Supplemental Table 1 All Adverse Events Reported with Tolvaptan in North American & Japanese Subjects

	Number of Subjects Reporting AE (%)		
MedDRA Adverse Event Term	156-05-002 or TEMPO[2-4]		
	15/15 mg/day N=17	45/15 mg/day N=22	90/30 mg/day N=24
Nasopharyngitis	13 (76)	2 (9)	1 (4)
Thirst	9 (53)	8 (36)	16 (67)
Pollakiuria	2 (12)	10 (46)	14 (58)
Renal Pain	0 (0)	10 (46)	9 (38)
Nocturia	2 (12)	9 (41)	3 (13)
Upper Respiratory Tract Infection	2 (12)	1 (5)	9 (38)
Polyuria	1 (6)	8 (36)	6 (25)
Dizziness	2 (12)	8 (36)	4 (17)
Contusion	6 (35)	1 (5)	0 (0)
Fatigue	1 (6)	6 (27)	8 (33)
Hypertension	5 (29)	4 (18)	4 (17)
Abdominal Pain	1 (6)	3 (14)	7 (29)
Diarrhea	2 (12)	2 (9)	7 (29)
Blood Antidiuretic Hormone Increased*	5 (29)	N/A	N/A
Urinary Tract Infection	1 (6)	3 (14)	6 (25)
Sinusitis	2 (12)	3 (14)	6 (25)
Headache	4 (24)	3 (14)	6 (25)
Blood Uric Acid Increased	4 (24)	0 (0)	0 (0)
Anemia	1 (6)	5 (23)	1 (4)
Back Pain	3 (18)	5 (23)	3 (13)
Dry Skin	2 (12)	5 (23)	2 (8)
Dyspnea	0 (0)	1 (5)	5 (21)
Constipation	1 (6)	0 (0)	5 (21)
Dehydration	3 (18)	0 (0)	2 (8)
Gastritis	3 (18)	0 (0)	0 (0)
Palpitations	3 (18)	3 (14)	1 (4)
Gastritis Erosive	3 (18)	0 (0)	0 (0)
Vertigo	3 (18)	0 (0)	0 (0)
Dental Caries	3 (18)	0 (0)	0 (0)
Bronchitis	1 (6)	4 (18)	2 (8)
Abdominal Distension	1 (6)	3 (14)	4 (17)
Nausea	1 (6)	1 (5)	4 (17)
Cough	0 (0)	0 (0)	4 (17)
Edema Peripheral	1 (6)	3 (14)	3 (13)
Hypotension	0 (0)	3 (14)	3 (13)
Arthralgia	1 (6)	3 (14)	3 (13)
Chest Pain	1 (6)	3 (14)	2 (8)
Dry Eye	0 (0)	3 (14)	2 (8)
Polydipsia	0 (0)	3 (14)	1 (4)
Erythema	0 (0)	3 (14)	0 (0)
Weight Increased	0 (0)	3 (14)	0 (0)
Blood Creatinine Increased	2 (12)	1 (5)	3 (13)
Viral Upper Respiratory Tract Infection	0 (0)	1 (5)	3 (13)
Dyspepsia	0 (0)	1 (5)	3 (13)

Dry Mouth	0 (0)	0 (0)	3 (13)
Vomiting	0 (0)	1 (5)	3 (13)
Insomnia	1 (6)	1 (5)	3 (13)
Rash	0 (0)	0 (0)	3 (13)
Muscle Spasms	0 (0)	0 (0)	3 (13)
Anxiety	0 (0)	0 (0)	3 (13)
Pain in Extremity	2 (12)	2 (9)	0 (0)
Blood Triglycerides Increased	2 (12)	0 (0)	2 (8)
Hyperuricemia	2 (12)	0 (0)	2 (8)
Tinea Pedis	2 (12)	1 (5)	0 (0)
Pharyngitis	2 (12)	0 (0)	1 (4)
Musculoskeletal Pain	2 (12)	0 (0)	1 (4)
Neck Pain	2 (12)	0 (0)	1 (4)
Arthropod Sting	2 (12)	0 (0)	0 (0)
Keratitis	2 (12)	0 (0)	0 (0)
Gastric Polyps	2 (12)	0 (0)	0 (0)
Malaise	2 (12)	0 (0)	0 (0)
Muscle Injury	2 (12)	0 (0)	0 (0)
Alanine Aminotransferase Increased	2 (12)	0 (0)	0 (0)
Blood Cholesterol Increased	2 (12)	0 (0)	0 (0)
Blood Glucose Increased	2 (12)	0 (0)	0 (0)
Hemoglobin Decreased	2 (12)	0 (0)	0 (0)
Blood Phosphorus Increased	2 (12)	0 (0)	0 (0)
Spinal Osteoarthritis	2 (12)	0 (0)	0 (0)
Intervertebral Disc Protrusion	2 (12)	0 (0)	0 (0)
Intracranial Aneurysm	2 (12)	0 (0)	0 (0)
Eczema	2 (12)	0 (0)	0 (0)
Pruritus	2 (12)	0 (0)	0 (0)
Upper Respiratory Tract Inflamation	2 (12)	0 (0)	0 (0)
Flank Pain	0 (0)	2 (9)	2 (8)
Influenza	1 (6)	2 (9)	1 (4)
Flatulence	0 (0)	2 (9)	1 (4)
Gastroenteritis Viral	0 (0)	2 (9)	1 (4)
Otitis Media	0 (0)	2 (9)	1 (4)
Nasal Congestion	0 (0)	2 (9)	1 (4)
Atrial Fibrillation	0 (0)	2 (9)	0 (0)
Umbilical Hernia	0 (0)	2 (9)	0 (0)
Decreased Appetite	0 (0)	2 (9)	0 (0)
Micturation Urgency	0 (0)	2 (9)	0 (0)
Renal Failure Acute	0 (0)	2 (9)	0 (0)
Menorrhagia	0 (0)	2 (9)	0 (0)
Depression	1 (6)	0 (0)	2 (8)
Abdominal Pain Upper	1 (6)	0 (0)	2 (8)
Pneumonia	0 (0)	1 (5)	2 (8)
Weight Decreased	0 (0)	1 (5)	2 (8)
Hematuria	0 (0)	1 (5)	2 (8)
Polycystic Liver Disease	0 (0)	0 (0)	2 (8)
Food Poisoning	0 (0)	0 (0)	2 (8)
Gastrointestinal Reflux Disease	0 (0)	0 (0)	2 (8)
Early Satiety	0 (0)	0 (0)	2 (8)
Mucosal Dryness	0 (0)	0 (0)	2 (8)
Fungal Infection	0 (0)	0 (0)	2 (8)

Viral Infection	0 (0)	0 (0)	2 (8)
Incision Site Pain	0 (0)	0 (0)	2 (8)
Hypertriglyceridemia	0 (0)	0 (0)	2 (8)
Micturation Disorder	0 (0)	0 (0)	2 (8)
Nephrolithiasis	0 (0)	0 (0)	2 (8)
Dysmenorrhea	0 (0)	0 (0)	2 (8)
Pharyngolaryngeal Pain	0 (0)	0 (0)	2 (8)
Hemorrhoids	1 (6)	1 (5)	0 (0)
Seasonal Allergy	1 (6)	1 (5)	0 (0)
Skin Papilloma	1 (6)	1 (5)	0 (0)
Breast Cyst	1 (6)	1 (5)	0 (0)
Hyperkeratosis	1 (6)	1 (5)	0 (0)
Diverticulitis	1 (6)	0 (0)	1 (4)
Laceration	1 (6)	0 (0)	1 (4)
Renal Impairment	1 (6)	0 (0)	1 (4)
Arrhythmia	1 (6)	0 (0)	0 (0)
Sinus Bradycardia	1 (6)	0 (0)	0 (0)
Asthenopia	1 (6)	0 (0)	0 (0)
Conjunctival Hemorrhage	1 (6)	0 (0)	0 (0)
Conjunctivitis	1 (6)	0 (0)	0 (0)
Eye Pruritis	1 (6)	0 (0)	0 (0)
Abdominal Discomfort	1 (6)	0 (0)	0 (0)
Enterocolitis	1 (6)	0 (0)	0 (0)
Irritable Bowel Syndrome	1 (6)	0 (0)	0 (0)
Periodontal Disease	1 (6)	0 (0)	0 (0)
Periodontitis	1 (6)	0 (0)	0 (0)
Gastrointestinal Telangiectasia	1 (6)	0 (0)	0 (0)
Mass	1 (6)	0 (0)	0 (0)
Inflammations	1 (6)	0 (0)	0 (0)
Vessel Puncture Site Hematoma	1 (6)	0 (0)	0 (0)
Anaphylactic Reaction	1 (6)	0 (0)	0 (0)
Drug Hypersensitivity	1 (6)	0 (0)	0 (0)
Acute Tonsillitis	1 (6)	0 (0)	0 (0)
Hordeolum	1 (6)	0 (0)	0 (0)
Paronychia	1 (6)	0 (0)	0 (0)
Tonsillitis	1 (6)	0 (0)	0 (0)
Urethritis	1 (6)	0 (0)	0 (0)
Oral Herpes	1 (6)	0 (0)	0 (0)
Clavicle Fracture	1 (6)	0 (0)	0 (0)
Foot Fracture	1 (6)	0 (0)	0 (0)
Head Injury	1 (6)	0 (0)	0 (0)
Muscle Injury	1 (6)	0 (0)	0 (0)
Tooth Injury	1 (6)	0 (0)	0 (0)
Mouth Injury	1 (6)	0 (0)	0 (0)
Wound	1 (6)	0 (0)	0 (0)
Aspartate Aminotransferase Increased	1 (6)	0 (0)	0 (0)
Blood Calcium Increased	1 (6)	0 (0)	0 (0)
Blood Creatinine Phosphokinase Increased	1 (6)	0 (0)	0 (0)
Blood Glucose Increased	1 (6)	0 (0)	0 (0)
Blood Lactate Dehydrogenase Increased	1 (6)	0 (0)	0 (0)
Blood Osmolality Decreased	1 (6)	0 (0)	0 (0)

Blood Osmolality Increased	1 (6)	0 (0)	0 (0)
Gamma-glutamyltransferase Increased	1 (6)	0 (0)	0 (0)
Lymphocyte Count Decreased	1 (6)	0 (0)	0 (0)
Monocyte Count Increased	1 (6)	0 (0)	0 (0)
Neutrophil Count Increased	1 (6)	0 (0)	0 (0)
Red Blood Cell Count Decreased	1 (6)	0 (0)	0 (0)
White Blood Cell Count Decreased	1 (6)	0 (0)	0 (0)
Blood Alkaline Phosphatase Decreased	1 (6)	0 (0)	0 (0)
Urine Output Increased	1 (6)	0 (0)	0 (0)
Lumbar Spinal Stenosis	1 (6)	0 (0)	0 (0)
Amnesia	1 (6)	0 (0)	0 (0)
Glossopharyngeal Neuralgia	1 (6)	0 (0)	0 (0)
Hyperaesthesia	1 (6)	0 (0)	0 (0)
Migrane	1 (6)	0 (0)	0 (0)
Sciatica	1 (6)	0 (0)	0 (0)
Subarachnoid Hemorrhage	1 (6)	0 (0)	0 (0)
Arachnoid Cyst	1 (6)	0 (0)	0 (0)
Adjustment Disorder with Depressed Mood	1 (6)	0 (0)	0 (0)
Asthma	1 (6)	0 (0)	0 (0)
Hemoptysis	1 (6)	0 (0)	0 (0)
Rhinorrhea	1 (6)	0 (0)	0 (0)
Oropharyngeal Pain	1 (6)	0 (0)	0 (0)
Dyshydrosis	1 (6)	0 (0)	0 (0)
Ingrowing Nail	1 (6)	0 (0)	0 (0)
Urticaria	1 (6)	0 (0)	0 (0)
Arthropod Bite	0 (0)	1 (5)	1 (4)
Abdominal Pain Lower	0 (0)	1 (5)	1 (4)
Hiatus Hernia	0 (0)	1 (5)	1 (4)
Cyst	0 (0)	1 (5)	1 (4)
Body Tinea	0 (0)	1 (5)	1 (4)
Kidney Infection	0 (0)	1 (5)	1 (4)
Tooth Infection	0 (0)	1 (5)	1 (4)
Vulvovaginal Mycotic Infection	0 (0)	1 (5)	1 (4)
Fall	0 (0)	1 (5)	1 (4)
Radius Fracture	0 (0)	1 (5)	1 (4)
Skin Laceration	0 (0)	1 (5)	1 (4)
Cardiac Murmur	0 (0)	1 (5)	1 (4)
Hyperlipidemia	0 (0)	1 (5)	1 (4)
Dysgeusia	0 (0)	1 (5)	1 (4)
Kidney Enlargement	0 (0)	1 (5)	1 (4)
Renal Cyst Ruptured	0 (0)	1 (5)	1 (4)
Dermatitis Contact	0 (0)	1 (5)	1 (4)
Eosinophilia	0 (0)	1 (5)	0 (0)
Tympanic Membrane Perforation	0 (0)	1 (5)	0 (0)
Vertigo Positional	0 (0)	1 (5)	0 (0)
Hypothyroidism	0 (0)	1 (5)	0 (0)
Eye Swelling	0 (0)	1 (5)	0 (0)
Ocular Hyperemia	0 (0)	1 (5)	0 (0)
Vision Blurred	0 (0)	1 (5)	0 (0)
Abdominal Hernia	0 (0)	1 (5)	0 (0)
Gastrointestinal Disorder	0 (0)	1 (5)	0 (0)

Reflux Esophagitis	0 (0)	1 (5)	0 (0)
Chest Discomfort	0 (0)	1 (5)	0 (0)
Irritability	0 (0)	1 (5)	0 (0)
Edema	0 (0)	1 (5)	0 (0)
Cholelithiasis	0 (0)	1 (5)	0 (0)
Hepatomegaly	0 (0)	1 (5)	0 (0)
Hypersensitivity	0 (0)	1 (5)	0 (0)
Ear Infection	0 (0)	1 (5)	0 (0)
Lower Respiratory Tract Infection	0 (0)	1 (5)	0 (0)
Respiratory Tract Infection	0 (0)	1 (5)	0 (0)
Rhinitis	0 (0)	1 (5)	0 (0)
Tooth Abscess	0 (0)	1 (5)	0 (0)
Joint Injury	0 (0)	1 (5)	0 (0)
Limb Injury	0 (0)	1 (5)	0 (0)
Rib Fracture	0 (0)	1 (5)	0 (0)
Soft Tissue Injury	0 (0)	1 (5)	0 (0)
Stress Fracture	0 (0)	1 (5)	0 (0)
Blood Prolactin Increased	0 (0)	1 (5)	0 (0)
Blood Urine Present	0 (0)	1 (5)	0 (0)
Liver Function Test Abnormal	0 (0)	1 (5)	0 (0)
Transaminases Increased	0 (0)	1 (5)	0 (0)
Hypercholesterolemia	0 (0)	1 (5)	0 (0)
Hypernatremia	0 (0)	1 (5)	0 (0)
Plantar Faciitis	0 (0)	1 (5)	0 (0)
Rotator Cuff Syndrome	0 (0)	1 (5)	0 (0)
Acrochordon	0 (0)	1 (5)	0 (0)
Lipoma	0 (0)	1 (5)	0 (0)
Melanocytic Nevis	0 (0)	1 (5)	0 (0)
Neuroma	0 (0)	1 (5)	0 (0)
Pituitary Tumor Benign	0 (0)	1 (5)	0 (0)
Seborrheic Keratosis	0 (0)	1 (5)	0 (0)
Nystagmus	0 (0)	1 (5)	0 (0)
Paraesthesia	0 (0)	1 (5)	0 (0)
Parosmia	0 (0)	1 (5)	0 (0)
Somnolence	0 (0)	1 (5)	0 (0)
Tremor	0 (0)	1 (5)	0 (0)
Abnormal Dreams	0 (0)	1 (5)	0 (0)
Azotemia	0 (0)	1 (5)	0 (0)
Breast Tenderness	0 (0)	1 (5)	0 (0)
Dysfunctional Uterine Bleeding	0 (0)	1 (5)	0 (0)
Menstruation Irregular	0 (0)	1 (5)	0 (0)
Ovarian Cyst Rupture	0 (0)	1 (5)	0 (0)
Pelvic Pain	0 (0)	1 (5)	0 (0)
Rhinitis Alergic	0 (0)	1 (5)	0 (0)
Sinus Congestion	0 (0)	1 (5)	0 (0)
Sleep Apnea Syndrome	0 (0)	1 (5)	0 (0)
Snoring	0 (0)	1 (5)	0 (0)
Alopecia	0 (0)	1 (5)	0 (0)
Cambell de Morgan Spots	0 (0)	1 (5)	0 (0)
Dermatitis	0 (0)	1 (5)	0 (0)
Psoriasis	0 (0)	1 (5)	0 (0)
Seborrheic Dermatitis	0 (0)	1 (5)	0 (0)

Skin Discoloration	0 (0)	1 (5)	0 (0)
Orthostatic Hypotension	0 (0)	1 (5)	0 (0)
Leukocytosis	0 (0)	0 (0)	1 (4)
Splenomegaly	0 (0)	0 (0)	1 (4)
Tachycardia	0 (0)	0 (0)	1 (4)
Ventricular Extrasystoles	0 (0)	0 (0)	1 (4)
Hyperparathyroidism Primary	0 (0)	0 (0)	1 (4)
Hyperparathyroidism Secondary	0 (0)	0 (0)	1 (4)
Ascites	0 (0)	0 (0)	1 (4)
Breath Odor	0 (0)	0 (0)	1 (4)
Epiploic Appendagitis	0 (0)	0 (0)	1 (4)
Gastrointestinal Edema	0 (0)	0 (0)	1 (4)
Rectal Hemorrhage	0 (0)	0 (0)	1 (4)
Tooth Impacted	0 (0)	0 (0)	1 (4)
Chills	0 (0)	0 (0)	1 (4)
Dyscomfort	0 (0)	0 (0)	1 (4)
Energy Increased	0 (0)	0 (0)	1 (4)
Generalized Edema	0 (0)	0 (0)	1 (4)
Granuloma	0 (0)	0 (0)	1 (4)
Influenza Like Illness	0 (0)	0 (0)	1 (4)
Localized Edema	0 (0)	0 (0)	1 (4)
Pain	0 (0)	0 (0)	1 (4)
Peripheral Coldness	0 (0)	0 (0)	1 (4)
Pyrexia	0 (0)	0 (0)	1 (4)
Temperature Intolerance	0 (0)	0 (0)	1 (4)
Cholecystitis Chronic	0 (0)	0 (0)	1 (4)
Alveolar Osteitis	0 (0)	0 (0)	1 (4)
Cystitis	0 (0)	0 (0)	1 (4)
Gastroenteritis	0 (0)	0 (0)	1 (4)
Pyelonephritis	0 (0)	0 (0)	1 (4)
Barotrauma	0 (0)	0 (0)	1 (4)
Foreign Body in Eye	0 (0)	0 (0)	1 (4)
Incisional Hernia	0 (0)	0 (0)	1 (4)
Nerve Compression	0 (0)	0 (0)	1 (4)
Wrist Fracture	0 (0)	0 (0)	1 (4)
Grip Strength Decreased	0 (0)	0 (0)	1 (4)
Kidney Palpable	0 (0)	0 (0)	1 (4)
Lipids Increased	0 (0)	0 (0)	1 (4)
Waist Circumference Increased	0 (0)	0 (0)	1 (4)
Hypokalemia	0 (0)	0 (0)	1 (4)
Bursitis	0 (0)	0 (0)	1 (4)
Groin Pain	0 (0)	0 (0)	1 (4)
Joint Range of Motion Decreased	0 (0)	0 (0)	1 (4)
Musculoskeletal Chest Pain	0 (0)	0 (0)	1 (4)
Osteoporosis	0 (0)	0 (0)	1 (4)
Trigger Finger	0 (0)	0 (0)	1 (4)
Malignant Melanoma In Situ	0 (0)	0 (0)	1 (4)
Uterine Leiomyoma	0 (0)	0 (0)	1 (4)
Hyperreflexia	0 (0)	0 (0)	1 (4)
Sinus Headache	0 (0)	0 (0)	1 (4)
Syncope	0 (0)	0 (0)	1 (4)
Transient Ischemic Attack	0 (0)	0 (0)	1 (4)

Visual Field Defect	0 (0)	0 (0)	1 (4)
Libido Decreased	0 (0)	0 (0)	1 (4)
Bladder Discomfort	0 (0)	0 (0)	1 (4)
Renal Failure	0 (0)	0 (0)	1 (4)
Erectile Dysfunction	0 (0)	0 (0)	1 (4)
Menopausal Symptoms	0 (0)	0 (0)	1 (4)
Ovarian Cyst	0 (0)	0 (0)	1 (4)
Vaginal Dyscharge	0 (0)	0 (0)	1 (4)
Dyspnea Exhertional	0 (0)	0 (0)	1 (4)
Paranasal Sinus Hypersecretion	0 (0)	0 (0)	1 (4)
Pharyngeal Erythema	0 (0)	0 (0)	1 (4)
Postnasal Drip	0 (0)	0 (0)	1 (4)
Productive Cough	0 (0)	0 (0)	1 (4)
Night Sweats	0 (0)	0 (0)	1 (4)
Petechiae	0 (0)	0 (0)	1 (4)
Rash Macular	0 (0)	0 (0)	1 (4)
Rash Papular	0 (0)	0 (0)	1 (4)
Rash Puritic	0 (0)	0 (0)	1 (4)
Skin Lesion	0 (0)	0 (0)	1 (4)
Skin Plaque	0 (0)	0 (0)	1 (4)
Flushing	0 (0)	0 (0)	1 (4)

Adverse Event is a new or worsening untoward symptom or sign occurring after receiving at least 1 dose of tolvaptan.

[1]Subjects receiving at least 1 dose from Japanese 156-05-002 (N=17) studies.

[2]Subjects receiving at least 1 dose from U.S. 156-04-250 “TEMPO$^2_4$” (N=46) who were randomized to separate dose groups.

*N/A = Not Applicable since Antidiuretic Hormone (vasopressin) was not assessed in TEMPO$^2_4$

Supplemental Table 2 Details of Tolvaptan Subjects Withdrawing Prior to 36 months of Therapy.		
Subject Study ID & Tolvaptan Dose	**Reason for Withdrawal**	**Comment**
156-04-250-0012004 60/30 mg/day	Adverse Event: Transient Ischemic Attack	44 year old woman diagnosed with atrial fibrillation on day 144. Study drug was discontinued on day 147 for a transient ischemic attack which resolved 8 days later. The investigator assessed relationship to therapy as possible
156-04-250-0012043 45/15 mg/day	Adverse Event: Benign Pituitary Tumor	28 year old woman placed on hormonal therapy for dysfunctional uterine bleeding on day 103. She developed blurred vision on day 164 and was found to have a pituitary microadenoma on day 238. Study drug was discontinued on day 414. The investigator assessed relationship to therapy as possible
156-04-250-0032038 60/30 mg/day	Subject Withdrew Consent	43 year old woman with a gradual increase in serum creatinine from a baseline of 2.4 mg/dL. On day 582, she decided to pursue pre-emptive transplantation. Serum creatinine peaked at 3.2 mg/dL and was 3.0 mg/dL at study withdrawal. The investigator deemed the increase in serum creatinine to be unrelated to therapy.
156-04-250-0042039 60/30 mg/day	Lost to Follow up	39 year old man with pollakiuria from day 1, worsening nocturia on day 466 and worsening fatigue on day 467. He became non-compliant with study medication and was lost to follow-up. The investigator assessed relationship to therapy as probable for pollakiuria, possible for nocturia, and unlikely for fatigue.
156-04-250-0132005 45/15 mg/day	Adverse Event: Acute Renal Failure	48 year old woman with an increase in serum creatinine from a baseline of 1.3-1.4 mg/dL to a peak 1.6-1.7 during titration (day 24-26), which returned to 1.3 on treatment interruption (day 52) and increased to 1.6 after resuming therapy (day 69). Study drug was discontinued on day 69 and serum creatinine returned to 1.4 mg/dL after 27 days. The investigator deemed relationship to therapy as definite.
156-04-250-0132026 45/15 mg/day	Adverse Event: Eye Swelling	49 year old woman complained of left eye periorbital swelling on day 93 and of seasonal allergies on day 99. The eye swelling resolved after 140 days. She discontinued the trial at day 189. The investigator deemed relationship to therapy as probable.
156-04-250-0132033 45/15 mg/day	Met Withdrawal Criteria	35 year old woman deemed to be non-compliant with study medication and withdrawn from the study on day 173.
156-05-002-0010001 15/15 mg/day	Adverse Event: Renal Impairment	45 year old woman with an increase in serum creatinine from 0.79 mg/dL at baseline to 0.93 at day 7. She developed itching on the lower back on day 35 and 73. Study drug was suspended on day 95. Serum creatinine values during this time ranged between 0.90 and 1.03 mg/dL. Two months later the itching resolved and serum creatinine following discontinuation of therapy ranged between 0.83 and 0.92 mg/dL The investigator deemed the adverse event related to treatment.
156-05-002-0020001 15/15 mg/day	Subject Requested Withdrawal	33 years old man withdrawn at his request on day 658 without having experienced adverse events.
156-05-002-0060002 15/15 mg/day	Adverse Event: Subarachnoid hemorrhage	38 year old woman suffered a subarachnoid hemorrhage due to a ruptured cerebral aneurysm on day 74 and died 18 days later. The event was assessed as not related to

Supplemental Table 2 Details of Tolvaptan Subjects Withdrawing Prior to 36 months of Therapy.		
		treatment.
156-05-002-0070001 15/15 mg/day	Subject Met Withdrawal Criteria: Serum creatinine ≥ 2.5 mg/dL	44 year old man with an increase in the serum creatinine from 2.13 mg/dL at screening and 1.88 mg/dL at baseline to 2.55 mg/dL on day 252. Study drug administration was discontinued. One month later serum creatinine was 2.49 mg/dL and remained high (2.55 and 2.57 mg/dL). Subject was withdrawn according to exclusion criteria. The increase was assessed as non-serious and possibly related to therapy.
156-05-002-0090002 15/15 mg/day	Subject Requested Withdrawal	40 year old woman withdrawn at her request on day 672 without having experienced adverse events.

Supplemental Table 3 Annualized Progression Rate of TKV and eGFR Projected Over 3 Years Data-in All Subjects

Annualized TKV Growth Rate[1]

Group	N	Annual Change %/year (± SD)	Ratio of Geometric Means (RGM, 95% CI) [1]	p-value
TKV Control	126	5.8 (4.1)	0.96 (0.95-0.97)	<0.001
Tolvaptan	62	1.7 (9.2)		

Annualized eGFR Slope[2]

Group	N	Annual Change mL/min/1.73m^2/year (± SD)	LS Mean Difference (mL/min/1.73m^2/year, 95% CI)	p-value
eGFR Control	126	-2.0 (3.2)	0.95 (0.13-1.8)	=0.02
Tolvaptan	63	-1.7 (11.9)		

N=Number of subjects, SD=Standard Deviation, CI=Confidence interval

[1] Summary Statistics derived by regressing logarithm transformed TKV against time, and then exponential the regression slopes, p-value of Ratio of Geometric Means derived from testing time:treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects. The Ratio of Geometric Means is an estimate of the ratio of the geometric mean of annualized growth rate of tolvaptan and control.

[2] Summary Statistics derived by slope of change by regressing estimated GFR data against time by subject. LS Means Difference derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects. Matching criteria were gender, hypertension status, age and CKD-EPI eGFR (using coefficient of 0.813 if Japanese).[15]

Supplemental Table 4 Change in Mean TKV and eGFR in All Completing Subjects by Visit											
	Control					Tolvaptan					
TKV mL	**N**	**Mean**	**SD**	**Mean % Change**	**SD**	**N**	**Mean**	**SD**	**Mean % Change**	**SD**	**Group Difference (95%CI) p-value**
Baseline	126	1362	680.7			63	1649.0	939.3			
Month 12	123	1448	731.2	5.0	6.6	54	1633.5	964.3	0.9	7.1	-4.67 (-1.28 to -8.06) p = 0.0071
Month 24	118	1579	843.0	13.8	10.6	51	1670.9	1015	1.6	8.5	-12.6 (-9.11 to -16.0) p < 0.0001
Month 36	126	1646	887.3	19.0	14.9	51	1733.5	1052	5.3	11.0	-14.3 (-10.9 to -17.7) p < 0.0001
eGFR ml/min/1.73m^2	**N**	**Mean**	**SD**	**Mean Change**	**SD**	**N**	**Mean**	**SD**	**Mean Change**	**SD**	**Group Difference (95%CI) p-value**
Baseline	126	62.1	18.9			63	61.4	19.7			
Month 12	123	60.4	21.6	-2.05	8.56	53	59.7	22.1	-1.68	12.3	0.4 (-2.7 to 3.5) p = 0.806
Month 24	123	56.7	22.4	-5.16	9.33	50	59.3	21.5	-2.55	8.82	2.3 (-0.9 to 5.4) p = 0.160
Month 36	125	55.8	22.4	-6.53	10.8	51	55.9	21.1	-5.70	9.23	0.7 (-2.4 to 3.9) p = 0.654

eGFR by MDRD = 186 x (Scr)-1.154x(age)-0.203 x (0.742 if female) x(1.21 if African American or 0.808 if Japanese).

Supplemental Table 5 Annualized Progression Rate of TKV and eGFR in Completing Subjects Projected Over 3 Years (TEMPO$^{2}_{4}$ only)

Annualized TKV Growth Rate[1]

Group	N	Annual Change %/year (± SD)	Ratio of Geometric Means (RGM, 95% CI)[1]	p-value
TKV Control	78	6.0 (4.4)	0.97 (0.95 to 0.98)	p<0.001
Tolvaptan	39	2.3 (3.5)		

Annualized eGFR Slope[2]

Group	N	Annual Change mL/min/1.73m2/year (± SD)	LS Mean Difference (mL/min/1.73m2/year, 95% CI)	p-value
eGFR Control	78	-2.4 (3.3)	1.5 (0.46 to 2.53)	p=0.005
Tolvaptan	39	-0.6 (2.5)		

N=Number of subjects, SD=Standard Deviation, CI=Confidence interval

[1] Summary Statistics derived by regressing logarithm transformed TKV against time, and then exponential the regression slopes, p-value of Ratio of Geometric Means derived from testing time:treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects. The Ratio of Geometric Means is an estimate of the ratio of the geometric mean of annualized growth rate of tolvaptan and control.

[2] Summary Statistics derived by slope of change by regressing estimated GFR data against time by subject. LS Means Difference derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects. eGFR by MDRD = 186 x (Scr)-1.154x(age)-0.203 x (0.742 if female) x(1.21 if African American).

Supplemental Table 6 Annualized Progression Rate of TKV and eGFR Projected Over 3 Years Data-in All Subjects (TEMPO$^{2}_{4}$ only)

Annualized TKV Growth Rate[1]

Group	N	Annual Change %/year (± SD)	Ratio of Geometric Means (RGM, 95% CI)[1]	p-value
TKV Control	92	6.1 (4.4)	0.97 (0.95 to 0.98)	p<0.001
Tolvaptan	46	2.2 (10.5)		

Annualized eGFR Slope[2]

Group	N	Annual Change mL/min/1.73m2/year (± SD)	LS Mean Difference (mL/min/1.73m2/year, 95% CI)	p-value
eGFR Control	92	-2.3 (3.3)	1.4 (0.41 to 2.40)	p = 0.006
Tolvaptan	46	-0.5 (9.4)		

N=Number of subjects, SD=Standard Deviation, CI=Confidence interval

[1] Summary Statistics derived by regressing logarithm transformed TKV against time, and then exponential the regression slopes, p-value of Ratio of Geometric Means derived from testing time:treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects. The Ratio of Geometric Means is an estimate of the ratio of the geometric mean of annualized growth rate of tolvaptan and control.

[2] Summary Statistics derived by slope of change by regressing estimated GFR data against time by subject. LS Means Difference derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects. eGFR by MDRD = 186 x (Scr)-1.154x(age)-0.203 x (0.742 if female) x(1.21 if African American).