Failed Trials and Design Considerations in Pediatric Type 2 Diabetes

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Related Financial Disclosures

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- AstraZeneca
- Boehringer Ingelheim
- Janssen
- Novo Nordisk
- Sanofi
- Takeda

The Problem

Treatment options are much more limited in adolescents than adults with T2D

- Metformin, insulin and intensive life-style interventions (ILI) are the only approved drugs in pediatric T2D
- Rosiglitazone and glimepiride failed non-inferiority tests vs metformin as monotherapy of T2D in adolescents due to inadequate sample sizes
- Due to a log-jam of studies, no DPP4, GLP1 agonist or SGLT2 inhibitor has been approved for use in youth with T2D

Outline

There are almost insurmountable challenges at every level that thwart completion of clinical trials required for approval of new drugs for youth with T2D, including

- Eligibility
- Study Design

This presentation will:

- Use the insights learned from the Pediatric Diabetes Consortium (PDC) T2D Registry to illustrate how these issues have contributed to the problems.
- Offer some possible solutions

Why the Log Jam of Studies?

Too Many Studies

EMA has approved 26 Pediatric Investigational Plans for medicines for the treatment of T2DM in children but

Last pivotal trial that was successfully completed was metformin in ~2002

Drug	Anticipated Completion Date
empagliflozin	February 2019
exenatide	July 2019
alogliptin	May 2020
insulin peglispro	June 2020
albiglutide	April 2021
omarigliptin	February 2022
dulaglutide	June 2022
lixisenatide	October 2022
sotagliflozin	February 2024
human recombinant interleukin-2	September 2024
ertugliflozin	March 2026
glucagon receptor antagonist	July 2027

Too Few Patients

- > 5,000 patients aged 10-17 years required to complete current and planned studies clinical trials
- Prevalence of T2D in youth <20 years of age in the USA:
  - SEARCH Study: ~20-25,000
  - Isn't that enough?

Demographic and Clinical Characteristics of PDC T2D Subjects Illustrate Challenges in Recruitment

Enrollment a 8 Pediatric T2D Treatment Centers in the US begun in 2011

- T2D by ADA criteria
- <21 years of age

Number of subjects: 660 as of 9/15/15

Age: 16.0 yrs

Duration: 2.0 yrs

BMI: 99%

A1c: 7.3%

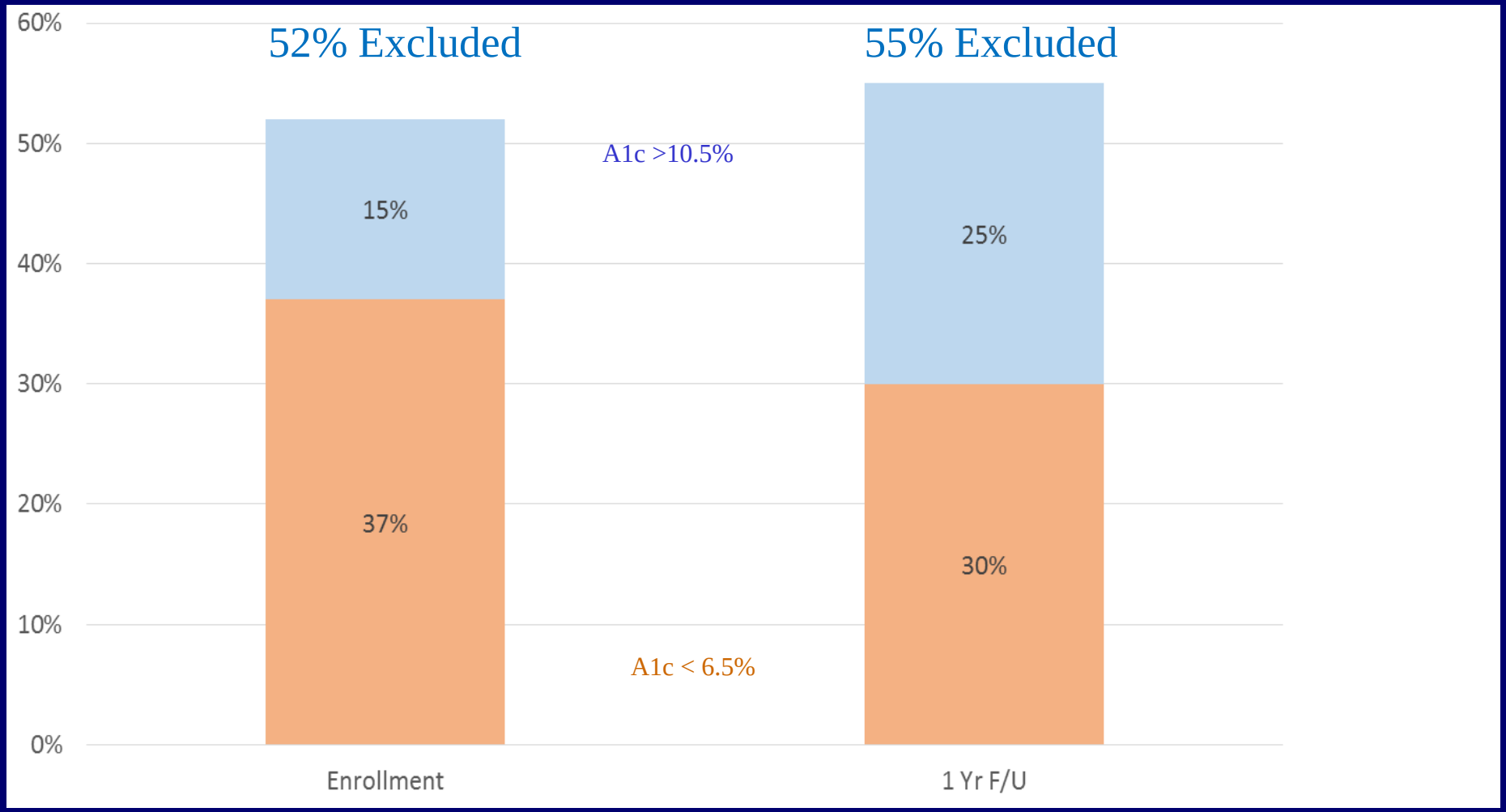
Demographic and Clinical Characteristics of PDC T2D Subjects Illustrate Challenges in Recruitment

Age	**10-17 yrs**
Female	**63%**
Minorities	**92%**
Low SES	
• Parent Education HS or Less:	70%
• Annual Family Income < $50,000	76%
• Family Income <$25,000	44%
• Medicaid/ Gov't Insurance	78%
Co-Morbidities	
• Dyslipidemia:	42%
• Hypertension:	31%
• Symptoms of Depression:	22%

Adverse Impact of Eligibility Criteria on Pool of Potential Subjects

Eligibility Criteria	PDC subjects eligible
Drug naïve + A1c > 7.0%	7%
Metformin + A1c > 7.0%	6%
D&E ± Met ± Insulin + A1c > 7.0%	48%

Current Standard: D/E ± Met ± Insulin A1c ≥ 6.5 and ≤ 10.5%



Is a lower limit of A1c ≥6.5% needed for add-on therapy trials vs placebo?

PDC Data: may only need a lower limit of T2D duration

Duration of T2D (months)	N with A1c <6.5%	Mean A1c at that visit (%)	Mean Change in A1c after 6 months (%)	P-value of change after 6 months
0	33	6.0	-0.2	0.03
3	188	5.8	+0.3	0.01
6	195	5.7	+0.6	<0.001
9	164	5.7	+0.4	0.002
12	138	5.7	+0.4	<0.001
15	136	5.6	+0.8	<0.001
18	107	5.7	+0.3	0.002
21	84	5.8	+0.4	0.003
24	80	5.7	+0.7	0.008
27	82	5.7	+0.4	0.002
30	54	5.7	+0.6	<0.001

Hypothesis: Add-on experimental drug treatment would prevent the rise in A1c over the following 6 months vs placebo in subjects with ≥ 6 months of T2D duration

Other Obstacles to Enrollment

- PDC subjects age18-20 years excluded even though they comprise 21.5% of the PDC population, have mean A1c >8.5% and most were diagnosed at <18 years of age
- Metformin-treated subjects excluded if on metformin XR
  - Some recent RCTs have eliminated this exclusion
- EMA has required at least 30% European-like subjects
  - Some new and modified PIPs have waived this requirement due to recruitment difficulties in these studies

Study Design Issues

FDA and EMA Pediatric T2D Investigation Plans usually require 2 separate studies:

- A stand alone PK/PD study
- A Phase III efficacy and safety study

Pros and Cons of PK/PD Studies

Pros:

- Usually a relatively small number of subjects
- May be important to establish dose-response relationships and tolerability

Cons:

- Some have required multiple overnight CRC admissions
- Recruitment rates have averaged $\leq$ 1 subject/ month
- Can delay the start of Phase III study for 1-2.5 years
- Most PK studies to date have resulted in Pediatric Phase III studies that utilize the same doses as in adults

Pivotal Randomized Clinical Trials

Phase III efficacy and safety studies

- Efficacy outcome at ~26 weeks
- Safety outcome through to 52 weeks

New Problem

- Recent phase III studies have required separate treatment arms using different doses of the experimental drug
- Lower than highest recommended adult dose is being tested as a separate arm, even though PK studies indicate that drug exposures in adolescents are almost always $\leq$ that in adults
  - Increases sample size by $\geq$50%
- Since in T2D, adults are simply smaller adolescents, testing lower doses of T2D drugs in pediatric studies will make it even more difficult to complete these studies.

Obstacles to Participation in T2D studies at Academic Pediatric Diabetes Centers in the US

Practical Issues

- Lack of administrative infrastructure to assist with IRB approval and budget negotiations
- Inadequate clinical research facilities and lack of experienced staff
- Short-term trials that enroll only a small number of patients and funded on a per-patient cost basis are not economically feasible
- Problems with study protocols designed by companies and regulatory agencies that are not “Kid-Friendly”

PES Survey of Barriers to Participation in Industry-Sponsored T2D Studies*

The Top 5 Answers were:

1. T2D Clinic caring for ≤ 50 patients with T2D under the age of 18 years
2. Lack of interest in participating in research by patients and families
3. Restrictive inclusion criteria
4. Exclusion of subjects due to past or current use glucose-lowering agents other than metformin
5. Inadequate reimbursement

* Survey prepared by R Gubitosi-Klug and K Bethin

Obstacles to Participation in T2D studies at Academic Pediatric Diabetes Centers in the US

Philosophical Issues:

—Limited scholarly value of industry-sponsored vs NIH or other investigator-initiated peer-reviewed studies

—Lack of a sense of ownership of prepackaged, industry-sponsored studies

Conclusion

In the absence of broader eligibility criteria and new study designs, metformin and insulin are likely to remain the only drugs approved for the treatment of youth with T2D for the foreseeable future.

Possible Solutions

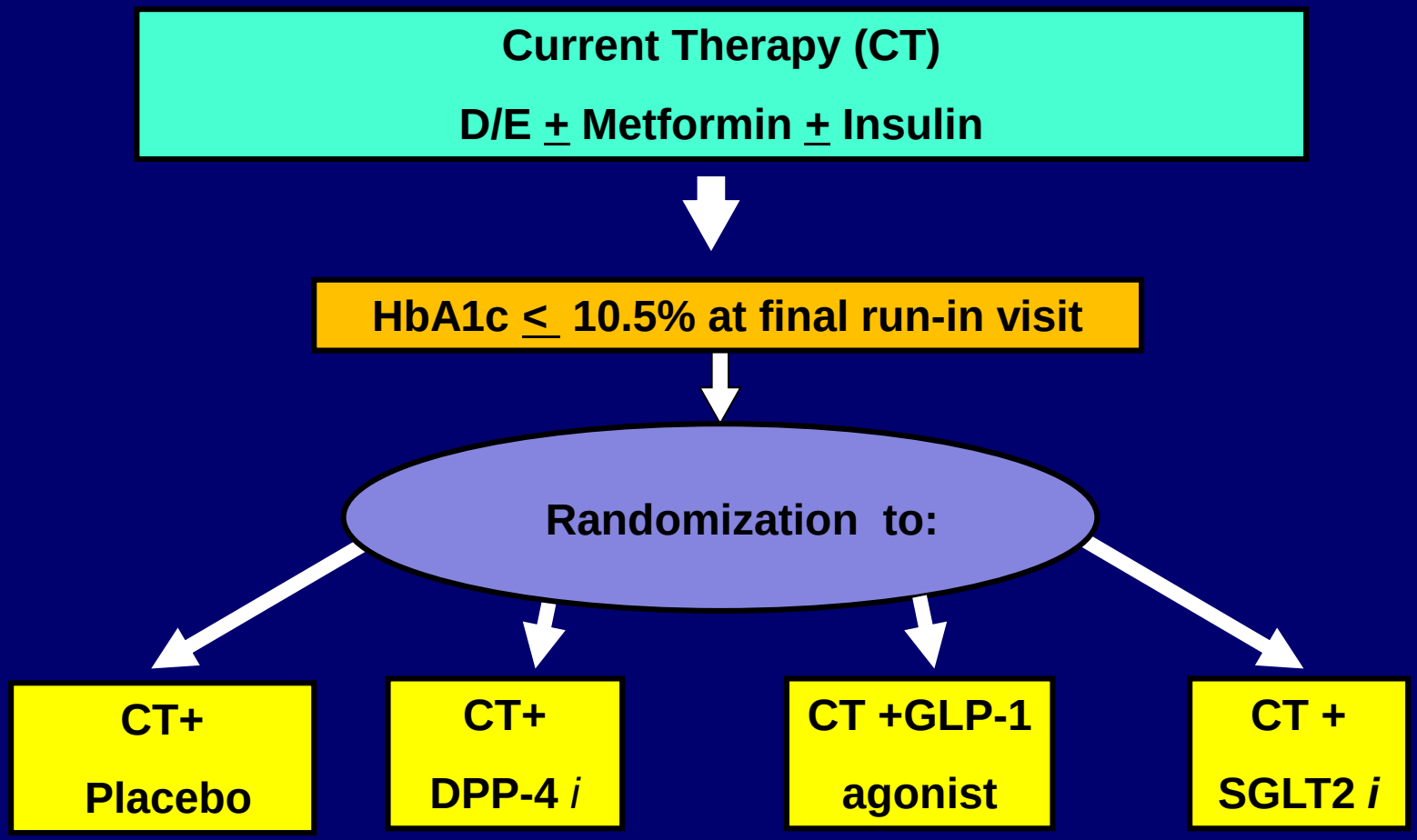
Increase the pool of subjects by:

- making patients with A1c <6.5% and duration of T2D ≥ 6 months eligible
- expanding the age range to ≥ 10 and ≤ 21 yrs
- simplifying protocols and eliminate unnecessary exclusion criteria

Decrease the number of required subjects by:

- Reducing the number of exposed subjects to 50-65 per arm
- Using multi-agent studies where each experimental arm is compared to a single control group

Multi-Arm Study of Experimental Drugs vs Placebo as Add-ons to Current Therapy



5-Arm RCT About to be Launched

DPP4*i*

— Two arms: one low dose and one high dose

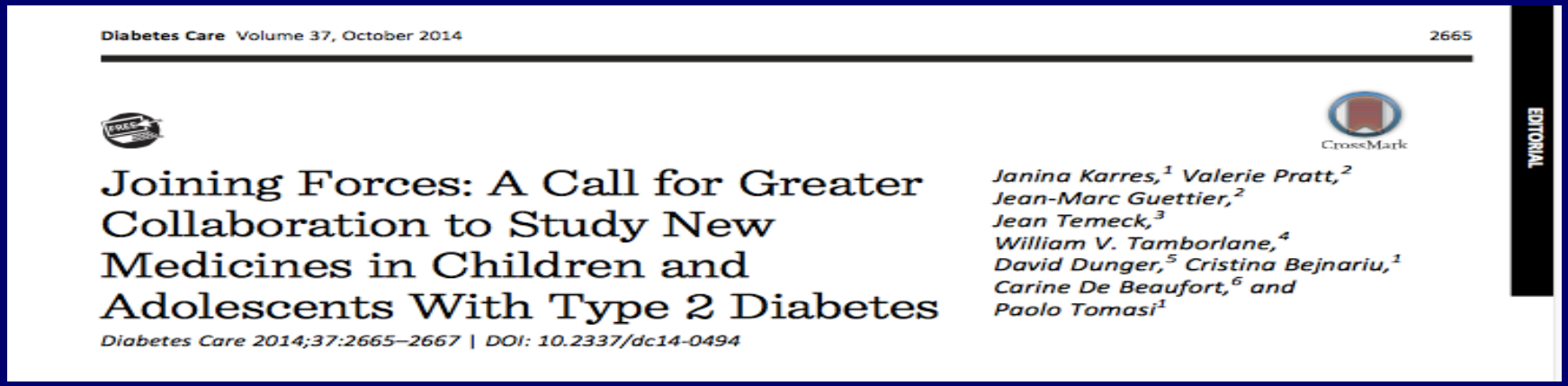
SGLT2*i*

— Two arms: one low dose and one high dose

Single Placebo Control Group

Total Sample size >300 subjects

Possible Solutions



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EDITORIAL

Joining Forces: A Call for Greater Collaboration to Study New Medicines in Children and Adolescents With Type 2 Diabetes

Janina Karres,[1] Valerie Pratt,[2] Jean-Marc Guettier,[2] Jean Temeck,[3] William V. Tamborlane,[4] David Dunger,[5] Cristina Bejnariu,[1] Carine De Beaufort,[6] and Paolo Tomasi[1]

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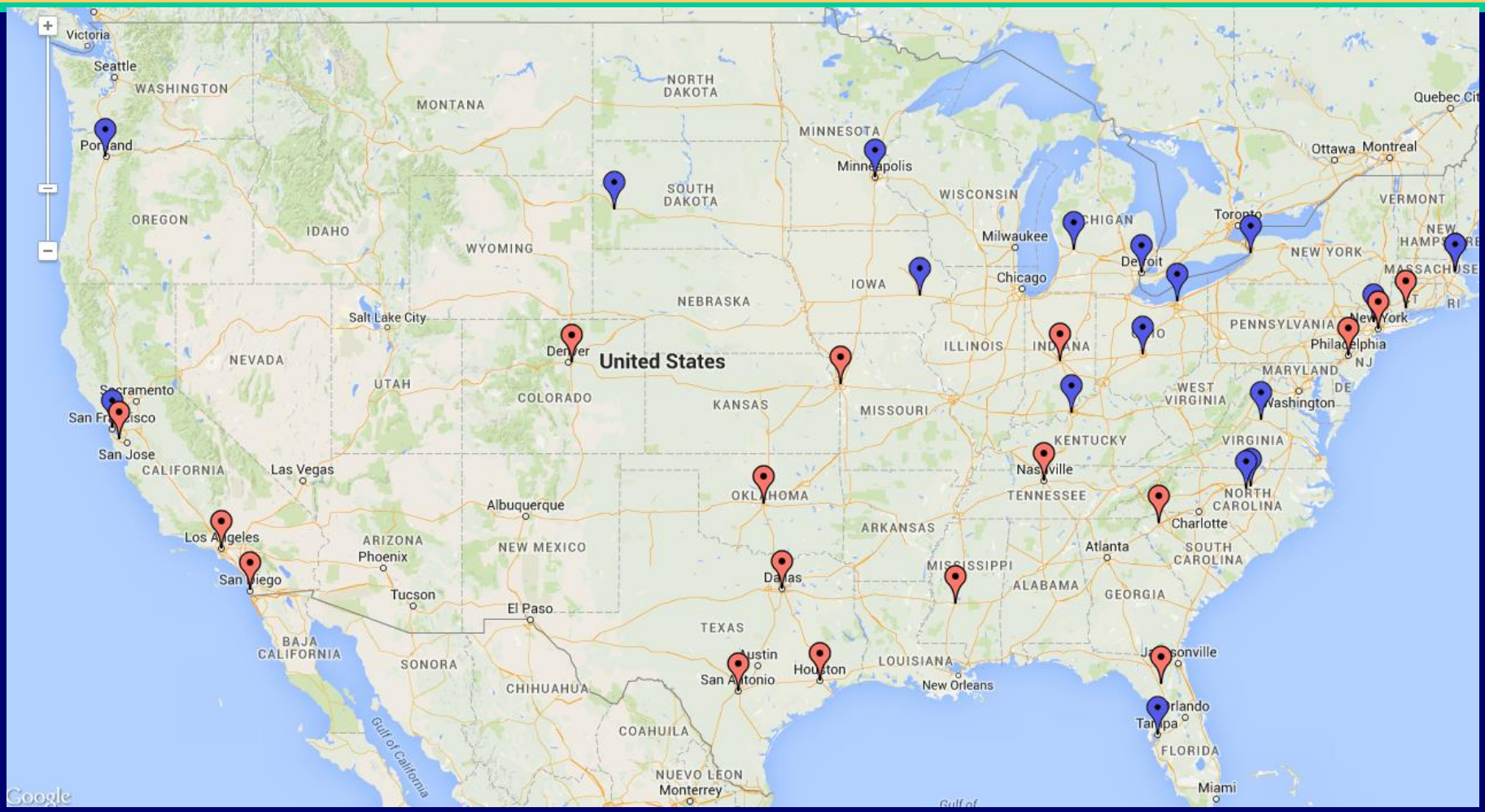
- Build a collaboration between academic medical centers, pharmaceutical-industry sponsors and regulatory agencies in carrying out multi-agent studies
- Develop national and international consortia of pediatric diabetes treatment centers to provide the infrastructure and patient populations to complete these trials

The New PDC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The New PDC

- Network of 43 leading pediatric T2D treatment centers in the US
- All 43 Centers have Master Contracts with the PDC Coordinating Center in Tampa re participation as a group in pivotal trials of new drugs for youth with T2D
- Number of patients: >4,500
- Number of new patients/yr: >1,200

Streamlining Center Participation In New Clinical trials

Utilize the Resources of the PDC Coordinating Center to negotiate:

- Single confidentiality agreement for all centers
- Single template clinical trial budget that adequately reimburses centers for their time and effort

Establish a Center Oversight Committee to:

- Monitor clinical center performance in screening, enrolling and retaining patients in each trial
- Hold monthly teleconference calls with Center PI's and Study Coordinators to discuss best practices

Establish a consulting group of experienced investigators to advise sponsors on study designs

Thank You

Failure of Prior Non-inferiority Studies of Rosiglitazone and Glimepiride vs Metformin as Initial Monotherapy (ΔA1c ≤ 0.4%)

Drug	N Exp Drug	N Met	ΔA1c *	95% CI
Rosiglitazone	77	83	0.35%	-0.2 to **+1.3**
Glimepiride	127	126	0.3%	-0.4 to **+1.2**

* Favoring metformin