2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Tarka®	**Volume:**	
Name of Active Ingredient: trandolapril and verapamil SR	**Page:**	
Title of Study: A Phase 4, Randomized, Open-Label, Active Controlled Study to Compare the Effects of Tarka® and Lotrel® on Albuminuria in Hypertensive, Type 2 Diabetic Subjects with Diabetic Nephropathy		
Investigator: Multicenter study. Coordinating investigator is Robert Toto, MD		
Study Sites: A total of 66 sites in the United States enrolled study subjects.		
Publications: None		
Studied Period (Years): **First Subject First Visit:** 07 Jan 2004 **Last Subject Last Visit:** 24 Jan 2006	**Phase of Development:** 4	
Objectives: The primary objective of this study was to determine if trandolapril/verapamil SR (Tarka®) was superior to amlodipine/benazepril (Lotrel®) in the reduction of albuminuria in hypertensive subjects with Type 2 diabetes mellitus (DM) and diabetic nephropathy. Albuminuria was to be determined as the urine albumin:creatinine ratio (UACR). The secondary objectives of this study were: 1. To compare the effects of Tarka and Lotrel on changes in blood pressure (BP) and BP control, proteinuria, estimated glomerular filtration rate (GFR). 2. To compare antihypertensive drug use in each treatment group by drug, dose, and class. 3. To compare the safety profile of Tarka and Lotrel by evaluating lipid parameters, glycemic control, quality of life using the 36-Item Short Form Health Survey (SF-36), and adverse events. 4. From a substudy, to explore the effects of Tarka and Lotrel on serum high-sensitivity C-reactive protein (hsCRP), urinary malondialdehyde (MDA) and carbonylated proteins as oxidative stress markers, urinary monocyte chemotactic protein-1 (MCP-1) as an inflammatory marker, transforming growth factor-β (TGF- β) as a profibrotic marker, proteinuria selectivity index, and ambulatory blood pressure parameters.		

Methodology: This was a Phase 4, open-label, active-controlled, randomized, multicenter study designed to determine if Tarka was superior to Lotrel in the reduction of albuminuria in subjects with Type 2 DM, hypertension (HTN), and diabetic nephropathy. At approximately 65 sites, 325 subjects were to be enrolled into the Run-in Period in order to randomize 300 subjects. Subjects meeting the inclusion and exclusion criteria were to be screened for eligibility for a period of up to two weeks. Subjects then began a 4-week Run-in Period during which all subjects were to replace their current antihypertensive medication with a combination of lisinopril 20 mg once daily (QD) and torsemide 10 mg QD. At Week -2, all the subjects were to return to be evaluated on vital signs, drug compliance, and provide a blood sample for chemistry (i.e., electrolytes). At the end of the Run-in Period, all subjects were to discontinue lisinopril and torsemide. Those subjects who satisfied the entry criteria at the screening visit, potassium criteria at Week -2, and the randomization criteria for BP and compliance were to be randomized to one of two treatment arms: Tarka 2/180 mg QD or Lotrel 5/10 mg QD for 4 weeks. Four weeks after randomization, subjects in the Tarka group were to have their dose increased to Tarka 4/240 mg QD, and subjects in the Lotrel group were to have their dose increased to Lotrel 10/20 mg QD. For subjects who did not achieve the target BP subsequent to the Week 4 visit (< 130/80 mmHg), torsemide could have been added incrementally by 10 mg, to a maximum dose of 40 mg QD. For those subjects in either treatment group who still did not achieve target BP, another antihypertensive agent could have been added, excluding an angiotensin receptor blocker (ARB), calcium channel blocker (CCB), aldosterone receptor inhibitor or another angiotensin-converting enzyme inhibitor (ACEI). Those subjects receiving an ARB, CCB, aldosterone receptor inhibitor or ACEI therapy to control HTN were to be withdrawn from the study.

Timed, overnight urine samples were to be collected prior to randomization (Baseline) and at 12, 24, and 36 weeks (Final Visit) after randomization to measure albuminuria (UACR). The investigators were to be blinded to the results of urinary albumin and protein excretion for all visits except the screening visit.

Approximately 80 subjects from up to 15 sites were to participate in a substudy in which disease biomarkers were to be collected, and ambulatory blood pressure (ABP) was to be monitored, at Baseline and the Final Visit. The sites participating in this substudy were to be selected prior to study initiation.

The duration of the study treatment was to be approximately 40 weeks, including the 4 week Run-in Treatment Period, and the 36-week Randomized Treatment Period. Subjects were to be followed for spontaneously reported adverse events (AEs) and serious adverse events (SAEs) for 30 days after the last dose of the study drugs.

Number of Subjects (Planned and Analyzed):

Planned: 300

Analyzed: 304 (Tarka treatment group: 152; Lotrel treatment group: 152)

Diagnosis and Main Criteria for Inclusion:

A subject was eligible for study participation if he/she: was at least 18 years of age, had documented essential hypertension requiring two or more medications to treat hypertension or had uncontrolled BP on monotherapy (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg); had diagnosed Type 2 Diabetes Mellitus, with diabetic nephropathy and albuminuria (Screening UACR ≥ 0.2 g/g); had a Screening estimated GFR ≥ 30 mL/min, based on the Modification of Diet in Renal Disease (MDRD) equation; if female, was either not of childbearing potential, defined as postmenopausal for at least one year or was surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or was of childbearing potential and used an approved method of birth control; if female, the results of a urine pregnancy test performed at Screening were to be negative; if female, subject was not breast-feeding; voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study had been explained and the subject had the opportunity to ask questions.

A subject was to be excluded from the study if he/she met any of the following criteria: had secondary forms of HTN (adrenocortical disease, Cushing Syndrome, primary aldosteronism, iatrogenic) or severe hypertension (requiring > 4 antihypertensive medications); had poorly controlled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg); was receiving ongoing treatment with medications that would substantially influence urinary protein excretion, such as chronic use of non-steroidal anti inflammatory drugs (NSAIDs, except aspirin ≤ 325 mg/day), COX-2 inhibitors, or immunosuppressive therapy (e.g., glucocorticosteroids, interferons or cyclosporins) that could not be discontinued at enrollment for the duration of the trial (occasional use of NSAIDs [less than 4×/week] was permitted); subject had clinically significant electrolyte abnormalities at Screening - serum potassium < 3.5 mmol/L or > 5.0 mmol/L (or > 5.5 mmol/L for subjects currently on ACEI or ARB therapy), or serum sodium < 130 mmol/L; had Type 1 DM; had severe hepatic dysfunction at Screening as determined by liver function tests – bilirubin > 2.0 mg/dL, ALT and /or AST > 3 × the upper limit of normal; had poorly controlled diabetes, based on HbA1c > 10% at Screening; had non-diabetic renal disease; had a stroke, myocardial infarction, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft) or transient ischemic attack (TIA) within 3 months prior to Screening; had diagnosed HIV, had known active drug or alcohol abuse; had arm circumference > 42 cm at Screening; survival was expected to be < 1 year, had previously demonstrated poor blood pressure response to treatment with Tarka or Lotrel; had a hypersensitivity to ACEI or CCB medication, including history of angioedema related to previous treatment with ACEI(s); had a hypersensitivity to torsemide or sulfonylureas; had any of the following cardiovascular abnormalities: sick sinus syndrome or second- or third-degree AV block except with a functioning pacemaker, significant left ventricular dysfunction (ejection fraction < 30%), diagnosed with New York Heart Association (NYHA) Class III or IV heart failure, Atrial flutter or atrial fibrillation and an accessory bypass track (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine Syndromes), unstable angina, systolic blood pressure (SBP) < 90 mmHg, severe bradycardia (< 50 beats/minute); had received any investigational drug within 4 weeks prior to Screening; for any reason, subject was considered by the investigator to be an unsuitable candidate to receive study drug. Exclusion Criteria During Run-in Period (Week -2): serum potassium < 3.5 mmol/L or > 5.5 mmol/L. Exclusion Criteria for Randomization: sitting systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 100 mmHg; drug compliance not within 80-120% during the last two weeks of Run-in Period.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Tarka, 2/180 mg and 4/240 QD, oral. Lot numbers are not available as study drugs were supplied via retail pharmaceutical supply.

Duration of Treatment:

4 week Run-in Treatment Period, and the 36-week Randomized Treatment Period

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Lotrel 5/10 mg or 10/20 mg QD, oral. Lot numbers are not available as study drugs were supplied via retail pharmaceutical supply.

Criteria for Evaluation

Efficacy: The primary efficacy variable was the percent change from baseline to endpoint in albuminuria, calculated as UACR. Secondary efficacy variables included absolute change in UACR from baseline to endpoint; absolute and percent change in urine protein: creatinine ratio from baseline to endpoint; absolute and percent change in UACR and urine protein: creatinine ratio from baseline to Week 12, Week 24 and Week 36; change in eGFR from baseline to endpoint; change in SBP and DBP from baseline to endpoint based on clinic measurement.

Safety: Safety was evaluated through the incidence of treatment-emergent adverse events, analysis of laboratory and vital signs variables, and through completion of a 36-Item Short Form Health Survey.

Statistical Methods

Efficacy: A 5% level of significance was used unless otherwise stated. One-way analysis of variance (ANOVA) or Fisher's exact tests were used to test the homogeneity of demographic data; analysis of covariance (ANCOVA) with terms for baseline value, treatment group, and center for changes from baseline to endpoint. The treatment-by-center interaction was added to the ANCOVA model and assessed at the 10% significance level. ANCOVA with log-transformed data was used for primary efficacy variable. Repeated-measures models were used for systolic and diastolic blood pressure over time. A logistic regression with terms for treatment and center was used for analysis of goal achievement.

Safety: Fisher's exact test was used to analyze the incidence of adverse events; one-way ANOVA was used to analyze the change from baseline in laboratory variables.

Summary/Conclusions

Efficacy Results: Based on available screening laboratory data, at least 342 subjects were screened for enrollment. Of these subjects, 12 were screening failures and 330 subjects were enrolled into the Run-In Period of the study. Twenty-six subjects were failures during the Run-In Period of the study. A total of 304 subjects were randomized and received at least one dose of study drug. Of these subjects 152/304 were randomized to receive Tarka and 152/304 were randomized to receive Lotrel. The proportion of male and female subjects enrolled in each treatment group and was comparable, as were findings for all remaining demographic variables. Baseline characteristics such as blood pressure, heart rate, eGFR, body temperature, weight, height, and body mass index were also comparable between treatment groups.

Efficacy Results (Continued)

With regards to the primary endpoint, the percent change in UACR from baseline to endpoint, no statistically significant differences between treatment groups were observed. Similarly, none of the secondary endpoints related to UACR or UPCR demonstrated statistically significant differences between treatment groups.

Analysis of systolic blood pressure indicated that subjects in the Tarka treatment group had a mean increase in systolic blood pressure of 1.50 (1.565) mmHg compared with a decrease of -4.93 (1.521) mmHg seen in the Lotrel treatment group. This difference was statistically significant (P = 0.002). Mixed model analyses supported the findings for absolute changes in systolic blood pressure. Results of the analysis of the change from baseline to endpoint in diastolic blood pressure indicated that subjects in the Tarka treatment group had a mean decrease in diastolic blood pressure of -1.35 (0.903) mmHg compared with a decrease of -4.69 (0.879) mmHg seen in the Lotrel treatment group. This difference was statistically significant (P = 0.005). Mixed model analyses of diastolic blood pressure also supported these findings. Categorical analysis of blood pressure control (< 130/80 mmHg) over the study demonstrated statistically significant differences favoring Lotrel-treated subjects at Week 6 (P = 0.002), Week 12 (P = 0.005), and at study endpoint (P = 0.042).

Analysis of the estimated glomerular filtration rate from baseline to endpoint indicated no statistically significant differences between treatment groups. Similarly, no statistically significant differences were observed between treatment groups with regards to the estimated glomerular filtration rate from baseline to endpoint with baseline albuminuria as a covariate. Substudies of disease biomarkers and ambulatory blood pressure were intended to be conducted on 80 subjects; however, enrollment in these substudies was not sufficient to provide meaningful results.

Safety Results: The mean (SD) total duration of treatment for subjects in the Tarka group was 206.1 (89.6) days while the mean total duration of treatment for subjects in the Lotrel group was 228.9 (67.5) days. The proportion of subjects who received the maximum dose of study drug during the study was similar between treatment groups (138/152 Tarka group; 143/152 Lotrel group).

Overall, 104/152 (68%) subjects in the Tarka group and 116/152 (76%) subjects in the Lotrel group reported one or more treatment-emergent adverse events during the study. The most commonly reported treatment-emergent adverse events were peripheral edema (Tarka: 9/152, 6% vs. Lotrel 21/152, 14%), urinary tract infection (Tarka: 13/152, 9% vs. Lotrel 11/152, 7%), upper respiratory tract infection (Tarka: 8/152, 5% vs. Lotrel 8/152, 5%), cough (Tarka: 8/152, 5% vs. Lotrel 7/152, 5%), dizziness (Tarka: 9/152, 6% vs. Lotrel 4/152, 3%), and hypoglycemia (Tarka: 8/152, 5% vs. Lotrel 5/152, 3%).

Safety Results (Continued)

Statistically significant differences between treatment groups were observed with the occurrence of bradycardia (Tarka: 6/152, 4% vs. Lotrel 0/152; P = 0.03), peripheral edema (Tarka: 9/152, 6% vs. Lotrel 21/152, 14%; P = 0.033), and hypotension (Tarka: 9/152, 6% vs. Lotrel 1/152, 1%; P = 0.019). For events of bradycardia occurring in the Tarka group, 3 events were considered probably related to study drug administration and 1 event was considered possibly related. No events of bradycardia were observed in Lotrel-treated subjects. For events of peripheral edema occurring in the Tarka treatment group, 2 events were considered probably related to study drug administration and 3 events were considered possibly related. However, within the Lotrel treatment group, 7 events of peripheral edema were considered probably related to study drug administration and 9 events were considered possibly related. For events of hypotension occurring in the Tarka group, 1 event was considered probably related to study drug administration and 5 events were considered possibly related. Within the Lotrel treatment group, 1 event of hypotension was considered possibly related to study drug administration. A similar number of subjects in either treatment group reported cough during randomized treatment (Tarka: 8/152, 5% vs. Lotrel 7/152, 5%). The incidence of cough associated with ACE inhibitors is well characterized in labeling and the literature, and was not an unexpected event.

The overall incidence of subjects reporting one or more treatment-emergent adverse events considered possibly or probably related to study drug administration was similar between treatment groups (possibly related: Tarka 20/152 vs. Lotrel 23/152 and probably related: Tarka 15/152 vs. Lotrel 18/152). Except for peripheral edema (probably related: Tarka 2/152, 1% vs. Lotrel 7/152, 5%; possibly related: Tarka 3/152, 2% vs. Lotrel 9/152, 6%;), no treatment-emergent adverse events occurred that were considered to have been possibly or probably related to study drug administration in ≥ 5% of subjects in either treatment group. The majority of treatment-emergent adverse events occurred that were considered to have been possibly or probably related to study drug administration were observed as single incidences.

Overall, 30/152 (20%) subjects in the Tarka group and 23/152 (15%) subjects in the Lotrel group reported one or more treatment-emergent adverse events considered to be severe in intensity. Within the Tarka group, except for bradycardia (3/152), myocardial infarction (2/152), fatigue (3/152), hypoglycemia (3/152), dizziness (2/152), and hypotension (4/152), all severe adverse events were observed as single incidences. Within the Lotrel group, except for anemia (2/152), hypoglycemia (3/152), and renal failure (2/152), all severe adverse events were observed as single incidences.

A total of 2 subjects died during the randomized treatment period of the study; one subject in each treatment group. Neither event was considered possibly or probably related to study drug administration. Overall, 56 subjects reported 120 serious adverse events. Twenty nine subjects in the Tarka group had 71 serious adverse events and 27 subjects in the Lotrel group had 49 serious adverse events. Within the Tarka treatment group, 13 events were considered possibly or probably related to study drug administration. Within the Lotrel treatment group, 10 events were considered possibly or probably related to study drug administration. The remaining serious adverse events in either treatment group were considered not related or probably not related to study drug. A total of 21 subjects in the Tarka treatment group reported 29 adverse events associated with permanent withdrawal of study drug. Twelve subjects in the Lotrel group reported 15 events associated with permanent withdrawal of study drug.

Safety Results (Continued):

At study endpoint, no statistically significant differences between treatment groups were observed in the absolute changes in hematology, chemistry, or urinalysis variables. Additional analyses conducted on the percent change from baseline for total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, fasting glucose, HbA_{1c} indicated trends of improvement favoring Tarka-treated subjects for fasting glucose and HbA_{1c}; however, neither finding was statistically significant.

Except for glucose, HbA_{1c}, and HDL cholesterol, evaluation of the transition from baseline values to the final observed values indicated, in general, that the majority of subjects in either treatment group had baseline values in the normal range for most chemistry hematology, and urinalysis variables and that few transitions to either high or low values occurred. For those values that did transition, changes from baseline status were comparable between treatment groups. Evaluations of transitions from baseline for glucose indicated that fewer Tarka subjects transitioned from normal glucose levels at baseline to high levels at the final observation (10 vs. 19) and that a greater number of Tarka subjects transitioned from high glucose levels to normal levels (15 vs. 9) compared with Lotrel-treated subjects. With regards to HbA1c, a similar number of subjects in either treatment group shifted from normal to high values; however, 20 subjects in the Tarka group compared with 11 subjects in the Lotrel group shifted from high baseline values to normal values at the final observation. With regards to HDL cholesterol, a similar number of subjects in either treatment group shifted from normal to low values; however, 9 subjects in the Tarka group compared with 17 subjects in the Lotrel group shifted from low baseline values to normal values at the final observation.

No statistically significant differences were observed between treatment groups with regards to any SF-36 subscale.

Conclusions: The hypothesis that Tarka is superior to Lotrel with regards to the reduction of albuminuria as determined by the percent change in UACR was not demonstrated by the results of this study. This outcome may be due to two factors. First, there was a significant difference in systolic BP in favor of Lotrel and second, this study used a fully exploited RAAS inhibition dose at run-in and at baseline. Whether both components (BP effect and RAAS inhibition) resulted in counteractive or additive effects remains unknown.

Date of the Report: 05 October 2006