EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Questionnaire Overview

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PATIENT POPULATION

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1. Do you consider inclusion of treatment naïve patients feasible and compatible with good clinical practice?

Mostly: Yes

- Patients with recent diagnosis & failing lifestyle interventions would benefit from intensification of the background lifestyle intervention & frequent clinical monitoring/ increases number of eligible patients.

- Only if :
  positive B/R balance in adults/ safety or efficacy advantage over metformin/ seeking a first line monotherapy indication in children/ good rescue criteria/ patients have reasonable metabolic control/ MF is not tolerated.

Several: No

- MF recommended first line treatment (together with lifestyle management- American Academy of Pediatrics) with good safety and efficacy/ monotherapy not well accepted by patients, parents, ethics committees.

PATIENT POPULATION

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2.a Do you consider inclusion of paediatric patients on stable insulin background therapy (without MF) compatible with good clinical practise?

Mostly: Yes

- This is in line with current clinical practice.

- Only if :

  MF not tolerated/ absence of pancreatic antibodies/ compatible with study drug/ study drug similar efficacy as MF/ for short term trials PK,PD/ only if low insulin doses are needed.

Few: No

- First drug of choice is MF/ before adding a New Drug to insulin try diet/exercise and metformin and weaning from insulin (IDF/ISPAD Guidelines 2011).

PATIENT POPULATION

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2.b Is there a potential need for triple pharmacotherapy (novel glucose lowering agent on top of metformin and insulin) in children to achieve glycaemic control?

Mostly: Yes

- Glucose dysregulation develops rapidly in children, not all patients tolerate MF at max. effective dose/ not all patients & MDs are willing to stop insulin/ TODAY study: 40% still inadequately controlled with dual therapy (MF & Rosiglitazone).

- Consider:
  aim should be reduction of insulin/ interesting for agents with glucagonostatic effect/ if scientific rationale and safe.

Few: No

- Very small population/ preferably triple therapy of glucose lowering agents without insulin (hypos and weight gain).

PATIENT POPULATION

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3. Depending on the duration of prior insulin therapy, how long should a wash out period at least be before including paediatric patients, weaned off insulin prior to inclusion, into a trial.

- Sufficient time to allow stabilisation of HbA1c to the new baseline level before entering trial/ 3-5 times the insulin half-life/ 1 week to 3 months

- Many patients poor glycaemic control, 'washout' difficult.
- Alternative: gradual insulin withdrawal by introduction of active agent/placebo (up-titration).

PATIENT POPULATION

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

- Monotherapy:
  6-6.5-7% to **9-10-11%**

- Add-on:
  6.5 - 7.5% to **9-11%** (even up to 12% in insulin pre-treated patients)

- Below 6.5% is therapeutic goal, so 6.5% and over.

TRIAL DURATION

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5. Should a paediatric study demonstrate sustainability of treatment effect or rather proof similar size of treatment effect as in adults?

Mostly: proof similar effect size

- Expect similar durability as adults/ conducting long-term trials in children with T2DM is challenging (i.e. ethical issue)/ post marketing studies better suited to address the question on effect durability/ better to focus on safety, tolerability, dose and formulation in children during the trials.

Few: proof durability

- Implication of TODAY study: failure rates on metformin in children with type 2 diabetes appear to be higher as compared with published adult data/ differences between children and adults in several aspects of the disease -> a trial designed to prove similarity of effect size between adults and children unlikely to inform safe and effective use of the therapy in children.

TRIAL DURATION

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6. What study duration (placebo controlled phase) could provide information on the durability of glucose lowering effects in children (6 months, 12 months, longer)?

Several: 12 months would be needed

- TODAY trial: median time to treatment failure was 11.5 months.
  (EMA GL for adults recommends: one trial to demonstrate maintenance of effect over at least 12 months).

Several: no need to test durability of effect during safety and efficacy studies

- Expect similar durability as adults/ post-marketing studies better suited for this.

Majority: 6 months
But only if HbA1c is not too high/ only in add-on studies
(-> otherwise 3 months acceptable as placebo controlled phase)

Suggestion: design a study with open label extension and / or switch to active drug in placebo arm after placebo controlled phase (done in all PIP studies).

TRIAL DURATION

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7. Is it ethically justified to have a placebo controlled trial period of more than 6 months within paediatric T2DM studies if children with HbA1c up to 11% are included (naïve and metformin/insulin treated patients)?

Mostly: No

- Ethically not justified/ probably not needed and counterproductive if great need for rescue medication and high dropout rates.

Several: Yes

- But need stringent rescue criteria.

Further comments:

- It depends on the type of trial being considered (i.e. time to failure trial), the type of patients recruited and the background intervention/therapy optimisation offered in the trial.

- Control: MF and/ or exercise and diet would be better than placebo.

- 12m: Naïve patients if HbA1c is below 9%
- 12m: patients on MR/insulin if HbA1c is below 10%

ENDPOINTS

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8. Which primary and key secondary endpoints do you consider most appropriate for a paediatric T2DM trial?

Primary endpoint:

Mostly: HbA1c

Few: Safety and tolerability

Secondary endpoints:

Most frequent:

- FPG,
- weight/BMI,
- hypoglycaemic episodes,
- CGMS (nocturnal hypoglycaemia risk)

Also mentioned:

- postprandial glucose (PPG),
- lipid profile,
- amount of rescue therapy required,
- IDAA1C,
- glucose variability,
- fructosamine,
- glucagon,
- beta cell function (drug dependent)

ENDPOINTS

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9. What is considered a minimally important clinical difference in terms of glucose lowering properties (% HbA1c lowering) of an investigational glucose lowering agent? Can we define responder criteria?

HbA1c lowering

Most: above 0.4% or at least 0.5% HbA1c lowering.

Some: at least 0.3% HbA1c lowering.

Few: at least 1 % HbA1c lowering.

Comment:
Using the same difference across drugs of different classes does not seem appropriate as this approach does not account for different therapeutic benefits/risks of drugs of different classes.

Responder criteria

- Target below 7%.
- Target below 7.5%.
- Maintain HbA1c level of at least 8%.

Comment:
Best is composite responder:
HbA1c drop and no weight gain.

ENDPOINTS

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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?

Comments:

- Endpoints have not been sufficiently validated to serve as clinical surrogates.
- Preservation of beta-cell function should translate into clinically meaningful benefits (i.e., improved glycaemic control or lower risk of hypoglycaemia).

Population:

- Onset less than 3y, naïve.
- HbA1cs between 7-8.5% on metformin.
- No-go: patients receiving exogenous insulin therapy.
- Population with exp. deterioration.
- N=30-50.

Endpoint:

- Difference in c-peptide during MMT.
- HOMA-B.
- Fasting glucagon.
- Proinsulin to insulin ratio.
- HOMA- IR.

Duration:

1 year
2 years
6 months

Suggestion:

Multi-company studies with same class of drug using same assessment technique and do meta-analysis.

STUDY DESIGN

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11. In light of the limited patient population, is a multi-company, multi-agent, academic led, pharma funded, CRO managed study considered feasible (comparison of several agents in the same class (Gliptin, GLP-1 analogues etc.) with one control group)?

Mostly: Yes

Suggestions / Comments:
Objective should be: demonstration of non-inferiority between agents.
SWEET to act as an intervention ARO/ funding from FP7 or IMI.

Several: Feasibility problems
Direct comparison between competitor compounds/ different outcomes on S&E/ different timelines of drug developments/ rescue therapy could be a problem for the placebo arm if multiple agents are compared in one trial, as to what agent could be used.

12. In light of the limited patient population, do you consider cross-over designs potentially appropriate for paediatric trials with investigational glucose lowering agents?

Many: Yes

- But only for Phase 1 studies to evaluate PK and short-term PD/ consider order effect, long wash-out period to get back to baseline, long study duration and high drop-out rate.

Many: No

- Disease modification: first two years decrease in endogenous insulin secretion -> influences outcome.

AND

- Short term (3 months) cross over studies may not give sufficient data to assess efficacy or safety.

Enpr-EMA Network discussion

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A. Would you be interested in supporting/participating in a European paediatric/endocrine research network?

All: Yes

B. Which data are captured/available from current European diabetes registries?

Mostly:
Very country dependent
Overall rather sparse information
Most information is on T1DM patients

Mentioned were:
EURODIAB, SWEET, DPV in Germany and Austria, Swediabkids, EHRs such as GPRD, Hvidore Study Group (Italy).

Captured are:
DPV: HbA1c, medication, anthropometric, co-medication etc.
?: ..and ketoacidosis at diagnosis, insulin regimen, number of severe hypoglycaemic events, centralised autoantibodies, BMI, BP, Lipids, pubertal status, microvascular complications, other medication, smoking.

Enpr-EMA Network discussion

EUROPEAN MEDICINES AGENCY

C. Could current European diabetes registries be used by a European paediatric/endocrine research network to capture patient outcome data and deliver long term surveillance of safety/efficacy around new glucose lowering drugs?

Mostly: Yes (hopefully in future).

Several: Not yet.

Several: Some countries only.

Enpr-EMA Network discussion

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D. Do specialized study centres have access to all potentially eligible paediatric T2DM patients?

Mostly: No.

Several: Yes.

Several: Country dependent.

Suggestion:
Form consortiums of a large number of sites that could facilitate recruitment of diabetic patients. Seek support from EU and US governments in partnership with pharma companies.