulin dose in Units per kilogram per 24 h takes into account the glycaemic consequences of a change in residual beta cell function. This parameter may even remove the need for mixed meal investigations, as it is related to the endogenous c-peptide secretion.

Although the primary endpoint may be measured at one to 1.5 years, regulatory studies should last at least 1-2 years, as intensive followup is considered necessary for two years (with a further followup for 2 years). It was discussed that even 6 months may be sufficient to evaluate the effect, because beta cell loss in children is very rapid. However, since some patients have prolonged remissions and may need two years to reach maximum benefit, the panel was split on the optimal time of evaluation of the primary endpoint, with 1 year to be considered as the minimum.

Need for markers of humoral or cellular immunity:

The panel agreed that for efficacy these are not necessary, but they may be needed for safety, according to the type of product (e.g. immune intervention or DPP4-inhibitors).

Quality of life outcome:

A QoL questionnaire may be interesting, because these measures may correlate with metabolic control. The problem is that the QoL questionnaire should ideally be completed by the patient, not the parents, so it may be more difficult to apply to young children. For that age group, no standardized tools are available at the moment. In any case, approval of a drugs is never based on QoL, but on efficacy or safety; therefore, QoL is not acceptable as a primary or co-primary endpoint.

Vascular endpoints:

The panel considered that these are not necessary in studies for T1DM.

Safety monitoring:

While the evaluation of efficacy may require 6 months for insulin (and 12 months for long-acting analogues), safety evaluation requires at least 12 months for insulins (including immunogenicity). However some experts considered that in some cases, for example for behavioural issues, tumorigenicity or immunogenicity, 2 years may be needed; this opinion was not shared by other members, for whom a 1-year study seemed sufficient.

Significant benefit:

less weight gain for the same HbA1c improvement could be an interesting significant benefit, and therefore a secondary endpoint, specifically in T2DM. Hypoglycaemia frequency could be useful, and also glucose variability. Finally, insulin sensitivity could be an interesting objective.

Type 2 diabetes

Question 8

Do you think that there is a need for additional long-acting insulin analogues in the treatment of type 2 DM in children?

See answer to question 3.

Question 9

When studying the efficacy of a new drug for type 2 diabetes in adolescents, vs. placebo, is it acceptable to include in the study both naïve patients (i.e. non-drug treated) and patients currently taking metformin?

The panel was divided on this issue. Although inclusion in placebo-controlled studies of patients both naïve and treated with metformin could facilitate recruitment, it makes interpretation of results less clear. Some experts suggested that it might be possible to avoid a washout period (see below) if metformin is discontinued before randomization to new agent or placebo, provided that the study duration is sufficient; this would obviate to the recruitment issue, while allowing for a placebo-controlled trial. The panel acknowledged that inclusion of both naïve and metformin treated patients is allowed by the FDA, as this is considered more representative of the real-life situation.

Question 10

Since post-prandial glucose levels have an estimated greater effect size than HbA1c, their use as primary endpoint may help in reducing the number of patients needed for clinical trials in paediatric type 2 diabetes. Would this be acceptable in paediatric studies, if data on HbA1c levels are available in adults?

Although postprandial glucose appears to be an interesting endpoint, most experts still considered that HbA1c should remain the primary endpoint in children and adolescents, at least until pilot studies are able to demonstrate the equivalence of the two. Postprandial glucose could see a limited use, for example as an interim analysis for futility, however, but only if taken after a standard meal in hospital. The panel could not reach a conclusion on whether alternative parameters (glucose AUC, CGMS, postprandial glucose) have a lower variation than HbA1c, thus possibly decreasing the sample size if proposed as primary endpoint, and therefore cannot be recommended at present.

Other issues discussed:

Run-in period:

Not always feasible, but if so it should be only 3 months. In any case there seems to be no need for a compulsory run-in period, as the efficacy of them in children is very limited and most children are treated with medications immediately.

Wash-out period:

A wash out before monotherapy, if included, should last at least three months. However stopping treatment in adolescents is usually difficult. It might be possible to switch products without washout, if the study is long enough.

Effect size vs. placebo:

As any reduction in HbA1c values is considered useful, particularly in patients in whom metformin fails to achieve a satisfactory metabolic control, the panel agreed that a minimum decrease of HbA1c% of 0.5 should be used in sample size calculations. However a greater effect size would allow for sample size reduction and may be applicable to at least some products.

Vascular endpoints:

Retinal photography at one year was considered not useful as the duration of treatment is too short. Although FAG could provide more information, it was considered too invasive in children. Microalbuminuria is an important parameter and should be included as it is a simple and non-invasive measurement, even if one year of treatment may be too short to demonstrate effects. However, ACE-inhibitor and statins are used more and more often, and this has to be taken into account.

Beta cell preservation:

The panel agreed that to estimate a possible preservation of beta-cell function in T2DM, stimulated C-peptide measurement is necessary. Basal measures such as HOMA-B or proinsulin/insulin ratio are not useful as surrogate measures of beta-cell function. The mixed-meal appears the best stimulus, both for T1DM and T2DM, even if the test may not be easy to do in children and blood glucose values can rise to high and symptomatic values during the test.

Main Participants

- Carine de Beaufort, Centre Hospitalier de Luxembourg, Luxembourg (L)
- Paolo Tomasi, European Medicines Agency, London (UK)
- Eberhard Blind, European Medicines Agency, London (UK)
- Marcel Th.B. Twickler, Academic Medical Centre, Amsterdam (NL)
- Henk-Jaan Aanstoot, Centre for Paediatric and Adolescent Diabetes Care and Research, Rotterdam (NL)
- Karen Tornoe, Danish Medicines Agency, Copenhagen (DK), and PDCO
- Mira Pavlovic, AFSSAPS, Paris (F), and EWP
- Henrik Bindesbol Mortensen, Glostrup (DK)
- Agnes Gyurasics, National Institute of Pharmacy, Budapest (H)
- Przemyslawa Jarosz-Chobot, Silesian University School of Medicine, Katowice (PL)
- Kristina Dunder, Medical Products Agency, Uppsala (S), and SAWP
- Zdenek Sumnik, University Hospital of Motol, Prague (CZ)
- Henriette Delemarre-Van de Waal*, VU University Medical Centre, Amsterdam (NL)
- Tadej Battelino*, University's Children Hospital, Ljubljana (SLO)
- Jean Jacques Robert*, Hopital Necker-Enfants-Malades, Paris (F)[*]
- FDA (via teleconference – afternoon only).

[*] *these experts could not attend the meeting, but provided answers to the list of questions.