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List of Principal Investigators and Study Sites

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SUPPLEMENTAL TABLES

Supplemental Table 1. Incidence of treatment-emergent adverse events occurring in ≥2% of subjects (safety sample)

System Organ Class Preferred Term n (%)	From REPRISE Tolvaptan (N=505)	From REPRISE Placebo (N=569)	From TEMPO 4:4 Tolvaptan (N=717)	From Other Tolvaptan (N=6)	From Other Placebo (N=3)	Total (N=1800)
Blood and Lymphatic System Disorders						
Anemia	23 (4.6)	21 (3.7)	24 (3.3)	0 (0.0)	0 (0.0)	68 (3.8)
Gastrointestinal Disorders						
Abdominal Pain	25 (5.0)	25 (4.4)	28 (3.9)	0 (0.0)	0 (0.0)	78 (4.3)
Abdominal Pain Upper	21 (4.2)	19 (3.3)	12 (1.7)	1 (16.7)	0 (0.0)	53 (2.9)
Constipation	17 (3.4)	28 (4.9)	10 (1.4)	0 (0.0)	1 (33.3)	56 (3.1)
Diarrhea	38 (7.5)	38 (6.7)	33 (4.6)	0 (0.0)	1 (33.3)	110 (6.1)
Dry Mouth	22 (4.4)	38 (6.7)	3 (0.4)	0 (0.0)	0 (0.0)	63 (3.5)
Dyspepsia	17 (3.4)	27 (4.7)	10 (1.4)	1 (16.7)	0 (0.0)	55 (3.1)
Gastroesophageal Reflux Disease	11 (2.2)	20 (3.5)	18 (2.5)	0 (0.0)	1 (33.3)	50 (2.8)
Nausea	37 (7.3)	52 (9.1)	39 (5.4)	0 (0.0)	1 (33.3)	129 (7.2)
Umbilical Hernia	12 (2.4)	6 (1.1)	20 (2.8)	0 (0.0)	0 (0.0)	38 (2.1)
Vomiting	24 (4.8)	38 (6.7)	32 (4.5)	0 (0.0)	0 (0.0)	94 (5.2)
General Disorders and Administration Site Conditions						
Fatigue	48 (9.5)	74 (13.0)	34 (4.7)	0 (0.0)	0 (0.0)	156 (8.7)
Edema Peripheral	33 (6.5)	39 (6.9)	42 (5.9)	0 (0.0)	0 (0.0)	114 (6.3)
Pyrexia	21 (4.2)	19 (3.3)	27 (3.8)	0 (0.0)	0 (0.0)	67 (3.7)
Thirst	139 (27.5)	184 (32.3)	91 (12.7)	4 (66.7)	0 (0.0)	418 (23.2)
Infections and Infestations						
Bronchitis	23 (4.6)	29 (5.1)	31 (4.3)	1 (16.7)	0 (0.0)	84 (4.7)
Gastroenteritis	16 (3.2)	25 (4.4)	41 (5.7)	1 (16.7)	0 (0.0)	83 (4.6)
Influenza	34 (6.7)	43 (7.6)	39 (5.4)	0 (0.0)	0 (0.0)	116 (6.4)
Nasopharyngitis	92 (18.2)	100 (17.6)	94 (13.1)	0 (0.0)	1 (33.3)	287 (15.9)
Sinusitis	22 (4.4)	31 (5.4)	35 (4.9)	1 (16.7)	0 (0.0)	89 (4.9)

Upper Respiratory Tract Infection	58 (11.5)	53 (9.3)	86 (12.0)	1 (16.7)	0 (0.0)	198 (11.0)
Urinary Tract Infection	53 (10.5)	59 (10.4)	67 (9.3)	1 (16.7)	0 (0.0)	180 (10.0)
Investigations						
Alanine Aminotransferase Increased	10 (2.0)	23 (4.0)	17 (2.4)	1 (16.7)	0 (0.0)	51 (2.8)
Blood Creatinine Increased	78 (15.4)	90 (15.8)	71 (9.9)	0 (0.0)	1 (33.3)	240 (13.3)
Metabolism and Nutrition Disorders						
Gout	28 (5.5)	25 (4.4)	30 (4.2)	0 (0.0)	1 (33.3)	84 (4.7)
Hyperkalemia	13 (2.6)	15 (2.6)	10 (1.4)	0 (0.0)	0 (0.0)	38 (2.1)
Hyperuricemia	16 (3.2)	15 (2.6)	19 (2.6)	0 (0.0)	0 (0.0)	50 (2.8)
Metabolic Acidosis	12 (2.4)	17 (3.0)	8 (1.1)	0 (0.0)	0 (0.0)	37 (2.1)
Polydipsia	27 (5.3)	53 (9.3)	14 (2.0)	0 (0.0)	0 (0.0)	94 (5.2)
Vitamin D Deficiency	16 (3.2)	11 (1.9)	11 (1.5)	0 (0.0)	0 (0.0)	38 (2.1)
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	33 (6.5)	25 (4.4)	26 (3.6)	0 (0.0)	0 (0.0)	84 (4.7)
Back Pain	53 (10.5)	57 (10.0)	51 (7.1)	1 (16.7)	0 (0.0)	162 (9.0)
Muscle Spasms	17 (3.4)	27 (4.7)	30 (4.2)	0 (0.0)	0 (0.0)	74 (4.1)
Myalgia	17 (3.4)	17 (3.0)	20 (2.8)	0 (0.0)	0 (0.0)	54 (3.0)
Pain in Extremity	18 (3.6)	27 (4.7)	12 (1.7)	0 (0.0)	0 (0.0)	57 (3.2)
Nervous System Disorders						
Dizziness	18 (3.6)	31 (5.4)	31 (4.3)	0 (0.0)	1 (33.3)	81 (4.5)
Headache	51 (10.1)	72 (12.7)	51 (7.1)	2 (33.3)	0 (0.0)	176 (9.8)
Psychiatric Disorders						
Insomnia	7 (1.4)	14 (2.5)	19 (2.6)	0 (0.0)	0 (0.0)	40 (2.2)
Renal and Urinary Disorders						
Acute Kidney Injury	11 (2.2)	14 (2.5)	13 (1.8)	0 (0.0)	0 (0.0)	38 (2.1)
Hematuria	27 (5.3)	52 (9.1)	48 (6.7)	0 (0.0)	2 (66.7)	129 (7.2)
Nocturia	77 (15.2)	124 (21.8)	58 (8.1)	3 (50.0)	1 (33.3)	263 (14.6)
Pollakiuria	27 (5.3)	35 (6.2)	12 (1.7)	2 (33.3)	0 (0.0)	76 (4.2)
Polyuria	117 (23.2)	180 (31.6)	53 (7.4)	2 (33.3)	0 (0.0)	352 (19.6)
Kidney Impairment	16 (3.2)	31 (5.4)	15 (2.1)	0 (0.0)	0 (0.0)	62 (3.4)
Kidney Pain	98 (19.4)	111 (19.5)	141 (19.7)	3 (50.0)	2 (66.7)	355 (19.7)

Respiratory, Thoracic and Mediastinal Disorders						
Cough	27 (5.3)	28 (4.9)	28 (3.9)	0 (0.0)	0 (0.0)	83 (4.6)
Oropharyngeal Pain	12 (2.4)	17 (3.0)	11 (1.5)	0 (0.0)	0 (0.0)	40 (2.2)
Skin and Subcutaneous Tissue Disorders						
Rash	12 (2.4)	16 (2.8)	12 (1.7)	0 (0.0)	0 (0.0)	40 (2.2)
Vascular Disorders						
Hypertension	87 (17.2)	77 (13.5)	140 (19.5)	4 (66.7)	1 (33.3)	309 (17.2)

Supplemental Table 2. Cross-trial comparison of treatment-emergent adverse events of skin malignancy and glaucoma over 12 months of tolvaptan exposure (long-term extension, REPRISE, TEMPO 4:4, and TEMPO 3:4 trials)

n (%)	**Long-term Extension (From REPRISE Placebo) (N=569)**	**Tolvaptan Arm of REPRISE (N=681)**	**TEMPO 4:4 (From TEMPO 3:4 Placebo) (N=314)**	**Tolvaptan Arm of TEMPO 3:4 (N=961)**
Skin malignant tumor	3 (0.5)	3 (0.4)	1 (0.3)	5 (0.5)
Skin tumors of unspecified malignancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Supplemental Table 3. Serious treatment-emergent adverse events of acute kidney injury and kidney impairment

Subject	Event	Prior Treatment Subgroup	Serum Creatinine Prior to the Event (mg/dL)	Time from Serum Creatinine Prior to the Event to Peak Serum Creatinine During the Event (Days)	Peak Serum Creatinine During the Event (mg/dL)	Serum Creatinine After the Event (mg/dL)	Action Regarding Study Drug	Outcome
1	Acute kidney injury	REPRISE placebo	2.04	n/a	Not available	1.90	Interrupted	Recovered/Resolved
2	Acute kidney injury	TEMPO 4:4 tolvaptan	3.53	79	4.59	Not available	Dose not changed	Not recovered/Not resolved
3	Acute kidney injury	TEMPO 4:4 tolvaptan	2.88	n/a	Not available	Not available	Dose not changed	Recovered/Resolved
4	Acute kidney injury	TEMPO 4:4 tolvaptan	3.72	n/a	Not available	3.25	Not applicable[a]	Recovered/Resolved
5	Acute kidney injury	REPRISE placebo	1.64	35	1.79	Not available	Withdrawn	Recovered/Resolved
6	Acute kidney injury	REPRISE tolvaptan	3.66	36	3.86	3.18	Interrupted	Recovered/Resolved
7	Acute kidney injury	TEMPO 4:4 tolvaptan	2.59	n/a	Not available	3.10	Not applicable[a]	Recovered/Resolved with sequelae
8	Acute kidney injury	TEMPO 4:4 tolvaptan	1.18	n/a	Not available	Not available	Not applicable[a]	Recovered/Resolved
9	Acute kidney injury	REPRISE placebo	2.84	n/a	Not available	2.94	Interrupted	Recovered/Resolved
10	Acute kidney injury	REPRISE placebo	2.73	n/a	Not available	2.40	Dose not changed	Recovered/Resolved
	Acute kidney injury	REPRISE placebo	3.01	n/a	Not available	4.47	Withdrawn	Recovered/Resolved with sequelae
11	Acute kidney injury	REPRISE placebo	1.48	n/a	Not available	Not available	Interrupted	Recovered/Resolved
12	Acute kidney injury	REPRISE placebo	4.00	n/a	Not available	3.44	Not applicable[a]	Recovered/Resolved
13	Acute kidney injury	REPRISE tolvaptan	2.87	102	3.09	Not available	Not applicable[a]	Recovered/Resolved
	Kidney impairment	REPRISE tolvaptan	2.87	n/a	Not available	3.09	Interrupted	Recovered/Resolved
14	Acute kidney injury	REPRISE tolvaptan	2.73	n/a	Not available	2.25	Interrupted	Recovered/Resolved
15	Acute kidney injury	REPRISE tolvaptan	2.46	34	2.37	2.38	Interrupted	Recovered/Resolved
16	Acute kidney injury	REPRISE tolvaptan	2.82	33	4.43	2.85	Interrupted	Recovered/Resolved with sequelae
17	Acute kidney injury	REPRISE placebo	1.55	28	1.62	Not available	Withdrawn	Recovered/Resolved
18	Acute kidney injury	TEMPO 4:4 tolvaptan	2.75	n/a	Not available	3.05	Interrupted	Recovered/Resolved
	Kidney impairment	TEMPO 4:4 tolvaptan	4.16	n/a	Not available	3.99	Interrupted	Recovered/Resolved with sequelae
19	Acute kidney injury[b]	TEMPO 4:4 tolvaptan	4.47	297	8.47	Not available	Dose not changed	Not recovered/Not resolved
20	Acute kidney injury	REPRISE placebo	1.61	n/a	Not available	1.43	Withdrawn	Recovered/Resolved
21	Kidney impairment	REPRISE tolvaptan	1.94	28	2.45	2.31	Withdrawn	Recovered/Resolved
22	Kidney impairment	REPRISE tolvaptan	2.33	74	2.62	Not available	Withdrawn	Not recovered/Not resolved
23	Kidney impairment	REPRISE tolvaptan	3.06	n/a	Not available	1.53	Withdrawn	Recovered/Resolved
24	Kidney impairment	REPRISE placebo	3.75	125	3.62	Not available	Withdrawn	Not recovered/Not resolved
25	Kidney impairment	REPRISE placebo	3.27	548	5.38	Not available	Interrupted	Not recovered/Not resolved
26	Kidney impairment	REPRISE tolvaptan	2.38	28	3.19	2.56	Interrupted	Recovered/Resolved
27	Kidney impairment	TEMPO 4:4 tolvaptan	5.43	91	7.13	Not available	Withdrawn	Not recovered/Not resolved
28	Kidney impairment	TEMPO 4:4 tolvaptan	4.48	54	4.14	Not available	Withdrawn	Not recovered/Not resolved
29	Kidney impairment	REPRISE tolvaptan	4.25	18	1.80	Not available	Withdrawn	Recovering/Resolving

[a]Indicates that the event occurred after the trial drug stop date; as such, no further action to the drug applied, since the trial drug was no longer being administered at the time of event onset.
[b]The event was considered by the investigator to be unrelated to the trial drug. The subject later progressed to kidney failure, also considered unrelated to the trial drug, and discontinued participation in the trial.
n/a, not applicable (peak serum creatinine during the event not available).

Supplemental Table 4. Serious treatment-emergent adverse events of end-stage kidney disease

Subject	Prior Treatment Subgroup	Serum Creatinine at Study Baseline (mg/dL)	Time From Baseline to Last Creatinine Measurement on Trial (Days)	Last Serum Creatinine on Trial (mg/dL)	Action Regarding Study Drug	Outcome
1	REPRISE tolvaptan	2.14	591	1.46	Withdrawn	Not recovered/Not resolved
2	TEMPO 4:4 tolvaptan	4.95	646	8.40	Withdrawn	Not recovered/Not resolved
3	TEMPO 4:4 tolvaptan	2.91	556	1.47	Withdrawn	Recovered/Resolved
4	REPRISE tolvaptan	3.27	460	4.65	Withdrawn	Not recovered/Not resolved
5	REPRISE tolvaptan	2.60	534	3.97	Withdrawn	Not recovered/Not resolved
6	TEMPO 4:4 tolvaptan	2.53	379	3.17	Withdrawn	Not recovered/Not resolved
7	TEMPO 4:4 tolvaptan	3.18	575	5.36	Withdrawn	Not recovered/Not resolved
8	TEMPO 4:4 tolvaptan	3.77	476	6.02	Withdrawn	Not recovered/Not resolved
9	TEMPO 4:4 tolvaptan	3.62	396	3.89	Withdrawn	Not recovered/Not resolved
10	TEMPO 4:4 tolvaptan	3.01	372	3.49	Withdrawn	Not recovered/Not resolved
11	TEMPO 4:4 tolvaptan	4.46	457	6.01	Dose not changed	Recovered/Resolved

Supplemental Table 5. Overview of adverse events in the long-term extension by cumulative tolvaptan exposure (i.e., exposure during prior trials and the long-term extension)

	Prior Trial Participation			
n (%[a])	**From REPRISE Tolvaptan**	**From REPRISE Placebo**	**From TEMPO 4:4 Tolvaptan**	**Total[b]**
Subjects treated	**505**	**569**	**717**	**1800**
<18 months	16	209	1	229
≥18 to <36 months	348	359	4	716
≥36 to <54 months	141	1	11	153
≥54 to <72 months	0	0	67	68
≥72 to <90 months	0	0	114	114
≥90 months	0	0	520	520
Subjects with AEs	**473 (94)**	**531 (93)**	**643 (90)**	**1656 (92)**
<18 months	14 (88)	194 (93)	1 (100)	212 (93)
≥18 to <36 months	321 (92)	336 (94)	3 (75)	665 (93)
≥36 to <54 months	138 (98)	1 (100)	9 (82)	148 (97)
≥54 to <72 months	0	0	63 (94)	64 (94)
≥72 to <90 months	0	0	101 (89)	101 (89)
≥90 months	0	0	466 (90)	466 (90)
AEs	**3567**	**4313**	**3963**	**11932**
<18 months	63	1266	8	1364
≥18 to <36 months	2237	3042	11	5350
≥36 to <54 months	1267	5	83	1355
≥54 to <72 months	0	0	539	541
≥72 to <90 months	0	0	431	431
≥90 months	0	0	2891	2891
Subjects with treatment-emergent AEs	**473 (94)**	**531 (93)**	**640 (89)**	**1653 (92)**
<18 months	14 (88)	194 (93)	1 (100)	212 (93)
≥18 to <36 months	321 (92)	336 (94)	3 (75)	665 (93)
≥36 to <54 months	138 (98)	1 (100)	9 (82)	148 (97)
≥54 to <72 months	0	0	63 (94)	64 (94)

≥72 to <90 months	0	0	100 (88)	100 (88)
≥90 months	0	0	464 (89)	464 (89)
Treatment-emergent AEs	**2965**	**3678**	**3297**	**10019**
<18 months	56	1099	6	1185
≥18 to <36 months	1860	2574	11	4499
≥36 to <54 months	1049	5	70	1124
≥54 to <72 months	0	0	431	432
≥72 to <90 months	0	0	362	362
≥90 months	0	0	2417	2417
Subjects with serious treatment-emergent AEs	**87 (17)**	**96 (17)**	**103 (14)**	**289 (16)**
<18 months	5 (31)	42 (20)	1 (100)	49 (21)
≥18 to <36 months	56 (16)	54 (15)	0	112 (16)
≥36 to <54 months	26 (18)	0	1 (9)	27 (18)
≥54 to <72 months	0	0	10 (15)	10 (15)
≥72 to <90 months	0	0	9 (8)	9 (8)
≥90 months	0	0	82 (16)	82 (16)
Subjects with severe treatment-emergent AEs	**74 (15)**	**78 (14)**	**83 (12)**	**238 (13)**
<18 months	2 (13)	38 (18)	1 (100)	42 (18)
≥18 to <36 months	47 (14)	40 (11)	1 (25)	90 (13)
≥36 to <54 months	25 (18)	0	3 (27)	28 (18)
≥54 to <72 months	0	0	13 (19)	13 (19)
≥72 to <90 months	0	0	8 (7)	8 (7)
≥90 months	0	0	57 (11)	57 (11)
Subjects with treatment-emergent AEs both serious and severe	**43 (9)**	**40 (7)**	**44 (6)**	**128 (7)**
<18 months	2 (13)	17 (8)	1 (100)	21 (9)
≥18 to <36 months	24 (7)	23 (6)	0	47 (7)
≥36 to <54 months	17 (12)	0	1 (9)	18 (12)
≥54 to <72 months	0	0	7 (10)	7 (10)
≥72 to <90 months	0	0	4 (4)	4 (4)
≥90 months	0	0	31 (6)	31 (6)

Subjects discontinued trial drug due to AEs	**33 (7)**	**65 (11)**	**38 (5)**	**137 (8)**
<18 months	7 (44)	59 (28)	1 (100)	67 (29)
≥18 to <36 months	22 (6)	6 (2)	1 (25)	30 (4)
≥36 to <54 months	4 (3)	0	1 (9)	5 (3)
≥54 to <72 months	0	0	3 (5)	3 (4)
≥72 to <90 months	0	0	1 (0.9)	1 (0.9)
≥90 months	0	0	31 (6)	31 (6)
Deaths	**1 (0.2)**	**5 (0.9)**	**3 (0.4)**	**9 (0.5)**
<18 months	0	3 (1)	0	3 (1)
≥18 to <36 months	1 (0.3)	2 (0.6)	0	3 (0.4)
≥36 to <54 months	0	0	0	0
≥54 to <72 months	0	0	0	0
≥72 to <90 months	0	0	0	0
≥90 months	0	0	3 (0.6)	3 (0.6)

[a]Percentages are based on the number of subjects treated for each cumulative exposure period; [b]The table has no column for subjects who entered the extension directly from TEMPO 3:4 or NOCTURNE due to the small number of subjects (n=9; 4 from TEMPO 3:4 tolvaptan and 2 from NOCTURNE tolvaptan; 3 from TEMPO 3:4 placebo) from those trials. Data from these subjects are included in the total column.
AE, adverse event.

Supplemental Table 6. Subjects with elevations ≥10 x upper limit of normal in alanine aminotransferase or aspartate aminotransferase

Subject	Prior Treatment Subgroup	Peak Fold Change x Upper Limit of Normal	Trial Day	Action Regarding Study Drug	Outcome
1	REPRISE PLC	ALT 22.6	189	Discontinued	Recovered/Resolved
2	REPRISE PLC	ALT 22.1 AST 18.5	204	Discontinued	Recovered/Resolved
3	REPRISE PLC	ALT 26.9 AST 17.7	35 49	Discontinued	Recovering/Resolving
4	REPRISE PLC	ALT 35.9 AST 23.3	539	Discontinued	Recovered/Resolved
5	REPRISE PLC	ALT 10.2	106	Discontinued	Recovered/Resolved

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLC, placebo.