# Avapritinib for the Treatment of GIST: Analysis of Efficacy, Safety, and Patient Management Strategies at the Recommended Phase 2 Dose

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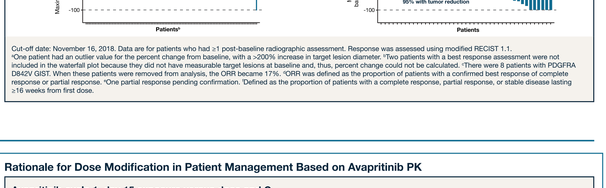
# BACKGROUND

- Treatment of metastatic GIST involves the sequential use of multi-targeted TKIs, which are associated with low response rates in patients with advanced disease and off-target effects. As secondary resistance mutations accumulate, multi-targeted TKIs lose activity[1–4]
- No effective therapy is approved for GIST after failure of imatinib, sunitinib, and regorafenib[1–7]
- Avapritinib is an investigational precision therapy designed to be a highly selective and potent inhibitor of KIT and PDGFRA mutant kinases[8]
- Avapritinib has received breakthrough therapy designation from the US FDA for the treatment of unresectable or metastatic GIST harboring the PDGFRA D842V mutation
- In the NAVIGATOR study, most AEs were grade 1 or 2, with a higher incidence of commonly reported AEs in the avapritinib 400 mg vs 300 mg QD dose group[9]
  - 8.3% of patients discontinued avapritinib for a treatment-related toxicity in the starting dose 300/400 mg QD group
- The most frequent AEs reported with avapritinib (such as fatigue, gastrointestinal events, fluid retention, and anemia) commonly occur with TKIs that inhibit KIT and PDGFRA, however cognitive effects were observed that have not typically been reported with agents used to treat GIST
  - Although manageable with intervention, this was determined to be an AE of special interest (AESI)
  - No anatomic changes were observed in patients who underwent brain imaging
- Supportive care and flexible dosing (including dose interruptions and/or reductions) are common strategies for managing AEs associated with oral multi-targeted TKIs,[10-13] and were likewise used to manage AEs occurring with avapritinib treatment, including cognitive effects

### Antitumor activity per central radiology review in NAVIGATOR

**Patient subgroups with (A) GIST administered avapritinib in the 4L+ setting and (B) GIST harboring mutations in exon 18 of PDGFRA. All patients received a starting avapritinib dose of 300 mg or 400 mg QD.**




Cut-off date: November 16, 2018. Data are for patients who had ≥1 post-baseline radiographic assessment. Response was assessed using modified RECIST 1.1.
[a]One patient had an outlier value for the percent change from baseline, with a >200% increase in target lesion diameter. [b]Two patients with a best response assessment were not included in the waterfall plot because they did not have measurable target lesions at baseline and, thus, percent change could not be calculated. [c]There were 8 patients with PDGFRA D842V GIST. When these patients were removed from analysis, the ORR became 17%. [d]ORR was defined as the proportion of patients with a confirmed best response of complete response or partial response. [e]One partial response pending confirmation. [f]Defined as the proportion of patients with a complete response, partial response, or stable disease lasting ≥16 weeks from first dose.

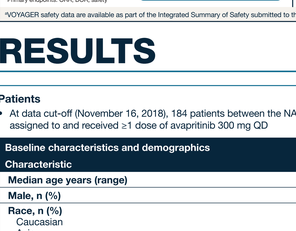
# OBJECTIVES AND STUDY DESIGN

- This post-hoc analysis of the safety and tolerability of avapritinib at the recommended starting dose of 300 mg QD included data from the completed NAVIGATOR study (NCT02508532) and ongoing VOYAGER study (NCT03465722)
- All clinical data are based on the data cut-off date of November 16, 2018, unless specifically noted otherwise

**Pooled analysis across two studies**

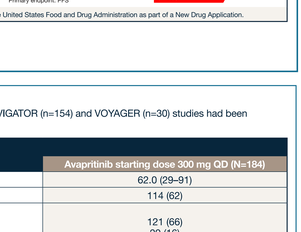
**NAVIGATOR Study Design (completed)**

**Dose Escalation**




Primary endpoints: ORR, DOR, safety

**VOYAGER Study Design (ongoing)[a]**

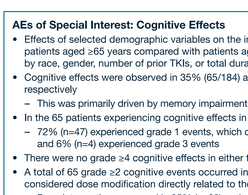



Primary endpoint: PFS

[a]VOYAGER safety data are available as part of the Integrated Summary of Safety submitted to the United States Food and Drug Administration as part of a New Drug Application.

### Rationale for Dose Modification in Patient Management Based on Avapritinib PK

**Avapritinib cycle 1, day 15 exposure versus dose and $C_{ave}$**




- As is typical of oral kinase inhibitors, intra-patient exposure variability was observed
- A trend was observed between increased $C_{ave}$ and the occurrence of grade 3 or 4 AEs as well as cognitive effect AEs (data not shown)
- Approximately 50% of patients at the 300 mg QD dose level had drug exposures extending into the 4th $C_{ave}$ quartile, suggesting that patients with higher grade AEs may be exposed to higher drug concentrations (data not shown)

Cut-off date: November 16, 2018. Box plots show day 15 $C_{ave}$ (day 15 $AUC_{0-24}$/24). $C_{ave}$ (average plasma concentration) was derived using population PK methods and considered to be more representative of drug exposure at the time of an event. Quartile 1: <25th percentile of exposure, Quartile 2: ≥25th percentile and <50th percentile of exposure, Quartile 3: ≥50th percentile and <75th percentile of exposure, Quartile 4: ≥75th percentile of exposure.

# RESULTS

### Patients

- At data cut-off (November 16, 2018), 184 patients between the NAVIGATOR (n=154) and VOYAGER (n=30) studies had been assigned to and received ≥1 dose of avapritinib 300 mg QD

**Baseline characteristics and demographics**

| Characteristic | Avapritinib starting dose 300 mg QD (N=184) |
|---|---|
| **Median age years (range)** | 62.0 (29–91) |
| **Male, n (%)** | 114 (62) |
| **Race, n (%)** | |
| Caucasian | 121 (66) |
| Asian | 29 (16) |
| Black/African American | 8 (4) |
| Other[a] | 8 (4) |
| Unknown | 18 (10) |
| **ECOG performance status, n (%)** | |
| 0 | 70 (38) |
| 1 | 107 (58) |
| 2 | 7 (4) |
| **Median time since diagnosis, years (range)** | 5.35 (0.1–20.0) |
| **Metastatic disease, n (%)** | 181 (98) |
| **GIST mutational subtype, n (%)** | |
| KIT | 143 (78) |
| PDGFRA D842V | 28 (15) |
| PDGFRA non-D842V | 4 (2) |
| **Largest target lesion size, n (%)** | |
| ≤10 cm | 147 (80) |
| >10 cm | 35 (19) |
| Unknown | 2 (1) |
| **Number of prior lines of TKIs, n (%)** | |
| 0 | 4 (2) |
| 1 | 42 (23) |
| 2 | 46 (25) |
| 3 | 40 (22) |
| ≥4 | 52 (28) |

[a]Includes individuals self-identified as American Indian or Alaska Native or as "other".

### Adverse Events

| Summary of adverse events, regardless of causality | Avapritinib 300 mg QD (n=184) | | Avapritinib 400 mg QD (n=50) | |
|---|---|---|---|---|
| | Any grade[a] | Grade ≥3[b] | Any grade[a] | Grade ≥3[b] |
| **Any AE, n (%)** | 181 (98) | 123 (67) | 49 (98) | 41 (82) |
| Nausea | 107 (58) | 3 (2) | 38 (76) | 3 (6) |
| Fatigue | 90 (49) | 8 (4) | 34 (68) | 8 (16) |
| Anemia | 85 (46) | 43 (23) | 26 (52) | 17 (34) |
| Decreased appetite | 62 (34) | 3 (2) | 21 (42) | 3 (6) |
| Periorbital edema | 62 (34) | 2 (1) | 26 (52) | 0 |
| Diarrhea | 59 (32) | 7 (4) | 19 (38) | 3 (6) |
| Vomiting | 56 (30) | 3 (2) | 27 (54) | 1 (2) |
| Lacrimation increased | 50 (27) | 0 | 21 (42) | 0 |
| Peripheral edema | 47 (26) | 2 (1) | 18 (36) | 1 (2) |
| Face edema | 43 (23) | 0 | 14 (28) | 1 (2) |
| Memory impairment | 43 (23) | 0 | 19 (38) | 1 (2) |
| Abdominal pain | 38 (21) | 12 (7) | 10 (20) | 1 (2) |
| Blood bilirubin increased | 38 (21) | 9 (5) | 11 (22) | 1 (2) |
| Constipation | 39 (21) | 3 (2) | 12 (24) | 0 |
| Hair color changes | 29 (16) | 0 | 14 (28) | 1 (2) |
| Headache | 30 (16) | 1 (<1) | 10 (20) | 0 |

[a]All AEs occurring in ≥15% of patients. [b]Grade ≥3 AEs occurring in ≥5% of patients.

### Related AEs

- Treatment-related AEs were reported in 95% (n=174) of patients, most commonly nausea (54%, n=99), fatigue (40%, n=74), and anemia (36%, n=67)
  - Among 184 patients treated with avapritinib 300 mg QD in NAVIGATOR and VOYAGER, 9% (n=16) experienced a treatment-related AE leading to discontinuation of avapritinib
  - Grade ≥3 AEs were considered to be treatment-related in 48% (n=89)
- AE incidence was generally higher with an initial avapritinib dose of 400 mg QD than 300 mg QD
- There were no treatment-related deaths

### Dose Modifications

- Dose modification was utilized for the management of a variety of AEs associated with avapritinib, including a subset of cognitive effects
- Dose modifications occurred in 73% (135/184) of patients in the 300 mg QD starting dose group
  - Dose interruptions or reductions were reported in 62% (n=115) and 42% (n=77) of patients, respectively
  - 14% (n=26) of patients were dose modified for cognitive effects; 5% (n=9) were dose reduced, and 9% (n=17) had dose interruptions
  - Despite dose modifications, the median dose intensity in patients in this group was 281 mg per day

### AEs and Dose Modification

| AEs | Avapritinib 300 mg QD (n=184) | | Avapritinib 400 mg QD (n=50) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| **AE leading to dose interruption, n (%)** | 118 (64) | NA | 34 (68) | NA |
| **AE leading to dose reduction, n (%)** | 75 (41) | NA | 33 (66) | NA |
| **AESI, n (%)** | | | | |
| Cognitive effects | 65 (35) | 4 (2) | 24 (48) | 4 (8) |
| Memory impairment | 43 (23) | 0 | 19 (38) | 1 (2) |
| Cognitive disorder | 23 (12) | 1 (<1) | 3 (6) | 1 (2) |
| Confusional state | 11 (6) | 2 (1) | 5 (10) | 2 (1) |
| Encephalopathy | 1 (<1) | 1 (<1) | 2 (4) | 1 (2) |
| Intracranial hemorrhage[a,b] | 2 (1) | 1 (<1) | 0 | 0 |

[a]An additional patient who received a starting avapritinib dose of 90 mg/day and had been escalated to avapritinib 200 mg/day experienced intracranial hemorrhage. [b]Grade ≥3 intracranial hemorrhage required permanent discontinuation of study drug per protocol dose modification guidelines. NA, not available.

**AEs leading to dose interruption (≥3% of patients) or dose reduction with avapritinib 300 mg QD (n=184)**

| Preferred term, n (%) | Dose interruption | Dose reduction |
|---|---|---|
| Anemia | 21 (11.4) | 10 (5.4) |
| Nausea | 15 (8.2) | 6 (3.3) |
| Fatigue | 13 (7.1) | 10 (5.4) |
| Vomiting | 11 (6.0) | 2 (1.1) |
| Diarrhea | 8 (4.3) | 2 (1.1) |
| Cognitive effect | 17 (9.2) | 9 (4.9) |
| Blood bilirubin increased | 7 (3.8) | 7 (3.8) |
| Pleural effusion | 6 (3.3) | 3 (1.6) |
| Periorbital edema | 6 (3.3) | 4 (2.2) |
| Dyspnea | 6 (3.3) | 3 (1.6) |
| Neutrophil count decreased | 6 (3.3) | 7 (3.8) |

### AEs of Special Interest: Cognitive Effects

- Effects of selected demographic variables on the incidence of cognitive effects were analyzed. The incidence was higher in patients aged ≥65 years compared with patients aged <65 years (44% vs 34%); however there was no difference in incidence by race, gender, number of prior TKIs, or total duration of prior TKI use
- Cognitive effects were observed in 35% (65/184) and 48% (24/50) of patients receiving avapritinib at 300 mg QD and 400 mg QD, respectively
  - This was primarily driven by memory impairment (300 mg: 23%; 400 mg: 38%)
- In the 65 patients experiencing cognitive effects in the 300 mg QD dose group
  - 72% (n=47) experienced grade 1 events, which did not affect activities of daily living and 22% (n=14) experienced grade 2 events, and 6% (n=4) experienced grade 3 events
- There were no grade ≥4 cognitive effects in either the 300 mg QD or 400 mg QD group
- A total of 65 grade ≥2 cognitive events occurred in 29 patients who received 300 mg or 400 mg QD (these analyses only considered dose modification directly related to the events)
  - Dose interruptions occurred in 35% (n=23), reductions in 9% (n=6), and both interruptions and reductions in 15% (n=10)
- All dose modification interventions improved grade ≥2 cognitive effects compared to no action
  - Median time to improvement to a lower grade was 12.0 days for any intervention vs 32.5 days for no intervention
  - Symptoms improved fastest with dose interruptions (median 8 days)

**Dose modification guidelines used in NAVIGATOR and VOYAGER studies**

| Grade | General AEs | Cognitive Effect AEs |
|---|---|---|
| 1 | No dose modification required | Consider interruption |
| 2 | Hold until improved; restart at reduced dose | Interrupt for 7 days; restart at reduced dose when improved |
| ≥3 | Hold until improved; restart at reduced dose | Interrupt for 14 days; restart at reduced dose when improved |

### Outcome of Cognitive Effects AEs

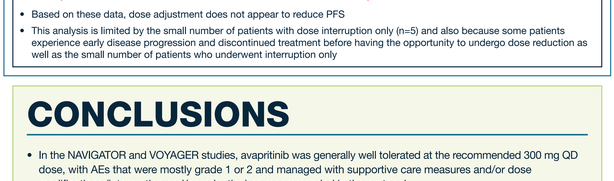
**Outcome of Cognitive Effect AEs**

| Category | | Dose reduction (n=6) | Dose interruption (n=23) | Dose reduction + dose interruption (n=10) | Any Intervention (n=39) | No Intervention (n=26) | Total (n=65) |
|---|---|---|---|---|---|---|---|
| **Grade ≥2 cognitive effects[a]** | | | | | | | |
| Improved to a lower grade | n, (%) | 4 (67) | 15 (65) | 7 (70) | 26 (67) | 12 (46) | 38 (58) |
| | Median, days | 53.0 | 8.0 | 22.0 | 12.0 | 32.5 | 15.0 |
| | Range | 36–224 | 2–37 | 7–28 | 2-224 | 7–170 | 2–224 |
| Worsened | n, (%) | 0 | 0 | 0 | 0 | 1 (4) | 1 (2) |
| | Median, days | - | - | - | | 11.0 | 11.0 |
| | Range | - | - | - | | 11.0–11.0 | 11.0–11.0 |
| Unchanged | n, (%) | 2 (33) | 8 (35) | 3 (30) | 13 (33) | 13 (50) | 26 (40) |
| | Median, days | 106.0 | 31.0 | 4.0 | 32.0 | 27.0 | 28.5 |
| | Range | 46–166 | 9–93 | 3–85 | 3-166 | 1–407 | 1–407 |

[a]Approximately a quarter of grade 1 events resolved, and the majority of events were ongoing no matter what action was taken (or no action). Grade ≥2 did not worsen if a patient dose modified. These analyses only considered dose modification directly related to the events. Modifications may have been made for reasons other than cognitive effects.

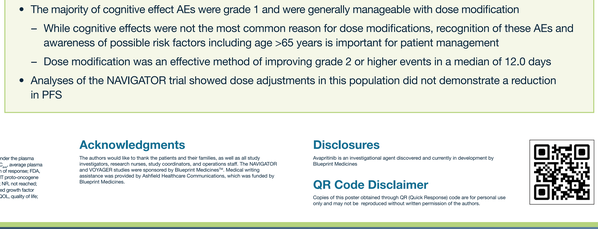
### Cognitive Effects: Time to Onset and Improvement

- Among the 29 patients experiencing a grade ≥2 cognitive effect whose starting dose was 300/400 mg QD, 50% of the patients had experienced an event by 9 weeks
- The probability of experiencing a cognitive effect increases over the first 7-8 months of treatment, and reaches a plateau
- If no cognitive effect AE was experienced by that time, it was unlikely to occur




### Dose Modification Does Not Appear to Affect PFS (NAVIGATOR Only)

**PFS duration in NAVIGATOR in the subgroup of patients with (A) non-PDGFRA D842V GIST receiving avapritinib in the 4L+ setting and (B) PDGFRA D842V GIST. All patients received a starting avapritinib dose of 300 mg QD.**




- Based on these data, dose adjustment does not appear to reduce PFS
- This analysis is limited by the small number of patients with dose interruption only (n=5) and also because some patients experience early disease progression and discontinued treatment before having the opportunity to undergo dose reduction as well as the small number of patients who underwent interruption only

# CONCLUSIONS

- In the NAVIGATOR and VOYAGER studies, avapritinib was generally well tolerated at the recommended 300 mg QD dose, with AEs that were mostly grade 1 or 2 and managed with supportive care measures and/or dose modifications (interruption and/or reduction) as recommended in the protocol
- This analysis supports early recognition of AEs and individually tailored dose adjustments of avapritinib as an effective way to manage treatment-related AEs and maintain patients on treatment
- Among AEs observed, cognitive effects emerged as an AESI not commonly reported with other agents used to treat GIST
- The majority of cognitive effect AEs were grade 1 and were generally manageable with dose modification
  - While cognitive effects were not the most common reason for dose modifications, recognition of these AEs and awareness of possible risk factors including age >65 years is important for patient management
  - Dose modification was an effective method of improving grade 2 or higher events in a median of 12.0 days
- Analyses of the NAVIGATOR trial showed dose adjustments in this population did not demonstrate a reduction in PFS

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### Abbreviations

AE, adverse event; AESI, adverse event of special interest; $AUC_{0-24}$, area under the plasma concentration-time curve over the dosing interval (n=24) at steady state; $C_{ave}$, average plasma exposure; CI, confidence interval; DLT, dose-limiting toxicity; DOR, duration of response; FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumor; KIT, KIT proto-oncogene receptor tyrosine kinase; L, line of therapy; MTD, maximum tolerated dose; NR, not reached; ORR, objective response rate; OS, overall survival; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; PO, orally; QD, once daily; QOL, quality of life; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

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### Disclosures

Avapritinib is an investigational agent discovered and currently in development by Blueprint Medicines

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