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Investment Highlights

APTOSE

**Clinical stage biotech company** developing first-in-class targeted agents
**Treating hematologic malignancies** life-threatening / orphan diseases
**Two clinical-stage targeted agents** with strong IP protection

**CG-806** Oral pan-FLT3 / pan-BTK Inhibitor

*All wild type & mutant forms of BTK and FLT3* potently inhibited
**Simultaneously targets** multiple essential pathways to kill cancer cells
**Phase 1a/b stage** for the treatment of CLL/SLL/NHL and planned for AML/MDS

**APTO-253** MYC Inhibitor

**Only clinical stage agent** directly targeting G-Quadruplex of MYC oncogene
**Phase 1B stage** for AML/MDS demonstrating clinical safety and MYC inhibition

**Market**

*1B+ commercial opportunity* in AML and CLL lead indications with two agents
**Rapid clinical POC and value creation** when treating hematologic malignancies

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Aptose Scientific Advisory Team

Dr. Brian J. Druker, MD
Collaborator & Chair of SAB
Key Role in Dev’t of Gleevec
- Member, National Academy of Medicine, National Academy of Sciences & American Academy of Arts & Sciences
- Winner of Karnofsky Award, Lasker “America’s Nobel” Award
- Winner of Japan Prize in Healthcare and Medical Technology and the Tang Prize in Biopharmaceutical Science
- Winner of the prestigious Sjöberg Prize
- Leader of Inter-institutional Beat AML Initiative

Dr. Michael Andreeff, MD, PhD
Collaborator & Member of SAB
- Professor of Medicine, Paul and Mary Haas Chair in Genetics
- Director, Flow Cytometry and Cellular Imaging Facility
- Director, Bone Marrow Aspiration Clinic
- Chief, Section of Molecular Hematology and Therapy
- MD Anderson Cancer Center
- Physician Scientist
- Expert in AML and other hematologic malignancies
- Expert in drug resistance and drug mechanisms
- Published over 450 peer-reviewed papers
- Published multiple books and chapters
1. Potently inhibits all known forms of FLT3 and BTK driver kinases
2. Suppresses other signaling pathways essential for cancer cell survival
3. Precision that spares targets and pathways associated with toxicity
**CG-806**

- Inhibits WT/mutant “Driver” BTK & FLT3
- Suppresses oncogenic “Rescue” Pathways
- Avoids many of kinases that cause toxicity
- Hope avoid rapid emergence of dug resistance

**B-Cell Cancers**

**CG-806**

**AML**

**BTK “Driver” Intracellular**

- Ibrutinib
- Acalabrutinib
- Zanubrutinib
- ARQ 531
- SNS-062

**FLT3 “Driver” Surface Receptor**

- Midostaurin
- Sorafenib
- Gilteritinib
- Quizartinib
- Crenolanib

**“Rescue” Pathways**

- FLT3, BCR, CSF1R, PDGFRα, RET, MET, ERK, MYC, AKT, H3S10

**Intolerance**

**Resistance**

**Refractory**

**pan-FLT3/pan-BTK Multi-Cluster Kinase Inhibitor**

- CG-806
  - Inhibits WT/mutant “Driver” BTK & FLT3
  - Suppresses oncogenic “Rescue” Pathways
  - Avoids many of kinases that cause toxicity
  - Hope avoid rapid emergence of dug resistance
“Multi-Cluster Kinase Inhibitor”: CG-806 Potently and Selectively Inhibits Clusters of Related Kinases

- Atypical inhibition profile
  - FLT3 / TRK receptor clusters
  - BTK / AURK intracellular clusters
- Inhibits oncogenic signal initiation and transmission
- Avoids other kinase clusters associated with toxicity
- NOT “dirty” or “single-hit” Ki
- Inhibits Multiple Kinases/Pwys Operative in Blood Cancers
  - BTK cluster → B-cell cancers
  - FLT3 cluster → AML
Medical Need for Next Generation BTK Inhibitor (BTKi)

Overexpressed BTK (Bruton’s Tyrosine Kinase)
- Drives B-cell cancers: CLL/SLL and NHL (FL, MCL, DLBCL, others)

Ibrutinib Covalent BTKi
- Standard of care therapy with >$6B annual sales
- Chemically targets Cys 481 residue in the active site of BTK

Ibrutinib Shortcomings: Patients Discontinuing
- 56% CLL Patients: Discontinue treatment with ibrutinib at 44 months\(^{(1,2)}\)
- Resistant (C481S mutant), intolerant or refractory to ibrutinib

CG-806 May Overcome Shortcomings of Ibrutinib
- “Non-covalent inhibitor” of BTK
- Retains activity against WT and C481S-BTK enzyme
- Well tolerated and inhibits “oncogenic rescue” pathways

**X-ray Crystal Structure of CG-806 in BTK WT and C481S mutant.** The co-crystal complex of CG-806 bound to BTK- wild type (WT) or -C481S at resolution of 1.84Å and 1.63Å, respectively, revealed a binding mode of an **atypical type II non-covalent inhibitor**. The DFG motif occupies an atypical conformation whereby the Phe540 is rotated out of the ATP binding pocket and the Asp539 side chain is tilted to hydrogen bond with CG-806. Moreover, CG-806 interacts with the hinge region and the αC-helix is in a partial out position. No electron density interaction was observed between CG-806 and the C481 residue. **A.** CG-806 binds BTK WT; **B.** CG-806 binds BTK C481S mutant; **C.** Overlay of CG-806 and ibrutinib binding in BTK WT.
CG-806 Non-Covalent Inhibitor Retains Potency Against C481S-BTK

Retains potency against C481S-BTK

But does not inhibit TEC, EGFR, ErbB2 kinases that are linked to ibrutinib related toxicities, including bleeding disorders, gut and skin toxicity and atrial fibrillation, respectively.

<table>
<thead>
<tr>
<th>Kinase</th>
<th>CG-806</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK-WT</td>
<td></td>
<td>8.4</td>
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<tr>
<td>BTK-C481S</td>
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<table>
<thead>
<tr>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>TEC</th>
<th>EGFR</th>
<th>ErbB2</th>
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<tbody>
<tr>
<td>ibrutinib</td>
<td>78</td>
<td>5.6</td>
<td>9.4</td>
</tr>
<tr>
<td>CG-806</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
</tbody>
</table>
CG-806 In Vitro Suppresses Multiple Oncogenic Signaling Pathways and Kills Malignant Cells (B-cells and AML)

- Inhibits BTK/BCR, FLT3, PI3K/AKT/mTOR/S6K, ERK signaling and MYC expression
- Pathway suppression is maintained in the presence of mesenchymal stem cells
- Induces caspase cleavage and PARP cleavage / apoptosis in malignant B-cells
- **CG-806 on average 1000x more potent than ibrutinib at killing B-cell lines**

**ABC-DLBCL Cell Lines**

**GCB-DLBCL Cell Lines**

CG-806 potently inhibits CFU potential in clonogenicity assay
CG-806 Exerts Broad & Superior Killing Potency Compared to Ibrutinib on Patient Samples

CLL and ALL Patient Samples: Determined Cell Killing IC\textsubscript{50}

“More Than Just a BTK Inhibitor”

- CG-806 shows superior killing relative to ibrutinib (SOC covalent BTK inhibitor)
- CG-806 on average 1000x more potent than ibrutinib at killing malignant B-cells
- CG-806 targets Driver (BTK) and Rescue Pathways in B-cell cancers
Impressive Combination of CG-806 with Venetoclax on Primary Samples from CLL or ALL Patients

- **CG-806 and Venetoclax (Bcl2i):**
  - Individually highly active agents

- **Combination Studies:**
  - Enhanced ex vivo killing of patient bone marrow cells in most samples

- **CG-806 + Venetoclax:**
  - Combination may become the preferred drug combination for patients with AML, MDS/MPN, CLL, ALL and other hematologic malignancies

Box plots show median and IQR; width is proportional to number of samples
Drugs are ordered from left to right by increasing median IC$_{50}$ across all diagnoses
**Aggressive Cancer of Blood and Bone Marrow (Orphan Disease)**

- **FLT3-ITD mutation** is key driver in 25-35% of AML patients.\(^2,3\)
- Approved: Sorafenib (Nexavar®); Midostaurin (Rydapt®); Gilteritinib (Xospata®)
- Development Stage: Quizartinib, Crenolanib, other FLT3 inhibitors

**Medical Need For a Superior FLT3 Inhibitor**

- “Dirty” agents (Midostaurin, Sorafenib, etc.) are limited → Toxicity
- “Selective” agents don’t provide durable responses → Resistance
- Need potent drug to inhibit all mutant forms of FLT3: ITD/TKD/GK/WT

**Inhibiting FLT3 Only is Not Enough to Control AML**

- Also need to target multiple other “rescue” pathways that compensate

**CG-806 Potently Inhibits All FLT3 + “Rescue” Pathways**

- FLT3, PDGFRα, CSF1R, MET, RET, ERK/MYC, AKT, BTK, SRC, MYC and H3S10 key pathways crippled

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CG-806 Inhibits FLT3-ITD and Kills Cells with FLT3-ITD Mutation More Potently than Other FLT3 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC$_{50}$ (nM)</th>
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<tbody>
<tr>
<td>CG-806$^{(1)}$</td>
<td>0.8</td>
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<tr>
<td>Quizartinib$^{(2)}$</td>
<td>8.8</td>
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<tr>
<td>Gilteritinib$^{(3)}$</td>
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<tr>
<td>Crenolanib$^{(4)}$</td>
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<tr>
<td>Midostaurin$^{(2)}$</td>
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</tr>
<tr>
<td>Nexavar$^{(2)}$</td>
<td>79</td>
</tr>
<tr>
<td>Sutent$^{(2)}$</td>
<td>1</td>
</tr>
</tbody>
</table>

(1) Reaction Biology Corp.
(2) Blood. 2009 Oct 1; 114(14): 2984–2992
(3) J Clin Oncol 32:5a, 2014 (suppl; abstr T070)
(4) Blood 2014 Jan 2; 123(1): 94-100 ; AACR Poster 2012
(5) ASH Oral Presentation 2016
N/A – Data not available / Not Applicable.

(1) Ba/F3 isogenic cells kindly provided by Dr. Michael Andreeff at MDACC
CG-806 Rapid and Sustained Antitumor Activity in Mouse Model of FLT3-ITD AML After Oral Dosing for 28 Days

- Observed no weight loss or any sign of toxicity at any dose level
- Tumor growth inhibition observed at all dose levels over 28 days of dosing
- Significant cure rates at two highest dose levels through 120 days
CG-806 Inhibits All Forms of FLT3 and Kills Cells with FLT3-D835Y Mutation More Potently than Other FLT3 Inhibitors

<table>
<thead>
<tr>
<th>FLT3 Proteins (Fragments)</th>
<th>CG-806 Kd (nM)</th>
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</thead>
<tbody>
<tr>
<td>FLT3 WT</td>
<td>0.24</td>
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<tr>
<td>FLT3 ITD</td>
<td>3.1</td>
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<tr>
<td>FLT3 D835Y</td>
<td>4.2</td>
</tr>
<tr>
<td>D835H</td>
<td>2.2</td>
</tr>
<tr>
<td>D835V</td>
<td>7.9</td>
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<tr>
<td>R834Q</td>
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<tr>
<td>N841I</td>
<td>0.8</td>
</tr>
<tr>
<td>K663Q</td>
<td>0.55</td>
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<tr>
<td>ITD / F691L</td>
<td>16</td>
</tr>
</tbody>
</table>

CG-806 Superior to Other FLT3 Inhibitors on AML Cells with FLT3-D835Y Mutation

(1) Ba/F3 isogenic cells kindly provided by Dr. Michael Andreeff at MDACC.
CG-806 Efficacy in PDX Model Against AML Patient Cells with FLT3 ITD + D835 Mutations

Patient information: AML patient (FLT3-ITD) received Sorafenib+Azacitidine Tx and experienced CR after one cycle therapy; relapsed after 3 cycles of treatment and acquired a D835 mutation (now FLT3-ITD/D835)

Patient Derived Xenograft (PDX) Model

Model implanted with FLT3 ITD+D835 mutated primary AML cells. CG-806 Tx initiated d27 (QDx5/wk Orally). hCD45+/mCD45- leukemic cells in peripheral blood were quantitated with flow cytometry.

CG-806

- Reduced leukemia cell burden
- Reduced splenomegaly
- Extended survival
- Active against patient-derived FLT3-ITD / D835 AML
- Potential to treat emerging FLT3i-resistant AML patients
More than 200 AML Patient Samples: Determined Cell Killing (Ex Vivo IC₅₀)

- Determined IC₅₀ for FLT3i’s: CG-806, Quizartinib, Gilteritinib, Dovitinib, Sorafenib, Midostaurin, Crenolanib
- **CG-806 demonstrated greater potency in killing primary AML cells bearing wild-type FLT3 or FLT3-ITD**

IC₅₀ for each drug against each patient sample: Expressed as a Heatmap
AML patient samples with FLT3 mutations (ITD or TKD), with or without concurrent mutations of NPM1, are highly sensitive to CG-806.

Sensitivity of AML patient samples generally related to FLT3 ITD high allelic ratio (IC50 = 0.03 µM) vs. low allelic ratio (IC50 = 0.11 µM).

AML patient samples with mutated IDH1 are more sensitive to CG-806 relative to the IDH WT or IDH2 mutations (p < 0.05).

AML patient samples with TP53 WT and TP53 mutations equivalently sensitive to CG-806.

AML patient samples with TP53 mutations were resistant to most other FLT3 inhibitors.

AML patient samples with ASXL1 WT and ASXL1 mutations equivalently sensitive to CG-806.

CG-806 has greater potency than other FLT3 inhibitors to kill Ba/F3 cells transfected with various FLT3 mutations.
Impressive Combination of CG-806 with Venetoclax on Primary Samples from AML and MDS/MPN Patients

- **CG-806 and Venetoclax (Bcl2i):**
  - Individually highly active agents

- **Combination Studies:**
  - Enhanced ex vivo killing of patient bone marrow cells in most samples

- **CG-806 + Venetoclax:**
  - Combination may become the preferred drug combination for patients with **AML**, **MDS/MPN**, and other hematologic malignancies

Box plots show median and IQR; width is proportional to number of samples
Drugs are ordered from left to right by increasing median IC_{50} across all diagnoses
CG-806 Oral Agent: Potential Best-In-Class BTKi and FLT3i

- Superior Inhibition of key “Oncogenic” Pathways
- Strong Inhibition on BTK (WT / Mutant)
- Superior Potency/Range on Cell Lines
- Combines Favorably Venetoclax (Bcl-2 inh), Mcl-1 inh, BETi, cytarabine, daunorubicin
- Strong Oral Efficacy Standard & PDX Models
- Robust Safety Window Xenografts & GLP IND-Enabling Studies
- Favorable Safety Profile In vitro and In vivo
- Superior Inhibition on FLT3 (WT / Mutant)
- Superior Potency/Range on Patient Samples
Well-Differentiated MOA and Superiority to Competitor Agents

- Suppresses Initiation and Transmission of Oncogenic Signals
- Delivers Robust Efficacy (“Cures”) and Safety Profiles in Animals

Plan to Develop Broadly for B-Cell Cancer and AML/MDS

Patients with Unmet Needs & Potential Paths to Rapid Approvals

- AML: FLT3i-R (Emerging resistance to FLT3 inhibitors)
- AML: IDH1-M (Sensitive or resistant to IDH1 inhibitors)
- AML: Elderly/fragile (Unable to tolerate other regimens)
- AML/CLL/SLL: Venetoclax-R (Emerging resistance to venetoclax)
- CLL/SLL/MCL: R/R/I to BTKi (Failed covalent &/or non-covalent BTKi)
- CLL/SLL: Richter’s (Richter’s Transformation/Richter’s Syndrome)

Phase 1a/b Clinical Trial Underway: CLL/SLL & NHL B-Cell Cancers

- Patient screening ongoing and only 1 patient required on lowest dose
Advanced CG-806 into First Phase 1a/b Clinical Trial: Patients with CLL/SLL or NHL

Relapsed or refractory CLL/SLL or NHL who failed or are intolerant to 2 or more lines of established therapy, or for whom no other treatment options are available

Includes Patients with WT or C481S BTK

Dose Escalation Phase

28-day cycle – Dose every 12 hours
Dose Level 1 – 150mg every 12 hours
Planned 6 dose levels

Dose Expansion will occur once MTD or Therapeutic Dose is Reached

Expansion Phase
25 Patients Each

Diffuse Large B-Cell Lymphomas
Mantle Cell Lymphomas
Indolent Lymphomas
CLL/SLL
CG-806 Phase I Clinical Development Plan: B-Cell Cancers AND AML/MDS

R/R B-Cell Cancer Patients: CLL/SLL and NHL

- Begin with B-cell cancer patients – these are less acutely ill than AML patients
- Dose escalating Phase I a/b trial – Define safety, tolerance, PK and PD profiles
- Continue dose escalation to define RP2D – Expand to sensitive subpopulations
- Seek a dose in B-cell cancer patients that delivers a “therapeutic exposure” for AML

Relapsed/Refractory AML/MDS

- AML patients are acutely ill and do not wish to dose sub-therapeutically
- Dose escalating Phase I a/b trial – Define safety, tolerance, PK and PD profiles
- Continue dose escalation to define RP2D
- Expand to sensitive subpopulations: FLT3iR, IDH1M, Unfit/elderly, other

Excited to move CG-806 into the clinic – Provide updates throughout the year
APTO-253

Phase 1b Stage Treatment of AML

Small Molecule MYC Inhibitor
MYC protein regulates multitude of key biological processes

- Transcription factor binds to hundreds of genes

Dysregulated in >50% of all human cancers

- Reprograms signaling pathways to support survival

Direct targeting of MYC protein is challenging

- Generally considered “undruggable” – no active site

Prior Strategies to Suppress MYC:

- Targeting transcription via BRD4 or CDK7/9

- Inhibit translation via inhibition of the PI3K/AKT/mTOR pathway

- Destabilize MYC by targeting deubiquitinases

- Inhibit AURKs and PLK1 that form activating complexes with MYC

- Inhibit activity by disrupting MYC:MAX complex
APTO-253 New Class of Small Molecule MYC Inhibitor: Inhibits MYC Transcription and Induces p21

- Targets DNA regulatory motif (G-Quadruplex) in promoter of MYC gene (NOT the MYC protein)
- Inhibits MYC gene expression (mRNA) → depletes cells of MYC protein → induces apoptosis

**MYC mRNA and Protein Inhibition**

![Graph showing MYC mRNA and Protein Inhibition](image)

**p21 (CDKN1A) Induction**

![Graph showing p21 (CDKN1A) Induction](image)

- APTO-253 inhibits MYC expression
- Causes induction of p21
- Triggers cell cycle arrest/apoptosis
APTO-253
Ongoing Phase 1b Dose Escalating Clinical Trial

R/R AML and High Risk MDS
• Planned up to 20 Patients
• Safety, PK, MTD, DLT, RP2D
• Biomarkers, Efficacy, Transfusions

Single Agent Expansions
AML – Up to 15 Patients
ORR, Efficacy, Biomarkers, Safety

Single Agent Expansions
MDS – Up to 15 Patients
ORR, Efficacy, Biomarkers, Safety

Drug Combination Trials

• Drug Product Employs Newly Modified Formulation
• Dosing Schedule: Day 1 of Each Week on 28-day Cycle
• Dosing Levels Planned: 20 (1pt), 40 (1pt), 66 (3x3pts), 100, 140, 180, 220mg/m²
  – 20mg/m² dose: Completed with 1 AML patient
  – 40mg/m² dose: Dosing ongoing with MDS patient
• Desired Outcomes: Safe, MYC inhibition, p21 induction, patient responses

Note: Phase 1b expansion cohorts and Phase 2 trials contingent on Phase 1b outcomes
Preliminary Data of Patient #1 Dosed Once Weekly for 28 Days: Observed MYC Inhibition and p21 Induction

- Patients may respond differently in the future
- Cycle one of APTO-253 treatment at 20mg/m² for 28 days
- Sampled pre-dose and 24 hr post-dose on day 1, 8, 15, and 22
- MYC and p21 gene expression analyzed in-house by qPCR analysis
## Aptose Executive Summary

### Developing Highly Differentiated / Targeted Drugs for Blood Cancers

#### CG-806 First-in-Class Pan-FLT3 / Pan-BTK Multi-Cluster Inhibitor
- Potently Inhibits all forms of FLT3, BTK and inhibits “oncogenic rescue” pathways
- Potential to treat FLT3i-resistant, IDH1-mutant, and elderly segments of AML population
- Potential to treat B cell cancer patients resistant to / discontinuing other BTKi
- Phase 1 with CLL/SLL/NHL trial underway and subsequent AML trial planned in 2019

#### APTO-253 First-in-Class MYC Expression Inhibitor in Phase Ib for AML
- Dosing of R/R-AML / hr-MDS patients ongoing and throughout 2019
- Demonstrated MYC inhibition: Watch for safety, tolerance, and patient responses
- Potential to expand into B cell malignancy patients (role of MYC)

### Strong Leadership and KOL Support

### Maintain Strong Financial Foundation
- > 12 Months operating capital on hand and availability
Thank You!