Safety, Pharmacokinetics (PK), and Clinical Activity of Bezuclastinib + Sunitinib in Previously-Treated Gastrointestinal Stromal Tumor (GIST): Results from Part 1 of the Phase 3 Peak Study

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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 arises in 60% of patients within 2 years.[1,2]
- Resistance to imatinib is driven by additional mutations in KIT exons 13/14 (ATP binding domain) or exons 17/18 (activation loop).[3,4] Mutations may be present in both exons 13/14 and 17/18 in the same patient.
- Additional FDA-approved sequential lines of therapy include the TKIs sunitinib, regorafenib, and ripretinib.
  - However, each TKI is only effective against a subset of resistance mutations and disease progression results from clonal heterogeneity.
- Bezuclastinib (CGT9486, formerly PLX9486) is an investigational TKI that inhibits mutations in KIT exons 9, 11, 17, and 18.[5]

Rationale for Treatment of GIST with Bezuclastinib in Combination with Sunitinib

- Broad KIT inhibition drives tumor regression in mutationally heterogeneous GIST patient-derived xenograft models.[6]
- While no single TKI inhibits all mutations, the combination of bezuclastinib (targeting exons 9, 11, 17, and 18) and sunitinib (targeting exons 9, 11, 13, and 14) targets the full spectrum of primary and secondary mutations.[6]
- In preclinical studies, bezuclastinib demonstrated no significant activity against closely related kinases (Table 1), inhibition of which has been linked to toxicities.[7,8]

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 (PDGFRa), NIH3T3 (PDGFRb), HEK293 engineered lines (CSF1R, FLT3, and VEGFR2).

- In a Phase 1/2 clinical study, pts with relapsed and/or refractory GIST and a median of 3 prior lines of therapy treated with bezuclastinib and sunitinib (n=15) experienced clinical benefit and an acceptable safety profile, warranting further evaluation in a randomized trial.[5]
- Prior to study initiation, an optimized formulation of bezuclastinib was developed to improve bioavailability and reduce pill burden.

MATERIALS AND METHODS

Figure 1. Study Design for the Global Phase 3 Randomized Peak Study (NCT05208047)

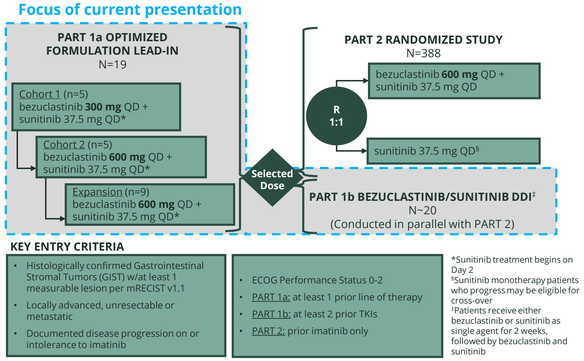


Table 2. Objectives, Endpoints, and Enrollment Status

Study Part	Objective	Primary Endpoint	Current Enrollment Status
1a	Identify a dose of an optimized formulation of bezuclastinib to be administered in combination with sunitinib that achieves target drug exposures defined based on previous Phase 1/2 clinical data with bezuclastinib and sunitinib in patients with GIST	PK of bezuclastinib	**Enrollment complete**
1b	To characterize the potential drug-drug interaction between bezuclastinib and sunitinib	PK of bezuclastinib, sunitinib, and the primary active metabolite of sunitinib	**Enrollment complete**
2	To determine the efficacy of bezuclastinib and sunitinib vs sunitinib in patients with GIST and prior imatinib only	PFS per mRECIST v1.1	**Now enrolling**

RESULTS

Part 1 Patient Disposition

Part 1a€ 19 pts: 5 patients received a starting dose of 300 mg QD bezuclastinib (3 of these patients elected to increase to 600 mg QD bezuclastinib as of data-cut).

14 patients received a starting dose of 600 mg QD bezuclastinib.

Part 1b€ 20 pts: Patients randomized 1:1 to receive 600 mg QD bezuclastinib or 37.5 mg QD sunitinib as a single agent for 2 weeks, followed by combination therapy.

Part 1 39 pts: Of 39 patients treated in Part 1, 25 remain on study treatment.

As of 29-Mar-2023 Data-cut
€Enrollment complete. Part 1b enrolled a total of 23 patients as of April 2023.

Demographic and Baseline Characteristics

- Baseline Characteristics: 39 patients enrolled in Part 1; median age 58 years (range: 33-77)

Table 3. Demographic and Baseline Characteristics

Baseline Characteristics	Part 1a N=19 (%)	Part 1b N=20 (%)	Total N=39 (%)
Male, n (%)	13 (68.4)	18 (90.0)	**31 (79.5)**
ECOG Performance Status (baseline)			
0	12 (63.2)	10 (50.0)	**22 (56.4)**
1	6 (31.6)	10 (50.0)	**16 (41.0)**
2	1 (5.3)	0 (0)	**1 (2.6)**
Total number of prior TKI therapies			
0	0 (0)	0 (0)	**0 (0)**
1	7 (36.8)	0 (0)	**7 (17.9)**
2	7 (36.8)	4 (20.0)	**11 (28.2)**
≥3	5 (26.3)	16 (80.0)	**21 (53.8)**

Baseline Characteristics	Part 1a N=19 (%)	Part 1b N=20 (%)	Total N=39 (%)
Primary Tumor Location at Diagnosis			
Stomach	4 (21.1)	4 (20.0)	**8 (20.5)**
Small Intestine	8 (42.1)	14 (70.0)	**22 (56.4)**
Other abdominal locations	7 (36.8)	2 (10.0)	**9 (23.1)**
Primary Mutation‡			
Exon 9^	2 (10.5)	7 (35.0)	**9 (23.1)**
Exon 11^	13 (68.4)	14 (70.0)	**27 (69.2)**
Other/unknown	4 (21.1)	0	**4 (10.3)**
Prior Radiotherapy	4 (21.1)	5 (25.0)	**9 (23.1)**
Prior anti-cancer surgery	15 (78.9)	19 (95.0)	**34 (87.2)**

As of 29-Mar-2023 Data-cut
Safety Analysis Set: All treated pts

‡Per archival samples taken any time from primary diagnosis to screening
^One patient in Part 1b with both exon 9 and exon 11 appears twice in the Part 1b and Total column

SAFETY

Combination therapy with bezuclastinib and sunitinib in Part 1 was well-tolerated and does not appear to add to the frequency or severity of adverse events associated with single agent sunitinib.

- Majority of TEAEs were of low CTCAE grade and reversible.
- Low rate of Grade 3+ events.
- Limited 9/39 (23%) dose reductions of any study medications due to TEAEs.
- Infrequent (n=2) discontinuations due to TEAEs (1 patient with Grade 2 Rash, 1 patient with Gr 1 abdominal pain and Gr 3 diarrhea).
- Only two patients experienced serious adverse events possibly associated with study medications.
  - One patient with Grade 2 neutrophil count decrease and pyrexia, and Grade 3 platelet count decrease.
  - One patient with Grade 2 bacterial peritonitis and Grade 3 febrile neutropenia.

Clinical Pharmacokinetics of Bezuclastinib

- Steady state exposure of bezuclastinib increased in an approximately dose proportional manner from 300 mg to 600 mg following once daily (QD) administration of bezuclastinib and 37. 5 mg sunitinib.[6]
- Part 1a data supports the selection of 600 mg bezuclastinib and 37.5 mg sunitinib as the dose for Part 1b and Part 2 of the Peak study.

Table 4. TEAEs ≥15% All Causality

Preferred Term	Part 1a N=19 (%)		Part 1b N=20 (%)		Total N=39 (%)
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades
TEAEs					
Diarrhea	11 (58)	2(11)	6 (30)	-	**17 (44)**
Fatigue	10 (53)	-	6 (30)	-	**16 (41)**
Nausea	9 (47)	-	4 (20)	-	**13 (33)**
Hair color changes	8 (42)	-	1 (5)	-	**9 (23)**
Hypertension	5 (26)	2 (11)	3 (15)	2 (10)	**8 (21)**
Taste disorder^	3 (16)	-	5 (25)	-	**8 (21)**
GERD	3 (16)	-	4 (20)		**7 (18)**
Abdominal pain	3 (16)	-	3 (15)	-	**6 (15)**
Headache	3 (16)	-	3 (15)	-	**6 (15)**
Rash¶	3 (16)	-	3 (15)	-	**6 (15)**

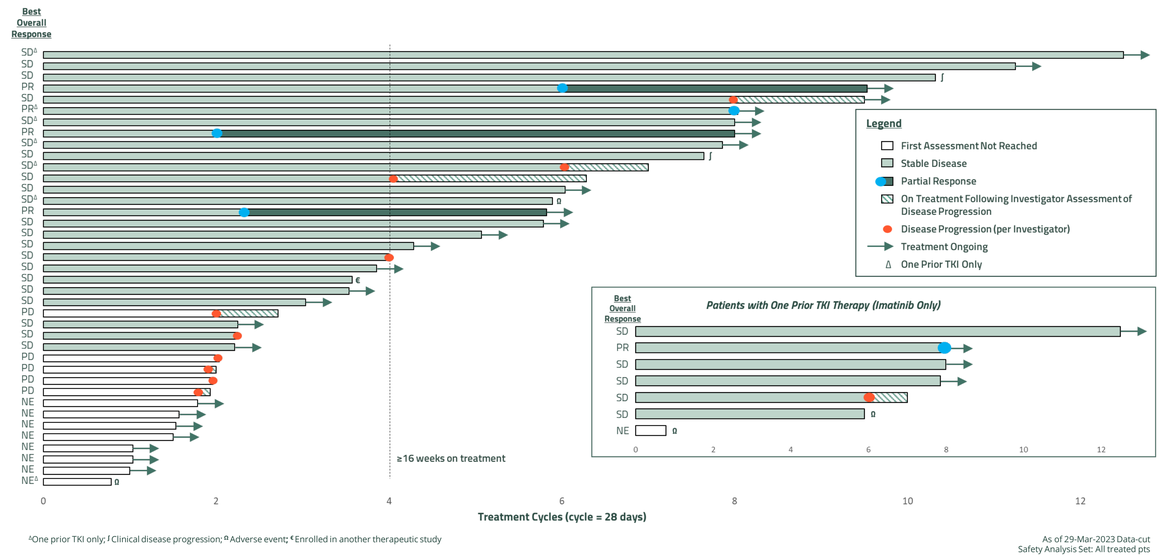
Preferred Term	Part 1a N=19 (%)		Part 1b N=20 (%)		Total N=39 (%)
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades
Laboratory TEAEs					
Neutropenia†	9 (47)	-	6 (30)	2 (10)	**15 (39)**
AST increased	9 (47)	1(5)	6 (30)	-	**15 (39)**
ALT increased	8 (42)	-	6 (30)	1 (5)	**14 (36)**
WBC count decreased	7 (37)	-	7 (35)	1 (5)	**14 (36)**
Anemia	5 (26)	1 (5)	3 (15)	-	**8 (21)**
Hypophosphatemia	4 (21)	-	3 (15)	-	**7 (18)**
Blood creatinine increased	4 (21)	-	2 (10)	-	**6 (15)**
Hyponatremia	5 (26)	-	1 (5)	-	**6 (15)**
Thrombocytopenia*	5 (26)	1 (5)	1 (5)	-	**6 (15)**

†Includes pooled PTs of Neutropenia, Neutrophil Count Decreased
^Includes pooled PTs of Taste disorder, Dysgeusia, Ageusia
*Includes pooled PTs of Thrombocytopenia and Platelet Count Decreased
¶Includes pooled PTs of Rash, Rash maculo-papular

As of 29-Mar-2023 Data-cut
Safety Analysis Set: All treated pts

EFFICACY

Figure 2. Treatment Duration and Disease Assessment in Part 1a/b



£One prior TKI only; ƒ Clinical disease progression; ¤ Adverse event; € Enrolled in another therapeutic study

As of 29-Mar-2023 Data-cut
Safety Analysis Set: All treated pts

- Median time to response was 4.2 cycles (range: 2.0 to 8.0 cycles).
- Data are immature to estimate median PFS.

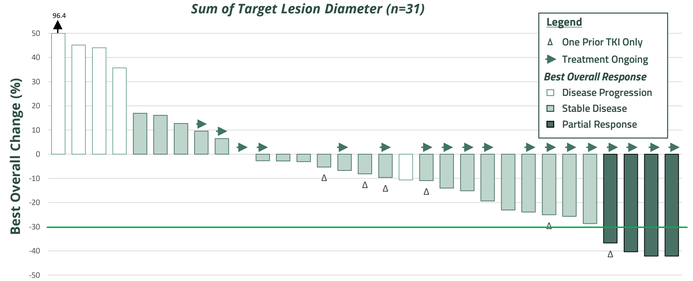
Table 5. Early Responses Observed Per Investigator Assessment

	One Prior TKI Therapy (imatinib treatment only)	2+ Prior TKI Therapies	Total
Part 1a + 1b, n	6	25	**31**
Disease Control Rate*, n (%)	6 (100.0)	11 (44.0)	**17 (54.8)**
Best Overall Response, n (%)			
Partial Response (PR)	1 (16.7) ‡	3 (12.0)	**4 (12.9)**
Stable Disease (SD)	5 (83.3)	17 (68.0)	**22 (71.0)**
Progressive Disease (PD)	0	5 (20.0)	**5 (16.1)**

*Disease Control Rate = CR + PR + durable SD [16 weeks]; EE analysis set includes patients who have not yet been on study for 16 weeks
‡Unconfirmed response

As of 29-Mar-2023 Data-cut
Efficacy Evaluable Analysis Set: All treated pts with ≥1 postbaseline tumor assessment

Figure 3. Best Overall Change (%) in Sum of Target Lesion Diameter



£One prior TKI only

As of 29-Mar-2023 Data-cut
Efficacy Evaluable Analysis Set: All treated pts with ≥1 postbaseline tumor assessment

CONCLUSIONS

- Encouraging safety, tolerability, and clinical activity in Part 1, consistent with previously reported clinical data (Ph 1/2 PLX121-01 trial).
  - Majority of adverse events were Grade 1-2 and reversible with a low rate of Grade 3 events reported.
  - Combination was well-tolerated with limited dose reductions and discontinuations due to adverse events.
  - Combination therapy does not appear to be adding to the frequency or severity of adverse events associated with single agent sunitinib.
- Clinical activity supports potential for durable disease control in imatinib-resistant GIST patients, including heavily pretreated patients.
  - 4 patients with partial responses at early stage of the trial.
  - Responses developing at later timepoints suggest response rate may continue to increase over time.
  - Data are immature to estimate median PFS.
- Part 2 is enrolling patients who have progressed on or are intolerant to imatinib only at the selected starting dose of 600 mg bezuclastinib QD and 37.5 mg sunitinib QD.

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References: [1]Gramza AW, et al. Clin Cancer Res, 2009;15(24):7510-7518. [2]Arshad J et al. *JCO Precis Oncol,* 2020;4:66-73. [3]Casali PG, et al. *JCO,* 2017;35(15):1713-1720. [4]Serrano C and George S. *CCR,* 2020;26(19):5078-5085. [5]Wagner AJ, et al. *JAMA Oncol.* 2021;7(9): 1343-1350. [6]Wagner et al. [abstract 1251848] 2022. In: CTOS 2022: 1251848. [7]Giles FJ et al. Leukemia. 2009;23(10):1698-1707. [8]Liu S, Kurzrock R. Seminars in Oncology. 2015;42(6):863-875.

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