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)

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Abstract 11533
Poster 459

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 first-line treatment standard for 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]
- In a Phase 1/2 trial (PLX121-01), combination of bezuclastinib + sunitinib was well-tolerated and demonstrated clinical activity in patients with relapsed/refractory GIST.[8]

Bezuclastinib is Highly Selective for KIT Compared to Other TKIs.[9-11]

- In preclinical studies, bezuclastinib demonstrated no significant activity against closely-related kinases which have been linked to toxicities including edema, hypertension, and pleural effusion.[9-10, 12]
- 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.

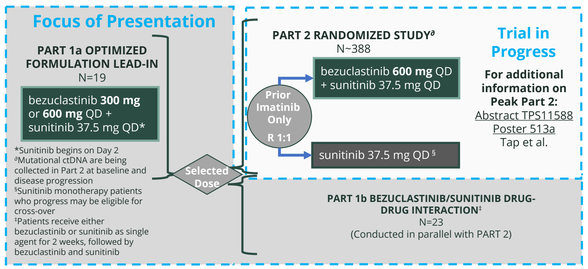
Table 1. Activity Against Closely Related Kinases

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).

MATERIALS AND METHODS

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



All data are as of 01-Apr-2024 data-cut

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 alone in patients with GIST and prior imatinib only	PFS per mRECIST v1.1	**Now enrolling**

Key Entry Criteria

- 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
- PART 1a: at least 1 prior line of therapy
- PART 1b: at least 2 prior TKIs
- PART 2: prior imatinib only

RESULTS

Disposition, Demographics, and Baseline Characteristics

Table 2. Disposition, Demographics, and Baseline Characteristics

Baseline Characteristics	Part 1a N=19	Part 1b N=23	Total N=42
Male, n (%)	13 (68.4)	21 (91.3)	**34 (81.0)**
Median Age in Years (range)	60 (42-77)	59 (33-77)	**59.5 (33-77)**
ECOG Performance Status (baseline)			
0	12 (63.2)	12 (52.2)	**24 (57.1)**
1	6 (31.6)	11 (47.8)	**17 (40.5)**
2	1 (5.3)	0 (0)	**1 (2.4)**
Median (range) Prior TKI therapies	2 (1-6)	3 (2-5)	**2.5 (1-6)**
Total Number of Prior TKI Therapies			
0	0 (0)	0 (0)	**0 (0)**
1	7 (36.8)	0 (0)	**7 (16.7)**
≥2	12 (63.2)	23 (100)	**35 (83.3)**
Prior TKIs			
Imatinib	19 (100)	23 (100)	**42 (100)**
Sunitinib	8 (42.1)	20 (87.0)	**28 (66.7)**
Ripretinib	7 (36.8)	14 (60.9)	**21 (50.0)**
Regorafenib	4 (21.1)	11 (47.8)	**15 (35.7)**
Prior Radiotherapy	4 (21.1)	6 (26.1)	**10 (23.8)**
Prior Anti-cancer Surgery	16 (84.2)	22 (95.7)	**38 (90.5)**
Primary Tumor Location at Diagnosis			
Stomach	4 (21.1)	3 (13.0)	**7 (16.7)**
Small Intestine	7 (36.8)	16 (69.6)	**23 (54.8)**
Other abdominal locations	8 (42.1)	4 (17.4)	**12 (28.6)**
Primary Mutation[‡]			
Exon 9	2 (10.5)	6 (26.1)	**8 (19.0)**
Exon 11	12 (63.2)	8 (34.8)	**20 (47.6)**
Other	5 (26.3)	9 (39.1)	**14 (33.3)**
Weeks on Treatment, median (range)	30.6 (3.1-102.7)	32.3 (1.9-76.9)	**32.1 (1.9-102.7)**
On Study Treatment as of Data Cut-off	3 (15.8)	8 (34.8)	**11 (26.2)**
Discontinued Study Treatment	16 (84.2)	15 (65.2)	**31 (73.8)**
Disease Progression	11 (57.9)	11 (47.8)	**22 (52.4)**
Withdrawn Consent	0	3 (13.0)	**3 (7.1)**
Clinical Progression	2 (10.5)	1 (4.3)	**3 (7.1)**
Adverse Event	2 (10.5)	0	**2 (4.8)**
Enrollment in Other Therapeutic Study	1 (5.3)	0	**1 (2.4)**

[‡]Per archival samples taken any time from primary diagnosis to screening

Safety Analysis Set: All treated pts

Encouraging Long-term Safety and Tolerability With Combination Bezuclastinib and Sunitinib Therapy in Part 1

- Majority of treatment-emergent adverse events (TEAEs) were of low CTCAE grade and reversible
- Only three patients experienced serious adverse events possibly associated with study medications:
  - Gr 2 neutrophil count decrease and pyrexia and Gr 3 platelet count decrease
  - Gr 2 bacterial peritonitis and Gr 3 febrile neutropenia
  - Gr 3 anemia, asthenia, and edema peripheral
- Dose reductions of any study medications due to TEAEs occurred in n=12 (29%) patients
- Infrequent (n=2) discontinuations due to TEAEs
  - Gr 2 rash; Gr 1 abdominal pain and Gr 3 diarrhea
- The combination of bezuclastinib and sunitinib does not appear to add to the severity of AEs associated with sunitinib monotherapy and is well-tolerated (median treatment duration of 32 weeks).

Table 3. TEAEs ≥15% of Patients All Causality

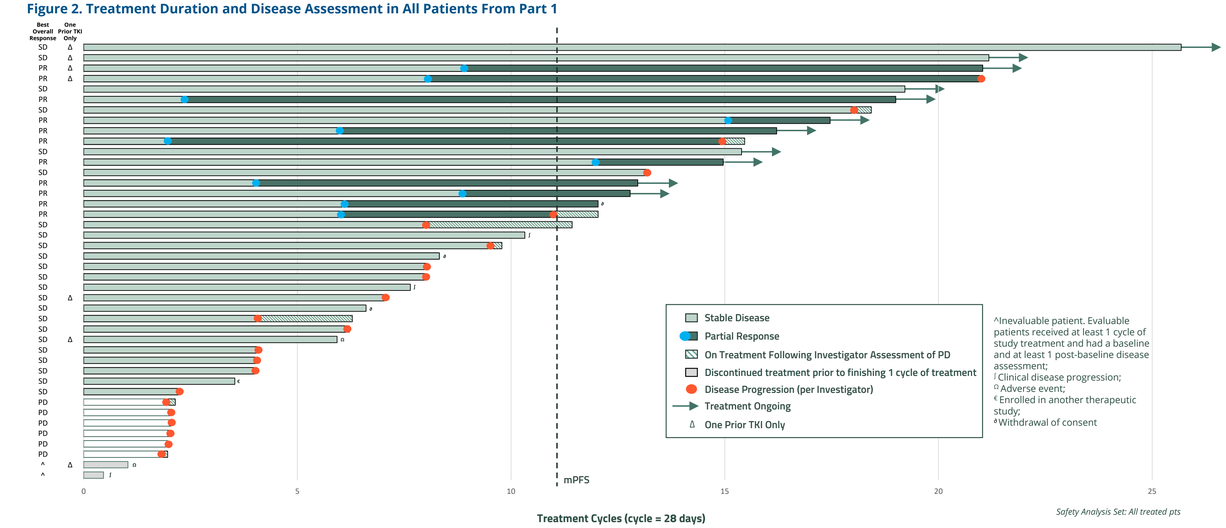
Preferred Term	Part 1a n=19 (%)		Part 1b n=23 (%)		Total n=42 (%)	
	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Diarrhea	12 (63)	2 (11)	17 (74)	-	**29 (69)**	**2 (5)**
Fatigue	10 (53)		13 (57)		**23 (55)**	
Hypertension	10 (53)	4 (21)	9 (39)	3 (13)	**19 (45)**	**7 (17)**
Nausea	8 (42)	-	9 (39)	-	**17 (40)**	-
Hair color changes	9 (47)	-	6 (26)	-	**15 (36)**	-
GERD	4 (21)	-	9 (39)	-	**13 (31)**	-
Taste disorder*	3 (16)	-	10 (43)	-	**13 (31)**	-
Decreased appetite	6 (32)	-	6 (26)	-	**12 (29)**	-
Rash*	5 (26)	-	6 (26)	-	**11 (26)**	-
Neutropenia*	4 (21)	-	5 (22)	3 (13)	**9 (21)**	**3 (7)**
ALT/AST increased	4 (21)	1 (5)	5 (22)	1 (4)	**9 (21)**	**2 (5)**
Anemia	3 (16)	-	6 (26)	3 (13)	**9 (21)**	**3 (7)**
Headache	4 (21)	-	5 (22)	-	**9 (21)**	-
Abdominal pain	6 (32)	-	2 (9)	-	**8 (19)**	-
PPE	5 (26)	-	3 (13)	-	**8 (19)**	-
Hypokalemia	5 (26)	1 (5)	2 (9)	-	**7 (17)**	**1 (2)**
Vomiting	3 (16)	-	4 (17)	-	**7 (17)**	-

* Includes pooled PTs
GERD, gastroesophageal reflux disease; ALT, alanine transaminase; AST, aspartate transaminase; PPE, Palmar-Plantar Erythrodysesthesia

Safety Analysis Set: All treated pts

Median Progression-Free Survival (PFS) Was 10.2 Months in All Patients

Figure 2. Treatment Duration and Disease Assessment in All Patients From Part 1



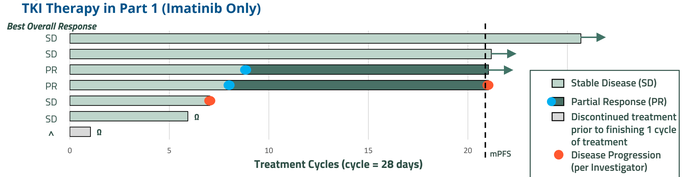
^Inevaluable patient. Evaluable patients received at least 1 cycle of study treatment and had a baseline and at least 1 post-baseline disease assessment; [‡] Clinical disease progression; [D] Adverse event; [E] Enrolled in another therapeutic study; [W] Withdrawal of consent

Safety Analysis Set: All treated pts

- Median (95% CI) progression-free survival was 10.2 (7.4, 19.4) months in all patients; the median (range) number of prior TKIs was 2.5 (1-6)

Median PFS Was 19.4 Months in Patients Receiving Bezuclastinib + Sunitinib Second Line

Figure 3. Treatment Duration and Disease Assessment in Patients with One Prior TKI Therapy in Part 1 (Imatinib Only)



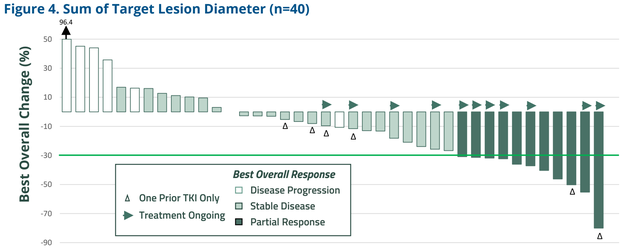
[A]Inevaluable patient. Evaluable patients received at least 1 cycle of study treatment and had a baseline and at least 1 post-baseline disease assessment; [D] Adverse event;

Safety Analysis Set with One Prior TKI

- Median (95% CI) progression-free survival was 19.4 (1.0, NE) months in patients with one prior TKI therapy (imatinib only)
- 3/7 patients with only one prior TKI remain on treatment beyond 19 months

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

Figure 4. Sum of Target Lesion Diameter (n=40)



Evaluable patients: received at least 1 cycle of study treatment and had a baseline and at least 1 post-baseline disease assessment

Treatment With Bezuclastinib and Sunitinib Resulted in an Objective Response Rate of 27.5% in All Patients and 33.3% in Patients With Prior Imatinib Only

Table 4. Responses Observed Per Investigator Assessment

	One Prior TKI Therapy (imatinib treatment only)	2+ Prior TKI Therapies	Total
Part 1a + 1b, n	6	34	**40**
Best Overall Response, n (%)			
Partial Response (PR)	2 (33.3)	9 (26.5) [‡]	**11 (27.5) [‡]**
Stable Disease (SD)	4 (66.7)	19 (55.9)	**23 (57.5)**
Progressive Disease (PD)	0	6 (17.6)	**6 (15.0)**
Disease Control Rate*, n (%)	6 (100)	26 (76.5)	**32 (80.0)**

*Disease Control Rate = CR + PR + durable SD [16 weeks]
[‡]Three patients had an unconfirmed partial response at time of data-cut

Evaluable patients: received at least 1 cycle of study treatment and had a baseline and at least 1 post-baseline disease assessment

CONCLUSIONS

Promising Efficacy and Favorable Safety Profile of Bezuclastinib and Sunitinib

Efficacy compares favorably to historical data in previously treated GIST

- The median PFS for all patients (median of 2.5 prior TKIs) in part 1 was 10.2 months and for the subset with one prior TKI, a population similar to that enrolling in Peak Part 2, was 19.4 months.
- The partial response rate was 27.5% in all patients in part 1 and 33.3% in the subset with one prior TKI.

Encouraging long-term safety and tolerability with combination bezuclastinib and sunitinib therapy in Part 1 with median treatment duration of 32 weeks

- Majority of TEAEs were low grade and reversible
- Combination was well tolerated with infrequent discontinuations due to adverse events

Part 2 of the Peak study is actively recruiting and enrolling patients globally

Presented at American Society of Clinical Oncology (ASCO) Annual Meeting
June 1, 2024 ▪ Chicago, IL

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