To become a fully integrated global biopharmaceutical company by extending our footprint in Korea and throughout the world
About CrystalGenomics

- Dedication to the discovery and development of novel pharmaceuticals in areas of unmet medical need using innovative platform technologies

- Commercial stage biopharmaceutical company with solid fundamentals and financial footing

CrystalGenomics


Certified by Korean Gov.

Launch of Acelex® in Korea
### CG Product and R&D Pipeline

#### PRODUCT

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Indication</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain &amp; Inflammation</td>
<td>Osteoarthritis</td>
<td>Acelex® (polmacoxib)</td>
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</table>

#### R&D PIPELINE

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Indication</th>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Infectious Disease</td>
<td>MRSA</td>
<td>First-in-class</td>
<td></td>
<td></td>
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<tr>
<td>Cancer</td>
<td>MDS</td>
<td>Best-in-class</td>
<td></td>
<td></td>
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<tr>
<td>Cancer</td>
<td>Pancreatic cancer</td>
<td>Best-in-class</td>
<td></td>
<td></td>
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<tr>
<td>Cancer</td>
<td>AML</td>
<td>First-in-class</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CNS</td>
<td>Alzheimer</td>
<td>First-in-class</td>
<td></td>
<td></td>
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<tr>
<td>Hematologic</td>
<td>Anemia</td>
<td>Best-in-class</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
CG Discovery Process and Platform Technology

**Lead Discovery (SCP™)**
- **SCPTM Library**
- **Virtual Screening**
- **SCP™ NMR**
- **In vitro Assay**

**Structure Determination (SPS™)**
- **Target Selection**
- **Synchrotron**

**Lead Optimization and Candidate Selection (SDF™)**
- **Drug Design & MediChem**
- **SDF™ X-ray**
- **SDF™ Informatics**
- **Parallel Synthesis**
- **Biological Evaluations**
- **In vivo Evaluation**
- **Pre-clinical Candidate**
- **Pre-clinical & Clinical Studies**

**In vitro DMPK**
- **Target Assays**
- **Cellular Assays**
- **DDoS**
Phosphodiesterase 5 inhibitors

- Viagra® (sildenafil)
- Cialis® (tadalafil)
- Levitra® (vardenafil)

CG Alliance Partners: Current and Past

- AstraZeneca
- DONG-A ST
- Hanmi
- TRPHARM
- Oxford Bioscience Partners
- Hanwha Venture Capital
- ProQuest Investments
- Bausch & Lomb
- AMOREPACIFIC
- yuyu
- KRICT
- KRB
- KIST
- DAIICHI SANKYO
- OncoTherapy Science, Inc.
- SBI Biotech
- CARNA BIOSCIENCES
- KISSEI PHARMACEUTICAL CO., LTD.
- ASAN Medical Center
Acelex® (polmacoxib)
Growth in Pain Therapeutics Market

- Pain therapeutics market growing due to aging of population and obesity epidemic
- Size of the Nonsteroidal Anti-inflammatory Drugs (NSAIDs) market, including COX-2 inhibitors, approx. $17.5B
## Acelex®: Tissue-Selective COX-2 Inhibitor

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
<th>Efficacy</th>
<th>Gastrointestinal Risk</th>
<th>Cardiovascular Risk</th>
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</thead>
<tbody>
<tr>
<td><strong>Traditional NSAID</strong></td>
<td>• naproxen, ibuprofen, diclofenac</td>
<td>Moderate ~ High</td>
<td>High</td>
<td>*Low</td>
</tr>
<tr>
<td></td>
<td>• COX-1 and COX-2 inhibition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dose: &gt; 1000mg/day TID or QID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Proton pump inhibitor combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Selective COX-2 Inhibitors</strong></td>
<td>• celecoxib, etoricoxib</td>
<td>Moderate ~ High</td>
<td>Low</td>
<td>*Low</td>
</tr>
<tr>
<td></td>
<td>• COX-2 selective inhibition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dose: 30–120 mg/day (etoricoxib) 200-800mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(celecoxib)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tissue-Selective COX-2 Inhibitor</strong></td>
<td>• Acelex® (polmacoxib)</td>
<td>High</td>
<td>Low</td>
<td><strong>Very low</strong></td>
</tr>
<tr>
<td></td>
<td>• Tissue-selective COX-2 inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dose: 2mg once a day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Occurrences are rare enough to be considered insignificant
**Acelex® has a mechanism of action that potentially allows for minimal cardiovascular risk
Acelex®: Developed Based on Global Standard

- Carcinogenicity (GLP-Tox)
- Drug-drug interaction
- Supra-therapeutic dose
- Phase IIb
- Phase III
- Long-term safety study

Phase IIa

GLP-Tox

Phase I

Pharmacodynamic
Overall improvement of signs and symptoms of osteoarthritis in terms of PGA* scores at week 3

*PGA (Physician’s Global Assessment)
Acelex® Shows Quicker Onset of Pain Relief

For WOMAC Physical Function, Acelex showed superior efficacy against celecoxib at Week 3 and non-inferiority to celecoxib at Week 6

*WOMAC: Western Ontario and McMaster Universities Arthritis Index
**Acelex® 2mg Capsule**  
Tissue-selective COX-2 inhibitor for relief of pain symptoms of OA

- Approved by the MFDS* (Feb. 2015),
- Launched in Korea by Dong-A ST (Sep. 2015)
- Partnered with TR-Pharm for Turkey & MENA (Jan. 2016)

<table>
<thead>
<tr>
<th>Category</th>
<th>Advantages of Acelex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>• Quicker onset of relief from the signs and symptoms of OA over celecoxib</td>
</tr>
<tr>
<td></td>
<td>• Superior PGA (Physicians Global Assessment) scores compared to celecoxib</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>• Lowest daily dose among all known NSAIDs</td>
</tr>
<tr>
<td></td>
<td>• Once-a-day dosing regimen unlike most traditional NSAIDs</td>
</tr>
<tr>
<td><strong>Gastrointestinal Side Effects</strong></td>
<td>• Better gastrointestinal (GI) safety in comparison to traditional NSAIDs</td>
</tr>
<tr>
<td><strong>Cardiovascular Side Effects</strong></td>
<td>• Cardiovascular (CV) safety to potentially minimize CV side effects</td>
</tr>
</tbody>
</table>

*MFDS: Ministry of Food and Drug Safety
**Acelex®: Export & Out-Licensing Status**

Acelex® to expand to global markets

<table>
<thead>
<tr>
<th>Territory</th>
<th>Partnership</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey (+MENA)</td>
<td>Product export</td>
<td>Partnered</td>
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<tr>
<td>China</td>
<td>Product export</td>
<td>Contract in progress</td>
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<tr>
<td>North America</td>
<td>Out-licensing</td>
<td>In discussion</td>
</tr>
<tr>
<td>Europe</td>
<td>Out-licensing</td>
<td>In discussion</td>
</tr>
<tr>
<td>Japan</td>
<td>Out-licensing</td>
<td>In discussion</td>
</tr>
<tr>
<td>South America</td>
<td>Product export</td>
<td>In negotiation</td>
</tr>
<tr>
<td>South East Asia</td>
<td>Product export</td>
<td>In negotiation</td>
</tr>
<tr>
<td>Russia &amp; CIS</td>
<td>Product export</td>
<td>In negotiation</td>
</tr>
</tbody>
</table>
Acelex®: Lifecycle Management (LCM) Strategy

Maintaining exclusive position up to 2034 to maximize revenues

Expansion of Acelex Product Portfolio

Launched 2015
Acelex 2mg Capsule

Combination products

Additional indications

New dosage forms

LCM through 2034
CG400549: Novel Antibiotic
MRSA is a Global Epidemic

- Methicillin Resistant *Staphylococcus aureus* (MRSA) is often referred to as the “Super Bug”
  - President Obama issued an executive order in 2014 to combat antibiotic resistance
- According to the CDC, over 72,000 invasive MRSA infections and 9,194 related deaths occurred in 2014
- Rate of MRSA infections recorded in hospitals doubled between 2003 to 2008 (Aug. 2012, UHC and Univ. of Chicago Medicine)

*Worldwide prevalence of hospital-acquired MRSA*  
(Global Epidemiology of MRSA, 2014)
CG400549: First-in-class FabI Inhibitor

- Fatty-acid biosynthesis inhibitor (FabI)
- Novel mechanism to block a key enzyme in the bacterial cell membrane formation pathway
CG400549-FabI Complex Structure Confirmation

S. aureus FabI

CG400549

Confirmation of binding mode for CG400549

X-ray Crystal Structure

Docking Structure
Phase IIa study for POC completed in the USA showed 100% of evaluable subjects had been clinically cured by the end of the study.

Formulations for both oral and IV.
## CG Seeking Global Partnership After Phase II

<table>
<thead>
<tr>
<th>Date</th>
<th>Licensor</th>
<th>Licensee</th>
<th>Product</th>
<th>Category</th>
<th>Deal Type</th>
<th>Territory</th>
<th>Deal Size US$ M</th>
<th>Upfront US$ M</th>
<th>Royalty US$ M</th>
<th>Milestone US$ M</th>
<th>Dev. Stage at signing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Meiji and Fedora</td>
<td>Roche</td>
<td>OP0595 (beta-lactamase inhibitor)</td>
<td>Bacterial Infections</td>
<td>Codevelopment, Commercialization, License</td>
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<td>Undisclosed</td>
<td>Undisclosed</td>
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<tr>
<td>2013</td>
<td>Trius</td>
<td>Cubist</td>
<td>tedizolid</td>
<td>Bacterial Infections</td>
<td>M&amp;A</td>
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<td>707</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>P3 completion</td>
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<td>2013</td>
<td>Optimer</td>
<td>Cubist</td>
<td>fidaxomicin</td>
<td>Bacterial Infections</td>
<td>M&amp;A</td>
<td></td>
<td>535</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>launched</td>
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<tr>
<td>2013</td>
<td>Polyphor</td>
<td>Roche</td>
<td>POL7080</td>
<td>Bacterial Infections</td>
<td>Co-development</td>
<td>Worldwide</td>
<td>547.4</td>
<td>38.3</td>
<td>-</td>
<td>509.1</td>
<td>P1 completed</td>
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<tr>
<td>2009</td>
<td>Zymogenetics</td>
<td>Bristol Myers Squibb</td>
<td>PEG-interferon</td>
<td>Infections</td>
<td>Codevelopment, Commercialization, License</td>
<td>Europe, USA</td>
<td>535</td>
<td>85+20</td>
<td>N/A</td>
<td>430</td>
<td>P1b</td>
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<tr>
<td>2009</td>
<td>Alnylam</td>
<td>Cubist</td>
<td>ALNRSV01, second gen. RNAi-based RSV inhibitors</td>
<td>Respiratory syncytial virus infection</td>
<td>50:50 Co-development, commercialization, license, sales</td>
<td>Worldwide</td>
<td>20</td>
<td>N/A</td>
<td>82.5</td>
<td>P2</td>
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</table>

*Worldwide
CG200745: Epigenetic Cancer Therapeutic
CG200745: Best-in-class Histone Deacetylase (HDAC) Inhibitor

- CG200745 has a superior pharmacokinetic (PK) and safety profile over other HDAC inhibitors (both approved & in development) due to its high level of drug exposure even at low doses
- Superb efficacy: 56% of all patients had stable disease in the Phase I study, an all-comer study which included a variety of solid tumor patients
- Phase Ib/Il in-progress for myelodysplastic syndrome (MDS) and pancreatic cancer in Korea

Cancer and epigenetics

Cancer’s epicentre
New understanding of how cancers work is yielding new treatments
Apr 7th 2012
Myelodysplastic Syndrome (MDS)

A group of rare & malignant hematopoietic disorders characterized by

• Bone marrow failure that results in cytopenia & related complications
• Dysplastic cytologic morphology is the hallmark of the disease
• No other options after current treatment failure (~80% failure rate, median overall survival = 4.3 months)
• Tendency to progress to AML

CG200745 designated as an orphan drug for treatment of MDS

• Orphan drug designation = premium pricing, quicker approval, market exclusivity
• CG200745 will target patients with MDS who have failed to respond to current therapies
  (i.e, hypomethylating agents: azacitidine, decitabine)
CG200745: Efficacy in Hematologic Cancers

- Superb efficacy shown in orthotopic animal model

WEHI-3 Leukemic syngenic model

**WBC (L/μL)**

- Survival (%)
  - control
  - Leukemia, untreated
  - Leukemia, 30mg/kg SAHA
  - Leukemia, 30mg/kg CG200745

**Body weight (g)**

- BALB/c nude mouse, n=10
  - vorinostat
  - CG200745

- Vehicle*
  - vorinostat
  - CG200745

*vehicle affected with splenomegaly
CG200745: Superior Efficacy in Disease Model

- CG200745 showed superior efficacy in the azacitidine (AZA) and decitabine (DEC) resistant xenograft myelodysplastic syndrome (MDS) mouse model.

**MOLM/AZA-1 model**

- Vehicle
- 45mpk CG20075

**MOLM/DEC-5 model**

- Vehicle
- 45mpk CG20075

Athymic nude, n=10, d1-5 on/6-7 off, 2weeks admin.

* Azacitidine resistant
** Decitabine resistant
• CG200745 treatment in patient derived cells shows significant efficacy
**Recent HDAC Inhibitor Deals**

- **NDA approval expected in Korea by 2019 (or earlier)**
- **CG to out-license ex-Korea global rights after Phase II**

<table>
<thead>
<tr>
<th>Date</th>
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<th>Milestone US$ M</th>
<th>Dev. Stage at signing</th>
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<tr>
<td>Feb.16'</td>
<td>HUYA</td>
<td>Eisai</td>
<td>HBI-8000 (HDACi)</td>
<td>Lymphoma &amp; solid tumors</td>
<td>Commercialization, Development, License</td>
<td>Japan, Korea &amp; SEA*</td>
<td>280</td>
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<td>Undisclosed</td>
<td>Undisclosed</td>
<td>P1 completed</td>
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<td>Apr.15'</td>
<td>4SC</td>
<td>Menarini</td>
<td>Resminostat (HDACi)</td>
<td>Solid tumors</td>
<td>Commercialization, Development, License</td>
<td>China &amp; APAC**</td>
<td>€95</td>
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<td>Jan.15'</td>
<td>Syndax</td>
<td>Kyowa Hakko Kirin</td>
<td>Entinostat (HDACi)</td>
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<td>Commercialization, Development, License</td>
<td>Japan &amp; Korea</td>
<td>100</td>
<td>25</td>
<td>Undisclosed</td>
<td>75</td>
<td>P3</td>
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<tr>
<td>Sep.13'</td>
<td>Syndax</td>
<td>Eddingpharm</td>
<td>Entinostat (HDACi)</td>
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<td>Commercialization, Development, License</td>
<td>China &amp; Asia</td>
<td>Undisclosed</td>
<td>Undisclosed</td>
<td>Undisclosed</td>
<td>Undisclosed</td>
<td>P3</td>
</tr>
<tr>
<td>Apr.11'</td>
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<td>Yakult Honsha</td>
<td>Resminostat (HDACi)</td>
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<td>Commercialization, Development, License</td>
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<td>€6</td>
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<tr>
<td>Feb.10'</td>
<td>Topotarget</td>
<td>Spectrum</td>
<td>Belinostat (HDACi)</td>
<td>Liquid tumors</td>
<td>Co-development, License</td>
<td>North America and India</td>
<td>350</td>
<td>30</td>
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<td>Approval</td>
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<td>Dec.09'</td>
<td>Gloucester</td>
<td>Celgene</td>
<td>Istodax (HDACi)</td>
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<td>640</td>
<td>340</td>
<td>-</td>
<td>300</td>
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* South East Asia

**Asia Pacific**
CG026806: Targeted Cancer Therapeutic
CG026806: First-in-class AML Therapeutic

- CG026806 is dual target inhibitor of FLT3 and BTK
- Recent publications highlight the importance of BTK in AML treatment

FLT3-ITD and TLR9 employ Bruton’s tyrosine kinase to activate distinct transcriptional programs mediating AML cell survival and proliferation

Thomas Osterhelch1,2, Sebastian Moh1, Jasmin Correa2, Julius Beck1, Carmen Dibello, Heline Braun1, Anjali Chawla3, Silvia Münch1, Johannes Wich1, Mark F. Osterhelch2, Gesine Bug1, Nathaniel Schonberger2, Christina Piskui, Ekhard Schütz1, Heini U. Uhl1, and Hubert Sepp1

Abstract
Acute myeloid leukemia (AML) is driven by oncogene mutations. With many cell autonomous drivers driving signaling in the context of the genetic disease burden, here, we analyzed the role of Bruton’s Tyrosine Kinase (BTK) in AML. BTK was frequently expressed and its inhibition inhibited proliferation and survival of AML cells - also in the stem cells. By interaction analysis of phosphoproteomics, we characterized BTK signaling networks, dependent signaling to highly context-dependent, in mediating FLT3-ITD dependent Myeloid and STAT3 axis of FLT3-ITD and BTK showed additive effects. In FLT-3 ITD and BTK, dual inhibition of FLT3-ITD and BTK showed additive effects. In FLT-3 ITD and BTK, dual inhibition of FLT3-ITD and BTK showed additive effects.

Key Points
- Two novel transcriptional modules, consisting of BTK, FLT3-ITD or TLR9, induce distinct oncogenic signaling
- The study suggests subtype-specific treatments considering combinations and chronology of AML affords

Introduction
Acute myeloid leukemia (AML) is primarily a disease of the elderly. In younger patients (<65 years, median diagnosis 72 years), there is improved survival over the decades; however, older patients have seen less improvement, with intensive cytotoxic treatment being a dilemma. AML is composed of heterogeneous groups of tumors. Despite this diversity, AML relies on common programs of self-renewal downstream of the driver oncogenes, suggesting that disease is caused by only a few mutations, and mechanistically common therapeutic approaches are broadly useful despite oncogenic involvement.

Tyrrosine kinases (TK) are attractive druggable targets in cancer. In AML, TK-inhibiting strategies occur in 55% of patients. Furthermore, TK-dependent cell survival pathways are dysregulated in most cases. Bruton’s TK (BTK) has been identified as functionally important in malignant hematopoietic cells. BTK was originally identified functionally in B-cell receptor signaling, with mutations blocking B-cell development. Other receptor tyrosine kinases (RTKs) such as SRC and AKT are also important. The inhibition of Bruton’s TK by BTK inhibitors has demonstrated promising activity and tolerability against TK-resistant AML, including chronic lymphocytic leukemia (CLL) mantle cell lymphoma, hairy cell leukemia, multiple myeloma, and diffuse large B-cell lymphoma. In addition to lymphoid cells, BTK expression has also been found in hematopoietic stem cells (HSCs), multipotent progenitors, and several other hematopoietic cells including erythroid and megakaryocytic cells. Furthermore, it is known that BTK deficiency/inhibition affects myeloid cells, including macrophage lipopolysaccharide (LPS)/TLR4-induced tumor necrosis factor (TNF) production.20-22 Bruton TK, via interleukin-6 (IL-6) and Stat3,23,24 nevrotrophil differentiation,25,26 and collagen-induced platelet aggregation.27,28 Moreover, high BTK phosphorylation and expression are observed in AML.29 Here we explore BTK function in human AML and describe the pharmacologic effects of BTK inhibition by Bruton’s TK, proliferation and bone marrow (BM) adhesion.

Methods
Materials
AML-derived cell lines were obtained from European Collection of Cell Cultures and authenticated by DNA fingerprinting. They were used at 1 passage for 4 months maximum and maintained, with regular DNA fingerprinting, in HCP media containing fetal bovine serum (FBS) and anti-BTK (D015) antibodies obtained from Cell Signaling Technologies. The phospho-pY223-BTK (FP403Y) and p-V514-BTK...
CG026806: Superior Efficacy Due to FLT3/BTK Dual Inhibition

(female BALB/c nude mouse, n=10 or 15 /group)

*: P<0.05 between vehicle control and CG026806 groups

δ: P<0.05 between vehicle control and lower doses of CG026806
Concluding Remarks
Concluding Remarks

1. CrystalGenomics has a **commercial product** that will allow for near-term profitability

2. CrystalGenomics has a promising development **pipeline** (two candidates in Phase II and one candidate in pre-clinical)

3. CrystalGenomics has a proprietary **platform technology** to continue to discover and develop new drug candidates
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Seongnamsi, Gyeonggido 463-400
Korea

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U.S.A.