CG100649, a Tissue-Specific Dual Inhibitor of COX-2 and Carbonic Anhydrase: Phase 2a Clinical Trial in Hip & Knee Osteoarthritis

William K. Schmidt[1], Klaus Lehnhardt[2], Johannes Hettwer[3], Oleg Nadashkevich[4], István Szombati[5], Vladislav Povoroznyuk[6], Bernard Chung[1], Hee Sook Nam[7], Sangsook Cho[1], Seonggu Ro[7], and Joong Myung Cho[7]
[1]CG Pharmaceuticals, Inc., Emeryville, CA, USA; [2]Orthopaedische Praxis, Bad Duerrheim, GERMANY; [3]Orthopaedische Praxis, Bad Hersfeld, GERMANY; [4]Lviv Natl. Med. Univ., Lviv, UKRAINE;
[5]Synexus Hungary Ltd., Budapest, HUNGARY; [6]Inst. of Gerontology AMS Ukraine, Kyiv, UKRAINE; [7]CrystalGenomics, Inc., Seoul, REPUBLIC OF KOREA

CrystalGenomics, Inc.
6th F., Asan Institute for Life Sciences
Asan Medical Center
Pungnap-2-dong, Songpa-gu
Seoul 138-736
Korea

PURPOSE

The aim of the study was to evaluate the clinical efficacy and safety of CG100649 administered in 3 different dosages. CG100649 is a first-in-class NSAID candidate with a new mode of "tissue-specific" activity designed to deliver sustained levels of drug to inflamed tissues while maintaining low systemic exposure by binding to carbonic anhydrase (CA) in red blood cells. Previous Phase I clinical studies have shown that CG100649 has a unique pharmacokinetic (PK) profile with 85-100x higher concentrations in whole blood (drug transport via erythrocytes that have high concentrations of CA) than in plasma (no CA). Synovial fluid has been shown to have little or no CA. Thus, CG100649 was hypothesized to achieve maximum efficacy in inflamed joints while minimizing its impact on the cardio-renal system or GI tract.

METHODS

Clinical trial CG100649-2-01 was a randomized, double-blind study in male subjects, 18-75 years old, with a 3 month or longer history of primary osteoarthritis (OA) of the hip or knee. The study was conducted in 248 subjects at 25 investigative sites in Germany, Hungary, and Ukraine. The trial was designed to evaluate the safety and efficacy of three parallel dose regimens of CG100649 vs. placebo in the treatment of OA. After a 5-14 day washout period from other pain relief medications, all doses were administered orally, once a day in the morning. Initial loading doses (Day 0) and maintenance doses (Days 1-20) were: High Dose (8 mg + 1.2 mg/day), Medium Dose (4 mg + 0.6 mg/day), and Low Dose (2 mg + 0.3 mg/day). Subjects returned to the study center once a week on Days 7, 14, and 21 during the treatment period and on Days 28 and 35 during the follow-up period for safety and efficacy assessments. Efficacy assessments included the Western Ontario and McMaster Universities (WOMAC™) OA index, Brief Pain Inventory (BPI), Subject's Global Assessment, Physician's Global Assessment, withdrawals due to lack of efficacy, and usage of paracetamol (acetaminophen) as a rescue medication. Blood pressure, ECG, and GI bleeding were monitored for potential adverse side effects.

TABLE 1: Demographics

	Placebo (N=63)	CG100649 2.0/0.3 mg N=62	CG100649 4.0/0.6 mg N=64	CG100649 8.0/1.2 mg N=59
Age (years)				
Mean ± SD	55 ± 13	55 ± 11	55 ± 11	54 ± 11
Minimum	26	29	28	26
Maximum	75	75	75	75
Length of time with OA (years)				
Median	3.6	4.0	4.2	3.3
Minimum	0.3	0.3	0.3	0.3
Maximum	29	29	24	18

*Subjects must have had chronic pain for ≥3 months from OA in order to fulfill the inclusion criteria for the study.

All subjects in the study were Caucasian men. Subjects in the study ranged from those who had only recently been diagnosed with OA to those who had suffered from the condition for over 29 years; the median length of time with OA was 3.9 years and was similar for each of the treatment groups. **Overall, 88% of the subjects completed the study. A greater proportion of subjects in the 8.0/1.2 mg CG100649 and placebo groups completed the study (98% and 92%, respectively) compared with the 2.0/0.3 mg and 4.0/0.6 mg CG100649 groups (81% and 80%, respectively).**

RESULTS

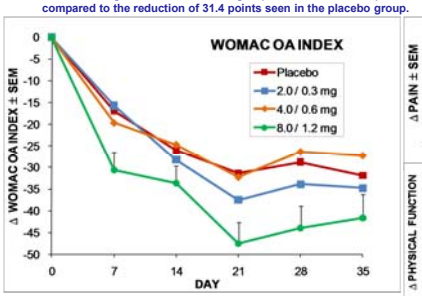
The CG100649 high dose group showed more than a 2-fold greater magnitude of improvement than the placebo group on the primary endpoint of change in the WOMAC score from baseline to Day 21 (median values were 37% vs. 17%, respectively; P=0.01). The study also met all key secondary endpoints, with the high dose demonstrating clinically and statistically significant superiority over the placebo group in the WOMAC OA score (p=0.009) and in the WOMAC subscales of pain, stiffness and physical function (p=0.016, p=0.023, and p=0.010, respectively) over the entire 35-day treatment and follow-up evaluation periods.

TABLE 2: Primary Efficacy Measurement: Sum of the WOMAC OA Index at Day 21 Compared to Baseline

Treatment Group	Mean sum of WOMAC OA index at baseline	Change in mean sum of WOMAC OA index at Day 21	Median % Improvement	p-value[1]
Placebo (n=60)	135	−31.4	17%	---
2.0/0.3 mg (n=57)	131	−37.5	24%	0.296
4.0/0.6 mg (n=62)	125	−32.3	22%	0.629
8.0/1.2 mg (n=58)	**132**	**−47.5**	**37%**	**0.010**

Statistical analysis is based on an ANCOVA model with terms for treatment and baseline score as fixed explanatory variables and pooled site (grouping of sites [within one country] with fewer than 8 subjects) as a random explanatory variable
[1] Pairwise comparison with placebo

The 8.0/1.2 mg CG100649 treatment group's reduction of 47.5 points was clinically relevant and statistically significantly different compared to the reduction of 31.4 points seen in the placebo group.



CG100649 (8.0 / 1.2 mg) compared to placebo: p=0.009

FIGURE 1: Mean Change in WOMAC OA Index at Days 7-21 (Active Dosing) and Days 28- 35 (Washout)

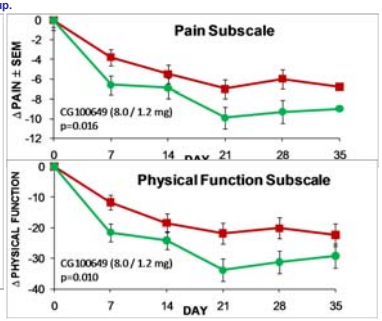


FIGURE 2: Mean Change in WOMAC Subscores at Days 7-21 (Active Dosing) and Days 28- 35 (Washout)

Daily Pain Intensity (DPI) scores were obtained as part of the Brief Pain Inventory (BPI) using hand-held eDiaries. All treatment groups had a decrease in mean average DPI score from Baseline to the final 7 days of treatment. The 8.0/1.2 mg CG100649 treatment group's reduction of 1.6 points was clinically meaningful and statistically significantly different compared to the reduction of 1.0 point seen in the placebo group (p=0.024). No statistically significant differences were found between placebo and any of the other treatment groups.

TABLE 3: Secondary Efficacy Measurement: Average Daily Pain Intensity (DPI) Score during the Final 7 Days of Treatment (Days 15-21) Compared to Baseline

Treatment Group	Mean average DPI at Baseline	Change in mean average DPI to the final 7 days of treatment	% Change	p-value[1]	95% Confidence interval
Placebo (n=60)	5.4	−1.0	-19%		
2.0/0.3 mg (n=57)	5.5	−1.5	-27%	0.145	−0.91 to 0.13
4.0/0.6 mg (n=62)	5.3	−1.3	-25%	0.300	−0.78 to 0.24
8.0/1.2 mg (n=58)	**5.4**	**−1.6**	**-30%**	**0.024**	**−1.1 to −0.078**

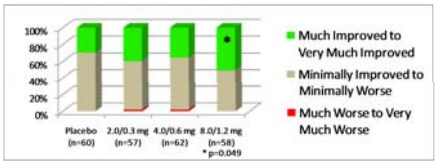
Statistical analysis is based on an ANCOVA model with terms for treatment and baseline score as fixed explanatory variables and pooled site (grouping of sites [within one country] with fewer than 8 subjects) as a random explanatory variable
[1] Pairwise comparison with placebo

In further analyses, the 8.0/1.2 mg CG100649 treatment group produced a clinically significant reduction in DPI pain scores during the entire 21-day treatment period compared to placebo (34% vs. 21%; p=0.008). Statistical significance was achieved at Days 7, 14, 21, and 28 (p=0.006, 0.031, 0.011, and 0.020, respectively), but not at Day 35. The Day 28 reduction in pain indicates that CG100649 continued to produce significant pain relief one week following the last dose which is equivalent to approximately one PK half-life of CG100649. This may have an advantage for patients who accidentally skip 1-2 doses.

At Day 21, a greater proportion of subjects in the 8.0/1.2 mg CG100649 treatment group (51%) reported being 'much improved' or 'very much improved' relative to their previous week's visit; this improvement was statistically significant (p=0.049) compared to the placebo group (29%). Comparable values were vs. 35-40% in the other CG100649 groups (not significant).

Subjects in the 8.0/1.2 mg CG100649 treatment group reported an early onset of 'much improved' or 'very much improved' at Day 7 (37%) compared to the placebo group (17%; p=0.040). This effect was not significant at Day 14 (31% vs. 24%; p=0.33), possibly due to a limited sample size.

On Day 28, 1 week after the treatment period had ended, subjects in the 8.0/1.2 mg CG100649 treatment group continued to report being 'much improved' or 'very much improved' (36%; p=0.044). Comparable values in the other CG100649 treatment groups were 22-26% (not significant) while the placebo group dropped to 11%.

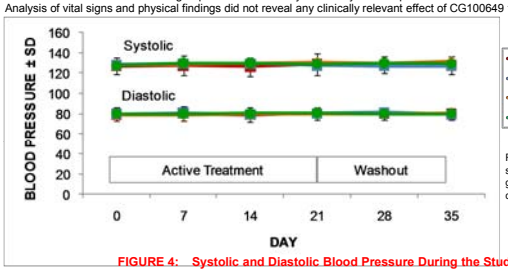


* p-value derived using Chi-square test with the three treatment groups compared to placebo at each visit.

FIGURE 3: Subject's Global Assessment (Day 21)

Statistical analyses of blood pressure no statistically significant differences between any of the active treatment groups and placebo at Day 21 (end of active treatment) or at Days 28 and 35 (washout period). A post-hoc analysis showed that there were no changes in cardiovascular parameters by treatment group among subjects who were less than 65 years of age (range 26-64 years) vs. those who were 65 years and older (range 65-75 years).

There were no relevant treatment group differences for any laboratory or ECG parameter.
Analysis of vital signs and physical findings did not reveal any clinically relevant effect of CG100649 treatment.



For clarity, ± SD Error Bars are shown only for the placebo group; all treatment groups had comparable variance.

FIGURE 4: Systolic and Diastolic Blood Pressure During the Study Period

CONCLUSIONS

These data show that an 8.0 mg loading dose of CG100649 followed by a 1.2 mg dose once daily for 3 weeks is well tolerated and efficacious in the treatment of OA pain in men. Further studies will evaluate higher CG100649 doses to determine maximum efficacious doses for reductions in OA pain and improvements in OA function, and maximum tolerated doses for preservation of normal cardiovascular, renal, and gastrointestinal function.

ACKNOWLEDGEMENT

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