FILSPARI® (sparsentan)
Safety in Clinical Trials

Summary

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[1,2]

Prescribing Information

- FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression[3]
- Because of the risks for hepatotoxicity and birth defects, FILSPARI is available only through a restricted program called the FILSPARI REMS[3]

Background

- The PROTECT study is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-control study of the efficacy and safety of sparsentan compared to irbesartan for the treatment of IgA nephropathy[4]
- The DUET study is a phase 2, randomized, multicenter, double-blind, active-control trial examining the safety and efficacy of sparsentan compared to irbesartan in patients with FSGS[2]
- The DUPLEX study is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial assessing the efficacy and safety of sparsentan as compared to irbesartan in 371 patients, ages 8 to 75 years, with primary and genetic FSGS[1,5]
- SPARTACUS is an open-label, multicenter, single-group phase 2 trial investigating the safety and efficacy of sparsentan in patients with IgA nephropathy at risk for disease progression despite treatment with combined RAASi and SGLT2 inhibitors[6,7]
- SPARTAN is a phase 2, open-label, single-arm trial investigating the safety, efficacy, and mechanism of action of sparsentan as first-line treatment for IgA nephropathy in newly diagnosed patients[8]
- The phase 2 EPPIK study is an open-label, single-arm, multicenter trial evaluating the safety, efficacy, and PK of liquid sparsentan in patients aged ≥1 to <18 years with FSGS or MCD and aged ≥2 to <18 years with IgAN, IgAV, or Alport syndrome[9]

Study Data

- In controlled clinical trials, sparsentan has been generally well tolerated[5,10]

Prescribing Information

- Adverse reactions reported in ≥2% in subjects treated with FILSPARI were hyperkalemia (17%), hypotension (including orthostatic hypotension) (16%), peripheral edema (16%), dizziness (16%), anemia (8%), acute kidney injury (6%), and transaminase elevations (3.5%)[3]
- Based on data from animal reproductive toxicity studies, FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy[3]
- In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the ULN have been observed in up to 3.5% of FILSPARI-treated patients, including cases confirmed with rechallenge[3]

For more information, please refer to the Prescribing Information, including Boxed Warning.

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2,11,12] Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT_1 pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.[13-15]

The PROTECT Study

The PROTECT study (NCT03762850) is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating long-term antiproteinuric and nephroprotective efficacy and safety of 400 mg of sparsentan in patients with IgA nephropathy compared to 300 mg of irbesartan.[16] The study includes 404 patients ages 18 years and older with biopsy proven IgA nephropathy who experience persistent proteinuria despite available ACEi or ARB therapy. Patients with urine protein ≥1 g/day at screening, eGFR ≥30 mL/min/1.73 m^2, SBP ≤150 mm Hg, and DBP ≤100 mm Hg were eligible.[17] The PROTECT study protocol provides for an unblinded interim analysis of at least 280 patients to be performed after 36 weeks of treatment to evaluate the primary efficacy endpoint, defined as change in proteinuria (UPCR) at Week 36 from baseline. Secondary efficacy endpoints include the rate of change in eGFR following the initiation of randomized treatment over 58-week and 110-week periods, as well as rate of change in eGFR over 52-week and 104-week periods following the first 6 weeks of randomized treatment.[4,17] The PROTECT study also examines change from baseline in UACR based on a 24-hour urine sample at Week 36, and prespecified exploratory endpoints of complete (UPE <0.3 g/day) and partial (UPE <1.0 g/day) proteinuria remission at least once at any time during the double-blind period. In addition, this study evaluates the proportion of patients in each group reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality. KF is defined as initiation of KRT or sustained eGFR value of <15 mL/min/1.73 m^2.[18] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[18,19]

The DUET Study

The DUET study (NCT01613118) is a phase 2, randomized, multicenter, double-blind, active-control trial in patients with biopsy-proven FSGS. Patients were randomized to 1 of 3 doses (200, 400, or 800 mg/day) of sparsentan or irbesartan (300 mg/day) and maintained through an 8-week double-blind phase. The primary endpoint was defined as reduction in UPCR after 8 weeks of treatment. The proportion of patients who achieved partial FSGS remission was evaluated as a secondary endpoint. Following the double-blind phase, patients had the option to continue into a 144-week OLE of treatment with sparsentan.[2]

The DUPLEX Study

The DUPLEX study (NCT03493685) is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial examining the safety and efficacy of sparsentan as compared to irbesartan in patients aged 8 to 75 years with biopsy-proven FSGS. Patients with UPCR ≥1.5 g/g at screening, eGFR ≥30 mL/min/1.73 m^2, and mean seated BP ≥100/60 mm Hg (patients ≥18 years) or above the 5th percentile for sex and height (<18 years) were eligible. After a 2-week washout period, 371 patients were randomized to receive either sparsentan or irbesartan, and subsequently dose titrated over 2 weeks to the maximum dose of either 800 mg/day sparsentan or 300 mg/day irbesartan, as tolerated.[1,5] Patients remained on maintenance doses of sparsentan or irbesartan during a 108-week double blind phase. Standard-of-care treatment, including RAASi, was resumed in Weeks 108-112. The primary efficacy endpoint was eGFR slope over 108 weeks of treatment, defined as eGFR total slope from Day 1 to Week 108 of treatment and eGFR chronic slope from Week 6 to Week 108 (following the initial acute effect of randomized treatment). The key secondary endpoint was percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112.[5] An additional interim endpoint was the proportion of patients achieving partial remission of proteinuria, defined as UPCR ≤1.5 g/g and a >40% reduction (FPRE) at Week 36. Proportion of patients achieving complete remission of proteinuria (UPCR <0.3 g/g) at any time in the double-blind period was also examined. Safety was assessed by double-blind monitoring of adverse events and safety endpoints.[1,5]

The SPARTACUS Study

The SPARTACUS study (NCT05856760) is a single-group, multicenter, open-label, exploratory phase 2 trial examining the safety and efficacy of sparsentan in adult patients with biopsy-proven IgA nephropathy at risk of disease progression despite ongoing treatment with RAASi and SGLT2 inhibitors.[7] Approximately 60 patients aged 18 years and older who are on stable doses of an ACEi/ARB and SGLT2 inhibitors will be enrolled. The primary outcome measure is change from baseline in UACR at Week 24. Secondary efficacy outcome measures include UACR <0.2 g/g at Week 24, ≥30% and ≥50% reduction from baseline in UACR at Week 24, and change from baseline in UACR, UPCR, eGFR, and BP at each study visit. Safety assessments throughout the study include TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest.[6,7,20]

The SPARTAN Study

The SPARTAN study (NCT04663204) is a phase 2, open-label, single-arm trial investigating the safety, efficacy, and mechanism of action of sparsentan as first-line treatment for IgA nephropathy in newly diagnosed patients, being conducted at 5 participating sites in the UK.[21] Patients aged ≥18 years diagnosed with biopsy-proven IgA nephropathy within 6 months of enrollment are eligible. Additional eligibility criteria include eGFR ≥30 mL/min/1.73 m^2, proteinuria ≥0.5 g/day, and no

exposure to ACEi or ARB treatment within 12 months of study screening. Sparsentan is initiated at a dose of 200 mg/day and titrated to 400 mg/day after 2 weeks. Treatment continues for 110 weeks, followed by a 4-week safety period. The primary efficacy endpoint is change in proteinuria (UPCR) from baseline at Week 36, based on a 24-hour urine sample. Secondary endpoints include complete remission of proteinuria defined as <0.3 g/day, rate of change in eGFR from Week 6 to Week 58, change in eGFR from Week 6 to Week 110, change in office and ambulatory BP from baseline, and change in UPCR and 24-hour protein excretion up to Week 114. Safety and tolerability assessments include abnormalities in clinical laboratory measures and vital signs, AEs, SAEs, AEs leading to discontinuation, and AEs leading to death.[8,22,23]

The EPPIK Study

The EPPIK study (NCT05003986) is a phase 2, global, open-label, single-arm, multicenter cohort study to evaluate the safety, efficacy, and PK of a once-daily oral suspension of sparsentan in pediatric patients with selected proteinuric glomerular diseases. The primary objective of the EPPIK study is to examine long-term antiproteinuric and nephroprotective potential and safety in this pediatric population.[24] Approximately 57 pediatric patients aged ≥1 to <18 years will be enrolled. EPPIK Population 1 will include ~30 patients aged 1 to <18 years with FSGS or treatment-resistant MCD. Population 2 will include ~27 patients aged 2 to <18 years with IgAN, IgAV, or Alport syndrome. Target exposure of sparsentan is equivalent to 800 mg in Population 1 and 400 mg in Population 2. Primary endpoints are the change from baseline in UPCR over a 108-week treatment period, incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest. Secondary endpoints include observed plasma PK concentration, steady-state PK parameters, change from baseline in UACR and eGFR over 108 weeks of treatment, and proportion of patients with FSGS or MCD histological patterns achieving partial remission (FPRE) in UPCR. Partial remission is defined as UPCR ≤1.5 g/g and >40% reduction in UPCR. Safety parameters are monitored throughout the duration of the study.[9,24,25]

Study Data

Safety of Sparsentan in IgA Nephropathy

The PROTECT Study

Safety data from the 2-year confirmatory analysis showed sparsentan to be well-tolerated, with a consistent safety profile comparable to irbesartan and no new safety signals. TEAEs were reported in 187 (93%) patients taking sparsentan and 177 (88%) irbesartan-treated patients. SAEs were reported by 75 (37%) patients taking sparsentan and 71 (35%) patients taking irbesartan.[26]

Peripheral edema was similar in both groups, with no increases in body weight. Change from no edema at baseline to severe edema occurred in 0 sparsentan-treated patients and 2 irbesartan-treated patients. Change from no edema to moderate edema occurred in 2 patients taking sparsentan and none taking irbesartan. Diuretic use initiated on or after beginning study drug was reported in 49 (24%) sparsentan patients and 54 (27%) irbesartan patients. The most frequently used class of diuretics was thiazides, utilized by 35 (17%) and 42 (21%) sparsentan and irbesartan patients, respectively. Transaminase elevations, defined as elevations in ALT or AST >3-fold the ULN, were observed in 7 (3.5%) patients taking sparsentan and 8 (4%) patients taking irbesartan. No cases of drug-induced liver injury occurred in either group. Rescue immunosuppressive therapy

was initiated sooner and more frequently in the irbesartan group (n=18; 9%) than with sparsentan treatment (n=7; 3%).[3,26]

Additional safety data is reported in **Table 1**.[26]

Table 1. TEAEs Over 2 Years of Sparsentan Treatment[a]

	Sparsentan (n=202)	Irbesartan (n=202)
Any TEAE, n (%)	187 (93)	177 (88)
TEAEs in ≥5% of patients in ≥1 group		
COVID-19	53 (26)	46 (23)
Hyperkalemia	32 (16)	26 (13)
Peripheral edema	31 (15)	24 (12)
Dizziness	30 (15)	13 (6)
Headache	27 (13)	26 (13)
Hypotension	26 (13)	8 (4)
Hypertension	22 (11)	28 (14)
Upper respiratory tract infection	18 (9)	18 (9)
Fatigue	17 (8)	11 (5)
Anemia	16 (8)	9 (4)
Nasopharyngitis	15 (7)	16 (8)
Blood creatinine phosphokinase increased	15 (7)	10 (5)
Cough	15 (7)	7 (3)
Muscle spasms	14 (7)	17 (8)
Arthralgia	14 (7)	13 (6)
Proteinuria	13 (6)	15 (7)
Backpain	12 (6)	16 (8)
Lipase increased	12 (6)	9 (4)
Acute kidney injury	12 (6)	5 (2)
Gout	11 (5)	10 (5)
Pruritus	11 (5)	8 (4)
Diarrhea	10 (5)	19 (9)
Blood creatinine increased	10 (5)	14 (7)
ALT increased	10 (5)	8 (4)
Gastroesophageal reflux disease	10 (5)	8 (4)
Nausea	10 (5)	5 (2)
Myalgia	10 (5)	4 (2)
Renal impairment	7 (3)	12 (6)
Urinary tract infection	7 (3)	12 (6)
Hyperuricemia	7 (3)	11 (5)
Pain in extremity	6 (3)	12 (6)
Serious TEAEs, n (%)	75 (37)	71 (35)
Serious TEAEs in ≥2 patients in ≥1 group, n (%)		
COVID-19	42 (21)	38 (19)
Chronic kidney disease	6 (3)	6 (3)
Acute kidney injury	4 (2)	1 (<1)
Dizziness	2 (1)	1 (<1)
Proteinuria	2 (1)	1 (<1)
Malaise	2 (1)	0 (0)
Appendicitis	1 (<1)	2 (1)
Cellulitis	1 (<1)	2 (1)
COVID-19 pneumonia	1 (<1)	2 (1)
IgAN	1 (<1)	2 (1)
Meniscus injury	1 (<1)	2 (1)
TEAEs leading to treatment discontinuation in ≥2 patients in ≥1 group, n (%)	21 (10)	18 (9)
Chronic kidney disease	3 (1)	3 (1)
Acute kidney injury	3 (1)	0 (0)
ALT increased	3 (1)	0 (0)
Hypotension	2 (1)	0 (0)
Lipase increased	2 (1)	0 (0)
Renal impairment	1 (<1)	4 (2)
TEAEs leading to death, n (%)	0 (0)	1 (<1)*

[a]Data presented in this table represents sparsentan and irbesartan groups individually and therefore differs from safety data representing the total study population.
*One patient in the irbesartan group died due to a severe AE of cardiorespiratory arrest that was considered not related to study drug.

The SPARTACUS Study

No unexpected safety signals occurred, and combined sparsentan and SGLT2 inhibitor therapy was generally well tolerated. TEAEs occurred in 12 (60%) patients, 5 (25%) of which were considered sparsentan-related. Additional safety information is described in **Table 2**.[20]

Table 2. TEAEs Reported in the SPARTACUS Study

	Sparsentan + SGLT2i (N=20)
Any TEAEs, n (%)	12 (60)
Sparsentan related	5 (25)
SGLT2i related	1 (5)
Any TEAE reported in >1 patient, n (%)	
Dizziness	2 (10)
Headache	2 (10)
Hypertension	2 (10)
Hypotension	2 (10)
Edema	2 (10)
Peripheral edema	2 (10)
Osteoarthritis	2 (10)
Any severe TEAE, n (%)	1 (5)
Gout	1 (5)
Any serious AE, n (%)	2 (10)
Acute kidney injury*,†	1 (5)
Cerebrovascular accident	1 (5)
Osteoarthritis*	1 (5)
Any abnormal liver function test results‡, n (%)	0 (0)
Any TEAE leading to treatment discontinuation, n (%)	1§ (5)

*Reported in the same patient.
†The incidence of acute kidney injury was mild, deemed unrelated to sparsentan or SGLT2i treatment, and was resolved after interruption of sparsentan and SGLT2i.
‡Abnormal liver function test results met the following criteria: (1) new elevation in ALT or AST >3× ULN with or without elevation of total serum bilirubin >2× ULN and (2) 2-fold increase in ALT or AST above the baseline value in patients who had elevated values prior to taking study medication.
§Patient discontinued treatment due to a TEAE of vertigo.

The SPARTAN Study

Sparsentan appeared to be generally well tolerated over 24 weeks of treatment. Among all patients (N=12) over 24 weeks of treatment, 1 patient discontinued treatment after 6 weeks due to hypotension. The most common AEs (occurring in >2 patients) were dizziness (n=6; 50%), urinary tract infection (n=3; 25%), dyspepsia (n=3; 25%), and vomiting (n=3; 25%). A serious AE, limb abscess, was reported in 1 (8%) patient.[21]

Safety of Sparsentan in FSGS

The DUET Study

In a post-hoc assessment through 240 weeks of the DUET OLE, no new or unexpected safety signals emerged. The most frequent TEAEs were headache, peripheral edema, upper respiratory tract infection, and hyperkalemia (**Table 3**). The most common TEAEs leading to discontinuation were glomerular filtration rate decreased, blood creatinine increased, pregnancy, acute kidney injury, and hepatic enzyme increased.[27]

Table 3. Most Common TEAEs by Year and Cases Per 100 Patient-Years for Total Study Duration

	n (%) Within Each Year					Total Study Duration Cases Per 100 Patient-Years, Cases/100 Patient Years
	Year 0 to <1 n=108	Year 1 to <2 n=87	Year 2 to <3 n=72	Year 3 to <4 n=60	Year 4 to <5 n=54	
Headache	25 (23.1)	5 (5.7)	1 (1.4)	4 (6.7)	2 (3.7)	11.7
Edema peripheral	15 (13.9)	10 (11.5)	3 (4.2)	2 (3.3)	2 (3.7)	11.2
Upper respiratory tract infection	9 (8.3)	5 (5.7)	6 (8.3)	5 (8.3)	2 (3.7)	10.6
Hyperkalemia	7 (6.5)	9 (10.3)	3 (4.2)	6 (10.0)	6 (11.1)	10.4
Hypotension	17 (15.7)	6 (6.9)	3 (4.2)	2 (3.3)	1 (1.9)	9.3
Nausea	17 (15.7)	3 (3.4)	2 (2.8)	4 (6.7)	1 (1.9)	8.5
Hypertension	6 (5.6)	7 (8.0)	2 (2.8)	3 (5.0)	6 (11.1)	7.6
Vomiting	12 (11.1)	2 (2.3)	5 (6.9)	2 (3.3)	1 (1.9)	7.6
Diarrhea	14 (13.0)	3 (3.4)	3 (4.2)	1 (1.7)	4 (7.4)	7.1
Dizziness	14 (13.0)	3 (3.4)	1 (1.4)	2 (3.3)	0	6.3
Blood creatinine increased	11 (10.2)	1 (1.1)	4 (5.6)	0	1 (1.9)	5.5
Blood creatine phosphokinase increased	8 (7.4)	2 (2.3)	0	3 (5.0)	2 (3.7)	4.9
Anemia	11 (10.2)	1 (1.1)	0	2 (3.3)	1 (1.9)	4.1

Among pediatric participants in the DUET OLE (n=26; mean age=15±4 years), no new or unexpected TEAEs occurred.[28]

The DUPLEX Study

Over 108 weeks of treatment, TEAEs were reported with similar frequency in the sparsentan (n=172; 93.5%) and irbesartan (n=174; 93%) treatment groups. Serious TEAEs occurred in 68 (37%) sparsentan-treated patients and 82 (43.9%) irbesartan-treated patients. ALT or AST elevations >3× ULN occurred in 5 (2.7%) patients taking sparsentan and 4 (2.2%) taking irbesartan; no cases were concurrent with elevated bilirubin levels ≥1.5× ULN. There were no drug-induced liver injuries with sparsentan; 1 was reported in the irbesartan group. Additional safety data is presented in **Table 4**.[5]

Table 4. Summary of TEAEs in the DUPLEX Study

Variable	Sparsentan (n=184)	Irbesartan (n=187)
	n (%)	
Any AE	172 (93.5)	174 (93)
TEAE*	88 (47.8)	88 (47.1)
SAE	68 (37)	82 (43.9)
AE leading to treatment discontinuation	26 (14.1)	22 (11.8)
AE leading to death†	4 (2.2)	3 (1.6)
AEs reported in ≥10% of patients‡		
COVID-19	41 (22.3)	50 (26.7)
Diarrhea	25 (13.6)	27 (14.4)
Nausea	10 (5.4)	18 (9.6)
Hyperkalemia	31 (16.8)	20 (10.7)
Peripheral edema	36 (19.6)	41 (21.9)
Blood creatine kinase increased	19 (10.3)	8 (4.3)
Muscle spasms	25 (13.6)	15 (8)
Back pain	15 (8.2)	20 (10.7)
Hypotension	33 (17.9)	21 (11.2)
Hypertension	20 (10.9)	24 (12.8)
Chronic kidney disease	13 (7.1)	22 (11.8)
Dizziness	23 (12.5)	21 (11.2)
Headache	20 (10.9)	23 (12.3)
Anemia	24 (13)	10 (5.3)

* Treatment-related adverse events were defined as events that were considered to be "related" or "possibly related" to the trial drug by the investigator. Events with missing relationship information were counted as treatment-related events.
† Adverse events that led to death included neuroendocrine carcinoma, subdural hematoma, coronavirus disease 2019 (COVID-19), and suicide (in 1 patient each) in the sparsentan group; and COVID-19 pneumonia, COVID-19, and respiratory distress (in 1 patient each) in the irbesartan group.
‡ If a patient had more than one event with a given preferred term, the patient was counted only once for that term.

Additional Studies in IgA Nephropathy and FSGS

The EPPIK Study

Sparsentan oral formulation appeared to be well tolerated by pediatric patients in the EPPIK study. Ten serious TEAEs were reported in 6 patients, and 1 patient discontinued study treatment due to worsening of nephrotic symptoms. The observed safety profile was consistent with that seen in adult FSGS and IgAN trials. Additional safety information is presented in **Table 5**.[9,25]

Table 5. TEAEs Reported in the EPPIK Study Over 12 Weeks of Sparsentan Treatment

Patients, n (%)	Population 1		Population 2		Total (N=34)
	MCD (n=10)	FSGS (n=11)	IgAN/IgAV (n=4)	AS (n=9)	
Any TEAE	**9 (90)**	**7 (64)**	**3 (75)**	**5 (56)**	**24 (71)**
Most common TEAEs (≥15% of the total population)					
Pyrexia	4 (40)	2 (18)	0 (0)	1 (11)	7 (21)
Vomiting	2 (20)	2 (18)	1 (25)	0 (0)	5 (15)
Fatigue	4 (40)	0 (0)	1 (25)	0 (0)	5 (15)
Any serious TEAE	**2 (20)**	**2 (18)**	**2 (50)**	**0 (0)**	**6 (18)***

*10 serious TEAEs occurred in 6 patients: acute kidney injury (n=1); nephrotic syndrome (n=1); vomiting (n=1); decreased activity (n=1); fluid retention (n=1); pleural effusion (n=1); hypotension (n=1); COVID-19 (n=1); SARS-CoV-2 positive antibody test (n=1); SARS-CoV-2 positive test (n=1).

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AS, Alport syndrome; AST, aspartate aminotransferase; AT1, angiotensin II type 1; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ETA, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; IRB, irbesartan; KF, kidney failure; KRT, kidney replacement therapy; MCD, minimal change disease; OLE, open-label extension; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitor; REMS, risk evaluation and mitigation strategy; SAE, serious adverse event; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter-2; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SPAR, sparsentan; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio; UPE, urinary protein excretion.

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