Study recruitment issues

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Opposing forces

- Providing access to medicines for children
- Improving on glycaemic control / tolerability afforded by diet and exercise and metformin
- Ensuring safety and tolerability is adequately assessed in the paediatric population

- Type 2 diabetes is a rare disease in children
- Metformin is a proven medicine with an extensive safety database
- Novel medicines may have untoward effects in the paediatric population

Just how rare is type 2 diabetes in children?

Country	Sample Size and Characte-ristics	No. of Cases of T2DM (%) (M/F ratio) Ethnic Origin	Estimated Incidence per 100000	Age (yr)	Obesity or over-weight (%)	Positive family history for T2DM (%)	Measured Parameters
		50% caucasian					age, heredity
UK [Haines, 2007]	Survey of 2665 consultant paediatric-icians	67 (0.53%) (29/38) 38 caucasian 29 ethnic minority (35% south asian, 45% black/blk british)	0.53	8.3-16.8	95	84	INS, C-peptide
UK [Ehtisham, 2004]	15255 diabetic pts	25 (0.16%) (7/17, 1 UNK) 11 caucasian 14 ethnic minority	0.21	9-15	92	84	OGTT, INS, C-peptide
UK [Drake, 2002]	Case report	4 (1/3) 4 caucasian	Not calculated	13-15	100	50	OGTT, INS, C-peptide, HbA1c>6.9%
UK [Feltbower, 2003]	677 diabetics	5 (0.6%) (2/3) 2 caucasian 3 south asian	prevalence 0.05/1000	10-19	No data	No data	Not described

1. Recreated primarily from data in [Malecka-Tendera, 2005], Pinhas-Hamiel, 2005] and [Haines, 2007].
2. Cannot ascertain from paper how many subjects <12 years

Just how many subjects are needed for a paediatric study?

- 80% power
- 0.5% difference vs placebo in HbA1c for investigational agent
- 2:1 randomisation (active vs placebo)
- Requires approxiately 120 active, 60 placebo subjects (function of likely effect size and variability of HbA1c)

Summary

- Metformin and weight loss are effective in managing paediatric Type 2 diabetes
- Despite increasing incidence, it is a rare disease in children
- Effect size and variability of HbA1c response necessitate recruitment to relatively large studies

Discussion points

- What is appropriate age banding for paediatric studies given the rareity of T2DM in children?
- Does the requirement for CV safety data (often post approval) affect the timing of paediatric studies?
- What weighting is given towards efficacy endpoints apart from HbA1c (e.g. Weight loss), in paediatric studies?

Enpr-EMA-Pharma Paediatric Type 2 Diabetes Mellitus Meeting Trial Recruitment Issues – a company perspective

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Innovative Medical Science for Children

Advancing the Development of Medicines for Children

Introduction

- The key goal of pediatric drug development is to get *'information'* about a drug to patients and their physicians as quickly as possible
- Limited opportunities for pediatric studies: studies need to be well conceived, global, **feasible** and answer pertinent and practical questions in a timely manner
- We are committed to accomplishing these goals but have encountered roadblocks to achieving them
- Need to define the roadblocks and innovate strategies to overcome them

Recruitment issues

- "Epidemic" of T2DM is relative
  - Small percentage of total DM patients in US,EU; numbers still small
- Enrollment criteria
  - Monotherapy: Placebo use is a barrier to enrollment (especially in light of AAP guidelines)
  - Add-on to Metformin: Enrollment only if not controlled on metformin, TODAY study
  - Concomitant insulin use: large number of patients taking insulin
  - 30% of patients should be recruited in EU member states or in countries with ethnicities and lifestyle that are analogous to those in EU countries. (not including US)
  - Only up through age 17 yrs
- Other enrollment considerations
  - Few registries to identify patients
- Number of studies being performed
  - industry, academic: over 2000 patients being sought
- Design and size of studies: requiring more patients to be screened
  - Similar to traditionally designed efficacy trials in adults
- New approach needed to provide dosing, efficacy, safety information
  - Formulation less of an issue in this population

Pediatric Trials in Type 2 Diabetes

Summary

- A review of clinicaltrials.gov and clinicaltrialsregister.eu reveals 10 prescription drugs are in clinical trials in pediatric T2DM patients
- In clinicaltrials.gov, there are 16 pediatric trials recruiting or not yet recruiting for 10 prescription drugs
  - The estimated pediatric patient population for these trials is approximately 2,000

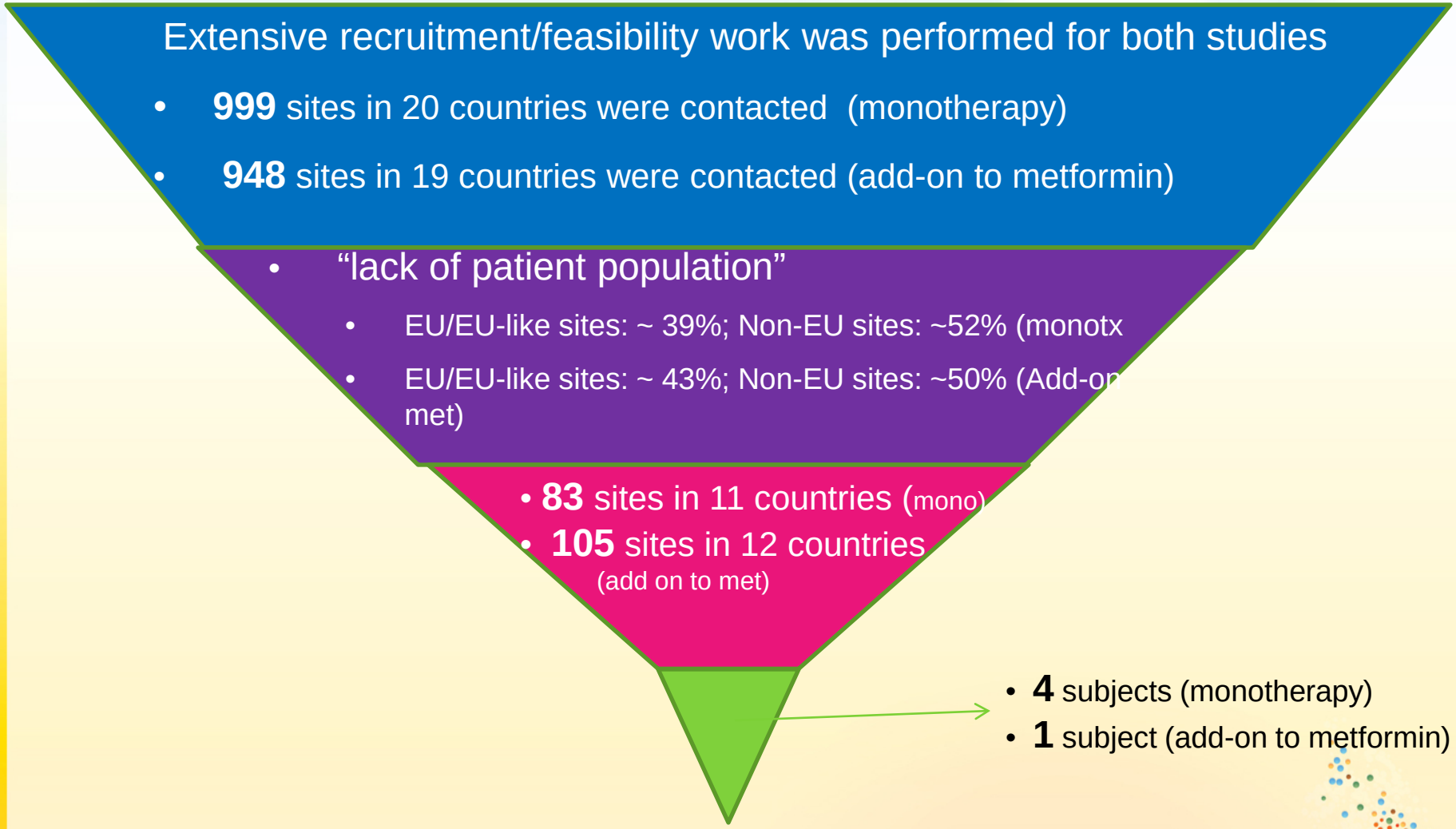
Drug (# trials)	Company	Class	Enrollment Total	Status
alogliptin	Takeda	DPP4 inhibitor	48	Recruiting
colesevelam	Daiichi Sankyo	Bile acid sequestrant	200	Recruiting
dapagliflozin	BMS / AZ	SGLT2 inhibitor	24	Not yet recruiting
exenatide (3)	Amylin / Lilly /Baylor / NIH	GLP-1 agonist	311	Recruiting
linagliptin	BI / Lilly	DPP4 inhibitor	117	Recruiting
liraglutide	Novo Nordisk	GLP-1 agonist	172	Not yet recruiting
lixisenatide	Sanofi	GLP-1 agonist	24	Recruiting
metformin	Univ. of Massachusetts	Biguanide antidiabetic	80	Recruiting
saxagliptin (3)	BMS / AZ	DPP4 inhibitor	372	Recruiting (1), Not yet recruiting (2)
sitagliptin (3)	Merck	DPP4 inhibitor	636	Recruiting
			1984	

- In clinicaltrialsregister.eu, there are 10 pediatric trials listed for 7 prescription drugs
  - The estimated pediatric patient population for these trials is approximately 2,000

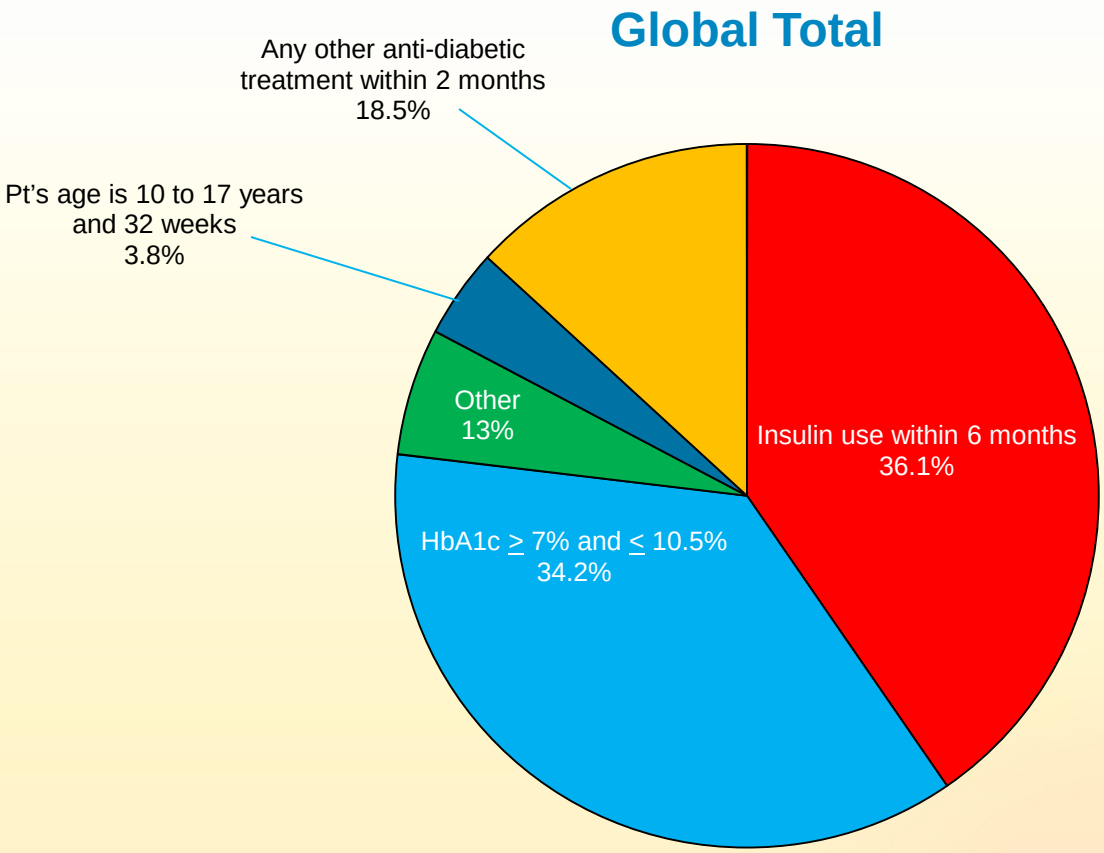
Drug (# trials)	Company	Class	Enrollment Total	Status
alogliptin	Takeda	DPP4 inhibitor	48	N/A
exenatide	Amylin	GLP-1 agonist	195	N/A
linagliptin	BI	DPP4 inhibitor	108	Ongoing
liraglutide (2)	Novo Nordisk	GLP-1 agonist	274	Ongoing
lixisenatide	Sanofi	GLP-1 agonist	24	Ongoing
saxagliptin (2)	BMS	DPP4 inhibitor	737	Ongoing
sitagliptin (2)	Merck	DPP4 inhibitor	600	Ongoing
			1986	

- Pediatric Investigation Plans (PIPs) have been approved for 16 drugs
  - Drugs are: albiglutide, alogliptin, bromocriptine, canagliflozin, dapagliflozin, dulaglutide, empagliflozin, exenatide, fasiglifam, insulin degludec, linagliptin, liraglutide, lixisenatide, saxagliptin, sitagliptin, taspoglutide (Roche discontinued taspoglutide in 2011)

Pediatric T2DM recruitment: saxagliptin experience



Prescreening Data in patients presumed to have T2DM



Possible Solutions

- Broaden entry criteria to enhance feasibility and reflect current clinical practice
  - Recent saxa PIP modification, (awaiting FDA feedback)
- Multi-company study with multiple agents within the same drug class using one control group
- Single company with multiple agents spanning different drug classes
- Study in related disease states (T1DM, pre-diabetes)
- Extrapolation Model