An Overview of the GRID Study: A Clinical Perspective on the Use of STIVARGA® (regorafenib)

Introduction

- STIVARGA (regorafenib) is an oral multikinase inhibitor approved by the US Food and Drug Administration in February 2013 for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate[1]
- This approval was based on data from GRID (GIST – Regorafenib in Progressive Disease), an international, multicenter, randomized, double-blind, placebo-controlled, phase 3 study which showed that the addition of STIVARGA to best supportive care (BSC) resulted in a statistically significant increase in progression-free survival (PFS) vs. the addition of placebo to BSC in patients with GIST[2]

Important Safety Information

WARNING: HEPATOTOXICITY

- Severe and sometimes fatal hepatotoxicity has been observed in clinical trials.
- Monitor hepatic function prior to and during treatment.
- Interrupt and then reduce or discontinue STIVARGA for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence.

Objectives

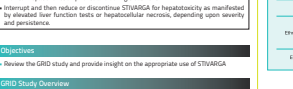
- Review the GRID study and provide insight on the appropriate use of STIVARGA

GRID Study Overview

Study Design

- GRID was an international, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial conducted at 57 hospitals in 17 countries [Figure 1. Pivotal Study Design]
- Between January 04, 2011, and August 18, 2011, 240 patients were screened, of whom 199 were ultimately randomized[2]
- A 2:1 randomization ratio was used to facilitate recruitment into this placebo-controlled trial

Figure 1. Pivotal Study Design[2]



- Primary endpoint: progression-free survival (PFS)
  - Based on disease assessment by independent radiological review using modified RECIST 1.1 criteria, in which lymph nodes and lesions/sites were not target lesions and progressively growing new tumor nodule within a pre-existing tumor mass was progression
- Key secondary endpoint: overall survival (OS)

Eligibility

- In the GRID trial, eligible patients had an ECOG PS ≤1 and had been previously treated with imatinib and sunitinib [Table 1. Patient Eligibility][2]

Table 1. Patient Eligibility[2]*

- Age ≥18 years and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1
- Histologically confirmed metastatic or unresectable GIST with ≥1 measurable lesion with CT or MRI according to RECIST v1.1
- Failure of at least previous imatinib (either disease progression or intolerance) and sunitinib (disease progression)
- No prior treatment with any VEGFR inhibitors other than sunitinib
- Resolution of all toxic effects of previous therapy to grade ≤1
- Adequate hematological, hepatic, cardiac and renal function
  - Total bilirubin, lipase, serum creatine, international normalized ratio, partial thromboplastin time and activated partial thromboplastin time ≤1.5x the upper limit of normal (ULN)
  - Alkaline phosphatase limit ≤2.5x the ULN
  - ALT and AST ≤2.5x the ULN
  - Glomerular filtration rate ≥30 mL/min/1.73m² according to the Modified Diet in Renal Disease abbreviated formula
  - Platelet count ≥100,000/mm³, hemoglobin ≥9.0 g/dL and absolute neutrophil count ≥1,500/mm³
- No major surgical procedure, open biopsy or significant traumatic injury ≤28 days before start of treatment
- No uncontrolled hypertension, unstable angina or myocardial infarction ≤6 months before start of study medication

*Additional eligibility criteria may apply.

Important Safety Information

Hepatotoxicity: Severe drug-induced liver injury with fatal outcome occurred in 0.3% of 1,200 STIVARGA-treated patients across all clinical trials. In gastrointestinal stromal tumor (GIST), fatal hepatic failure occurred in 0.8% of patients in the STIVARGA arm.

Liver Function Monitoring: Obtain liver function tests (ALT, AST, and bilirubin) before initiation of STIVARGA and monitor at least every 2 weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the upper limit of normal (ULN) or baseline values. Temporarily hold and then reduce or permanently discontinue STIVARGA, depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis.

GRID Study Overview

Baseline Characteristics

- In the GRID trial, baseline patient and disease characteristics were balanced between treatment groups [Table 2. Baseline Patient Characteristics; Table 3. Baseline Disease Characteristics][2]
- Slightly more patients were male and Caucasian with a median age of 61 years[2]
- The stomach and small intestine were the most common sites of the primary tumor[2]
- All patients had been previously treated with both imatinib and sunitinib [Table 4. Baseline Treatment Characteristics][2]

Table 2. Baseline Patient Characteristics*

- Demographic characteristics were similar between arms

	STIVARGA (N=133)	Placebo (N=66)
Median age, years (interquartile range)	60 (51-67)	61 (54-69)
Sex, n (%)		
Men	85 (64)	42 (64)
Women	48 (36)	24 (36)
Ethnic group, n (%)		
White	99 (74)	48 (73)
Black or African-American	0	1 (2)
Asian	34 (26)	16 (24)
Not reported or missing	0 (?)	1 (2)
ECOG PS, n (%)		
0	73 (55)	37 (56)
1	60 (45)	29 (44)

Table 3. Baseline Disease Characteristics*

	STIVARGA (N=133)	Placebo (N=66)
Location of primary tumor at initial diagnosis, n (%)		
Stomach	59 (44)	33 (50)
Other or missing	27 (20)	21 (32)
Jejunum	22 (17)	10 (15)
Ileum	15 (12)	7 (11)
Duodenum	11 (8)	4 (6)
Rectum	4 (3)	1 (2)
Colon (ascending or sigmoid)	3 (2)	0

Table 4. Baseline Treatment Characteristics*

	STIVARGA (N=133)	Placebo (N=66)
Previous therapy lines, n (%)		
2 lines	74 (56)	39 (59)
≥3 lines	59 (44)	27 (41)
Imatinib	133 (100)	66 (100)
Sunitinib	133 (100)	66 (100)
Previous therapies, n (%)		
Nilotinib	29 (22)	19 (29)
Other tyrosine kinase inhibitor	2 (2)	1 (2)
mTOR inhibitor	3 (2)	1 (2)
Cytotoxic chemotherapy	13 (10)	2 (3)
Other	5 (4)	1 (2)

Important Safety Information

Hemorrhage: STIVARGA caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) for GIST was 11% with STIVARGA compared to 3% with placebo. Fatal hemorrhage occurred in 4 of 632 (0.6%) STIVARGA-treated patients and involved the respiratory, gastrointestinal, or genitourinary tracts. Permanently discontinue STIVARGA in patients with severe or life-threatening hemorrhage and monitor INR levels more frequently in patients receiving warfarin.

Dermatological Toxicity: STIVARGA caused an increased incidence of hand-foot skin reaction (HFSR) (also known as palmar-plantar erythrodysesthesia [PPE]) and severe rash, frequently requiring dose modification. The overall incidence of HFSR (67% vs 7.2%) and the incidence of Grade 3 HFSR (22% vs 0%) were increased with STIVARGA compared to placebo for GIST. The incidence of Grade 3 rash (7% vs 0%) was higher in STIVARGA-treated patients in GIST. Toxic epidermal necrolysis occurred in 0.17% of 1200 STIVARGA-treated patients across all clinical trials. Withhold STIVARGA, reduce the dose, or permanently discontinue depending on the severity and persistence of dermatologic toxicity.

Hypertension: STIVARGA caused an increased incidence of hypertension (59% with STIVARGA vs 27% with placebo in GIST). Hypertensive crisis occurred in 0.25% of 1,200 STIVARGA-treated patients across all clinical trials. Do not initiate STIVARGA until blood pressure is adequately controlled. Monitor blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Temporarily or permanently withhold STIVARGA for severe or uncontrolled hypertension.

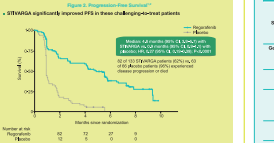
GRID Study Overview

Efficacy

- In the GRID trial, STIVARGA plus BSC significantly improved PFS relative to placebo plus BSC [Figure 2. Progression-Free Survival][2]

Figure 2. Progression-Free Survival[2]*

- STIVARGA significantly improved PFS in these challenging-to-treat patients



- At the time of disease progression, as assessed by central review, 56 (85%) patients randomized to placebo and 41 (31%) patients randomized to STIVARGA received open-label STIVARGA[2]
  - If, in the investigator's opinion, treatment with STIVARGA was providing a clinical benefit to a subject experiencing disease progression, the subject could continue open-label treatment[2]
- No significant difference between treatment arms was noted for overall survival [Table 5. Overall Survival][2]

Table 5. Overall Survival*

	STIVARGA (N=133)	Placebo (N=66)
Number of deaths, n (%)	89 (69)	47 (76)
Median OS, months (95% CI)	Not reached	Not reached
	0.77 (0.49-1.41)	
P-value	0.2	

Safety

- In the GRID trial, common adverse events (AEs) of any grade occurring in ≥30% of patients were hand-foot skin reaction (HFSR), hypertension, asthenia/fatigue, diarrhea, mucositis, dysphonia, infection, decreased appetite and food intake, and rash [Table 6. Common Adverse Events][2]
- The majority of these AEs were classified as either grade 1 or 2, that is, they were considered to be mild or moderate in severity[2]

Important Safety Information

Cardiac Ischemia and Infarction: STIVARGA increased the incidence of myocardial ischemia and infarction (1.2% with STIVARGA vs 0.4% with placebo). Withhold STIVARGA in patients who develop new or acute cardiac ischemia or infarction, and resume only after resolution of acute cardiac ischemic events if the potential benefits outweigh the risks of further cardiac ischemia.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS occurred in 1 of 1200 STIVARGA-treated patients across all clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Confirm the diagnosis of RPLS with MRI and discontinue STIVARGA in patients who develop RPLS.

Gastrointestinal Perforation or Fistula: Gastrointestinal perforation or fistula occurred in 0.8% of 1,200 patients treated with STIVARGA across all clinical trials; this included 4 fatal events. In GIST, 2.1% (4/189) of STIVARGA-treated patients developed gastrointestinal fistula or perforation; of these, 2 cases of gastrointestinal perforation were fatal. Permanently discontinue STIVARGA in patients who develop gastrointestinal perforation or fistula.

Wound Healing Complications: Treatment with STIVARGA should be stopped at least 2 weeks prior to scheduled surgery. Resuming treatment after surgery should be based on clinical judgment of adequate wound healing. STIVARGA should be discontinued in patients with wound dehiscence.

GRID Study Overview

Table 6. Common Adverse Events*†**

Adverse drug reactions (ADRs) reported in patients treated with STIVARGA and reported more commonly than in patients receiving placebo

	STIVARGA (N=132)			Placebo (N=66)		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Skin and subcutaneous tissue disorders						
HFSR/PPE, %	67	22	0	15	2	0
Rash‡, %	30	7	0	3	0	0
Alopecia, %	24	2	0	2	0	0
General disorders and administration site conditions						
Asthenia/fatigue, %	52	4	0	39	2	0
Fever, %	21	0	0	11	2	0
Vascular disorders						
Hypertension, %	59	27	<1	27	5	0
Hemorrhage, %	11	2	2	3	0	0
Gastrointestinal disorders						
Diarrhea, %	47	2	0	6	0	0
Mucositis, %	40	3	0	8	0	0
Nausea, %	30	2	0	12	2	0
Vomiting, %	17	<1	0	6	0	0
Respiratory, thoracic and mediastinal disorders						
Dysphonia, %	39	0	0	8	0	0
Infections and infestations						
Infection, %	32	4	<1	6	0	0
Metabolism and nutrition disorders						
Decreased appetite and food intake, %	31	<1	0	21	3	0
Hypothyroidism**, %	18	0	0	6	0	0
Nervous system disorders						
Headache, %	16	0	0	9	0	0
Investigations						
Weight loss, %	14	0	0	3	0	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal stiffness, %	14	0	0	3	0	0

*The term "rash" represents reports of events of rash, erythematous rash, macular rash, maculopapular rash, papular rash, and pruritic rash.
**Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

Important Safety Information

Embryo–Fetal Toxicity: STIVARGA can cause fetal harm when administered to a pregnant woman. Use effective contraception during treatment and up to 2 months after the last dose of therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers: Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from STIVARGA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Most Frequently Observed Adverse Drug Reactions in GIST (≥30%): The most frequently observed adverse drug reactions (≥30%) in STIVARGA-treated patients vs placebo-treated patients in GIST, respectively, were: HFSR/PPE (67% vs 15%), hypertension (59% vs 27%), asthenia/fatigue (52% vs 39%), diarrhea (47% vs 6%), mucositis (40% vs 8%), dysphonia (39% vs 9%), infection (32% vs 6%), decreased appetite and food intake (31% vs 21%), and rash (30% vs 3%).

References

1. STIVARGA Prescribing Information. 2013.
2. Demetri GD, et al. Lancet. 2013;381(9863):295-301.
3. Data on file, Bayer HealthCare Pharmaceuticals.

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Stivarga® (regorafenib) tablets

100 Bayer Boulevard, Whippany, NJ, USA

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