SUPPLEMENTARY MATERIAL

Contents

Definition of rapid correction of hyponatremia used in the reanalysis

- Too rapid correction of hyponatremia (serum sodium increase ≥ 12 mmol/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, or death. Therefore, after initiation of tolvaptan, patients should be closely monitored for serum sodium and volume status.

- Due to these risks, more precautionary limits to the rise of serum sodium apply in the early treatment phase. If sodium correction exceeds 6 mmol/L during the first 6 hours of administration or 8 mmol/L during the first 6-12 hours, respectively, the possibility that serum sodium correction may be overly rapid should be considered. These patients should be monitored more frequently regarding their serum sodium and administration of hypotonic fluid is recommended. In case serum sodium increases ≥12 mmol/L within 24 hours or ≥18 mmol/L within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid.

Differences in serum sodium of 4 mmol/L or less if they occurred within 4 hours or less were not taken into account.

Supplemental Table S1. Summary of thresholds used to define rapid correction of hyponatremia and the extrapolation used for measures between defined timelines

Threshold for serum sodium increase from SmPC	Time interval between 2 tests (hours)	Extrapolation used for time interval between defined values
6 mmol/L at 6 hours	$4 < T < 6$ hours	$Na/T \geq 1$
8 mmol/L at 12 hours 12 mmol/L at 24 hours	$6 \leq T < 24$ hours	$Na/([T/3] + 4) \geq 1$
18 mmol/L at 48 hours	$24 \leq T \leq 72$ hours	$Na/([T/4] + 6) \geq 1$

Na, sodium; SmPC, Summary of Product Characteristics; T, time in hours between the predose and postdose tests.

Patient disposition

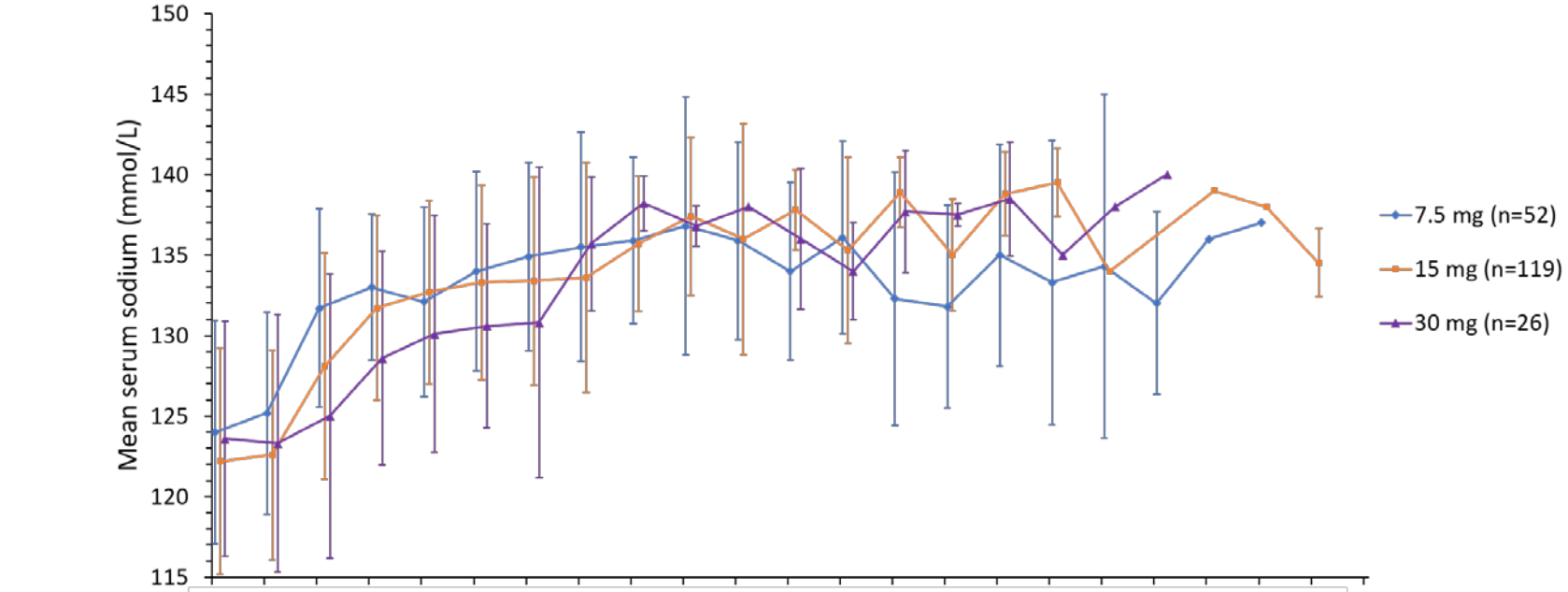
Supplemental Table S2. Patient disposition and reasons for discontinuation

n (%)	Population (N=252)
Total number of enrollment periods	271
Patients with >1 enrollment period	18
Completed treatment[a]	41 (15.1)
Discontinued treatment	176 (64.9)
Lack of efficacy	5 (1.8)
Adverse event	5 (1.8)
Patient withdrew consent	3 (1.1)
Patient lost to follow-up	31 (11.4)
Patient passed away	47 (17.3)
Discretion of the investigator	21 (7.7)
Other	64 (23.6)
Condition resolved[a]	3 (1.1)
Discretion of the patient	1 (0.4)
Disease progression	5 (18.0)
General practitioner decision	7 (2.6)
Lack of follow-up	2 (0.7)
N/A study completed	1 (0.4)
Non-compliance	2 (0.7)
Other	5 (1.8)
Other treatment	1 (0.4)
Other: N/A	1 (0.4)
Physician decision	5 (1.8)
Physician decision (discretion of other physician)	1 (0.4)
Serum sodium normalized[a]	16 (5.9)
Unknown	14 (5.2)

[a]The category "Completed treatment" in principle includes states of "Condition resolved" and "Serum sodium normalized." In some cases, however, the reporter entered corresponding free text, which is the reason for the presence of the categories "Condition resolved" and "Serum sodium normalized" in this table.

Serum sodium over time

Supplemental Figure S1. Mean (SD) serum sodium (mmol/L) in patients grouped by stable daily tolvaptan dose received



Number of evaluable subjects	BSL	D1	D2	D4	D7	W2	W4	M2	M4	M6	M8	M10	M12	M14	M16	M18	M20	M22	M24	M26	M28	M30
	Time of assessment																					
7.5 mg	44	45	41	35	22	29	17	21	11	9	8	5	8	4	4	5	4	3	2	1	1	0
15 mg	97	104	95	105	75	77	40	35	16	13	11	6	7	7	7	5	2	1	0	1	1	2
30 mg	24	25	21	24	21	21	16	12	6	4	1	3	3	3	2	2	1	1	1	0	0	0

Patients who did not enter a stable treatment phase were grouped according to their most used dose. Data are not shown for patients who received tolvaptan 45 mg/day (n=1) or 60 mg/day (n=1) as a stable dose, given the small number of patients in each treatment group.

BSL, baseline; D, day; M, month; SD, standard deviation; W, week.

Treatment-emergent adverse events by concomitant medication use and timing of event in relation to concomitant medication use

Supplemental Table S3. Patients with treatment-emergent adverse events by prior or concomitant use of cytochrome P450 3A4 inhibitors (system organ classes with ≥10% of patients of any subgroup reporting an event in the system organ class are shown)

	TEAEs With CYP3A4 Administration [N=98]		TEAEs Without CYP3A4 Administration [N=154]
	TEAEs During Concomitant Use	TEAEs Not During Concomitant Use	
Patients with any adverse events	n=72	n=43	n=93
Blood and lymphatic system disorders	12 (12.2%)	8 (8.2%)	5 (3.2%)
Gastrointestinal disorders	26 (26.5%)	20 (20.4%)	25 (16.2%)
General disorders and administration site conditions	21 (21.4%)	15 (15.3%)	24 (15.6%)
Infections and infestations	24 (24.5%)	15 (15.3%)	19 (12.3%)
Investigations	14 (14.3%)	12 (12.2%)	9 (5.8%)
Metabolism and nutrition disorders	17 (17.3%)	12 (12.2%)	17 (11.0%)
Musculoskeletal and connective tissue disorders	12 (12.2%)	6 (6.1%)	1 (0.6%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	11 (11.2%)	10 (10.2%)	22 (14.3%)
Nervous system disorders	10 (10.2%)	7 (7.1%)	16 (10.4%)
Psychiatric disorders	12 (12.2%)	15 (15.3%)	15 (9.7%)
Respiratory, thoracic, and mediastinal disorders	17 (17.3%)	15 (15.3%)	13 (8.4%)
Surgical and medical procedures	13 (13.3%)	6 (6.1%)	31 (20.1%)

CYP3A4, cytochrome P450 3A4 inhibitor; TEAE, treatment-emergent adverse event.

Supplemental Table S4. Patients with treatment-emergent adverse events by prior or concomitant use of cytochrome P450 3A4 inducers (system organ classes with ≥10% of patients of any subgroup reporting an event in the system organ class are shown)

	TEAEs With CYP3A4 Administration [N=59]		TEAEs Without CYP3A4 Administration [N=193]
	TEAEs During Concomitant Use	TEAEs Not During Concomitant Use	
Patients with any adverse events	n=34	n=30	n=126
Blood and lymphatic system disorders	5 (8.5%)	6 (10.2%)	12 (6.2%)
Gastrointestinal disorders	16 (27.1%)	13 (22.0%)	40 (20.7%)
General disorders and administration site conditions	15 (25.4%)	9 (15.3%)	34 (17.6%)
Infections and infestations	10 (16.9%)	11 (18.6%)	36 (18.7%)
Investigations	9 (15.3%)	4 (6.8%)	18 (9.3%)
Metabolism and nutrition disorders	13 (22.0%)	6 (10.2%)	26 (13.5%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	5 (8.5%)	12 (20.3%)	24 (12.4%)
Nervous system disorders	12 (20.3%)	5 (8.5%)	16 (8.3%)
Psychiatric disorders	9 (15.3%)	7 (11.9%)	24 (12.4%)
Respiratory, thoracic, and mediastinal disorders	10 (16.9%)	8 (13.6%)	25 (13.0%)
Surgical and medical procedures	12 (20.3%)	6 (10.2%)	33 (17.1%)

CYP3A4, cytochrome P450 3A4 inducer; TEAE, treatment-emergent adverse event.

Supplemental Table S5. Patients with treatment-emergent adverse events by prior or concomitant use of serum potassium concentration increasing substances (system organ classes with ≥10% of patients of any subgroup reporting an event in the system organ class are shown)

	TEAEs With Serum Potassium Concentration Increasing Substances [N=43]		TEAEs Without Serum Potassium Concentration Increasing Substances [N=209]
	TEAEs During Concomitant Use	TEAEs Not During Concomitant Use	
Patients with any adverse events	n=24	n=27	n=139
Blood and lymphatic system disorders	3 (7.0%)	6 (14.0%)	15 (7.2%)
Cardiac disorders	0 (0.0%)	9 (20.9%)	9 (4.3%)
Gastrointestinal disorders	9 (20.9%)	13 (30.2%)	45 (21.5%)
General disorders and administration site conditions	9 (20.9%)	12 (27.9%)	37 (17.7%)
Infections and infestations	8 (18.6%)	12 (27.9%)	36 (16.7%)
Injury, poisoning, and procedural complications	0 (0.0%)	5 (11.6%)	8 (3.8%)
Investigations	5 (11.6%)	5 (11.6%)	20 (10.0%)
Metabolism and nutrition disorders	9 (20.9%)	9 (20.9%)	28 (13.4%)
Musculoskeletal and connective tissue disorders	2 (4.7%)	6 (14.0%)	11 (5.3%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	3 (7.0%)	11 (25.6%)	28 (13.4%)
Nervous system disorders	3 (7.0%)	6 (14.0%)	24 (11.5%)
Psychiatric disorders	3 (7.0%)	8 (18.6%)	30 (14.4%)
Respiratory, thoracic, and mediastinal disorders	3 (7.0%)	7 (16.3%)	31 (14.8%)
Surgical and medical procedures	3 (7.0%)	5 (11.6%)	41 (19.6%)
Vascular disorders	3 (7.0%)	7 (16.3%)	16 (7.7%)

TEAE, treatment-emergent adverse event.

Supplemental Table S6. Patients with treatment-emergent adverse events by prior or concomitant use of either warfarin or antiplatelet agents (system organ classes with ≥10% of patients of any subgroup reporting an event in the system organ class are shown)

	TEAEs With Either Warfarin or Antiplatelet Agents [N=83]		TEAEs Without Either Warfarin or Antiplatelet Agents [N=169]
	TEAEs During Concomitant Use	TEAEs Not During Concomitant Use	
Patients with any adverse events	n=49	n=28	n=115
Gastrointestinal disorders	16 (19.3%)	9 (10.8%)	42 (24.9%)
General disorders and administration site conditions	21 (25.3%)	8 (9.6%)	31 (18.3%)
Infections and infestations	18 (21.7%)	8 (9.6%)	32 (18.9%)
Investigations	11 (13.3%)	4 (4.8%)	17(10.1%)
Metabolism and nutrition disorders	17 (20.5%)	5 (6.0%)	22 (13.0%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	8 (9.6%)	5 (6.0%)	28 (16.6%)
Nervous system disorders	12 (14.5%)	3 (3.6%)	18 (10.7%)
Psychiatric disorders	15 (18.1%)	5 (6.0%)	21 (12.4%)
Respiratory, thoracic, and mediastinal disorders	15 (18.1%)	6 (7.2%)	22 (13.0%)
Surgical and medical procedures	8 (9.6%)	2 (2.4%)	38 (22.5%)
Vascular disorders	10 (12.0%)	4 (4.8%)	12 (7.1%)

TEAE, treatment-emergent adverse event.

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