Case Report and Review of Preclinical Studies: Successfully Fathering a Child Following Avapritinib for Indolent Systemic Mastocytosis

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Introduction

- Indolent systemic mastocytosis (ISM) is a clonal mast cell disease driven by the *KIT* D816V gene mutation in ~95% of cases[1–4]
- Avapritinib is an orally bioavailable, highly selective, and potent inhibitor of KIT D816V[5]
- Avapritinib is approved in the USA and EU for the treatment of ISM, based on the outcomes of the phase 2, randomized, blinded, placebo-controlled PIONEER study (NCT03731260)[6,7]
- Extensive clinical experience with other tyrosine kinase inhibitors that can inhibit wild-type KIT, such as imatinib, have shown no significant impact on fertility[8–11]
- However, as avapritinib was initially studied in patients with gastrointestinal stromal tumor or advanced SM, two older patient populations, little is known about its effect on human fertility[12,13]
- Here, we provide data from two animal toxicity studies that assessed the potential effects of avapritinib on fertility in rats or male reproductive organs in dogs
- We also report the successful outcome of a pregnancy fathered by a patient treated with avapritinib for 13 months prior to interrupting treatment due to intention to conceive

Methods

- Two animal toxicology studies assessed the potential effects of avapritinib on fertility and male reproductive organs

Preclinical study 1

- The first study was a male and female rat (Sprague Dawley) fertility study that assessed impact on fertility
- Avapritinib was administered prior to mating and for a period following mating to males at doses of 3, 10, and 30 mg/kg/day and to females at doses of 3, 10, and 20 mg/kg/day
- Mating performance and estrous cycling were evaluated, and sperm parameters were assessed in male rats post euthanasia

Preclinical study 2

- The second study was a 9-month chronic repeat-dose toxicology study in dogs (Beagle)
- Avapritinib was administered to males and females at doses of 0.5, 1.5, and 5 mg/kg/day
- Dogs were dosed for 9 months prior to euthanasia
- Testicular histopathology was assessed post euthanasia

PIONEER clinical case study

- We also present one case study of a male patient who received avapritinib 25 mg once daily (QD) for the treatment of ISM on the PIONEER study
- The study design of PIONEER has been reported previously[14]
- Primary endpoints:
  - Total symptom score (TSS) as assessed by the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF; ©2018 Blueprint Medicines Corporation)[15]
  - Long-term safety and efficacy
- Secondary endpoints:
  - Change in tryptase levels
  - Change in *KIT* D816V variant allele frequency (VAF)
  - Changes in use of concomitant best supportive care medications
  - Changes in quality of life measures
- Exploratory endpoints:
  - Changes in skin lesion extent and coloration

Results

Preclinical study 1

- There was no impact of avapritinib on male or female fertility in rats as assessed by reproductive performance (mating and conception), sperm parameters (motility, morphology, and concentration), and estrous cycling up to the highest dose level tested (30 mg/kg/day and 20 mg/kg/day for males and females, respectively)
- The exposures associated with these dose levels were equivalent to 100.8 and 62.6 times the human exposure (area under the curve [AUC]) at a dose of 25 mg for males and females, respectively

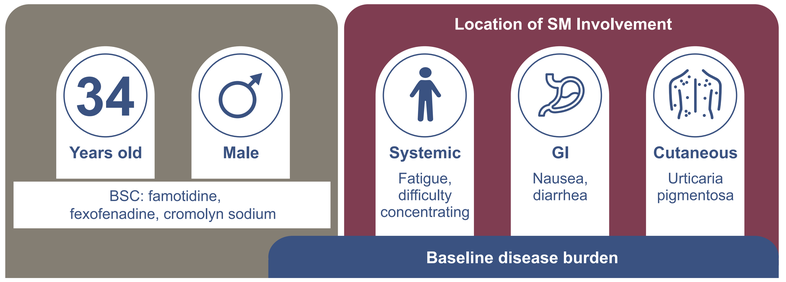
Preclinical study 2

- In the second study in dogs, three cases of hypospermatogenesis were observed histologically at the highest dose level tested of 5 mg/kg/day (with an associated exposure of 5.7 times the human exposure [AUC] at a dose of 25 mg). Zero cases were observed at 1.5 mg/kg/day, and one case was observed at 0.5 mg/kg/day
- Of note, minimal to mild hypospermatogenesis is one of the most common spontaneous findings identified in the testes of dogs 6–7 months of age[16,17]

PIONEER clinical case study

- Although previous studies regarding avapritinib involved older patient populations, patients as young as 18 years old have enrolled in the PIONEER study of avapritinib in ISM
- In June 2020, a 34-year-old man presented with symptoms of ISM (including urticaria pigmentosa, flushing, fatigue, nausea, and diarrhea)
- Baseline characteristics can be seen in **Figure 1**
- A skin biopsy showed increased mast cells in the dermis, and the patient had a serum tryptase of 27.6 ng/mL, suggestive of mastocytosis. Cromolyn sodium had no benefit
- Bone marrow examination in May 2021 showed a hypercellular marrow with focal atypical mast cell aggregates expressing CD117 and CD25, and cytogenetic analysis showed a normal karyotype
- Digital droplet polymerase chain reaction testing on peripheral blood showed a *KIT* D816V mutation. Next-generation sequencing did not reveal any pathogenic mutations
- Consistent with ISM, the patient did not have any evidence of end-organ mast cell infiltration such as cytopenias, hepatosplenomegaly, or osteopenia
- The patient enrolled in the PIONEER study and was randomized to the avapritinib treatment arm in October 2021
- The patient experienced an immediate drop in serum tryptase levels (from 27.6 to 8.8 ng/mL) and *KIT* D816V VAF in the peripheral blood (from 0.08 to 0.04; **Figures 2** and **3**)

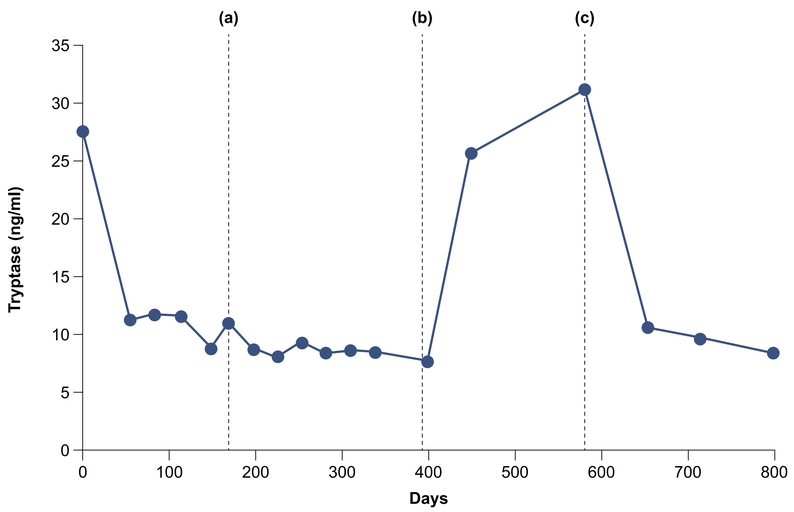
Figure 1. Baseline characteristics



ISM-SAF TSS	40
Serum tryptase	27.6 ng/mL
KIT D816V VAF	0.08%

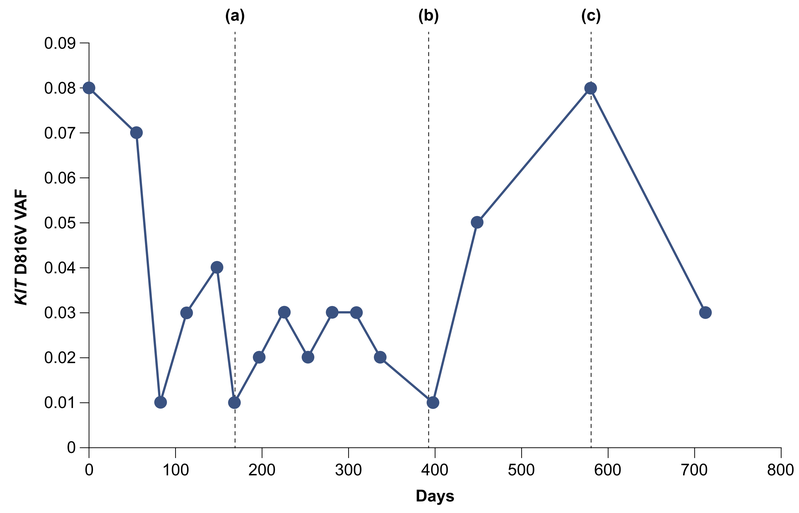
BSC, best supportive care; GI, gastrointestinal; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; SM, systemic mastocytosis; TSS, total symptom score; VAF, variant allele frequency.

Figure 2. Tryptase levels



Vertical lines denote: (a) rollover to open-label 25 mg avapritinib; (b) interruption of avapritinib; (c) restarting of avapritinib.

Figure 3. *KIT* D816V VAF



Vertical lines denote: (a) rollover to open-label 25 mg avapritinib; (b) interruption of avapritinib; (c) restarting of avapritinib.

- Maximum reduction in TSS was 45% and occurred after about 250 days on therapy
- The patient tolerated treatment very well
- The patient interrupted therapy with avapritinib in November 2022 (after 393 days on avapritinib) with the intent to father a child
- The patient and treating team elected to have a washout period of 3 months off drug before attempting to conceive. In March 2023, shortly after the 3-month washout period was over, the female partner of the patient became pregnant
- While off avapritinib, the patient noted worsening symptoms, reflected by a rising TSS, and serum tryptase increased to 31.2 ng/mL with a corresponding increase in *KIT* D816V VAF
- The patient resumed avapritinib 25 mg QD in May 2023 and experienced a rapid improvement in symptoms, which led to the discontinuation of antihistamines by August 2023. Additionally, within 3 months of restarting avapritinib, serum tryptase decreased to 10.6 ng/mL
- A healthy male was born in November 2023 after the patient's partner successfully carried the pregnancy to term

Conclusions

- To our knowledge, the presented case study is the first example of a patient attempting and successfully achieving fatherhood after treatment with avapritinib
- Notably, while the patient's symptoms and disease burden worsened following the interruption of avapritinib, they improved rapidly once the treatment was resumed
- As this is a single case study, further study regarding the impact of avapritinib on fertility is merited
- Separately, it is important to note that because of the potential risk to the fetus, per US Prescribing Information guidance,[6] avapritinib should be held for at least 6 weeks prior to conception, as a precaution

References

1. Pardanani A. *Am J Hematol*. 2023;98:1097–1116.
2. Ungerstedt J et al. *Cancers*. 2022;14:3942.
3. Kristensen T et al. *Am J Hematol*. 2014;89:493–498.
4. Garcia-Montero AC et al. *Blood*. 2006;108:2366–2372.
5. Evans EK et al. *Sci Transl Med*. 2017;9:eaao1690.
6. Ayvakit (avapritinib) Prescribing Information. Cambridge, MA: Blueprint Medicines Corporation; 2023.
7. Ayvakyt (avapritinib) Summary of Product Characteristics. Cambridge, MA; Blueprint Medicines Corporation; 2023.
8. Abu-Tineh M et al. *Cureus*. 2023;15:e33407.
9. Ault P et al. *J Clin Oncol*. 2006;24:1204–1208.
10. Ramasamy K et al. *Br J Haematol*. 2007;137:374–375.
11. Cortes JE et al. *Am J Hematol*. 2015;90:1111–1115.
12. Kang YK et al. *J Clin Oncol*. 2021:39:3128–3139.
13. Gotlib J et al. *Nat Med*. 2021;27:2192–2199.
14. Gotlib J et al. *NEJM Evidence*.2023;2:EVIDoa2200339.
15. Taylor F et al. *Orphanet J Rare Dis*. 2021;16:414.
16. Rehm S. *Toxicol Pathol*. 2000;28:782–787.
17. Goedken MJ et al. *Toxicol Pathol*. 2008;36:465–471.

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Conflicts of interest/disclosures

Dr Lampson is an employee and/or shareholder of Blueprint Medicines Corporation.

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