**Supplementary Material**

**SUPPLEMENTARY APPENDIX 1**

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## SUPPLEMENTAL METHODS

### Eligibility criteria

*Inclusion criteria*

1. End-stage renal disease maintained on outpatient hemodialysis at a healthcare center for > 3 months from Screening with hemodialysis using heparin (unfractionated heparin or low-molecular weight heparin) 3 times per week for a minimum of 3 hours per dialysis session and planned to continue this throughout the study.

2. Males or females 18 to 80 years of age at the time of informed consent.

3. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), postmenopausal (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 FSH levels in the postmenopausal range for the laboratory involved), abstinent, or if engaged in sexual relations of childbearing potential, subject was using an acceptable contraceptive method (specified in the protocol) from the time of signing the informed consent form until at least 84 days (approximately 5 half-lives of ISIS 416858) after the last dose of Study Drug.

   Males: Surgically sterile, abstinent or if engaged in sexual relations with a female of childbearing potential, subject was utilizing an acceptable contraceptive method (specified in the protocol) from the time of signing the informed consent form until at least 84 days (approximately 5 half-lives of ISIS 416858) after the last dose of Study Drug.

4. Must have given written informed consent (signed and dated) and any authorizations required by local law and have been able to comply with all study requirements.

*Exclusion criteria*

1. Documented thrombotic event (acute coronary syndrome, stroke or transient ischemic attack, venous thromboembolic event) in the past 3 months.

2. Active bleeding within the past 3 months from Screening or documented bleeding diathesis (history of bleeding disorder) or screening values of:

   - Platelet count < 150,000 cells/mm3
   - International normalized ratio (INR) > 1.4
   - Activated partial thromboplastin time (aPTT) > upper limit of normal (ULN)

3. Abnormal liver function at Screening:

   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x ULN
   - Total bilirubin > ULN

4. Active infection requiring systemic antiviral or antimicrobial therapy that would not have been completed prior to Study Day 1.

5. Attending nephrologist answered “no” to the question, “Would you be surprised if this patient died in the next year?”

6. Within 6 months prior to screening, had any of the following:

- More than 3 episodes of severe hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
- One (1) event of hypoglycemia in which the subject required hospitalization

7. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C, or chronic hepatitis B.

8. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever was longer.

9. Any history of previous treatment with an oligonucleotide (including small interfering ribonucleic acid [siRNA]).

10. Planned major surgery in the next 6 months (e.g., renal transplant surgery).

11. Recent history of, or current drug or alcohol abuse.

12. Concomitant medication restrictions: Concomitant use of anticoagulant/antiplatelet agents (e.g., warfarin, dabigatran, rivaroxaban, clopidogrel) that may have affected coagulation (except low-dose aspirin [≤ 100 mg/day] during treatment and post-treatment evaluation periods was not allowed. No allowed medications were to be administered within 1 hour of Study Drug administration.

13. Uncontrolled hypertension as judged by the Investigator. Subjects with a pre- or post dialysis blood pressure (BP) that was > 160 mmHg on at least 3 of the last 5 dialysis treatments were to be discussed with the Medical Monitor.

14. Had any other conditions that, in the opinion of the Investigator or Sponsor, would have made the subject unsuitable for inclusion (for example, atrial fibrillation), or could have interfered with the subject participating in or completing the study.

**SUPPLEMENTARY TABLES**

**Table S1.** Clotting assessment scale

| **Inspection site** | **Category 1** | **Category 2** | **Category 3** | **Category 4** |
|---|---|---|---|---|
| Air Trap | No clotting | Fibrinous ring with no clot formation on venous chamber filter | Clot formation on venous chamber | Coagulated system (treatment cannot continue without new setup) |
| Dialyzer | Clean dialyzer | Blood stripes affecting less than 5% of the fibers seen at the surface of the dialyzer | Blood stripes affecting 5% or more of the fibers seen at the surface of the dialyzer | Coagulated filter |

Overall score is the highest of the individual component scores

**Table S2.** Summary of plasma PK parameters of IONIS-FXI$_{Rx}$ following dose on day 1 (after the end of dialysis) and day 29 (prior to the start of dialysis) in ESRD subjects (PK cohort)

| Cohort | Dose (mg) | Study Day | N | $C_{max}$ (µg/mL) | $T_{max}$ (h) | $AUC_{0-3h}$ (h*µg /mL) | $AUC_{0-4h}$ (h*µg /mL) | $AUC_{last}$[a] (h*µg /mL) |
|---|---|---|---|---|---|---|---|---|
| PK | 300 | 1 | 6 | 11.0 (50.9) | 6.03 (2.98, 10.0) | 15.3 (65.6) | 24.7 (61.0) | 142 (39.7) |
| | | 29 | 5b | 9.36 (59.2) | 5.97 (4.00, 9.95) | 12.4 (50.1) | 20.3 (54.5) | 136 (45.6) |

Data are presented as geometric mean (geometric %CV), except $T_{max}$, which is presented as median (range).

N = Number of subjects

a $T_{last}$ = 23.9 to 24.4 h for PK cohort. $AUC_{last}$ is equivalent to $AUC_{0-24hr}$ as the nominal $T_{last}$ = 24 h.

b One (1) subject experienced a non-Study Drug-related SAE and could not participate in the Day 29 dosing and PK collection.

**Table S3.** IONIS-FXI$_{Rx}$ $C_{max}$ for repeated doses of 200 mg and 300 mg twice weekly for 15 days then weekly for 78 days

| **Dose (mg)** | **Study Day** | **N** | **$C_{max}$ (µg/mL)** | **$t_{1/2\lambda z}$ (Day)** |
|---|---|---|---|---|
| 200 | 1 | 14 | 8.24 (42.0) | NA |
| | 78 | 12 | 10.3 (36.8) | 16.9 (39.9) |
| 300 | 1 | 13 | 14.3 (46.5) | NA |
| | 78 | 10 | 12.3 (41.1) | 13.1 (35.1) |

Data are presented as geometric mean (geometric % CV)

**SUPPLEMENTARY FIGURES**

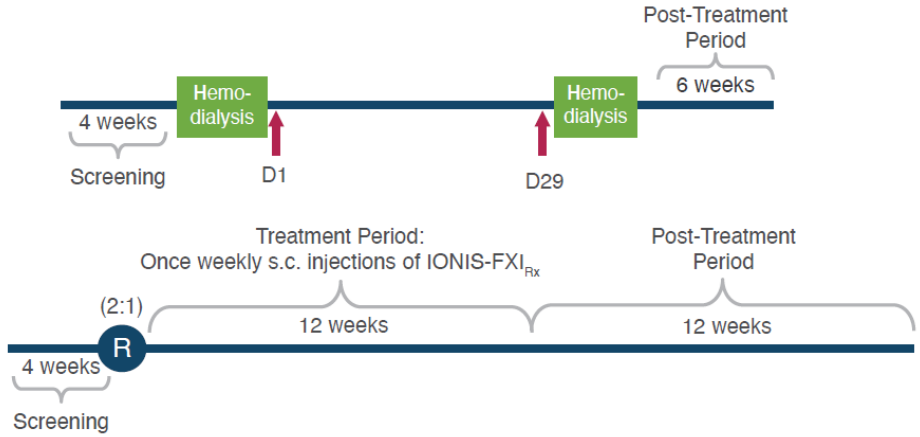
**Figure S1.** Study design

**PK Cohort**

| Dose | N |
|---|---|
| 300 mg | 6 |

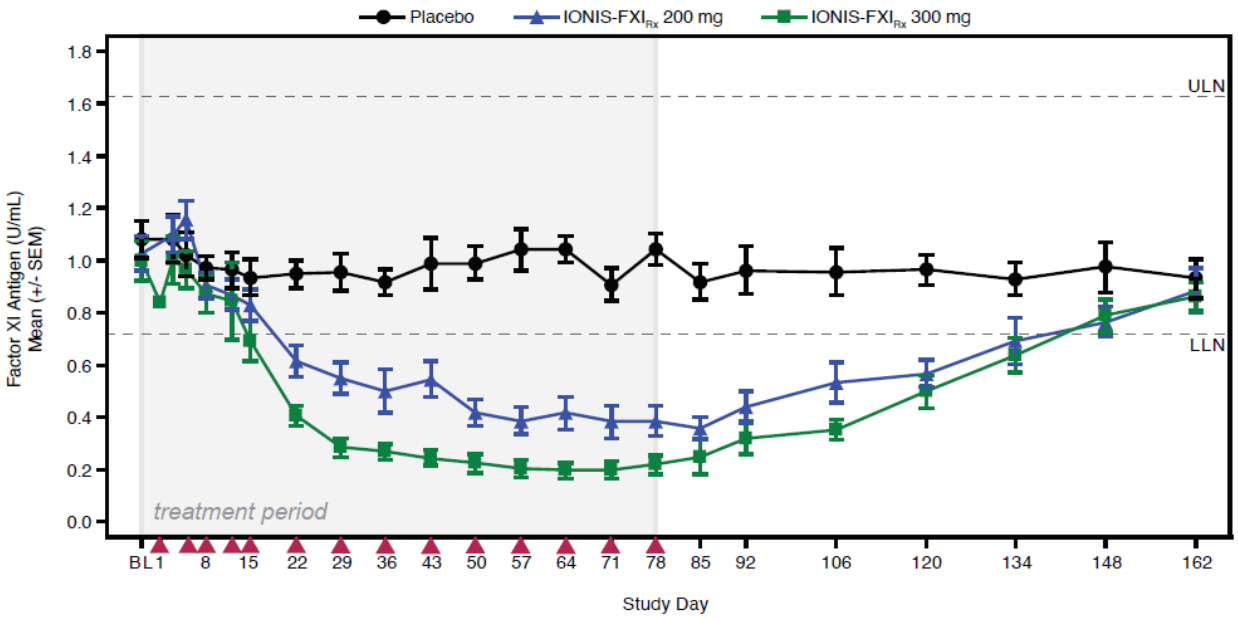
**Cohort A and B**

| Dose | N |
|---|---|
| 200 mg | 13 |
| 300 mg | 15 |
| Placebo | 15 |



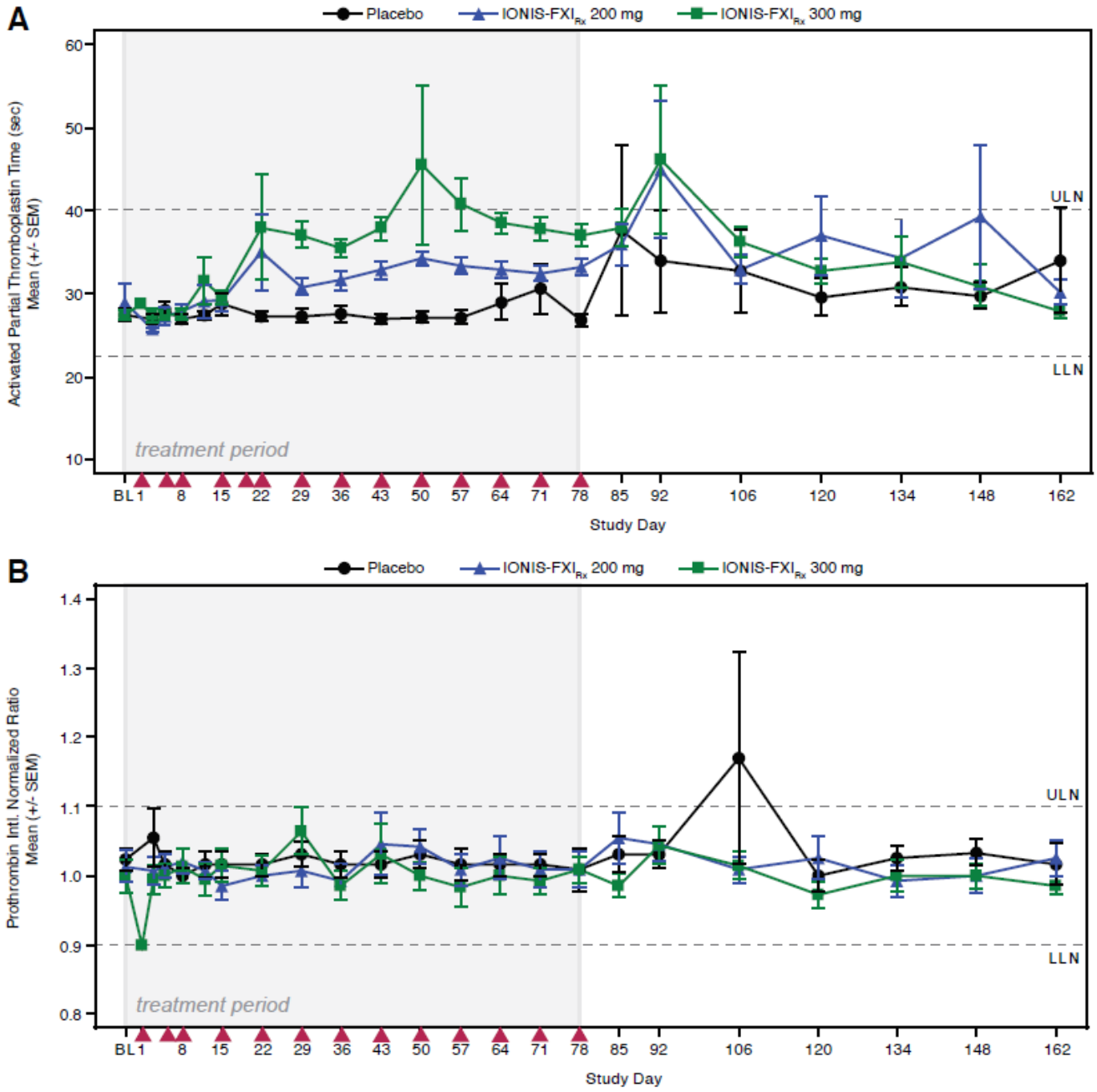

Dosing for the PK cohort occurred on day 1 (D1) and day 29 (D29). Dosing in Cohort A and B occurred twice weekly for weeks 1 and 2, then weekly to week 12.

**Figure S2.** Effect of IONIS-FXI$_{Rx}$ 200 mg and 300 mg on FXI antigen compared to placebo during the 78-day treatment period and subsequent 85-day washout period




Points represent mean and whiskers represent SEM (ITT population). Red arrowheads indicate dosing day.

**Figure S3.** Mean (± SEM) of (A) activated partial thromboplastin time (aPTT) and (B) international normalized ratio (INR) over 78-day treatment and 85-day washout of IONIS-FXI$_{Rx}$ (ITT population)




Red arrowheads indicate dosing day.

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 3 |
| | 2b | Specific objectives or hypotheses | 3 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 4 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | N/A |
| Participants | 4a | Eligibility criteria for participants | 4 |
| | 4b | Settings and locations where the data were collected | 4 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 4-5 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 5-6 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | N/A |
| Sample size | 7a | How sample size was determined | 6 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | N/A |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 4 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 4 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 4 |

| | | | |
|---|---|---|---|
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 4 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | 4-5 |
| | 11b | If relevant, description of the similarity of interventions | 4 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 6-7 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 7 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | 7 and Fig 1 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | Fig 1 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 7 |
| | 14b | Why the trial ended or was stopped | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | Table 1 |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | Fig 1 legend |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | 8-10 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | N/A |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | 7 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | 9 |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 11 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 11 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 11-12 |
| **Other information** | | | |

| | | | |
|---|---|---|---|
| Registration | 23 | Registration number and name of trial registry | 1 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | 4 |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 4, 13 |