Preclinical Characterization of CGT1145 a Novel, Wild-type-sparing, JAK2 V617F Mutant-selective Inhibitor

John Robinson, Shannon Winski, Kim Alley, Tanna Bettendorf, Abiezer Blandon, Alexandra Born, Richard Brizendine, Paul Carlson, Payal Chatterjee, Mark J Chicarelli, Michelle Crow,, Brad Fell, John Fischer, Jennifer Fulton, Anna Guarnieri, Ravi Jalluri, Amber Johnson, Keith Koch, Vijay Kumar, Cori Malinky, Matt McDonald, Colin McHugh, Maralee McVean, Brad Newhouse, Scott Niman, Rob Rieger, Mareli Rodriguez, Leah Salituro, Patrick Salvo, Francis Sullivan, John Trujillo, Brooklynn Venteicher, Logan Vine, Hannah Work, Yeyun Zhou

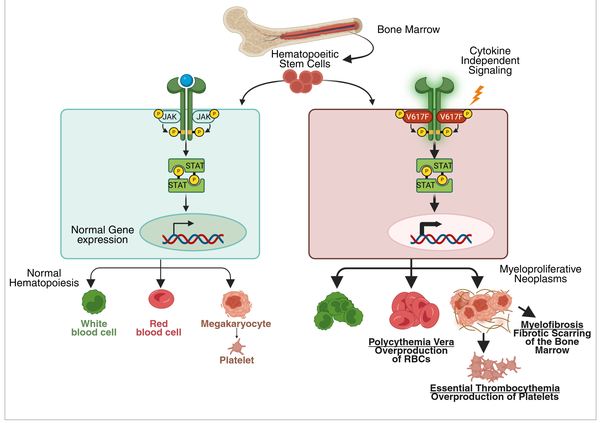
Cogent Biosciences, Inc., Boulder, CO and Waltham, MA

EHA-2129

INTRODUCTION

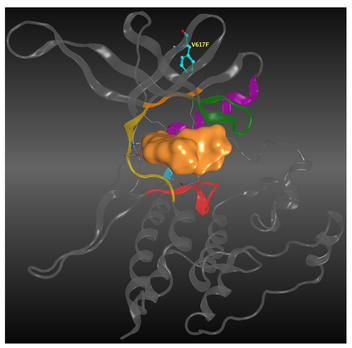
- JAK2 V617F is the most prevalent molecular abnormality in BCR-ABL-negative myeloproliferative neoplasms (MPNs), occurring in approximately 95% of patients with polycythemia vera and 50% of patients with essential thrombocythemia or primary myelofibrosis[1]
- This acquired point mutation in the JAK2 JH2 pseudokinase domain results in the constitutive activation of JAK2 kinase signaling leading to cytokine-independent growth of hematopoietic cells (Figure 1)[1,2,3,4]
- Clinically approved JAK2 inhibitors, such as ruxolitinib, are JAK2 JH1 kinase domain binders that effectively alleviate symptoms and improve outcomes in patients with MPNs. However, these inhibitors rarely lead to significant reductions in variant allele frequency or molecular remission due to dose-limiting hematologic toxicities.[5,6]
- A JAK2 V617F mutant-selective inhibitor that spares wild-type JAK2 has the potential to target and eliminate mutant clones, and induce molecular remission while avoiding hematologic tolerability issues

Figure 1 | JAK2 V617F Leads to Aberrant JAK/STAT Signaling and Drives MPN Disease



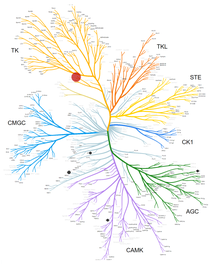
RESULTS

X-Ray Crystallography Shows CGT1145 Bound in the JAK V617F JH2 Pseudokinase Domain



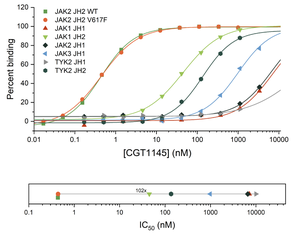
- Crystal structure of JAK2 JH2 pseudokinase domain co-crystallized with CGT1145 (orange surface) at 1.62 Å resolution
- Confirms binding in the JH2 ATP pocket near the V617F mutation
- CGT1145 binds at the hinge region between the C- & N-lobes of JAK2 JH2 forming two hydrogen bonding interactions with the backbone NH and C=O of Val629. It also forms hydrogen bonds with Lys581 and the backbone C=O of Lys677. Additionally, CGT1145 forms several hydrophobic interactions with sidechains from both the C- & N-lobes of JAK2-JH2 as well as hydrogen bonds with water molecules.

CGT1145 is Highly Selective Across the Kinome



- CGT1145 was screened at a concentration of 100 nM, >200x IC_{50} for binding to the JAK2 V617F JH2 domain, against a panel of 377 kinases using 10 uM ATP assay conditions
- CGT1145 was highly selective, inhibiting only four kinases greater than 50% (black circles on the kinome tree image)
- 100% target occupancy for the JAK2 V617F JH2 domain represented by red dot on the kinome tree image

CGT1145 is Selective for the JAK2 JH2 Domain



- CGT1145 binds to the JAK2 JH2 domain with sub-nM potency and is over 100x selective to JAK1 JH2, JAK1/2/3 JH1, and TYK2 enzymes

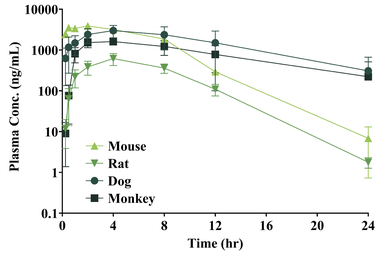
CGT1145 is a Potent JAK2 V617F Inhibitor with Best-In-Class Selectivity vs. JAK2 WT and JAK family Isoforms

Compound	JAK2 V617F IC_{50} (nM)		JAK2 WT IC_{50} (nM)		JAK1/3 IC_{50} (nM)		TYK2/JAK1 IC_{50} (nM)	
	HEL 92.1.7	SET-2	TF-1	WT Selectivity	HuT 78	JAK1/3 Selectivity	TF-1	TYK2/JAK1 Selectivity
CGT1145	81	76	13,300	164x-175x	8,800	110x-115x	3,300	41x-43x
Ruxolitinib	63	13	35	0.3x-2x	16	0.3x-1x	6.3	0.1x-0.5x
Momelotinib	500	68	340	0.4x-5x	270	1x-4x	56	0.1x-1x
Pacritinib	1,300	190	1,200	0.6x-6x	2,400	2x-13x	310	0.2x-2x
Fedratinib	620	150	260	0.4x-2x	260	0.4x-2x	120	0.2x-1x
Ajax patent example 1-4*	140	280	840	3x-6x	3,900	14x-28x	3,700	21x-26x

pSTAT5 was measured via HTRF in HEL 92.1.7 cells (JAK2 V617F), GM-CSF stimulated TF-1 cells (JAK2 WT), and IL-2 stimulated HuT 78 cells (JAK1/3) or via AlphaLISA in SET-2 cells (JAK2 V617F) or IFNα stimulated TF-1 (TYK2/JAK1) *WO2023086319

- CGT1145 was evaluated in multiple cell assays measuring pSTAT5 in HEL 92.1.7, and SET-2 (JAK2 V617F), GM-CSF stimulated TF-1 (JAK2 WT), IL-2 stimulated HuT 78 cell lines (JAK1/3), and IFNα stimulated TF-1 cells (TYK2/JAK2)
- CGT1145 is a potent inhibitor of JAK2 V617F signaling mechanistic cellular assays (avg IC_{50}= 79 nM), with consistent potency observed across HEL 92.1.7 and SET-2 mutant cell lines.
- CGT1145 is selective for JAK2 V617F over JAK2 WT, JAK 1/3, and TYK2 containing signaling pairs in cellular assays
- Improved JAK isoform selectivity compared with approved JAK inhibitors is anticipated to reduce JAK family related hematologic toxicities

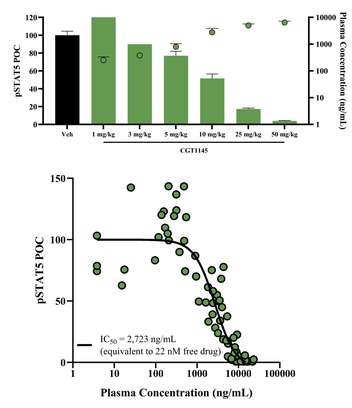
CGT1145 has High Oral Bioavailability and Low Clearance Across Preclinical Species



- A single dose of CGT1145 was administered orally at 10 mg/kg to male CD-1 mice, SD rats, beagle dogs, and cynomolgus monkeys (n=3 animals per group)
- CGT1145 exhibited low clearance across preclinical species tested, extraction ratio (ER) = 4% to 21%
- High oral bioavailability (>80%) was achieved in cynomolgus monkey and beagle dog
- Based on modeling, CGT1145 is predicted to have low human clearance and high oral bioavailability

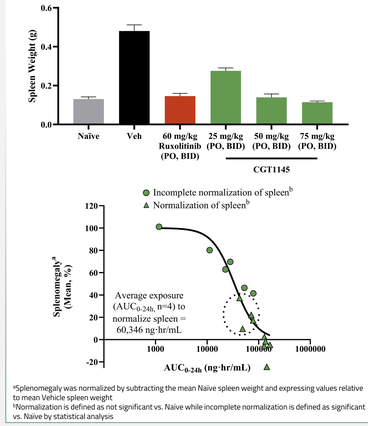
RESULTS

CGT1145 Dose-Dependently Inhibits pSTAT5 in a JAK2 V617F PK/PD Model



- Athymic nude mice bearing subcutaneous JAK2 V617F HEL 92.1.7 tumors were administered a single oral dose of CGT1145 ranging from 1 to 50 mg/kg
- At 4 hours postdose, CGT1145 showed a dose dependent reduction in tumor pSTAT5 levels measured by AlphaLISA with 96% inhibition achieved at 50 mg/kg
- Data from multiple studies were used to generate a curve to examine the impact of CGT1145 plasma concentration on tumor pSTAT5. The resulting in vivo observed IC_{50} value was calculated to be 2,723 ng/mL (equivalent to 22 nM free drug)

CGT1145 is Efficacious at 50 mg/kg BID in a JAK2 V617F Splenomegaly Model

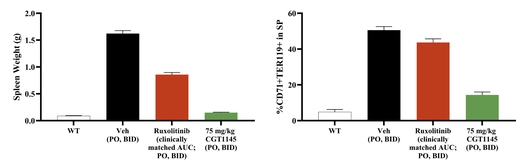


- In a mouse model of splenomegaly which mimics human MPN, athymic nude mice were implanted intravenously with Ba/F3-EPOR-JAK2-V617F cells. After 24 hours, CGT1145 was administered orally twice daily for 10 days. At the end of treatment, spleens were collected and weighed
- CGT1145 treatment led to a dose dependent inhibition of splenomegaly with normalization of spleen weight achieved at 50 mg/kg BID and was roughly equivalent to the activity of 60 mg/kg BID ruxolitinib
- The average plasma exposure ($AUC_{0\text{-}24h}$) of CGT1145 needed to normalize spleens in this model was calculated by averaging the plasma exposures across data points which demonstrated statistically comparable spleen weights to Naïve animals and was determined to be 60,346 ng·hr/mL

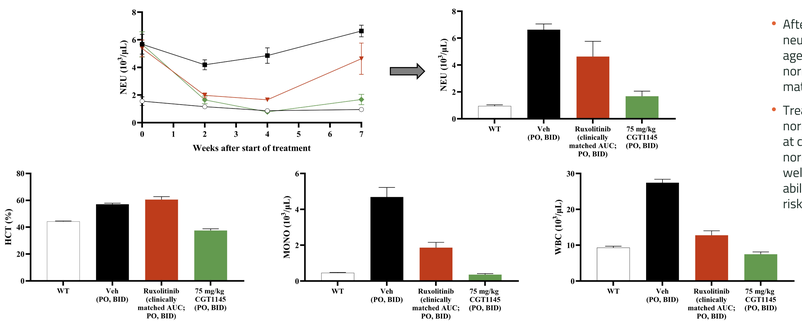
[a]Splenomegaly was normalized by subtracting the mean Naïve spleen weight and expressing values relative to mean Vehicle spleen weight
[b]Normalization is defined as not significant vs. Naïve while incomplete normalization is defined as significant vs. Naïve by statistical analysis

CGT1145 Decreases Erythroid Precursors in Spleen and Normalizes Hematologic Parameters in a Transgenic Mouse Model of JAK2 V617F Driven MPN

Spleen Outcomes



Hematologic Parameters



- Transgenic mice heterozygous for JAK2 V617F and exhibiting a classic MPN-like phenotype were administered CGT1145 orally twice daily for 7 weeks vs. ruxolitinib dosed at clinically matched AUC/exposure. Blood was collected for CBC analysis and spleens were measured for weight and CD71+TER119+ erythroid precursor fraction
- Treatment with CGT1145 led to normalization of spleen weight and decreased CD71+TER119+ erythroid precursor fraction in the spleen supporting the potential of CGT1145 as a disease modifying therapy through restoration of bone marrow function and attenuation of extramedullary hematopoiesis
- After 7 weeks of treatment, CGT1145 restored neutrophil counts to levels comparable to those of WT age-matched littermates, while ruxolitinib led to a brief normalization followed by re-elevation at clinically matched AUC/exposure
- Treatment with CGT1145 also led to restoration of normal HCT and MONO levels compared with ruxolitinib at clinically matched AUC/exposure. WBC was normalized in this study with CGT1145 treatment as well. These data collectively suggest an enhanced ability of CGT1145 to mitigate thrombosis risk, fibrotic risk and inflammation

CONCLUSIONS

CGT1145, a Potential Best-In-Class JAK2 V617F Mutant-Selective Inhibitor

- CGT1145 is a potent inhibitor of the JAK2 V617F mutation and is >100x selective over JAK2 WT and the JAK1/3 isoforms
- High oral bioavailability and low clearance seen in mouse, rat, dog, and cyno pharmacokinetic studies
- CGT1145 provides dose-dependent inhibition of pSTAT5 in a JAK2 V617F PK/PD model with complete inhibition seen at 50 mg/kg and an observed in vivo IC_{50} of 2,723 ng/mL
- In a JAK2 V617F splenomegaly model, CGT1145 administered at 50 mg/kg BID restored spleen weight to that of naïve animals and was roughly equivalent to the activity of 60 mg/kg BID ruxolitinib The average plasma exposure ($AUC_{0\text{-}24h}$) of CGT1145 needed to normalize spleens in this model was determined to be 60,346 ng·hr/mL
- CGT1145 normalizes blood cell counts and spleen weights in a transgenic mouse model of JAK2 V617F driven MPN
- CGT1145 is a potential best-in-class JAK2 V617F mutant selective inhibitor that has the potential to eradicate JAK2 V617F myeloproliferative neoplasm propagating cells and induce molecular remission with improved hematologic tolerability
- **Cogent plans to submit an IND application in 2026**

Presented at the European Hematology Association (EHA) 2026 Congress
June 11-14, 2026, Stockholm, Sweden

References: **1.** Baxter. 2005. Lancet. **2.** James. 2005. Nature. **3.** Levine. 2005. Cancer Cell. **4.** Kralovics. 2005. N. Engl. J. Med. **5.** Harrison. 2016. Leukemia. **6.** Deininger. 2015. Blood.
Acknowledgments/Disclosures: This study was funded by Cogent Biosciences. Poster layout support provided by PIXACORE.