Plasma concentrations were measurable up to 480 hr after the 1st dose and up to 360 hr after the 8th dose. There was statistically significant evidence for a linear dose-proportional increase, on average, in systemic exposure to CG100649 as measured by Cₚ₀. Single-dose CG100649 demonstrates a long terminal elimination half-life of approximately 5 days. Multiple dose cohorts consisting of a single loading dose followed by daily maintenance doses were given over 7 days (Group 1: 3 mg / 0.4 mg/day; Group 2: 6 mg / 0.8 mg/day). No adverse reactions or deaths occurred. Following repeated daily dosing, the degree of accumulation of CG10069 in plasma (Ro) on Day 8 was not appreciably different from that observed on Day 1. On average, Ro values ranged from 1.1 to 1.2, consistent with rapid achievement of steady-state following a loading dose. Plasma CG100649 concentrations of 4 to 5 ng/mL (Group 1) and 6 to 9 ng/mL (Group 2) were maintained during the repeat-dose regimen. Maximum plasma concentrations of CG100649 were reached at approximately 3 to 12 hr post-dose; thereafter, plasma concentrations exhibited terminal half-life of approximately 100 to 109 hr. Extrapolating from the preclinical efficacy data, the plasma concentrations with the higher maintenance dose regimen exceeded probable therapeutic concentrations by at least four fold. All doses were well tolerated. Use of a dose + reduced maintenance dose regimen may reduce the time to reach steady state plasma concentrations to approximately one day.

CG100649 is a novel dual-acting cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA) inhibitor which is being developed for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain. Single oral doses of 1, 5, 8, or 12 mg of CG100649 were well tolerated when given to healthy male subjects (N=4 and 2 placebo subjects per dose). There was statistically significant evidence for a linear dose-proportional increase, on average, in systemic exposure to CG100649 as measured by Cₚ₀. Single-dose CG100649 demonstrates a long terminal elimination half-life of approximately 5 days. Multiple dose cohorts consisting of a single loading dose followed by daily maintenance doses were given over 7 days (Group 1: 3 mg / 0.4 mg/day; Group 2: 6 mg / 0.8 mg/day). No adverse reactions or deaths occurred. Following repeated daily dosing, the degree of accumulation of CG10069 in plasma (Ro) on Day 8 was not appreciably different from that observed on Day 1. On average, Ro values ranged from 1.1 to 1.2, consistent with rapid achievement of steady-state following a loading dose. Plasma CG100649 concentrations of 4 to 5 ng/mL (Group 1) and 6 to 9 ng/mL (Group 2) were maintained during the repeat-dose regimen. Maximum plasma concentrations of CG100649 were reached at approximately 3 to 12 hr post-dose; thereafter, plasma concentrations exhibited terminal half-life of approximately 100 to 109 hr. Extrapolating from the preclinical efficacy data, the plasma concentrations with the higher maintenance dose regimen exceeded probable therapeutic concentrations by at least four fold. All doses were well tolerated. Use of a dose + reduced maintenance dose regimen may reduce the time to reach steady state plasma concentrations to approximately one day.

INTRODUCTION

CG100649 is a novel dual-acting cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA) inhibitor which is being developed for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain. The CA inhibitor activity of CG100649 is unlikely to affect CG100649’s intended therapeutic effects since CG100649 is believed to dissociate from CA and increase its local concentration in tissues which have low CA activity, such as inflamed joints. Given that CAs are abundantly present in a variety of tissues and cells, the high affinity of CG100649 for CAs may significantly affect the tissue distribution profile. CG100649 is expected to show reduced renal excretion following a loading dose. CG10069 was well tolerated. There were 24 treatment-emergent adverse events; 16 were reported by 8 of the 24 subjects; 25% of subjects in the treatment group and 50% of subjects in the placebo. There were no deaths reported. Figure 1 shows the mean plasma concentrations following multiple ascending dose study. Max plasma concentrations were reached at approximately 5.5 to 72.0 hr (median estimates), then declined with a mean apparent terminal half-life of approximately 111 hr (6 mg) and 133 hr (12 mg).

RESULTS

Sing Dose Study: CG100649 was well tolerated. A total of 14 treatment-emergent adverse events were reported by 8 of the 24 subjects: 25% in the treatment group and 50% in subjects in the placebo. These adverse events were gastrointestinal (vomiting, diarrhea, anorexia) not related to treatment with CG10069. There was no evidence of occult gastrointestinal blood loss. No clinically significant laboratory abnormalities were reported. There were no obvious trends in any of the laboratory data or in other safety including physical examination, vital signs, and 12-lead ECG. Following single administration, plasma concentrations of CG100649 were generally measurable up to 144 hr (1 mg), 240 hr (5 mg), 384 hr (8 mg) and 480 hr (12 mg) post-dose. Max plasma concentrations were reached at approximately 5.5 to 72.0 hr (median estimates), then declined with a mean apparent terminal half-life of approximately 111 hr (6 mg) and 133 hr (12 mg). There was statistically significant evidence for a dose-proportional increase, on average, in systemic exposure to CG100649 as measured by Cₚ₀. The prolonged half-life would result in steady state plasma concentrations being reached over approximately 20 days following a loading dose. However, plasma concentrations of CG100649 were significantly higher than loading dose to be used to reduce the time to reach steady state plasma concentration in future clinical studies.

CONCLUSIONS

1. CG100649 was well tolerated by the healthy male subjects participating in this study.
2. The subject incidence of adverse events was higher in subjects receiving the lower dose (83% of subjects receiving 1 mg), 58% of subjects receiving 2 mg, and 43% of subjects receiving 4 mg. Adverse events were mild in intensity.
3. Plasma CG100649 concentrations of 4 to 5 ng/mL (Group 1) and 6 to 9 ng/mL (Group 2) were maintained during the repeat-dose regimen. Maximum plasma concentrations of CG100649 were reached on average, at approximately 3 to 12 hr post-dose.
4. The mean apparent terminal half-life was 100 to 109 hr.
5. Between-subject (inter-individual) variability in the extent of systemic exposure was generally low, with coefficients of variation ranging from 12% to 30%.
6. Systemic exposure to CG100649 on Day 8 was not appreciably different to that observed on Day 1.

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**ABSTRACT**

CG100649 is a novel Dual-Acting COX-2 and Carbonic Anhydrase Inhibitor: Multi-Dose Pharmacokinetics and Safety Evaluation in Healthy Male and Female Subjects

**INTRODUCTION**

CG100649, a novel dual-acting cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA) inhibitor which is being developed for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain. Given that CAs are abundantly present in a variety of tissues and cells, the high affinity of CG100649 for CAs may significantly affect its local concentration in tissues which have low CA activity, such as inflamed joints. CG100649 is currently in phase II clinical trials in Europe.

**METHODS**

A Phase I double-blind, multi-dose, placebo-controlled study was conducted in 47 healthy male and female volunteers. CG100649 was developed by the United States Food and Drug Administration (FDA) through its overall safety profile by reducing effective free drug concentrations in tissues with high CA activity.

**CONCLUSIONS**

1. CG100649 was well tolerated in this U.S. Phase I study in 47 healthy male and female subjects.
2. A Phase II clinical trial in Europe was conducted in healthy volunteers. Cohort B; F
   - Male; 2 mg + 0.3 mg/day
   - Female; 2 mg + 0.3 mg/day
3. CG100649 showed approximately 85-100 times higher concentrations in whole blood than plasma due to its preferential high-affinity binding to red blood cell carbonic anhydrase. The most frequently reported adverse events were headaches (37% of active treatment subjects and 42% of placebo subjects) and edema (11% of active treatment subjects and 6% of placebo subjects), and pain in extremity (9% of active treatment subjects and 0% of placebo subjects).

**ACKNOWLEDGMENT**

This study was supported by Bio-Star project of Ministry of Knowledge Economy of Korea.

Supported by a grant from CrystalGenomics, Inc.
CG100649 is a novel dual-acting cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA) inhibitor which is being developed for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain. CG100649 has moderate to high potency inhibition of COX-2, ranging from 15-fold in human cells (whole blood, platelets and macrophages) to 45-fold in mouse peritoneal macrophages. In the in vitro COX-2 activity assay, CG100649 showed weaker COX-2 inhibitory activity than indomethacin in rat whole blood. CG100649 was a potent inhibitor of inflammation in adjunctive animals and collagen-induced arthritis in Lewis rats (paw swelling ED50s were 0.10 and 0.22 mg/kg/day). CG100649 and indomethacin showed similar potencies in the mouse acute air pouch and rat naïve paws edema inflammatory animal models. CG100649 was 5x more potent than indomethacin in the thermal hyperalgesia rat model and had significantly greater anti-inflammatory potency than Aspirin. CG100649 inhibited iNOS and is active with IC50s of 0.33 μM and 0.062 μM respectively (acetazolamide were 0.68 μM and 0.0091 μM, respectively). The CA inhibitory activity of CG100649 is likely to affect inflammation more than COX-2. We hypothesized that it may be possible to avoid GI and CV side effects by tissue-specific inhibition of COX-2. CG100649 is an orally available, small molecule dual inhibitor of COX-2 and CA. Oral administration of CG100649 produces significant levels of free active drug in joints, synovial fluid, and the CNS which are devoid of CA activity, but it is sequestered in an inactive form in many other tissues because the drug is tightly bound to CA-I and CA-II, a known family of proteins that are prevalent in the blood and in sites of potential COX-2 toxicity. The high affinity of CG100649 for CA could produce a reduction in blood pressure similar to the potent CA inhibitor acetazolamide. CG100649 is expected to show reduced COX-2 inhibition in tissues or organs of toxicity concern for NSAIDs. It is possible that the high affinity of CG100649 for CA could significantly affect the tissue distribution profile. CG100649 is expected to show reduced COX-2 inhibition in tissues or organs highly enriched with CAs (GI tract, blood, and kidney) due to substantial uptake of CG100649 by CAs, this may provide protection for organs of toxicity concern. CG100649 is currently in phase II clinical trials in Europe.

INTRODUCTION

Many NSAIDs are available for treating arthritic pain through the inhibition of COX-2 or COX-2. However, there is still a large unmet medical need for better antiinflammatory treatments because adverse effects in the gastrointestinal (GI) tract and cardiovascular (CV) system are related to inhibition of COX-2. Despite these issues, the therapeutic benefits of NSAIDs are significant, and these drugs have been widely prescribed, mainly because of the high efficacy of COX-2 inhibitors in the treatment of inflammatory conditions. We hypothesized that it may be possible to avoid GI and CV side effects by tissue-specific inhibition of COX-2. CG100649 is an orally available, small molecule dual inhibitor of COX-2 and CA. Oral administration of CG100649 produces significant levels of free active drug in joints, synovial fluid, and the CNS which are devoid of CA activity, but it is sequestered in an inactive form in many other tissues because the drug is tightly bound to CA-I and CA-II, a known family of proteins that are prevalent in the blood and in sites of potential COX-2 toxicity. The high affinity of CG100649 for CA could produce a reduction in blood pressure similar to the potent CA inhibitor acetazolamide. CG100649 is expected to show reduced COX-2 inhibition in tissues or organs of toxicity concern for NSAIDs. It is possible that the high affinity of CG100649 for CA could significantly affect the tissue distribution profile. CG100649 is expected to show reduced COX-2 inhibition in tissues or organs highly enriched with CAs (GI tract, blood, and kidney) due to substantial uptake of CG100649 by CAs, this may provide protection for organs of toxicity concern. CG100649 is currently in phase II clinical trials in Europe.

IN VITRO PHARMACOLOGY

Table 1. Inhibitory activity of CG100649 against COX

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cells</th>
<th>COX-2 IC50, nM</th>
<th>COX-2 Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG100649</td>
<td>PBMCS (COX-2)</td>
<td>0.97</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>Platelets (COX-1)</td>
<td>230</td>
<td>3,300</td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>1.8</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>Rosofebic</td>
<td>2.5</td>
<td>41</td>
</tr>
</tbody>
</table>

CG100649 is an orally available small molecule dual inhibitor of COX-2 and CA. The compound is a highly active inhibitor for COX-2 and is moderately selective for COX-2 over COX-1. It inhibits CA at nM concentrations.

Table 2. Inhibitory activity of CG100649 against CAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cells</th>
<th>CA-I</th>
<th>CA-II</th>
<th>CA-III</th>
<th>Remak **</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG100649</td>
<td>204</td>
<td>63</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>21</td>
<td></td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>50.000</td>
<td></td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Celecoxib inhibits CA-I &amp; CA-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>** Values of in-house study unless noted otherwise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Inhibitory activity of CG100649 against AcP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cells</th>
<th>IC50, μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG100649</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

CG100649 is a potent inhibitor of AcP & CA. The compound is a highly active inhibitor of AcP in AcP-rich tissues.

CG100649 is a dual inhibitor of COX-2 and carbonic anhydrase. The working hypothesis is that CG100649 cannot inhibit COX-2 in CA-rich tissues such as inflammatory joints. Thus, CG100649 should have reduced COX-2 effects in blood, blood vessels and kidneys by binding to CA and not binding to COX-2.

Table 4. Efficacy of CG100649 in the standard preclinical animal models.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Model</th>
<th>Foot Volume (ml)</th>
<th>Remak **</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG100649</td>
<td>* Celecoxib &amp; Indomethacin &amp; Rofecoxib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>** values of in-house study unless noted otherwise</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Plasma PK Data in Male SD Rats for CG100649 (pp)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cmax, ng/ml</th>
<th>AUC0-24h, ng•h/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG100649</td>
<td>1.0</td>
<td>728</td>
<td>4456</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>350</td>
<td>1750</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>4</td>
<td>22</td>
</tr>
</tbody>
</table>

Thus, the projected OA therapeutic plasma level of CG100649 is 4 ng/ml and the OA therapeutic plasma exposure is (4 ng/ml x 24 hr) or about 100 ng•h/ml.

CONCLUSIONS

1) CG100649 is a highly active inhibitor of COX-2 which is moderately selective for COX-2 over COX-1. It also inhibits CAs in the nanomolar level. Such dual inhibition is designed to avoid COX-2 inhibition in CA-rich tissues (CV & GI) but fully inhibit COX-2 in CA-lacking tissues such as inflammatory joints.

2) The OA therapeutic plasma level of CG100649 is projected to be 4 ng/ml.

Supported by a grant from CrystalGenomics, Inc.
CG100649 is a novel dual-acting COX-2 and carbonic anhydrase (CA) inhibitor which is currently in phase II clinical trials for the treatment of the bacterial Arthritis. Oral dosing produced large GI safety margins in rats and monkeys despite its modest COX-2 selectivity. 

**Safety pharmacology** studies showed that CG100649 produced no inhibition of hERG tail current. In whole body radiography (QWBPI) studies in rats, the highest actual dose (5.0 mg/kg/day) was well tolerated and produced no obvious signs of toxicity. Female rats showed sex related difference in systemic exposure is commonly observed in rats and is usually attributed to a lower metabolizing capacity of female rats. In male and female monkeys, following single and repeat oral doses of up to 30 mg/kg CG100649 to females rats which is commonly observed in rats due to a lower metabolizing capacity in females. The general activity and behavior in rats was not altered by the oral administration of CG100649 at single dose levels up to 30 mg/kg. Similarly, oral treatment of CG100649 did not significantly affect the respiratory rate or end tidal volume in conscious rats. Administration of oral doses up to 30 mg/kg CG100649 to awake cynomolgus monkeys had no marked effect on arterial blood pressure, heart rate or lead II ECG parameters (RR, QT, QTC and QRS intervals or QRS duration), waveform or rhythm in the 8 hours following dosing. Treatment with 2 μg/ml CG100649 in HEK293 cells stably transfected with hERG (DNA produced in CHO's binds to hERG) in whole body radiography (QWBPI) studies in rats, the highest activity was associated with white blood and tissues with high blood perfusion such as liver, lung, kidney, and bone marrow which also have the highest CA activity. These data project a favorable safety profile for CG100649 in humans.

**INTRODUCTION**

COX-2 inhibition by classical non-steroidal anti-inflammatory drugs (NSAIDs) effectively treats acute and chronic pain. However, 2% to 4% of patients taking NSAIDs have symptomatic gastrointestinal (GI) pain and their complications. Further studies suggest that COX-2 inhibition mediates the anti-inflammatory effects of NSAIDs, whereas COX-1 inhibition is responsible for adverse effects on the GI tract. This led to the development of COX-2 selective inhibitors (coxibs) that have the same anti-inflammatory benefits of nonselective NSAIDs but fewer GI side effects.

Effects of COX-2 inhibition on the cardiovascular (CV) system are not straightforward. Inhibition of COX-2-derived PG2, which reduces a protective effect on thrombogenesis, hypertensive, and hypoxia induced vasoconstriction in vivo (2) in rats, the highest risk of myocardial infarction and stroke. Thus, all commercially available NSAIDs and coxibs produce adverse GI or CV side effects in susceptible patients. Since the GI side effects of NSAIDs may be generated by COX-2 inhibition, we hypothesized that tissue-specific inhibition of COX-2 in inflamed joints may be a novel way to prevent adverse CV side effects in vascular tissues.

CG100649 achieves tissue specific inhibition of COX-2 through dual inhibition of COX-2 and 3-carboxylic anhydrase (CA). As summarized in the Figure 1, the working hypothesis is that COG100649 cannot inhibit COX-2 in CA-rich tissues & GI, but it can fully inhibit COX-2 in tissues that lack CA activity such as inflammatory joints. CG100649 binds preferentially to CA in blood, blood vessels, and kidneys. In inflamed tissues, CG100649 is a highly active COX-2 inhibitor which is moderately selective for COX-2 over COX-1. The tight binding of CG100649 to carbonic anhydrase (CA) in the GI tract may be hypothesized that tissue-specific inhibition of COX-2 in inflamed joints may be a novel way to prevent adverse CV side effects in vascular tissues.

CG100649 is a novel dual-acting cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA) inhibitor which is currently in phase II clinical trials for the treatment of the bacterial Arthritis. Oral dosing produced large GI safety margins in rats and monkeys despite its modest COX-2 selectivity. In vivo genotoxicity studies showed that CG100649 does not induce reverse mutations in the Ames test. However, it increased chromosomal aberrations in CHO cells at 500 μg/ml, which also produced 50% cellular toxicity. In vivo genotoxicity studies showed that CG100649 did not produce genotoxic effects in the mouse bone marrow microculture test or in the unscheduled DNA synthesis (UDS) assay in rat liver. The weight of evidence suggests that the genotoxicity is low. Oral 4-week toxicokinetic studies in rats at doses up to 3.5 mg/kg/day showed that systemic exposure in females was greater than in males due to the longer half-life in females (0.12-hr) compared to males (4.7-hr). A related difference in systemic exposure is commonly observed in rats and is usually attributed to a lower metabolizing capacity of female rats. In male and female monkeys, following single and repeat oral doses of 12 mg/kg/day, Cmax was generally reached in 2-4 hours post dose and the terminal halflife was shown to approx 60 hr. Systemic exposure at week 4 was greater than on day 1 (the degree of accumulation, P RU was approximately 1.6 to 3.8). The overall extent of exposure was not appreciably different in male and female monkeys.

**RESULTS**

The oral maximum tolerated dose (MTD) for CG100649 was determined to be approximately 1500 mg/kg in mice. In rats, the MTD was 125 mg/kg in males and 15 mg/kg in females. Clinical findings were generally of GI origin.

Oral safety studies were conducted in rats and monkeys for 28 days. In male rats, target doses up to 5.0 (3.6 actual dose) mg/kg/day were well tolerated and produced no obvious signs of toxicity. Female rats showed treatment-related histopathological findings in the intestines at target doses of 1.0, 1.5 and 3.0 mg/kg/day. Cytotoxic effects treated at 12 mg/kg/day showed a low incidence pathological finding in the stomach and in blood chemistry. At 5 mg/kg/day, blood chemistry changes were noted in only one rat. On the basis of these findings it was concluded that 2 mg/kg/day was a no observed effect level (NOEL), and 5 mg/kg/day was a no observed adverse effect level (NOAEL).

**CONCLUSIONS**

1) Safety pharmacology, genetic toxicity, single and repeat dose toxicity (4-week and 90-day studies in rats and monkeys), developmental toxicity, reproductive toxicity, and dog renal studies show a favorable safety profile for CG100649.

2) CG100649 produced large GI safety margins in rats and monkeys despite its modest COX-2 selectivity over COX-1. The tight binding of CG100649 to carbonic anhydrase (CA) in the GI tract may be responsible for its good GI safety.

3) Small effects on the renal hemodynamics suggest negligible COX-2 inhibition in the renal vasculature owing to the significant enrichment of CA in the renal vasculature. Likewise, COX-2 inhibition is too low to induce other types of blood vessels, developing a benefit on CV safety.

**REFERENCES**
