SUPPLEMENTAL MATERIAL

A randomized trial of tenapanor and phosphate binders as a dual mechanism treatment for hyperphosphatemia in patients on maintenance dialysis (AMPLIFY)

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Supplemental Information 1. Selection of trial population

Inclusion criteria

A patient was eligible for trial participation if he/she met the following criteria:

1. Signed and dated informed consent prior to any study specific procedure.

2. Men or women aged 18 to 80 years, inclusive, at screening (visit 1).

3. Women must have been non-pregnant, non-lactating, and fulfilling one of the following.

    a. Post-menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle stimulating hormone levels in the laboratory defined post-menopausal range.

    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation.

    c. Use of acceptable contraceptive method: intrauterine device (IUD) with spermicide, a female condom with spermicide, contraceptive sponge with spermicide, an intravaginal system (e.g. NuvaRing®), a diaphragm with spermicide, a cervical cap with spermicide, or oral, implantable, transdermal or injectable contraceptives, sexual abstinence, or a sterile sexual partner from screening (visit 1) until 30 days after the last patient visit.

4. Men must have agreed to avoid fathering a child (or donating sperm), and therefore have been either sterile (documented) or agreed to use, from the time of enrollment until 30 days after end of trial, one of the following approved methods of contraception: a male condom with spermicide, a sterile sexual partner, use of an IUD with spermicide by female sexual partner, a female condom with spermicide, contraceptive sponge with spermicide, an intravaginal system (e.g. NuvaRing), a diaphragm with spermicide, a cervical cap with spermicide, or oral, implantable, transdermal, or injectable contraceptives.

5. Chronic maintenance hemodialysis three times per week for at least 3 months or chronic maintenance peritoneal dialysis for a minimum of 6 months. If the modality of dialysis had then been changed, the patient must have received the new modality of dialysis for a minimum of 1 month.

6. If receiving active vitamin D or calcimimetics, the dose should have been unchanged during the 4 weeks preceding screening (visit 1).

7. Kt/V (a measure of dialysis adequacy) ≥1.2 at most recent measurement before screening (visit 1).

8. Prescribed and taking phosphate binder medication at least three times per day. The prescribed dose should have been unchanged during the 4 weeks preceding screening (visit 1).

9. Serum phosphorus levels ≥5.5 and ≤10.0 mg/dL at screening (visit 1) and at the end of the run-in period (visit 3), analyzed at the central laboratory used in the trial.

10. Able to understand and comply with the protocol.

Exclusion criteria

A patient was not eligible for trial participation if he/she met any of the following exclusion criteria, or was discontinued at the discretion of the investigator if he/she developed any of the following medical conditions during the trial.

1. Severe hyperphosphatemia defined as having a serum phosphorus level >10.0 mg/dL on phosphate binders at any time point during routine clinical monitoring for the 3 months preceding screening (visit 1).

2. Serum/plasma parathyroid hormone >1200 pg/mL. The most recent value from the patient's medical records was used.

3. Clinical signs of hypovolemia at screening (visit 1) as judged by the investigator.

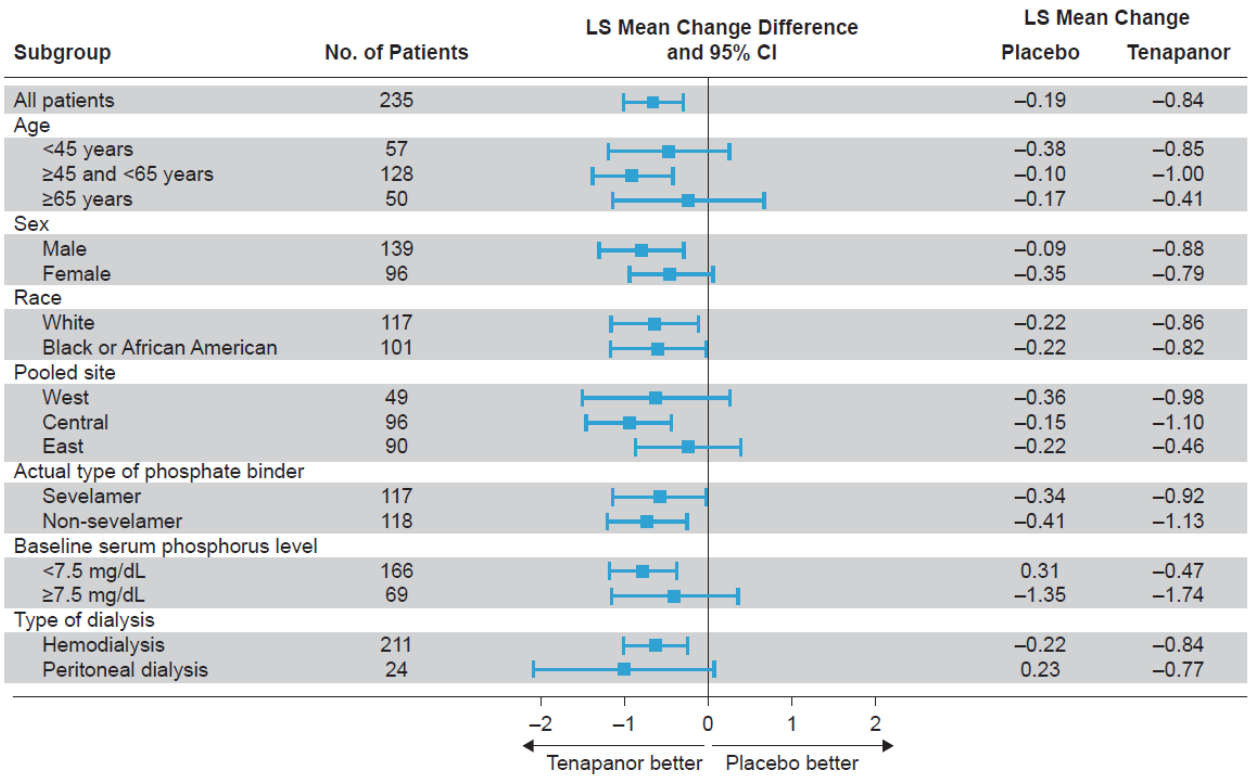
4. History of inflammatory bowel disease or irritable bowel syndrome with diarrhea.

5. Scheduled for living donor kidney transplant or planned to relocate to another center during the trial period.

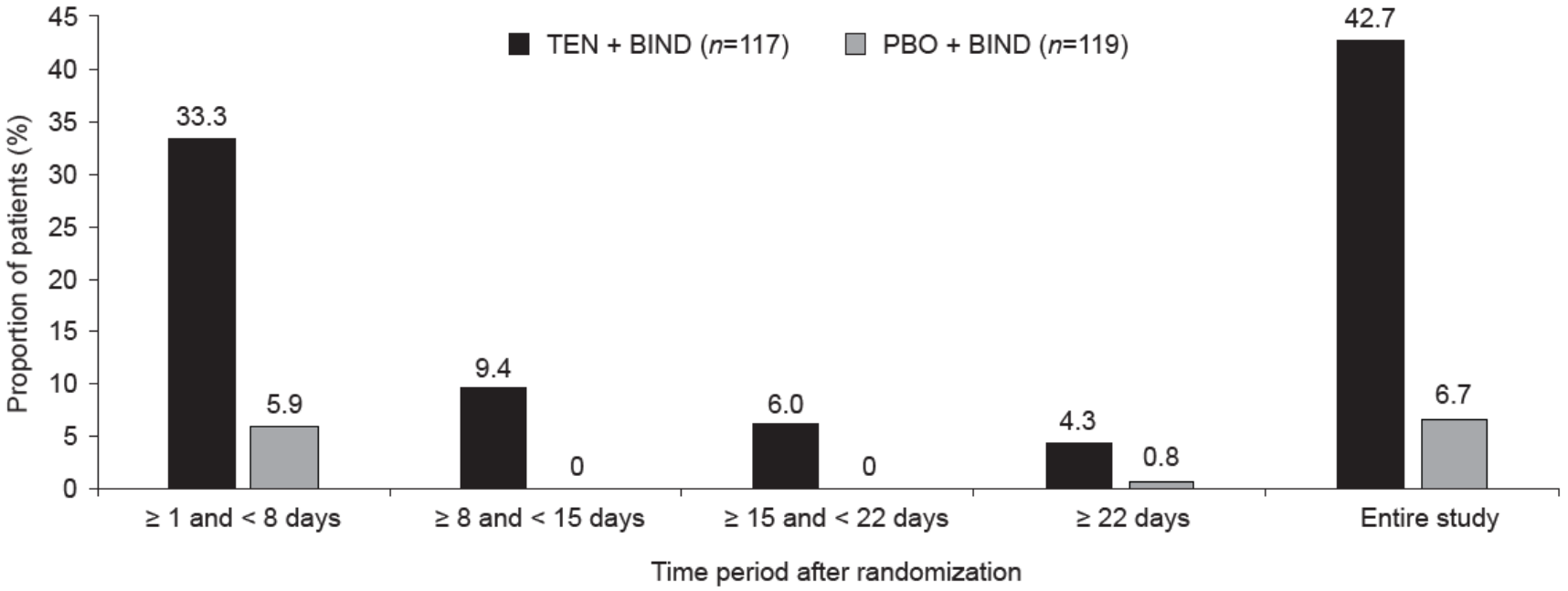
6. Use of an investigational agent within 30 days prior to screening (visit 1).

7. Involvement in the planning and/or conduct of the trial (applied to both Ardelyx/contract research organization staff and/or staff at the trial site).

8. If, in the opinion of the investigator, the patient was unable or unwilling to fulfil the requirements of the protocol or had a condition which would have rendered the results uninterpretable.



Supplemental Figure 1. Forest plot of LS mean difference in change in serum phosphorus (mg/dL) from baseline at week 4 (subgroup analysis of full analysis set). The LS means and standard errors come from a mixed-effects model for repeated measures (MMRM), with change from baseline as the dependent variable; type of binder (sevelamer or non-sevelamer), serum phosphorus level at baseline (<7.5 mg/dL or ≥7.5 mg/dL), treatment, visit (week 1 through to week 4) and treatment-by-visit interaction as fixed effects; baseline serum phosphorus level and baseline-by-visit interaction as covariates; and patient as a random effect. Baseline is defined as the measurement collected at day 1. If missing, the last measurement prior to the first dose of study drug is used. CI, confidence interval; LS, least-squares.



Supplemental Figure 2. Reports of any treatment-emergent diarrhea event. Data show the proportion of patients with any treatment-emergent diarrhea (reported as an AE by preferred term) that started during a specific time period and over the entire study. Patients with multiple reported diarrhea events may be counted in more than one time-interval, depending on the date that diarrhea was reported. AE, adverse event; BIND, binder; ITT, PBO, placebo; TEN, tenapanor.

Type of phosphate binder	**TEN + BIND (*n*=117)**	**PBO + BIND (*n*=119)**	**Overall (*N*=236)**
Sevelamer only			
n (%)	46 (39.3)	45 (37.8)	91 (38.6)
Mean daily dose	6313.0	5297.8	5811.0
Median daily dose	4800.0	4800.0	4800.0
Sevelamer + non-sevelamer			
n (%)	15 (12.8)	12 (10.1)	27 (11.4)
Mean daily dose	10334.2	10507.1	10411.0
Median daily dose	12600.0	10200.0	10350.0
Calcium acetate			
n (%)	25 (21.4)	23 (19.3)	48 (20.3)
Mean daily dose	3949.8	4610.9	4266.0
Median daily dose	2001.0	4002.0	4002.0
Calcium carbonate			
n (%)	2 (1.7)	2 (1.7)	4 (1.7)
Mean daily dose	2250.0	3300.0	2775.0
Median daily dose	2250.0	3300.0	2250.0
Ferric citrate			
n (%)	9 (7.7)	13 (10.9)	22 (9.3)
Mean daily dose	5000.0	7384.6	6409.1
Median daily dose	6000.0	8000.0	6000.0
Lanthanum carbonate			
n (%)	3 (2.6)	1 (0.8)	4 (1.7)
Mean daily dose	6500.0	3000.0	5625.0
Median daily dose	6000.0	3000.0	5250.0
Sucroferric oxyhydroxide			
n (%)	5 (4.3)	17 (14.3)	22 (9.3)
Mean daily dose	3000	2220.6	2397.7
Median daily dose	3000.0	1500.0	1875.0
Multiple non-sevelamer			
n (%)	12 (10.3)	6 (5.0)	18 (7.6)
Mean daily dose	6023.9	10001.2	7349.7
Median daily dose	6001.0	10002.0	7753.0

Supplemental Table 1. Summary of type of phosphate binder and mean daily dose in use at baseline (intent-to-treat set). Baseline was defined as the measurement collected at day 1. If this value was missing, the last measurement before the first dose of study drug was used. BIND, binder; ITT, intent-to-treat; PBO, placebo; TEN, tenapanor.