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

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Abstract #1251848

INTRODUCTION

Gastrointestinal Stromal Tumor (GIST)

- Most common mesenchymal tumor of the gastrointestinal tract, with about 4,000-6,000 new cases/year in the United States[1]
- Activating mutations in KIT are found in 80% of tumors, most commonly in exon 11 or exon 9
- These mutations are inhibited by the tyrosine kinase inhibitor (TKI) imatinib, but in the metastatic setting resistance ultimately arises in 60% of patients[1,2]
- Resistance to imatinib is usually from additional mutations in KIT exons 13/14 (ATP binding domain) or exons 17/18 (activation loop) [3,4]
- Additional FDA-approved sequential lines of therapy include the tyrosine kinase inhibitors (TKIs) sunitinib, regorafenib, and ripretinib
  - However, each are only effective against a subset of tumors with resistance mutations and disease progression results from clonal heterogeneity
- Bezuclastinib (formerly PLX9486 or CGT9486) is an investigational TKI that inhibits mutations in KIT exons 9, 11, 17, and 18 [5]

Bezuclastinib

- In preclinical studies, bezuclastinib demonstrated *no significant activity against closely related kinases,* unlike other KIT inhibitors (**Table 1**)
  - Inhibition of these closely-related kinases have been linked to toxicities[6,7]

Table 1. 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 (PDGFRα), NIH3T3 (PDGFRß), HEK293 engineered lines (CSF1R, FLT3, and VEGFR2).

Rationale for Combination of Bezuclastinib with Sunitinib

- Broad KIT inhibition drives tumor regression in mutationally heterogeneous GIST patient-derived xenograft models (**Figure 1**)
- Together, bezuclastinib and sunitinib target commonly occurring primary (exons 9, 11) and secondary (exons 13, 14, 17, 18) mutations (**Table 2**)

Figure 1. Tumor Volume Changes in GIST Patient-Derived Xenograft Models Following Treatment with Sunitinib, Bezuclastinib, or Combination

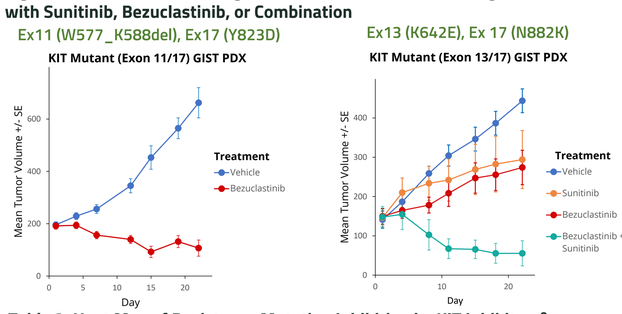
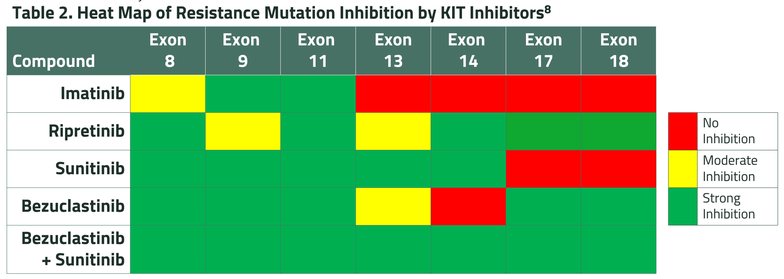


Table 2. Heat Map of Resistance Mutation Inhibition by KIT Inhibitors[8]



→ *The selectivity profile of bezuclastinib allows for combination with sunitinib, resulting in broad complementary activity against a spectrum of KIT primary and secondary resistance mutations, and ultimately may provide more durable response in patients with imatinib-resistant GIST*

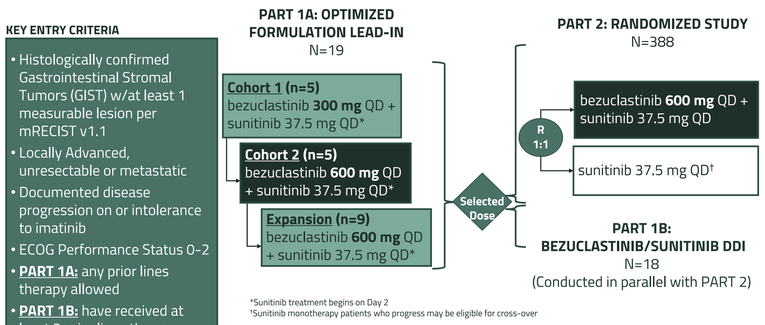
Bezuclastinib in GIST

- Bezuclastinib has been administered as both monotherapy and in combination with sunitinib in a completed Phase 1/2 clinical study in 51 patients with advanced solid tumors, including 46 patients with GIST (PLX121-01)[5]
  - Recommended Phase 2 dose[5]: bezuclastinib 1000 mg + sunitinib 37.5 mg PO QD
  - Patients treated with monotherapy bezuclastinib reported mostly grade 1 and 2 adverse events; the safety profile of combined bezuclastinib and sunitinib therapy was similar to that expected for sunitinib as a single agent
  - In 15 previously-treated patients receiving bezuclastinib doses of ≥500 mg daily in combination with sunitinib, the ORR was 20%, including 1 subject with CR (7%) and 2 patients with PR (13%); the disease control rate was 80% and median PFS was approximately 12 months
- A modified formulation (formulation B) was created in order to:
  - Increase proportion of active ingredients in the tablet and enable a higher strength presentation
  - Improve bioavailability and reduce pill count
- Part 1A of the Peak study is designed to confirm the dose of the optimized formulation (formulation B) to be used in the randomized portion of the study

MATERIALS AND METHODS

- Peak Study (NCT05208047) is a global, phase 3, multi-part open-label, multicenter clinical study of bezuclastinib + sunitinib vs. sunitinib in subjects with locally advanced, unresectable, or metastatic gastrointestinal stromal tumors (**Figure 2**)

Figure 2. Study Design for the Global Phase 3 Randomized Peak Study (NCT05208047)



*Sunitinib treatment begins on Day 2
†Sunitinib monotherapy patients who progress may be eligible for cross-over

Objectives and Endpoints for Peak Study

Part	Objective	Primary Endpoint
Part 1A	Identify a dose of bezuclastinib formulation B to be administered in combination with sunitinib that achieves target drug exposures defined based on previous Phase 1/2 clinical data with bezuclastinib + sunitinib in patients with gastrointestinal stromal tumor (GIST)	PK of bezuclastinib
Part 1B	To characterize the potential effect of sunitinib and its primary active metabolite on bezuclastinib PK, and vice versa	PK of bezuclastinib, sunitinib, and the primary active metabolite of sunitinib
Part 2	To determine the efficacy of bezuclastinib + sunitinib vs sunitinib in patients with GIST	PFS per mRECIST v1.1

RESULTS*

Disposition: Trial Part 1A

- Of 21 patients screened for the trial, 19 were enrolled and treated
  - Excluded: no progression on or intolerance to imatinib (n=1) and death (cardiac failure) prior to enrollment (n=1)
- 5 patients received 300 mg QD bezuclastinib and 37.5 mg QD sunitinib in Cohort 1
  - 1 patient discontinued bezuclastinib and sunitinib due to an adverse event
- 14 patients received 600 mg QD bezuclastinib and 37.5 mg QD sunitinib in Cohort 2 (n=5) and the Expansion Cohort (n=9)
  - 1 patient discontinued bezuclastinib and sunitinib due to disease progression

Baseline Characteristics

- 19 patients enrolled as of 26-Sep-2022; median age 60 years (range: 42-77) (**Table 3**)

Table 3. Demographic and Baseline Characteristics

Baseline Characteristics	Bezuclastinib (300 mg QD) + Sunitinib N=5 (%)	Bezuclastinib (600 mg QD) + Sunitinib N=14 (%)	Total N=19 (%)
Male, n (%)	3 (60)	10 (71)	**13 (68)**
ECOG Performance Status			
0	2 (40)	10 (71)	**12 (63)**
1	3 (60)	3 (21)	**6 (32)**
2	0	1 (7)	**1 (5)**
Status at Screening			
Locally advanced	0	1 (7)	**1 (5)**
Metastatic	5 (100)	13 (93)	**18 (95)**
Total Number of Prior Systemic Anti-cancer Treatments			
1	1 (20)	5 (36)	**6 (32)**
2	2 (40)	4 (29)	**6 (32)**
3	1 (20)	1 (7)	**2 (11)**
>3	1 (20)	4 (29)	**5 (26)**
Prior Radiotherapy	2 (40)	2 (14)	**4 (21)**
Prior Anti-cancer Surgery	3 (60)	11 (79)	**14 (74)**

Treatment Duration

- Median treatment duration is 6 weeks (range: 3.1, 23.9 weeks)
- 17 of 19 patients remain on study treatment

Summary of Safety and Tolerability

- Majority of TEAEs were of low CTCAE grade (**Table 4**)
- No Grade 4 or fatal events reported and low rate of grade 3 events
- One patient experienced SAEs: Grade 2 neutrophil count decrease, Grade 2 pyrexia, and Grade 3 platelet count decrease
- Combination was well tolerated across dosing cohorts; 1 patient requiring dose reduction of bezuclastinib due to Grade 3 diarrhea and 1 subject discontinued due to Grade 2 rash

RESULTS*

Table 4. Treatment-Related Adverse Events (TRAEs) Occurring in >15% of Total Population

Preferred Term	Bezuclastinib (300 mg QD‡) + Sunitinib N=5 (%)		Bezuclastinib (600 mg QD‡) + Sunitinib N=14 (%)		Total N=19(%)
	Grade 1 / 2	Grade 3	Grade 1 / 2	Grade 3	
Diarrhea	3 (60)	0	3 (21)	1 (7.1)	**7 (37)**
Neutropenia∫	3 (60)	0	4 (2()	0	**7 (37)**
ALT increased	2 (40)	0	4 (29)	0	**6 (32)**
AST increased	2 (40)	0	2 (14)	1 (7)	**5 (26)**
Fatigue	2 (40)	0	2 (14)	0	**4 (21)**
Hypertension	0	1 (20)	2 (14)	1 (7)	**4 (21)**
Dry mouth	2 (40)	0	1 (7)	0	**3 (16)**
Palmar plantar erythrody saesthesia	2 (40)	0	1 (7)	0	**3 (16)**
Thrombocytopenia*	1 (20)	0	1 (7)	1 (7)	**3(16)**
Nausea	0	0	3 (21)	0	**3 (16)**

‡Patients are included in the column according to their original dose at study entry; some patients had dose reductions and escalations during Part 1A of the study.
∫Includes pooled preferred terms of Neutropenia, Neutrophil Count Decreased and WBC Decreased
*Includes pooled preferred terms of Thrombocytopenia and Platelet Count Decreased

Summary of Clinical Pharmacokinetics of Bezuclastinib

- Steady state (C1D15) exposure to bezuclastinib increased with increase in dose from 300 mg to 600 mg following once daily administration of bezuclastinib + 37. 5 mg sunitinib (**Figure 3**)
- Similar PK profile and steady state exposure (C_{max} and AUC_{0-24h}) in patients who received QD doses of 600 mg bezuclastinib formulation B + 37.5 mg sunitinib in the Peak study Part 1A compared with patients who received QD doses of 1000 mg bezuclastinib formulation A + 37.5 mg sunitinib in the PLX121-01 study with exposure ratio of 1.1 (**Figure 3, Table 5**)

Figure 3. Mean (± SD) Steady State (C1D15) Bezuclastinib Concentration vs. Time Profile

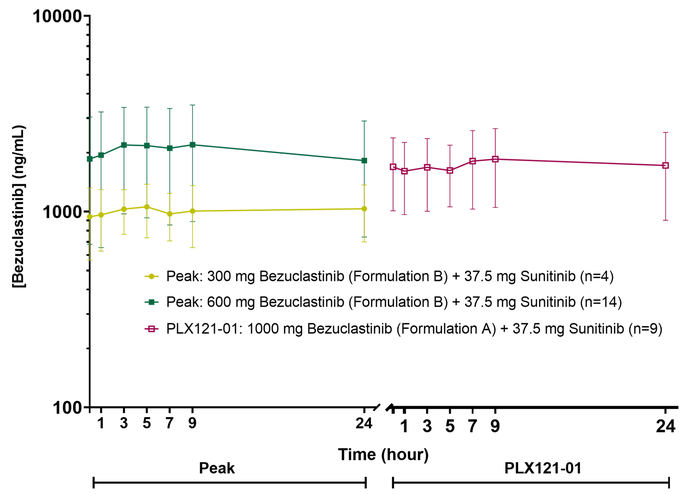


Table 5. Steady State Exposure of Bezuclastinib (Geometric Mean of C_{max} and AUC_{0-24h}) in Peak Part 1A In Comparison with the Target Exposure Previously Established in PLX121-01

Study	Formulation/Dose	C_{max} (ng/mL)	AUC_{0-24h} (h*ng/mL)
Peak	B/600 mg (N=14)	2090	42100
PLX121-01	A/1000 mg (N=9)	1850	38300
	Exposure Ratio (B/A)	1.1	1.1

CONCLUSIONS

- Based on clinical pharmacology and safety of the optimized formulation (formulation B) in Part 1A, a dose of 600 mg bezuclastinib QD + 37.5 mg sunitinib QD has been confirmed for use in the ongoing Peak randomized study
  - Both study Part 1B and Part 2 are actively recruiting, Part 1B is currently enrolling patients who have previously received two or more TKIs, and Part 2 is enrolling patients who have progressed on or are intolerant to imatinib only
- Encouraging safety and tolerability profile consistent with the previous study (Phase 1/2, n=18; Phase 3 lead-in, n=19) and no new safety signals identified.
  - Treatment is ongoing in 17 of 19 patients
  - The safety profile of the combination appears similar to the known safety profile for sunitinib monotherapy

*As of 26 Sept 2022 Data-cut

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