Peak Study: A Phase 3, Randomized, Open-label Multicenter Clinical Study of Bezuclastinib (CGT9486) and Sunitinib Combination Versus Sunitinib in Patients with Gastrointestinal Stromal Tumors (GIST)

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INTRODUCTION

Rationale for Treatment of GIST with Bezuclastinib in Combination with Sunitinib

- Gastrointestinal Stromal Tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract, with about 4,000-6,000 new cases/year in the United States.[1,2]
- Primary activating mutations in KIT are found in 80% of tumors, most commonly in exon 11 or exon 9.[3,4]
- Majority of the primary mutations are inhibited by the tyrosine kinase inhibitor (TKI) imatinib, the worldwide standard for first-line KIT mutated GIST[5,6]
- In the metastatic setting resistance to imatinib arises in 60% of patients within 2 years driven by additional mutations in KIT exons 13/14 (ATP binding domain) or exons 17/18 (activation loop).[5,6] Mutations may be present in both exons 13/14 and 17/18 in the same patient.
- While no single TKI inhibits all mutations, the combination of bezuclastinib, an investigational TKI inhibiting mutations in exons 9, 11, 17, and 18, and sunitinib, inhibiting mutations in exons 9, 11, 13, and 14, targets the full spectrum of primary and secondary resistance mutations.[7]

Table 1. Bezuclastinib + Sunitinib Combination Targets the Full Spectrum of Primary and Secondary Mutations

KIT Exon Mutations	Primary		Secondary				Broad Coverage of Spectrum of Mutations
	9	11	13	14	17	18	
Imatinib	√	√	-	-	-	-	-
Ripretinib	~	√	~	√	√	√	~
Sunitinib	√	√	√	√	-	-	-
Bezuclastinib	√	√	~	-	√	√	-
Bezuclastinib + Sunitinib	√	√	√	√	√	√	√

√ = strong inhibition ~ = moderate inhibition - = no inhibition

Bezuclastinib is highly selective whereas other TKIs targeting KIT affect closely related kinases.[8-10]

- In preclinical studies, bezuclastinib demonstrated no significant activity against closely-related kinases which have been linked to toxicities including edema, hypertension, and pleural effusion.[8-9, 11]
- The selectivity profile of bezuclastinib allows for combination with sunitinib, resulting in broad activity against a spectrum of KIT mutations, and ultimately may provide more durable response in patients with imatinib-resistant GIST.

Table 2. Activity Against Closely Related Kinases

Compound	Cell IC_{50}(nM)*				
	PDGFRα	PDGFRß	CSF1R	FLT3	VEGFR2
Bezuclastinib	**>10,000**	**>10,000**	**>10,000**	**>1000**	**>1000**
Imatinib	75	247	1027	>1000	>1000
Sunitinib	23	14	313	1	4
Regorafenib	138	1180	473	237	101
Avapritinib	53	10	249	305	>1000
Ripretinib	20	34	312	534	110

* Off-target assays were performed using phospho ELISAs (R&D Systems). The following cell lines were used for analysis: H1703 (PDGFRa), NIH3T3 (PDGFRb), HEK293 engineered lines (CSF1R, FLT3, and VEGFR2).

Bezuclastinib in Combination with Sunitinib Has Demonstrated Promising Efficacy and Favorable Safety Profile[12]

Please see: Wagner et al. Peak Part 1 Summary: A Phase 3, Randomized, Open-label Multicenter Clinical Study of Bezuclastinib (CGT9486) and Sunitinib Combination Versus Sunitinib in Patients with Gastrointestinal Stromal Tumors (GIST) . ASCO 2024

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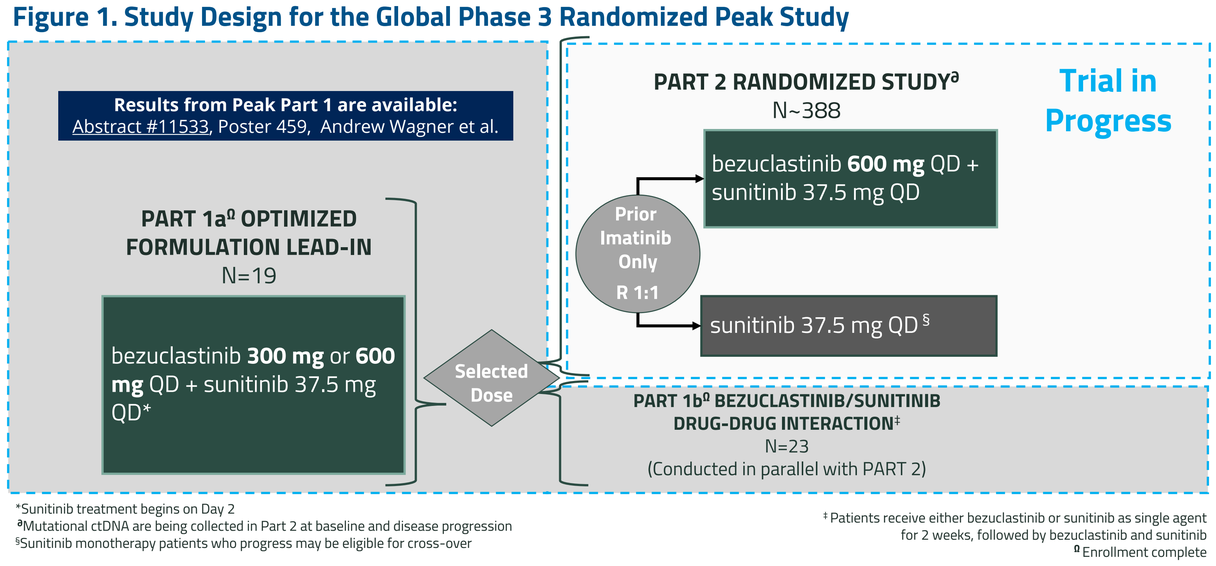
PEAK PART 2 TRIAL IN PROGRESS (NCT05208047)

Global, randomized, open-label, multi-part Phase 3 study evaluating the efficacy and safety of bezuclastinib + sunitinib versus sunitinib as second-line treatment in adult patients who were intolerant to imatinib or whose tumors had imatinib-resistance (NCT05208047)

- Based upon PK and safety, a dose of bezuclastinib 600 mg QD + sunitinib 37.5 mg QD has been determined for Part 2 of the Peak study.
- The primary endpoint for Part 2 is progression-free survival (PFS) confirmed by blinded independent central review per mRECIST v1.1.
  - Additional efficacy (including overall survival and objective response rate) and safety endpoints will be evaluated.

Figure 1. Study Design for the Global Phase 3 Randomized Peak Study

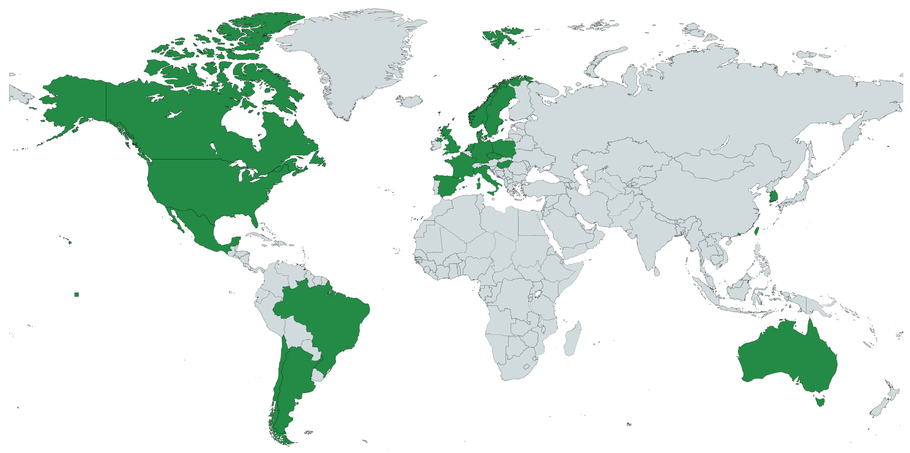


*Sunitinib treatment begins on Day 2
[a]Mutational ctDNA are being collected in Part 2 at baseline and disease progression
[§]Sunitinib monotherapy patients who progress may be eligible for cross-over
[‡] Patients receive either bezuclastinib or sunitinib as single agent for 2 weeks, followed by bezuclastinib and sunitinib
[Q] Enrollment complete

Study Design (Figures 1 and 2)

- Part 1a: Optimized Formulation Lead-In (n=19)
  - Patients were assigned to receive bezuclastinib 300 mg QD or 600 mg QD + sunitinib 37.5 mg QD.
- Part 1b: Bezuclastinib/Sunitinib DDI (n=23)
  - Patients were randomized to receive bezuclastinib 600 mg QD or sunitinib 37.5 mg QD as a single agent for 2 weeks, followed by combination therapy.
- Part 2: Randomized Study (n~388)
  - Patients are randomized to receive sunitinib 37.5 mg QD as a single agent or bezuclastinib 600 mg QD in combination with sunitinib 37.5 mg QD.

Figure 2. Selected Countries for the Peak Study



- Current Peak study sites are located in North America (3 countries), South America (3 countries), Europe (12 countries), and Asia-Pacific (4 countries).

Table 3. Peak Study Objectives and Endpoints for Part 2

Primary Objective	Determine the efficacy of bezuclastinib + sunitinib vs sunitinib alone as second-line treatment in adult patients with GIST who were intolerant to imatinib or whose tumors had imatinib resistance
Primary Endpoint	PFS based on blinded independent central review (BICR) per mRECIST v1.1
Secondary Endpoints	• Overall survival • Objective response rate based on BICR per mRECIST v1.1 • Safety and tolerability • Other efficacy parameters based on BICR: Disease control rate, time to response, and duration of response • PFS assessed by Investigator • Quality of Life
Exploratory Endpoints	• ctDNA for mutational analysis • Pharmacodynamics

Table 4. Key Entry Criteria for Part 2

Histologically confirmed Gastrointestinal Stromal Tumors (GIST) w/at least 1 measurable lesion per mRECIST v1.1
Locally advanced, unresectable or metastatic disease
Documented disease progression on or intolerance to imatinib
ECOG Performance Status 0-2
Prior imatinib only

SUMMARY

- The heterogeneity of KIT resistance mutations in patients with GIST necessitates a therapeutic approach that can provide broad activity against a spectrum of mutations.
- Peak is a global, randomized, open-label, multi-part Phase 3 study evaluating the efficacy and safety of bezuclastinib + sunitinib versus sunitinib as second-line treatment in adult patients with GIST who were either resistant to or intolerant of imatinib therapy.
- Data from the Peak study will determine the potential of bezuclastinib as a therapeutic option to improve outcomes in patients with imatinib-resistant GIST when used in combination with sunitinib.
- Part 2 of the Peak study is actively recruiting and enrolling patients at the selected starting dose of 600 mg bezuclastinib QD and 37.5 mg sunitinib QD.

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