

Enabling Integrated Analyses of Hypoglycemic Agents through Standards and Technology



Patel T, Tesfaldet B, Sviglin H, Witczak B, Rosario L, Navarro EE
FDA, Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Computational Science

Background: Section 907 of FDASIA directed FDA to report an integrated summary of safety and efficacy by demographic subgroups (age, gender, and race). However, the limited representation of subgroups in submitted new drug applications (NDAs) is often insufficient to enable required safety and efficacy analyses by subgroup. One possible way to overcome this limitation is to pool data from clinical trials across an NDA or across multiple NDAs. The Office of Translational Sciences in the Center for Drug Evaluation and Research (CDER) at the FDA converted legacy data from 51 pivotal clinical diabetes trials submitted in support of NDAs into the Analysis Data Model (ADaM). However, these studies were not prospectively designed to support a specific meta-analytic intent, and even if standards and technologies enable data integration, use of the data for other analyses may still be limited. We represent the methods through which we chose trials to pool for comparison, and describe the challenges in understanding subgroup outcomes because of differences in baseline demographic and clinical characteristics.

Methods: We reviewed the design of studies submitted in support of TZD drugs to determine whether it was feasible to isolate the new drug effect within the studies submitted in an NDA. We identified studies with a placebo treatment arm from a database of 51 studies converted to SDTM from TZD and non TZD new diabetes drug applications. We excluded studies where the placebo treatment arms contained background therapy with titration or a TZD. We describe the population attributes within the placebo controlled groups that limit the ability to compare outcomes to the active treatment arms. We compared the safety outcomes in the pooled TZD to the outcomes in the pooled placebo group as well as the outcomes by add-on background therapy in the TZD treated groups.

Results:

The study designs of trials within an NDA either consisted of monotherapy or add on therapy compared to placebo plus add on therapy; or dose ranging studies without an internal control. There were too few event rates for the endpoints of death, pancreatitis or hospitalization to describe outcomes by subgroup in the NDA. There were sufficient events of hypoglycemia to describe, but too few in any small subgroup category. However, event rates of hypoglycemia were observed to vary based on the concomitant medication. Observed event rates of hypoglycemia for TZD were greatest in the TZD + Insulin treated group and lowest in the TZD + metformin treated group. When a safety signal is observed in these studies, the effect of the new drug is difficult to isolate.

The studies that can contribute to a pooled placebo comparator generally consisted of patients who had not received nor donated blood for transfusion, were not pregnant nor planned to be pregnant, had normal liver function tests, had normal renal function, did not have a history of ketoacidosis nor require intensive therapy for their diabetes. Most studies excluded patients with significant peripheral vascular, cerebrovascular or cardiac disease, except for those studies designed to capture that patient population.

Compared to the TZD treated patients, participants in pooled placebo were observed to be older (Mean $\pm$ SD: 59y $\pm$ 9.5 vs 55y $\pm$ 10.4), and have a lower baseline HBA1C (Mean $\pm$ SD: 8.2% $\pm$ 1.3 vs 9.8% $\pm$ 1.5) in the aggregated database (N=7858). Patients who self identified as White, Black/ African American and Asian represented the majority of the race groups enrolled in the studies; there were too few American Indian/ Alaskan Natives and Pacific Islanders to represent in the analysis of outcomes by race.

Table 1: Treatment arms compared in TZD NDA clinical trials

NEW Drug A
Study A – TZD low dose + Insulin vs TZD high dose + Insulin
Study B – TZD low dose + Metformin vs TZD high dose + Metformin
Study C – TZD low dose + Sulfonyleurea vs TZD high dose + Sulfonyleurea
Study D – TZD titration + background vs Placebo + background
NEW Drug B
Study A – TZD low dose + Sulfonyleurea vs TZD high dose + Sulfonyleurea vs Placebo + Sulfonyleurea
Study B – TZD low dose + Placebo vs TZD low dose + Sulfonyleurea vs Placebo + Sulfonyleurea
Study C – TZD low dose + Sulfonyleurea vs TZD high dose + Sulfonyleurea vs Placebo + Sulfonyleurea
Study D – TZD high dose + Sulfonyleurea titration vs Placebo + Sulfonyleurea titration
Study E – TZD low dose + Metformin and Sulfonyleurea titration vs TZD high dose + Metformin and Sulfonyleurea titration vs Placebo + Metformin and Sulfonyleurea titration
Study

Table 2: Trial Summary of the Placebo Controlled Studies*

N	Randomization Quotient	Region of the Trial	Visits				Inclusion Criteria	Exclusion Criteria
			BL	Wk6	Wk12	Wk24		
4296	0.5	Non-U.S.	x			x	Objective evidence of CAD, CABG, stroke or MI 6 mo pre entry	
316	0.67	U.S.	x	x	x	x	Diabetes for at least 3 years appropriate for monotherapy	Pts with acidosis, requiring parenteral therapy for diabetes, LFT abnormalities
352	0.67	U.S.	x	x	x	x	Receiving half the recommended glyburide dose	Evidence of acidosis, CAD, neuropathy, LFT abnormality; Insulin
279	0.8	Non-U.S.	x	x	x	x	On SU for at least 6 mo	Pts with severe angina, coronary insufficiency, heart failure, renal/hepatic disease
419	0.67	U.S.	x	x	x	x	On metformin for 3 mo	H/o of cardiac disease, MI within 1 yr; Pts treated with insulin
436	0.67	U.S.	x	x	x	x	Included only those on Placebo	H/o of cardiac disease, MI within 1 yr; Pts treated with insulin
							Included only those on Placebo except on metformin and sulfonyleurea	
921	0.67	U.S.	x	x	x	x	On insulin for 3 months with metformin, pioglitazone, or combo	H/o cardiac disease, MI within 1 yr; Pts treated with insulin
135	0.5	U.S & non-U.S.	x	x	x	x		Previous hypoglycemia, on a weight reduction diet
866	0.67	U.S & non-U.S.	x	x	x	x		H/o ketoacidosis, insulin within 12 wks
473	0.67	U.S & non-U.S.	x	x	x	x		H/o ketoacidosis, insulin within 8 wks , on a weight loss program within 8 wks
460	0.67	U.S & non-U.S.	x	x	x	x		
610	0.5	U.S & non-U.S.	x	x	x	x		
1170	0.5	U.S & non-U.S.	x	x	x	x	Pts on intermediate acting insulin	Treated with sulfonyleurea and TZD in last 3 months; Severe PVD, liver disease, CHF, ketoacidosis, CAD diagnosis; On a weight loss program,
337	0.78	U.S & non-U.S.	x	x	x	x	Normal EKG, BMI<40, drug naïve	Normal kidney function, no raised LFT, no ketoacidosis, no insulin for a year, no significant CAD
262	0.8	U.S & non-U.S.	x	x	x	x	Drug naïve	Chronic steroid therapy, abnormal LFT, elevated creatinine, CVD, h/o ketoacidosis, poorly controlled diabetes
584	0.67	U.S & non-U.S.	x	x	x	x	Placebo+ metformin in pretreatment, on stable insulin dose or stable metformin	Renal disease, poorly controlled diabetes, ketoacidosis, liver disease, cardiovascular disease, steroid therapy
10	0.75	U.S & non-U.S.	x	x	x	x		Hypoxic states such as cardiac or respiratory failure, MI
411	0.67	U.S & non-U.S.	x			x		
509	0.5	U.S & non-U.S.	x	x	x	x		
486	0.5	U.S & non-U.S.	x	x	x	x		
365	0.67	U.S & non-U.S.	x	x	x	x		H/o ketoacidosis, chronic insulin therapy within 6 mo

*All the studies are randomized and double blind phase III trials.

Table 3: Subjects Attributes in the trials for one TZD application and within product placebo and the pooled placebo.

	TZDLI	TZDLM	TZDLS	TZDHI	TZDHM	TZDHS	Pooled TZD	Within Product Placebo	Pooled Placebo
	(N = 344)	(N = 411)	(N = 351)	(N = 346)	(N = 416)	(N = 351)	(N = 2219)	(N = 2633)	(N = 5639)
BMI (Mean $\pm$ SD)	33.5 $\pm$ 5.5	32.4 $\pm$ 5.4	32.6 $\pm$ 5.4	32.9 $\pm$ 5.4	32.4 $\pm$ 5.3	33 $\pm$ 5.5	32.8 $\pm$ 5.4	31 $\pm$ 4.8	31.3 $\pm$ 5.2
HBA1C (Mean $\pm$ SD)	9.9 $\pm$ 1.6	9.9 $\pm$ 1.5	9.8 $\pm$ 1.5	9.7 $\pm$ 1.5	9.9 $\pm$ 1.5	9.9 $\pm$ 1.4	9.8 $\pm$ 1.5	8.1 $\pm$ 1.4	8.2 $\pm$ 1.3
Age (Mean $\pm$ SD)	56.6 $\pm$ 10.9	53.7 $\pm$ 10.2	55.3 $\pm$ 10	56.3 $\pm$ 10.5	53.9 $\pm$ 10.1	54.5 $\pm$ 10.5	55 $\pm$ 10.4	61.6 $\pm$ 7.8	59 $\pm$ 9.5
Age Group, N(%)									
65+	86 (25)	59 (14.4)	57 (16.2)	79 (22.8)	58 (13.9)	63 (17.9)	402 (18.1)	1055 (40.1)	1743 (30.9)
<65	258 (75)	352 (85.6)	294 (83.8)	267 (77.2)	358 (86.1)	288 (82.1)	1817 (81.9)	1578 (59.9)	3851 (68.3)
Missing	-	-	-	-	-	-	-	-	45 (0.8)
Sex, N(%)									
Female	156 (45.3)	172 (41.8)	136 (38.7)	158 (45.7)	176 (42.3)	156 (44.4)	954 (43)	905 (34.4)	2190 (38.8)
Male	188 (54.7)	239 (58.2)	215 (61.3)	188 (54.3)	240 (57.7)	195 (55.6)	1265 (57)	1728 (65.6)	3449 (61.2)
Race, N(%)									
American Indian/ Alaskan	1 (0.3)	-	2 (0.6)	7 (2)	2 (0.5)	2 (0.6)	14 (0.6)	-	22 (0.4)
Asian	34 (9.9)	53 (12.9)	66 (18.8)	32 (9.2)	59 (14.2)	57 (16.2)	301 (13.6)	23 (0.9)	334 (5.9)
Black/ African American	84 (24.4)	80 (19.5)	48 (13.7)	84 (24.3)	77 (18.5)	41 (11.7)	414 (18.7)	7 (0.3)	247 (4.4)
Pacific Islanders	-	-	-	-	-	-	-	-	7 (0.1)
White	219 (63.7)	271 (65.9)	226 (64.4)	218 (63)	265 (63.7)	242 (68.9)	1441 (64.9)	2600 (98.7)	4924 (87.3)
Missing	4 (1.2)	4 (1)	7 (2)	4 (1.2)	5 (1.2)	5 (1.4)	29 (1.3)	-	-
Other	2 (0.6)	3 (0.7)	2 (0.6)	1 (0.3)	8 (1.9)	4 (1.1)	20 (0.9)	3 (0.1)	105 (1.9)
Source of Subjects, N(%)									
TZD NDAs	344 (100)	411 (100)	351 (100)	346 (100)	416 (100)	351 (100)	2219 (100)	2633 (100)	2964 (52.6)
GLP1 Rec Agonist NDAs	-	-	-	-	-	-	-	-	624 (11.1)
DPP4 Inhibitor NDAs	-	-	-	-	-	-	-	-	1308 (23.2)
Meglitinide NDAs	-	-	-	-	-	-	-	-	743 (13.2)

Table 4: Safety Observed

Dictionary Derived Term N(%)	TZD + Insulin (N = 690)	TZD + Metformin (N = 827)	TZD + SU (N = 702)	Pooled TZD (N = 2219)	Pooled Placebo (N = 5639)
Hypoglycemia	306 (44.3)	24 (2.9)	94 (13.4)	424 (19.1)	517 (9.2)
Death	1 (0.1)	-	-	1 (<0.1)	8 (0.1)
Hospitalization	-	-	-	-	8 (0.1)
Pancreatitis	-	-	-	-	4 (0.1)

LEGEND:

TZDLI – low dose TZD + Insulin
TZDLM – low dose TZD + Metformin
TZDLM – low dose TZD + Sulfonyleurea
TZDHI – high dose TZD + Insulin
TZDHM – high dose TZD + Metformin
TZDHM – high dose TZD + Sulfonyleurea

Conclusion:

- Populations enrolled in the aggregated database do not reflect the full range of patients with the disease in the US populations.
- Study designs for new TZDs render it challenging to isolate the effect attributable to a new drug particularly for individual safety events. The event rates of hypoglycemia with TZD appears to differ with the add on background therapy.
- Patients in the pooled placebo arm differed in age, sex and racial distribution from the TZD treated group and had a lower mean baseline HBA1C compared to patients in the TZD treated group. These baseline attributes and the varying randomization ratios for the studies from which these patients are derived render it challenging to perform comparisons across studies, even when made feasible by tools and technologies.
- The pooled placebo database may contain sufficient patient enrollments to enable comparisons that are designed to match patient attributes, as applied to observational studies. Other meta-analytic approaches can also be explored as new analysis capabilities are developed.