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Sparsentan for Treatment of Patients With Focal Segmental Glomerulosclerosis (FSGS): Design of the Phase 3 DUPLEX Study

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INTRODUCTION

- Sparsentan is a first-in-class, orally active, dual-acting compound combining angiotensin II type 1 (AT_1) receptor blockade with endothelin type A (ET_A) receptor antagonism in development for the treatment of primary or genetic focal segmental glomerulosclerosis (FSGS)[1,2]
- Data from the ongoing phase 2 DUET study established the antiproteinuric effect and safety profile of sparsentan (over the pooled 200, 400, and 800 mg/d dose range) in patients with FSGS
  - Combined sparsentan groups resulted in greater reduction in proteinuria versus the active control AT_1 blocker, irbesartan, 300 mg/d over an 8 week double-blind period[2]
  - At Week 8, a greater percentage of sparsentan versus irbesartan patients achieved the FSGS partial remission endpoint (FPRE), defined as urinary protein-to-creatinine ratio (UP/C) ≤1.5 g/g and a >40% reduction in UP/C from baseline[2,3]
  - Sparsentan continues to be evaluated in an open-label extension of the DUET study
- The actively enrolling phase 3 DUPLEX study will examine the long-term antiproteinuric efficacy, nephroprotective potential through slowing the decline of eGFR, and safety profile of sparsentan compared with irbesartan in patients with FSGS

OBJECTIVE

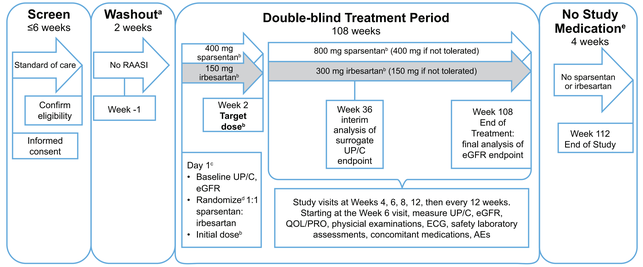
- To describe the study design and methodology of the DUPLEX phase 3 trial, including the novel approach of using FPRE as a surrogate endpoint

METHODS

Study Design

- DUPLEX (NCT03493685) is a multicenter, international, phase 3, randomized, double-blind, active-controlled study of sparsentan vs irbesartan in patients with primary or genetic FSGS (**Figure 1**)
  - Patients receiving renin-angiotensin-aldosterone system inhibitors (RAASI) will undergo a 2-week washout
  - Patients will be randomized 1:1 to sparsentan or irbesartan
  - Randomization is stratified by estimated glomerular filtration rate (eGFR) and UP/C at screening:
    - eGFR (≥30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2 for all patients)
    - UP/C (≤3.5 g/g and >3.5 g/g [patients ≥18 years of age] or ≤2 g/g and >2 g/g [patients <18 years of age])
  - Antihypertensive agents, except RAASI or endothelin inhibitors, are allowed to maintain blood pressure control
  - After a 108-week blinded treatment period, patients will undergo final on-treatment evaluations, discontinue study medication, and undergo final evaluations at Week 112 (study end)

Figure 1. DUPLEX study design



[a]For patients who are undergoing washout from RAASI. [b]Patients whose body weight is ≤50 kg at screening will receive half the otherwise specified doses of sparsentan or irbesartan (active control). Weight will be measured at each visit, and the dose increased at the Investigator's discretion if the patient's weight reaches >50 kg. [c]Day 1 events shown will occur in the order in which they are listed. [d]Randomization will be stratified by eGFR value (≥30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2 for all patients) and UP/C (≤3.5 g/g and >3.5 g/g [patients ≥18 years of age] or ≤2 g/g and >2 g/g [patients <18 years of age]) at screening. [e]Following the 108-week blinded treatment period, treatment with study medication will be discontinued. At this time, the Investigator should resume standard-of-care treatment, including treatment with RAASI (with the exception of irbesartan) provided there are no contraindications for their use. The Investigator may make additional adjustments in antihypertensive medications as clinically indicated to adequately control the patient's blood pressure.

AEs, adverse events; ARB, angiotensin receptor blocker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; PRO, patient-reported outcome; QOL, quality of life; RAASI, renin-angiotensin-aldosterone system inhibitor; UP/C, urinary protein-to-creatinine ratio.

Inclusion/Exclusion Criteria

- Key patient inclusion and exclusion criteria for enrollment in DUPLEX are shown in **Table 1**

Table 1. Key patient inclusion and exclusion criteria for DUPLEX

Key Inclusion criteria
• The patient or parent/legal guardian (as appropriate) is willing and able to provide signed informed consent, and where required, the patient is willing to provide assent, prior to any screening procedures
• The patient has biopsy-proven FSGS or documentation of a genetic mutation in a podocyte protein associated with FSGS
• *Sites within the US:* The patient is male or female aged 8 to 75 years, inclusive • *Sites outside the US:* The patient is male or female aged 18 to 75 years, inclusive
• The patient has a UP/C ≥1.5 g/g at screening
• The patient has an eGFR ≥30 mL/min/1.73 m^2 at screening
• Patients must agree to protocol-mandated and medically accepted methods of birth control
Key Exclusion Criteria
• The patient has FSGS secondary to another condition
• The patient has positive serological tests of primary or secondary glomerular injury not consistent with a diagnosis of primary or genetic FSGS
• The patient has a history of type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus
• The patient has undergone any organ transplantation, with the exception of corneal transplants, or has received certain immunosuppressive medications
• The patient has a documented history of heart failure, coronary artery disease, or cerebrovascular disease
• The patient has significant liver disease
• The patient is positive at screening for HIV or markers indicating acute or chronic hepatitis B infection or hepatitis C infection
• The patient has a history of malignancy other than adequately treated basal cell or squamous cell skin cancer or cervical carcinoma within the past 2 years
• The patient has disqualifying laboratory abnormalities during a screening
• The patient is >18 years of age with a BMI >40, or is ≤18 years of age with a BMI in the 99th percentile plus 5 units at screening
• The patient has a history of alcohol or illicit drug use disorder
• The patient has a history of serious side effect or allergic response to any angiotensin II antagonist or endothelin receptor antagonist
• The female patient is pregnant, plans to become pregnant during the course of the study, or is breastfeeding
• The male patient plans to father a child during the course of the study
• The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study, including the ability to swallow the study medication capsules whole

BMI, body mass index; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; UP/C, urinary protein-to-creatinine ratio.

Study Drug

- The treatment period includes dose titration in the first 2 weeks
  - At the Week 2 visit, patients who are able to tolerate the initial dose are prescribed the target dose (ie, sparsentan 800 mg or irbesartan 300 mg daily)
  - Patients who weigh ≤50 kg at screening receive 50% of the initial or target dose
  - Dose reductions from the target dose back to the initial dose are permitted at any time based on safety concerns

Study Measures

- Efficacy measures include UP/C and eGFR
- Safety measures include adverse events, vital signs, physical exams, body weight, electrocardiograms, peripheral edema, and clinical laboratory parameters

Data Analysis

- The study has appropriate power (≥90% power at a 2-sided α=0.05) to test the surrogate FPRE endpoint at the interim analysis and the primary eGFR endpoint at the final analysis
- Overall type-1 error at 2-sided α=0.05 is controlled using a prespecified multiple testing procedure
- The interim analysis for the surrogate endpoint after 36 weeks will be conducted by an independent statistical team (with controlled disclosure of analysis results) and the study team will remain blinded to the interim data

RESULTS

- Enrollment of approximately 300 patients globally is planned
- DUPLEX primary, surrogate, and secondary efficacy endpoints are shown in **Table 2**

Table 2. DUPLEX efficacy endpoints

Primary Efficacy Endpoint	Surrogate Efficacy Endpoint	Secondary Efficacy Endpoints
• The slope of eGFR, assessed from Week 6 to Week 108 at the final analysis	• The proportion of patients achieving a UP/C ≤1.5 g/g and a >40% reduction from baseline in UP/C (ie, FPRE[3]) at Week 36 (interim analysis)	• The percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112 • The percent change in eGFR from Week 6 to Week 108

eGFR, estimated glomerular filtration rate; FPRE, FSGS partial remission endpoint; UP/C, urinary protein-to-creatinine ratio.

- DUPLEX exploratory endpoints include:
  - Slope of eGFR assessed from Week 6 to Week 60
  - Absolute and percent change in eGFR from baseline at each visit
  - Percent change in eGFR from Week 6 at each visit
  - Proportion of patients achieving FPRE at each visit
  - Percent change in UP/C from baseline at each visit
  - Time to achieve FPRE
  - Patients reaching a confirmed 40% reduction in eGFR, ESKD, or death
  - Change from baseline in blood pressure at each visit
  - Patients undergoing initiation/intensification in immunosuppressive medication
  - Patients undergoing reduction in immunosuppressive medication
  - Change from baseline in quality of life at each visit beginning at Week 12
  - Frequency and duration of hospitalizations (any reason; kidney-related reasons)
  - Trough plasma PK concentrations
- Clinic visits during the double-blind treatment period will occur at Weeks 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, and 108 (end of treatment), with a final assessment at Week 112 (end of study) (**Table 3**)

Table 3. DUPLEX core study assessment schedule

	Screening	Washout[a]	Randomization & Blinded Treatment Period	End of Study
Visit	1	2	3 to 16[b] (EOT/ET)	17
Week	-6	-1	Day 1 to Week 108	112
Inclusion/Exclusion	●		●	
Physical examination, including peripheral edema assessment	●	●	●	●
Vital signs	●	●	●	●
Clinical laboratory assessments	●	●	●	●
12-lead electrocardiogram	●		●	
Quantitative urinalysis[c]	●		●	●
QOL[d]			●	●
Adverse event assessment	----------Continuous Monitoring----------			

[a]Patients taking RAASIs at screening (Visit 1) will complete a 2-week (14-day) washout from these medications prior to Day 1/Randomization. [b]The frequency of each assessment during the blinded treatment period varies across assessment categories. [c]Patients will collect the first morning void on 3 mornings within 5 days prior to the visit and bring them to the site visit. [d]Patients ≥18 years of age will complete the KDQOL-36 and EQ-5D-5L, and patients <18 years of age will complete the PedsQL and EQ-5D-Y.

EOT, end of treatment; EQ-5D, EuroQol 5-dimension quality of life instrument, version 5L; EQ-5D-Y, EuroQoL 5-dimension quality of life instrument, version Y; ET, early termination; KDQOL, Kidney Disease Quality of Life instrument; PedsQL, Pediatrics Quality of Life Inventory; QOL, quality of life; RAASIs, renin-angiotensin-aldosterone system inhibitors.

CONCLUSIONS

- The phase 3 DUPLEX study will enable the evaluation of the long-term antiproteinuric efficacy, nephroprotective effects, and safety of sparsentan compared with the active control irbesartan in primary or genetic FSGS
- DUPLEX also will provide valuable information on the novel approach of using FPRE as a surrogate efficacy endpoint

REFERENCES

1. Komers R, et al. *Kidney Int Rep.* 2017;2:254-264.
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3. Troost JP, et al. *Clin J Am Soc Nephrol.* 2018;13:414-421.

Disclosures

HT: Has received consultancy fees from Kaneka Inc., Otsuka, and ChemoCentryx and was previously a consultant to Genzyme and Optherion. HT is an unpaid consultant to Retrophin, Inc. and has an agreement with Goldfinch Biopharma through NYU.
JI: Is an employee of IQVIA and was hired by Retrophin, Inc. to conduct the research. She did not receive any payment or honoraria directly from Retrophin, Inc. for services rendered.
UD, AL, WR, RK: Employees of Retrophin, Inc. and may have an equity or other financial interest in Retrophin, Inc.

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