Final Results from the First in Man Phase 1 Clinical Trial of CRN00808, an Orally Bioavailable sst2-Selective, Nonpeptide Somatostatin Biased Agonist for the Treatment of Acromegaly: Safety, Pharmacokinetics, Pharmacodynamics, and Midazolam Drug Interaction in Healthy Volunteers

Ajay Madan[1], Yun Fei Zhu[1], Stacy Markison[1], Stephen F. Betz[1], Alan Krasner[1], Rosa Luo[1], Tilman Oltersdorf[1], Theresa Jochelson[1], Jason Lickliter[2], R. Scott Struthers[1]

[1]Crinetics Pharmaceuticals, San Diego, CA; [2]Nucleus Network, Melbourne, Victoria, Australia

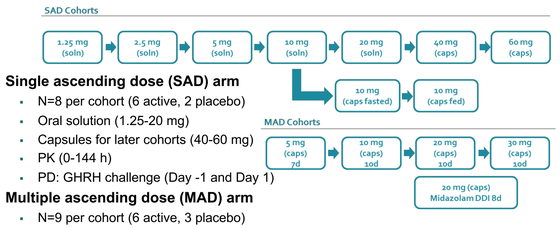
SAT-429

Injected depot formulations of somatostatin peptide analogs are routinely used to treat acromegaly and neuroendocrine tumors (NETs). CRN00808 is a small molecule nonpeptide selective somatostatin receptor 2 (SST2) agonist whose safety, pharmacokinetics (PK), and pharmacodynamics (PD) has been characterized in preclinical studies. This study describes the final results from a first-in-human, single and multiple ascending dose Phase 1 study in healthy volunteers to measure the safety, PK, PD, and midazolam drug interaction potential of CRN00808 (NCT03276858; preliminary results with blinded safety data presented at ENDO 2018). In the single dose arm of the study, cohorts of 8 subjects (6 active: 2 placebo) received CRN00808 as an oral solution or capsules (1.25 mg to 60 mg, or placebo). The effect of food on CRN00808 PK was also evaluated. In the multiple dose arm, cohorts of 9 subjects (6 active: 3 placebo) received CRN00808 capsules once daily (5 mg to 30 mg, or placebo) for 7-10 days. In the drug-interaction arm, a single cohort of 8 subjects received 20 mg of CRN00808 for 7 days; midazolam PK was assessed before (Day -2) and after (Day 7) administration of CRN00808. Safety and PK were assessed in all phases of the study. Suppression of GHRH-induced GH secretion and suppression of serum IGF-1 were measured as PD endpoints in the single and multiple dose phases of the study, respectively. Once daily administration of 5-30 mg CRN00808 capsules exhibited dose-dependent increases in peak (C_{max}) and total (AUC) plasma exposures. The apparent terminal elimination half-life was determined to be of 42-50 hours and steady state was achieved in 3-5 days. Capsules taken with a standard high fat, high calorie meal resulted in a markedly lower plasma CRN00808 AUC (83%). Oral administration of CRN00808 resulted in dose-dependent suppression of both GHRH stimulated GH and IGF-1 secretion; a single 10 mg dose was found to cause 91% suppression of GHRH-stimulated GH and 10 mg once per day for 10 days resulted in maximal suppression of serum IGF-1. Midazolam PK was unaffected by co-administration of 20 mg CRN00808, suggesting little or no risk of drug interaction with CYP3A4/5 substrates. Treatment emergent adverse events associated with CRN00808 were generally mild and transient, and consistent with those reported with other somatostatin agonists. In conclusion, results from this Phase I clinical trial in healthy volunteers support further clinical development of CRN00808 as a once-daily oral treatment of patients with acromegaly.

This work was supported in part by SBIR grants from the NIH awarded to Dr. Struthers (R44DK088501).

ClinicalTrials.gov Identifier: NCT03276858

Phase 1 trial design



Single ascending dose (SAD) arm
- N=8 per cohort (6 active, 2 placebo)
- Oral solution (1.25-20 mg)
- Capsules for later cohorts (40-60 mg)
- PK (0-144 h)
- PD: GHRH challenge (Day -1 and Day 1)

Multiple ascending dose (MAD) arm
- N=9 per cohort (6 active, 3 placebo)
- Capsules (5-30 mg), once-a-day for 7 (5 mg) or 10 days (10-30 mg)
- PK (Day 1 through Day last; up to 168 h postdose)
- IGF-1 levels (Day 1 through Day last)

Midazolam arm to assess the potential for drug-drug-interactions (DDI)
- N=8 per cohort (8 active), Day 1: 2 mg oral midazolam
- Day 3-9: 20 mg CRN00808: 2 mg Midazolam + 20 mg CRN00808)

Figure 1. Design of Phase 1 trial.
caps=capsules, GHRH=growth hormone releasing hormone, IGF-1=insulin-like growth factor-1, PD=pharmacodynamics, PK=pharmacokinetics, soln=solution

Single-dose pharmacokinetics of CRN00808:

Dose dependent increase in plasma concentrations

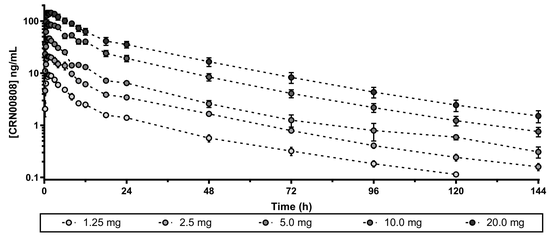


Figure 2. Single-dose pharmacokinetics of CRN00808 administered as an oral solution. CRN00808 concentrations measured using a validated sensitive (LLOQ = 0.1 ng/mL) LC/MS/MS based method.

Pharmacodynamics of single-dose CRN00808:

Potent dose- and concentration-dependent inhibition of GHRH stimulated GH release

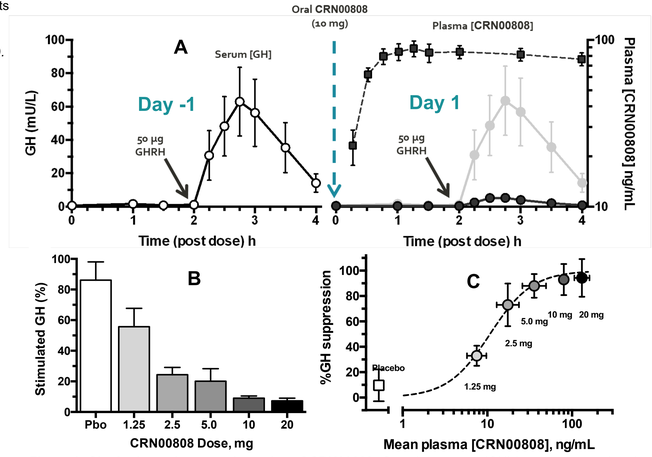


Figure 3. Single-dose pharmacodynamics of CRN00808. Growth hormone (GH) levels measured at the same time of the day after a growth hormone releasing hormone (GHRH) challenge on Day -1 (open and gray circles) and on Day 1 (closed circles). Plasma [CRN00808] in shown in black squares. On Day 1, GHRH was administered 2 hours post CRN00808 dose. A: Data at 10 mg dose with experimental details. B. % Suppression of GH $AUC_{0\text{-}2\,h}$ post GHRH. C. Concentration-dependent suppression of GH $AUC_{0\text{-}2h}$ post GHRH. Data shown are mean ± SEM.

Steady state pharmacokinetics of CRN00808 capsules:

Dose dependent increase in plasma concentrations

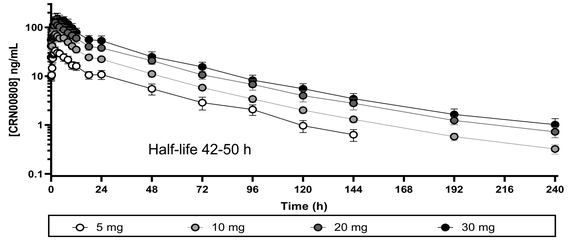


Figure 4. Day last (steady state) pharmacokinetics of CRN00808 administered as the capsule formulation. CRN00808 concentrations measured using a validated sensitive (LLOQ = 0.1 ng/mL) LC/MS/MS based method. Half-life reported for 10-30 mg dose range.

Pharmacodynamics of multiple-dose CRN00808:

Dose-dependent suppression of IGF-1; new steady state of IGF-1 achieved by Day 7

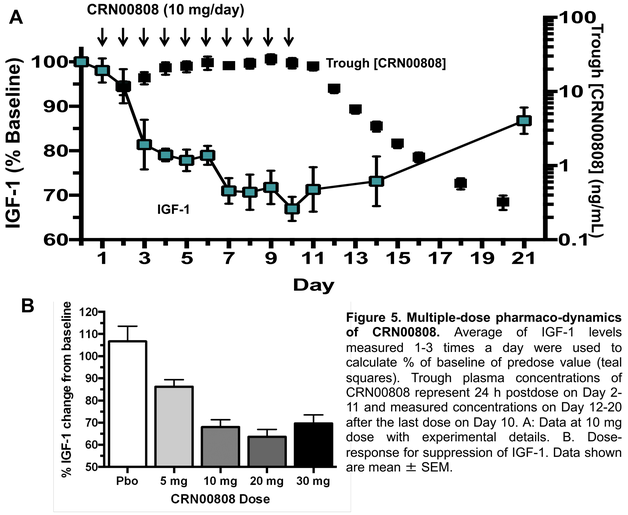


Figure 5. Multiple-dose pharmaco-dynamics of CRN00808. Average of IGF-1 levels measured 1-3 times a day were used to calculate % of baseline of predose value (teal squares). Trough plasma concentrations of CRN00808 represent 24 h postdose on Day 2-11 and measured concentrations on Day 12-20 after the last dose on Day 10. A: Data at 10 mg dose with experimental details. B. Dose-response for suppression of IGF-1. Data shown are mean ± SEM.

Comparison of oral solution and CRN00808 capsules:

Similar plasma [CRN00808] between oral solution and capsules

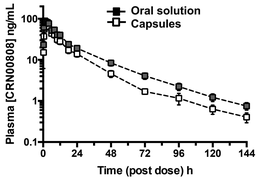


Figure 6. Comparison of oral solution and CRN00808 capsules. CRN00808 (10 mg) was administered either as a oral solution or capsule to fasted subjects in a crossover fashion with a 7-day washout (See Figure 1). Administration of CRN00808 (1st generation capsules) with a high-fat, high calorie meal resulted in marked decrease in systemic exposure (83% ↓ in AUC). Data shown are mean ± SEM.

Midazolam drug-interaction evaluation:

Steady state qd CRN00808 (20 mg) had little or no effect on midazolam PK

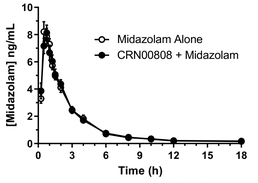


Figure 7. Effect of CRN00808 administration on midazolam (a sensitive CYP3A4 substrate) pharma-cokinetics. CRN00808 (20 mg) was administered either as a capsule for 7 days. Midazolam pharmacokinetics were assessed prior to CRN00808 administration (Day -3; Midazolam alone) and on 7th day of dosing with CRN00808 (CRN00808 + midazolam). Data shown are mean ± SEM.

Safety summary

- Tolerability and AE profile was consistent with approved peptide somatostatin analogs (abdominal pain, flatulence, abdominal distension, and diarrhea in approximately ~30% of subjects and mild elevations of pancreatic enzymes in approximately ~10% of subjects)
- Additional adverse events included: headache, dizziness and cardiac rhythm abnormalities (including NSVT). One serious adverse event of moderate NSVT was observed following a single 1.25 mg dose and was considered unlikely to be related to CRN00808. These AEs were not dose dependent and also observed in placebo subjects and/or prior to dosing.

Conclusions

Pharmacokinetics
- CRN00808 appears to be suitable for once daily oral administration (half-life 42-50 hours)
- Systemic exposure was markedly reduced when first generation capsule was taken with food
- Formulation studies are underway to mitigate the negative food effect

Pharmacodynamics
- Potent suppression of GH axis in Phase 1 provided clinical proof of concept
- Clear exposure response relationship observed for GH suppression
- Maximum GH and IGF-1 suppression observed with 10 mg dose

Safety
- CRN00808 was well tolerated with a safety profile consistent with somatostatin agonist activity

Midazolam-drug interaction
- No change in midazolam (a CYP3A4 substrate) pharmacokinetics with co-administration

Crinetics Pharmaceuticals