**Supplementary Appendix**

**ApoC-III reduction in subjects with moderate hypertriglyceridemia**

**and at high cardiovascular risk**

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for the Olezarsen Study Investigators

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# SITES AND INVESTIGATORS

|  |  |
| --- | --- |
| **Principal Investigatora** | **Site** |
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| Eric St. Amour | Q and T Research Outaouais Inc, Gatineau, QC |
| Karen Aspry | Miriam Hospital, Providence, RI |
| Christie Ballantyne | Center for Cardiovascular Disease Prevention, Baylor College of Medicine and DeBakey Heart and Vascular Center, Houston, TX |
| Cathy Barnes | Suncoast Clinical Research, New Port Richey, FL |
| Scott Baron | Capitol Interventional Cardiology, Carmichael, CA |
| Seth Baum | Excel Medical Clinical Trials, LLC, Boca Raton, FL |
| Harold Bays | L-MARC Research Center, Louisville, KY |
| Ravi Bhagwat | Cardiovascular Research of Northwest Indiana, LLC, Munster, IN |
| Samuel Butman | Verde Valley Medical Center, Cottonwood, AZ |
| Deanna Cheung | Long Beach Center for Clinical Research, Long Beach, CA |
| James Crenshaw | The Jackson Clinic, PA, Jackson, TN |
| Anthony DeMaria | University of California San Diego, La Jolla, CA |
| Isaac Dor | Clinical Investigation Specialists, Inc., Gurnee, IL |
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| Stephen Miller | Advanced Clinical Research Center, Murray, UT |
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| Patrick Moriarty | University of Kansas Medical Center, Kansas City, KS |
| Paul Norwood | Valley Research, Fresno, CA |
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| Jean-Claude Tardif | Montreal Heart Institute, University of Montreal |

a List includes Principal Investigators who randomized at least one patient, in alphabetical order by last name.

# METHODS

## Independent Data Safety Monitoring Board

|  |  |
| --- | --- |
| **Name** | **Address/Affiliation** |
| John L. Reid, BM, BCh (Chairperson) | University of Glasgow, Glasgow, UK (retired) |
| Richard C. Becker, MD | Cincinnati Heart, Lung, and Vascular Institute, OH |
| Jamie Dwyer, MD | Vanderbilt University Medical Center, Nashville, TN |
| Willis C. Maddrey, MD | University of Texas Southwestern Medical Center, Dallas, TX |
| Rodney Sleith, MS (Statistician) | Veristat In., Southborough, MA |

## Inclusion and Exclusion Criteria

**Inclusion Criteria:**

Patients were eligible to participate in this study if they met the following inclusion criteria:

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Males or females aged ≥18 and ≤ 80 years old at the time of informed consent
3. a. Clinical diagnosis of CVD (defined as documented coronary artery disease, stroke, or peripheral artery disease), OR

b. High risk for CVD defined as:

* Type 2 Diabetes Mellitus requiring treatment, and
* Age ≥ 50 years, and
* at least one additional CV risk factor:
  + men ≥ 55 years of age and women ≥ 65 years of age, or
  + current cigarette smoker, or stopped smoking within 3 months prior to screening, or
  + hypertension requiring antihypertensive treatment

1. Fasting serum TG ≥ 200 mg/dL (≥ 2.3 mmol/L) and ≤ 500 mg/dL (≥ 5.7 mmol/L) at Screening. If the fasting TG value at Screening is < 200 mg/dL (< 2.3 mmol/L) but ≥ 150 mg/dL (≥ 1.7 mmol/L) one additional test may have been performed in order to qualify
2. Fasting TG ≥ 200 mg/dL and ≤ 500 mg/dL at Qualification visit. If fasting TG is < 200mg/dL but ≥ 150 mg/dL one additional test may have been performed in order to qualify
3. Must have been on standard-of-care preventative therapy for their known CVD risk factors (e.g., hyperlipidemia, hypertension, diabetes)
4. Patients on the following medications must have been on a stable regimen for at least 4 weeks prior to Screening and expected to remain on a stable regimen through the end of the post-treatment follow-up period:
   1. Lipid lowering drugs (statins, ezetimibe, PCSK9 inhibitors, niacin, fibrates, fish oil or other products containing omega-3 fatty acids including over the counter preparations)
   2. Antiplatelet drugs
   3. Testosterone, estrogens, progesterone, growth hormone or progestins
5. Females: must have been non-pregnant and non-lactating and either:
   1. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy),
   2. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved),
   3. Abstinent\*, or
   4. If engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (olezarsen or placebo)

\* Abstinence was only acceptable as true abstinence, i.e., when this was in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal were not acceptable methods of contraception

1. Males must have been surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must have been using an acceptable contraceptive method from the time of signing the informed consent form until at least 13 weeks after the last dose of olezarsen

**Exclusion Criteria:**

Patients were excluded from enrolling in the study if they had any of the following exclusion criteria:

1. Within 3 months of Screening: acute coronary syndrome, major cardiac surgery, or stroke/transient ischemic attack
2. Within 3 months of Screening: coronary, carotid, or peripheral arterial revascularization, major non-cardiac surgery, or lipoprotein apheresis
3. Heart failure New York Heart Association (NYHA) class III and IV
4. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mmHg)
5. History of acute kidney injury within 12 months of Screening
6. Uncontrolled hyper or hypothyroidism
7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
8. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
10. Patients at high-risk of bleeding diathesis
11. Recent history of, or current drug or alcohol abuse
12. Hypersensitivity to the active substance or to any of the excipients
13. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:
    1. Positive test (including trace) for blood on urinalysis. In the event of a positive test, eligibility may have been confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
    2. Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg.
    3. Estimated glomerular filtration rate (GFR) ˂ 60 mL/min/1.73 m2 (as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation
    4. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN)
    5. Bilirubin > 1.2 x ULN, unless prior diagnosis and documentation of Gilbert’s syndrome in which case total bilirubin must have been ≤ 3 mg/dL
    6. Alkaline phosphatase (ALP) > 1.5 x ULN
    7. Platelet count ˂ lower limit of normal (LLN)
    8. LDL-C > 130 mg/dL (> 3.4 mmol/L)
14. Type 1 diabetes mellitus
15. Type 2 diabetes mellitus with any of the following:
    1. Newly diagnosed within 12 weeks of Screening
    2. Glycated hemoglobin (HbA1c) ≥ 9.0% at Screening
    3. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Screening [with the exception of ± 10 units of insulin])
    4. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units for insulin)
    5. Current use of glucagon-like peptide-1 (GLP-1) agonists, if patient had history of pancreatitis
16. Use of warfarin or other vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors
17. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever was longer
18. Treatment with any non-Akcea/non-Ionis oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of Screening. Patients who previously received only 1 dose of an Ionis oligonucleotide as part of a clinical study may have been included as long as ≥ 4 months had elapsed since dosing
19. Body mass index (BMI) > 40 kg/m2
20. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening
21. Unwillingness to comply with study procedures, including follow-up, as specified by the protocol, or unwillingness to cooperate fully with the Investigator
22. Had any other conditions, which, in the opinion of the Investigator or Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the Study

# Statistical analysis

**Power Calculations:**

***Efficacy***

Based upon prior clinical trial experience with olezarsen (formerly AKCEA-APOCIII-LRx), it was estimated that the standard deviation (SD) of the percent change in TG was approximately 25%. With 17 patients in each olezarsen treatment group and 17 in the placebo group there would be approximately 80% power to detect as little as 25% difference in percent change in TG levels between the olezarsen treatment groups and placebo group at an alpha level of 0.05, assuming 35% reduction in the olezarsen patients and 10% reduction in the placebo patients. Therefore, approximately 100 patients (20 patients in each of the 4 olezarsen treatment groups and 20 patients in the placebo group) were to be enrolled.

***Safety***

Based upon prior clinical trial experience with Ionis ASOs, assuming the incidence rate of platelet count below LLN in placebo treated patients is 1.9%, in the olezarsen treated patients is 3.8%, twice the incidence rate observed in placebo, with 80 patients treated with olezarsen (20 patients in each olezarsen treatment group), there would be at least 80% power to detect at least 1 event.

Therefore, a total of approximately 100 patients (25 patients per cohort, including 20 patients per cohort treated with olezarsen) were to be randomized 4:1 to receive olezarsen or placebo.

# Safety Monitoring and Stopping Rules for Platelet Count, Liver, and Renal Function

Confirmation Guidance: At any time during the study (treatment or post-treatment follow-up periods), the clinical laboratory results meeting any of the safety monitoring criteria **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens prior to administering the next dose of Study Drug. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection).

***Liver Chemistry Tests***

Liver chemistry tests were monitored every 14 days (±2 days) during the first 3-months of the study treatment, and monthly thereafter during the Treatment Period, and at Week 4, 8 and 13 of the Follow-Up Period. In the event of appearance of symptoms or signs of hepatic injury liver enzymes and bilirubin should had been tested as soon as possible, testing at a local lab was permissible.

Lab alerts for abnormal liver chemistry tests (set to anticipate the risk of a combined elevation of aminotransferases and bilirubin) were issued for:

1) ALT or AST > 3 x ULN;

2) ALT or AST > 2 x Baseline;

3) Total bilirubin > ULN;

4) ALP >ULN.

All these lab alerts must had been promptly reviewed by the Investigator (within 48 hours of receipt) and Medical Monitors (within 24 hours of receipt) to ensure that the result had not met the stopping rules.

For patients with confirmed ALT or AST levels > 3 x ULN, the following evaluations should had been performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases

2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets

3. Obtain a history of exposure to environmental chemical agents and travel

4. Serology for viral hepatitis (hepatitis A virus [HAV] immunoglobulin M [IgM], hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV] antibody, Cytomegalovirus [CMV] IgM, and EBV antibody panel)

5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Dosing of a patient with Study Drug had to be stopped permanently in the event of confirmed laboratory results meeting any of the following criteria:

1. ALT or AST > 8 x ULN, which is confirmed

2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks

3. ALT or AST > 3 x ULN (or the greater of 2 x Baseline value or 3 x ULN if the Baseline value was > ULN), which is confirmed and total bilirubin > 2 x ULN or INR > 1.5

4. ALT or AST > 3 x ULN (or the greater of 2 x Baseline value or 3 x ULN if the Baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation/injury

***Renal Function***

Renal function tests were monitored every 14 days (±2 days) during the first 3-months of the study treatment, and monthly thereafter during the Treatment Period, and at Week 4, 8 and 13 of the Follow-Up Period. They included serum creatinine and cystatin-C, extended urinalysis with urine/protein creatinine ratio (UPCR), urine/albumin creatinine ratio (UACR), and microscopy examination for urine red blood cells (RBCs), and biomarkers of acute renal injury. In the event of appearance of symptoms or signs consistent with renal dysfunction, renal function should had been tested as soon as possible, testing at a local lab was permissible.

Lab alerts for abnormal renal tests (set to anticipate and prevent the risk of a medically significant change in renal function while receiving Study Drug) were issued for:

1. Estimated GFR (eGFR) (by CKD-EPI formula) decrease from Baseline > 25%,
2. UACR > 250 mg/g,
3. UPCR > 500 mg/g,
4. Increase in serum creatinine from Baseline > 0.3 mg/dL,

All these lab alerts must had been promptly reviewed by the Investigator (within 48 hours of receipt) and Medical Monitors (within 24 hours of receipt) to ensure that the result had not met the stopping rules.

In the event that any of the renal monitoring rules above were met, treatment should had been immediately interrupted and the abnormal result should had been confirmed as soon as possible, but no later than 7 days after the initial event. In addition, upon consultation with the Study Medical Monitor, site had to obtain any additional lab assessments necessary to determine any alternative etiologies that might had accounted for the abnormal result. If results from additional testing confirmed the initial abnormal lab result, future treatment of the patient was determined per the guidelines below:

* An alternative etiology was identified that might accounted for abnormal results:
  + Patient had treatment interrupted until either:
    - Lab values have returned to baseline, and/or
    - Alternative etiology had resolved/recovered, AND
    - Study Medical Monitor had approved treatment to resume
* An alternative etiology was not identified that might accounted for abnormal results:
  + Patient was permanently withdrawn from treatment

***Platelet Count***

Hematology labs should had been sent in parallel to the central and local laboratory for analysis.

Platelet counts were monitored every 14 days (±2 days) for the duration of the Treatment Period. During the Follow-up period platelets were monitored every 2 weeks for the first 6 weeks and then at Week 8 and 13 weeks post last dose. Patients must not receive Study Drug without an interpretable platelet count result in the prior 14 days.

All platelet count results must had been reviewed promptly (within 48 hours of receipt) by the Investigator or the designee and Medical Monitors to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose interruption rule of 75,000/mm3.

Lab alerts related to platelet monitoring/stopping rules were issued when:

1) platelet counts are < 140,000 mm3,

2) platelet count is ≥ 30% decreased from Baseline, or

3) the hematology sample is unreportable.

All lab alerts were reviewed promptly by the Medical Monitor, and instructions are communicated to the Investigator and the study personnel within 24 hours of receiving an actionable lab alert.

In the event of a platelet count ˂ 140,000/mm3 platelet count had to be monitored weekly until the platelet count returned to the normal range (≥140,000/mm3) for 2 successive values. In the event of a platelet count ˂ 100,000/mm3 and ≥ 75,000/mm3 dose had to be permanently reduced to half dose.

In the event of a platelet count ˂ 75,000/mm3 and ≥ 50,000/mm3, dosing of a patient with Study Drug had to be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm3. If dosing were to continue, it must had been at a reduced dose. The suitability of the patient for continued dosing were to be determined by the Investigator in consultation with the Study Medical Monitor and were to be based on factors such as the original rate of decline in the patient’s platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count after interruption of dosing. If, after reintroduction of Study Drug, the platelet count again falls below 75,000/mm3, then dosing of the patient with Study Drug were to be stopped permanently.

Dosing of a patient with Study Drug had to be stopped permanently in the event of any platelet count < 50,000/mm3, or a platelet count less than 75,000/mm3 that occurred while the patient was already on a reduced dose. Platelet count had to be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Any case of a platelet count reduction to levels below 50,000/mm3 was considered an adverse event of special interest and had to be reported in an expedited fashion to the Sponsor.

# SUPPLEMENTARY FIGURES

## Figure S1. Study Design



Primary endpoint was the percent change from baseline to the primary analysis time point of 25-27 in fasting TG.

## Figure S2. Consort Diagram of Patient Recruitment

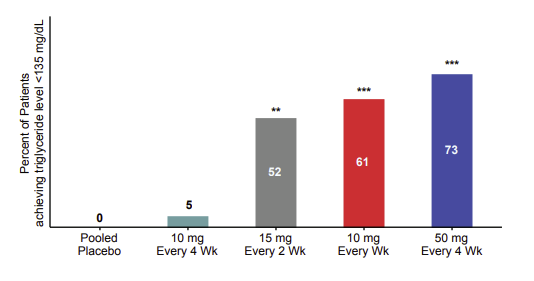


AE, adverse event; Q4W, every 4 weeks; Q2W, every 2 weeks; QW, every week. Each patient may have multiple reasons for failing screening.

aThe three most common reasons for patient ineligibility included failing to meet inclusion 4 (low TG at screening) = 171, and meeting exclusion criteria 13b (high UPCR) = 47 and 13c (low eGFR) = 40, see Table S1 for other reasons of patient ineligibility.

bReasons for withdrawal of consent included lost interest, frequent study visits or did not have time to participate.

**Figure S3. Percent of Patients Achieving Fasting Triglyceride Levels <135 mg/dL (B) at the Primary Analysis Timepoint (PAT).**



\*\* p-value <0.01; \*\*\* p-value <0.001

## Table S1. Reasons for Patient Ineligibility

|  |  |
| --- | --- |
| **Reasons for patient ineligibility** | **Number of Patients failing criteria\*** |
| ***Inclusion Criteria not met:*** |  |
| 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements | 1 |
| 3a. Clinical diagnosis of CVD (defined as documented coronary artery disease, stroke, or peripheral artery disease)  b. High risk for CVD | 5 |
|  |  |
| 4. Fasting serum TG ≥ 200 mg/dL (≥ 2.3 mmol/L) and ≤ 500 mg/dL (≥  5.7 mmol/L) at Screening. | 171 |
| 5. Fasting TG ≥ 200 mg/dL and ≤ 500 mg/dL at Qualification visit. | 34 |
| 7. Patients on the following medications must be on a stable regimen for  at least 4 weeks prior to Screening and expected to remain on a stable  regimen through the end of the post-treatment follow-up period:  a. Lipid lowering drugs (statins, ezetimibe, PCSK9 inhibitors, niacin, fibrates, fish oil or other products containing omega-3 fatty acids including OTC preparations)  b. Antiplatelet drugs  c. Testosterone, estrogens, progesterone, growth hormone or progestins | 10 |
| 8. Females must be non-pregnant and non-lactating and agree to contraception if they are of child bearing potential | 1 |
| ***Exclusion Criteria met:*** |  |
| 4. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg) | 3 |
|  |  |
| 6. Uncontrolled hyper or hypothyroidism | 1 |
| 7. Active infection requiring systemic antiviral or antimicrobial therapy  that will not be completed prior to Study Day 1 | 1 |
| 8. Known history of or positive test for human immunodeficiency virus  (HIV), hepatitis C or chronic hepatitis B | 5 |
| 9. Malignancy within 5 years, except for basal or squamous cell  carcinoma of the skin or carcinoma in situ of the cervix that has been  successfully treated | 1 |
| 13a. Positive test (including trace) for blood on urinalysis. | 19 |
| 13b.Urine protein/creatinine ratio (UPCR) ≥ 0.25 mg/mg. | 47 |
| 13c. Estimated GFR ˂ 60 mL/min/1.73 m2 (as determined by the CKD-  EPI Equation) | 40 |
| 13d. ALT or AST > 2 x ULN | 4 |
| 13e. Bilirubin > 1.2 x ULN, unless prior diagnosis and documentation of Gilbert’s syndrome in which case total bilirubin must be ≤ 3 mg/dL | 3 |
| 13f. | 2 |
| 13g. Platelet count ˂ LLN | 7 |
| 13h. LDL-C > 130 mg/dL (> 3.4 mmol/L) | 13 |
| 15a. Newly diagnosed Type 2 diabetes mellitus within 12 weeks of  Screening | 1 |
| 15b. HbA1c ≥ 9.0% at Screening | 8 |
| 15c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Screening [with the exception of ± 10 units of insulin]) | 3 |
| 16. Use of warfarin or other vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors | 1 |
| 19. BMI > 40 kg/m2 | 7 |
| 20. Blood donation of 50-499 mL within 30 days of Screening or of > 499 mL within 8 weeks of Screening | 1 |
| 21. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator | 4 |
| 22. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the Study | 5 |

**Table S2. Exploratory Endpoints. Percent Change from Baseline to the Primary Analysis Timepoint in Lipoprotein(a) and Angiopoietin-like 3.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Pooled Placebo (N=24)** | **APOCIII-LRX** | | | |
| **10 mg**  **every 4 Wk (N=22)** | **15 mg**  **every 2 Wk (N=23)** | **10 mg**  **every Wk (N=23)** | **50 mg**  **every 4 Wk**  **(N=22)** |
| **Lipoprotein(a)**  n  PAT/baseline, LSM (95% CI)  % Change from baseline  PAT/baseline, LSM (95% CI) vs placebo  % Change from baseline vs placebo  P- value | 20  0.99 (0.86, 1.13)  -1% | 18  0.89 (0.76, 1.03)  -11%  0.90 (0.73, 1.10)  -10%  0.2981 | 19  0.98 (0.85, 1.12)  -2%  0.99 (0.81, 1.21)  -1%  0.9238 | 18  1.22 (1.05, 1.41)  +22%  1.23 (1.01, 1.51)  +23%  0.0396 | 21  1.00 (0.87, 1.14)  0%  1.01 (0.83, 1.23)  +1%  0.9099 |
| **Angiopoietin-like 3**  n  PAT/baseline, LSM (95% CI)  % Change from baseline  PAT/baseline, LSM (95% CI) vs placebo  % Change from baseline vs placebo  P- value | 20  1.02 (0.92, 1.13)  +2% | 18  1.08 (0.97, 1.20)  +8%  1.06 (0.91, 1.22)  +6%  0.4533 | 19  1.06 (0.95, 1.17)  +6%  1.03 (0.89, 1.20)  +3%  0.6627 | 18  1.00 (0.90, 1.12)  0%  0.98 (0.85, 1.14)  -2%  0.8112 | 21  1.01 (0.92, 1.12)  +1%  0.99 (0.86, 1.14)  -1%  0.8831 |

CI denotes confidence interval, LSM least squares mean, PAT primary analysis timepoint.