TH-PO999

Impact of Sparsentan on Quality of Life (QoL) in Focal Segmental Glomerulosclerosis (FSGS) Patients in DUET: an Interim Analysis

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Introduction

- The DUET study examines sparsentan, a novel, orally active, dual-acting, selective antagonist of the angiotensin II AT_1 receptor and the endothelin type A receptor, versus irbesartan for the treatment of primary and genetic FSGS[1,2]
  - Sparsentan (over the pooled 200, 400, and 800 mg/day dose range) resulted in greater reduction in proteinuria versus irbesartan 300 mg/day over an 8-week double-blind period[2]
  - The incidence of treatment-emergent adverse events (TEAEs) in the double-blind period was 76.7% (56/73) in the sparsentan-treated patients and 72.2% (26/36) in the irbesartan-treated patients[2]
    - Sparsentan-treated patients experienced more frequent hypotension, dizziness, edema, and gastrointestinal TEAEs
  - Sparsentan continues to be evaluated in an open-label extension (OLE) phase of the DUET study,[1,2] and based on the most recently presented 84-week interim analysis (data cut in November 2017),[3] further clinical development of sparsentan is appropriate

Objective

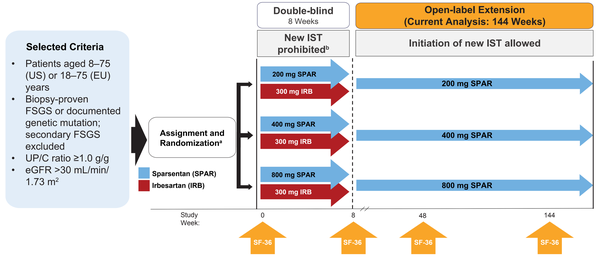
To examine the potential impact of sparsentan on quality of life (QoL) in patients with FSGS in the DUET study during both the double-blind and OLE (Weeks 48 and 144) periods

Methods

Study Design

- DUET (NCT01613118) is a phase 2, randomized, double-blind, active-controlled study (**Figure 1**)[1,2]
- The key features of the study design have been previously published[1,2]
- The SF-36 questionnaire was administered to adults at multiple time points, including baseline and at Weeks 8, 48, and 144

Figure 1. DUET study design[1]



Note: Patients were assigned to dose cohort, then randomized to sparsentan or irbesartan within the dose cohort. Study drug was administered orally once daily. Patients who weighed ≤50 kg received half the assigned daily dose of sparsentan or irbesartan. In the OLE period, patients were placed on the sparsentan dose they would have received according to the double-blind dose group in which they were enrolled.

[a]After 2 weeks of RASI washout.

[b]If a patient was taking ISTs (except rituximab or cyclophosphamide), the dose and/or levels must have been stable for 1 month before randomization and the investigator should not have had plans to alter the regimen during the first 8 weeks of treatment, except to stabilize levels.

eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; IST, immunosuppressive therapy; OLE, open-label extension; RASI, renin-angiotensin system inhibitor; SPAR, sparsentan; UP/C, urinary protein-to-creatinine ratio.

Study Measures

- The SF-36 includes 8 scales (4 physical and 4 mental), which are aggregated into the physical component score and mental component score[4]
- Norm-based scoring was used for the SF-36 physical and mental component scores at each completion time point
  - General population norm-based scores have a mean ± standard deviation (SD) of 50 ± 10[4]
  - Changes of 2 to 4 points in the physical component score or mental component score have been reported as important changes[4]

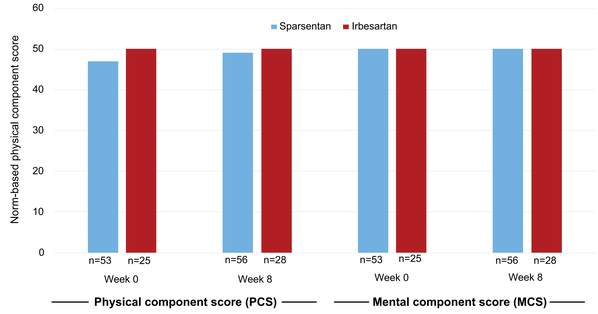
Data Analysis

- The full analysis set for the double-blind period (FAS) includes all randomized patients who received at least one dose of study drug and had at least one post-baseline efficacy evaluation
- The full analysis set for the OLE (OLE FAS) includes all patients who received open-label sparsentan and had efficacy assessments after receiving open-label sparsentan
- Cross-sectional SF-36 physical and mental component scores at baseline and Weeks 8, 48, and 144 were analyzed in adults
- Longitudinal changes from baseline in the physical and mental component scores were examined using descriptive statistics
  - Least squares mean (LSM) and standard error of the mean (SEM) for the change from baseline to Week 8
  - Mean ± SD and 95% confidence interval (CI) for the mean change from baseline to Week 48 and 144
    - OLE baseline for SPAR:SPAR was Week 0 and OLE baseline for IRB:SPAR was Week 8

Results

- The DUET study FAS consisted of 73 patients who were randomized to the sparsentan group and 36 patients who were randomized to the irbesartan group
- Patient demographics and baseline characteristics were similar between groups in the FAS[2]

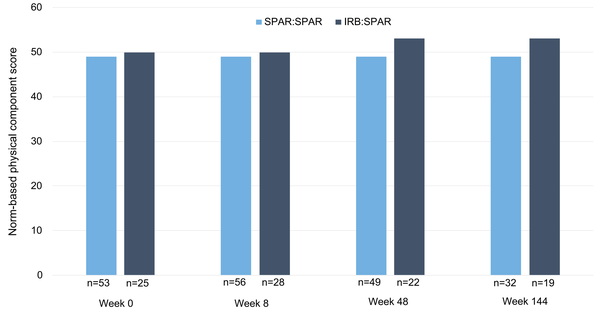
Figure 2. Cross-sectional SF-36 physical and mental component scores at baseline and Week 8 did not differ between sparsentan and irbesartan groups (FAS)



FAS, full analysis set.

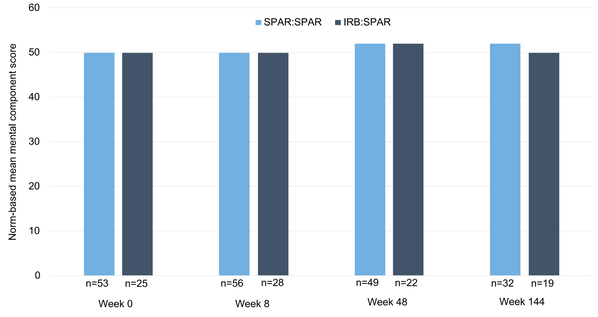
- The LSM change in component scores from baseline to Week 8 did not differ between the sparsentan and irbesartan groups
  - Physical component score LSM (SEM) change from baseline to Week 8 was -0.3 (0.9) in the sparsentan group (n=49) and 0.7 (1.2) in the irbesartan group (n=25) (*P*=0.5103)
  - Mental component score LSM (SEM) change from baseline to Week 8 was -0.1 (1.0) in the sparsentan group (n=49) and 0.2 (1.5) in the irbesartan group (n=25) (*P*=0.8725)

Figure 3. Cross-sectional mean physical component score up to Week 144 did not change (OLE FAS)



IRB:SPAR, irbesartan:sparsentan; OLE FAS, open-label extension full analysis set; SPAR:SPAR, sparsentan:sparsentan.

Figure 4. Cross-sectional mean mental component score up to Week 144 did not change (OLE FAS)



IRB:SPAR, irbesartan:sparsentan; OLE FAS, open-label extension full analysis set; SPAR:SPAR, sparsentan:sparsentan.

Table 1. Mean change from baseline in physical and mental component scores during the OLE (OLE FAS)

SF-36 Dimension	Baseline to Week 48		Baseline to Week 144	
	SPAR:SPAR (n=42)	IRB:SPAR (n=21)	SPAR:SPAR (n=29)	IRB:SPAR (n=18)
PCS Mean ± SD (95% CI)	0.0 ± 7.1 (-2.2, 2.2)	1.9 ± 6.0 (-0.8, 4.7)	1.6 ± 6.5 (-0.9, 4.0)	1.5 ± 4.9 (-1.0, 3.9)
MCS Mean ± SD (95% CI)	1.3 ± 7.2 (-1.0, 3.5)	1.5 ± 6.7 (-1.6, 4.5)	3.1 ± 8.4 (-0.1, 6.3)	-0.2 ± 10.8 (-5.6, 5.2)

OLE baseline for SPAR:SPAR was Week 0 and OLE baseline for IRB:SPAR was Week 8.

CI, confidence interval; MCS, mental component score; OLE FAS, open-label extension full analysis set; PCS, physical component score.

Conclusions

- Evaluation of QoL using the SF-36 showed that the physical and mental component scores reported by DUET patients with FSGS were higher than those previously reported by patients with steroid-resistant FSGS in the FSGS Clinical Trial (2011) and were similar to healthy subjects[5]
  - In a prior study, healthy subjects had composite physical and mental component scores (mean ± SD norm-based) of 50.0 ± 10.0, respectively, whereas patients with steroid-resistant FSGS had a composite physical component score of 44.3 ± 10.3 and a composite mental component score of 44.1 ± 12.6[5]
  - FSGS patients in the DUET study appear to have a better QoL than steroid-resistant patients previously reported in the FSGS Clinical Trial[5]
- The mean physical and mental component scores in DUET were similar in sparsentan- and irbesartan-treated patients during the double-blind period and remained stable over 2 years during the OLE period, regardless of original randomization group
- Sparsentan does not appear to have a negative effect on QoL

References

1. Komers R, et al. *Kidney Int Rep.* 2017;2:654-664.
2. Trachtman H, et al. *J Am Soc Nephrol.* 2018;29:2745-2754.
3. Hogan J, et al. Oral presentation at Kidney Week, October 23-28, 2018, San Diego, CA.
4. Finkelstein FO, et al. *Health Qual Life Outcomes.* 2018;16:111.
5. Gipson DS, et al. *Kidney Int.* 2011;79:678-685.

Disclosures

HT: Has received consultancy fees from Kaneka Inc., Otsuka, and ChemoCentryx and was previously a consultant to Genzyme and Optherion, is a consultant to Retrophin, Inc. through an agreement with NYU, and has an agreement with Goldfinch Biopharma through NYU.

JH: Has received consultancy and advisory board honoraria from Retrophin, Inc., Mallinckrodt, Aurinia Pharmaceuticals, Zyversa (Variant) Pharmaceuticals, Goldfinch Bio, Dimerix, and GSK. He is also a site principal investigator for the DUET and DUPLEX studies.

BF: Former employee of Retrophin, Inc. and may have an equity or other financial interest in Retrophin, Inc.

RK: Employee of Retrophin, Inc. and may have an equity or other financial interest in Retrophin, Inc.

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