Rilpivirine Shows Efficacy, Safety in HIV Patients

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FROM THE 18TH INTERNATIONAL AIDS CONFERENCE

VIENNA – Rilpivirine, an investigational non-nucleoside reverse transcriptase inhibitor for treating HIV, matched the efficacy of the benchmark agent in the class, efavirenz, and edged efavirenz for safety in a pair of phase III studies with more than 1,300 patients combined.

The results showed virologic failure to be the only parameter by which rilpivirine fell short of efavirenz, with rilpivirine's rate nearly twice that of efavirenz, Dr. Calvin J. Cohen said at the meeting.

Despite that, rilpivirine "had significant tolerability advantages over efavirenz," said Dr. Cohen, research director of the Community Research Initiative of New England in Boston. The HIV-infected patients randomized to 25 mg of oral rilpivirine once daily had a lower rate of discontinuations for adverse events; half the rate of grade 2-4 adverse events; and reduced rates of dizziness, rash, abnormal dreams and nightmares, and grade 3 and 4 lipid abnormalities, compared with those randomized to 600 mg of efavirenz once daily.

"These studies provide valuable information on the safety and tolerability of TMC278 [rilpivirine] and specifically its metabolic and CNS side effect profiles," Dr. Cohen said in a written statement.

The study was sponsored by Tibotec Pharmaceuticals, a subsidiary of Johnson & Johnson that is developing the drug. Tibotec has filed a New Drug Application with the Food and Drug Administration based on the data Dr. Cohen presented.

The Efficacy Comparison in Treatment-Naive HIV-Infected Subjects of TMC278 and EFV (ECHO) study and

the TMC278 Against HIV in a Once Daily Regimen vs. Efavirenz (THRIVE) study had very similar results, differing only in the type of treatment added to each of the two study agents.

In ECHO, all patients also received the standard initial combination of tenofovir and emtricitabine. In THRIVE, each participating physician could decide which dual nucleoside reverse transcriptase inhibitors to prescribe. Their choice was tenofovir and emtricitabine in 60% of the THRIVE patients, zidovudine and lamivudine in 30%, and abacavir and lamivudine in 10%. Both trials enrolled treatment-naive patients with a baseline viral load of more than 5,000 copies/mL.

The median age of all patients in both trials was 36 years, and three-quarters were men. About half of the patients had viral loads greater than 100,000 copies/mL, and their average CD4 cell count was roughly 250 cells/mm^3.

The primary end point of both studies was the percentage of patients with an undetectable viral load (fewer than 50 copies/mL) after 48 weeks on treatment. The end point occurred in 84% of the 686 rilpivirine patients and 82% of the 682 patients who got efavirenz, showing rilpivirine's noninferiority. Curves depicting the rate at which patients attained undetectable viral loads during 48 weeks of treatment showed virtually identical kinetics, Dr. Cohen said. Virologic failure occurred in 9% of the rilpivirine patients and 5% of those on efavirenz.

Discontinuation of treatment for an adverse event occurred in 3% of those on rilpivirine and 8% of those on efavirenz. A grade 2-4 adverse event at least possibly related to treatment occurred in 16% of patients on rilpivirine and 31% of those on efavirenz. Neurologic adverse events appeared in 17% of the rilpivirine patients and 38% of those on efavirenz. Dizziness incidence was 8% with rilpivirine and 26% with efavirenz.

Tibotec also announced that it is collaborating with Gilead Sciences in developing a single-pill, once-daily formulation that combines rilpivirine, tenofovir, and emtricitabine.

Dr. Cohen has received research support from, has served on the speakers bureau for, and has been a consultant to Tibotec, Bristol-Myers Squibb, Gilead Sciences (maker of tenofovir and emtricitabine), and Merck. He has also been a consultant to Abbott. ■

Table 1: Treatment –emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency ≥ 5%) (continued)

	LANTUS, % (n=1257)	NPH, % (n=1070)
Accidental injury	5.7	6.4
Headache	5.5	4.7

*Body System not Specified

Table 2: Treatment –emergent adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency ≥ 5%)

	LANTUS, % (n=849)	NPH, % (n=714)
Upper respiratory tract infection	11.4	13.3
Infection*	10.4	11.6
Retinal vascular disorder	5.8	7.4

*Body System not Specified

Table 3: Treatment –emergent adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency ≥ 10%)

	LANTUS, % (n=514)	NPH, % (n=503)
Upper respiratory tract infection	29.0	33.6
Edema peripheral	20.0	22.7
Hypertension	19.6	18.9
Influenza	18.7	19.5
Sinusitis	18.5	17.9
Cataract	18.1	15.9
Bronchitis	15.2	14.1
Arthralgia	14.2	16.1
Pain in extremity	13.0	13.1
Back pain	12.8	12.3
Cough	12.1	7.4
Urinary tract infection	10.7	10.1
Diarrhea	10.7	10.3
Depression	10.5	9.7
Headache	10.3	9.3

Table 4: Treatment –emergent adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency ≥ 5%)

	LANTUS, % (n=174)	NPH, % (n=175)
Infection*	13.8	17.7
Upper respiratory tract infection	13.8	16.0
Pharyngitis	7.5	8.6
Rhinitis	5.2	5.1

*Body System not Specified

• *Severe Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LANTUS *[See Warnings and Precautions (5.3)]*. Tables 5 and 6 summarize the incidence of severe hypoglycemia in the LANTUS individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤56 mg/dL in the 5-year

trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

The rates of severe symptomatic hypoglycemia in the LANTUS clinical trials (see Section 14 in the full prescribing information for a description of the study designs) were comparable for all treatment regimens (see Tables 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes. (see Table 5) *[See Clinical Studies (14) in the full prescribing information].*

Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes

	Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	10.6 (31/292)	15.0 (44/293)	8.7 (23/264)	10.4 (28/270)	6.5 (20/310)	5.2 (16/309)	23.0 (40/174)	28.6 (50/175)

Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes

	Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin		Study G Type 2 Diabetes Adults 5 years In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	1.7 (5/289)	1.1 (3/281)	0.4 (1/259)	2.3 (6/259)	7.8 (40/513)	11.9 (60/504)

• *Retinopathy*

Retinopathy was evaluated in the LANTUS clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes.

LANTUS was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 yrs) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified post-baseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are shown in Table 7 for both the per-protocol and Intent-to-Treat populations, and indicate similarity of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome.

Table 7. Number (%) of patients with 3 or more step progression on ETDRS scale at endpoint

	Lantus (%)	NPH (%)	Difference*,† (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-2.0% (2.6%)	-7.0% to +3.1%
Intent-to-Treat	63/502 (12.5%)	71/487 (14.6%)	- 2.1% (2.1%)	-6.3% to +2.1%

*Difference = Lantus – NPH

†using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function