Discovery of ABBV/GLPG-2222, a potent CFTR corrector for the treatment of Cystic Fibrosis

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Outline

1. Background
2. Lead identification
3. Optimization of C1 corrector
4. ABBV-2222 attributes and characterization
5. ABBV-2222 clinical status
6. Summary
Cystic Fibrosis Disease Overview

An Orphan Disease with High Unmet Need

- Cystic fibrosis (CF) is a life-shortening, monogenic disease affecting ~75,000 worldwide
  - Caused by mutations in CFTR
- Multi-organ disease with progressive lung disease the main cause of mortality
- Complex treatment regimens target downstream symptoms
  - huge treatment burden (2-4 hrs/day).
- Median age of death is only 27.5 years

Source: CF Foundation 2011 Patient Registry Annual Data Report
Cystic Fibrosis is Driven by Defects in CFTR

272 Disease-related Mutations Categorized into 6 Classes

Severe Mutations:
- Class I, II, III
- Reduced survival
- Pancreatic insufficient
- ≥ 90% of population

Mild Mutations:
- Class IV, V, VI
- Pancreatic sufficient
Developing Therapies for the Most Severe Mutations

Two Main Approaches to Fix CFTR

**Potentiators** restore the flow of ions through activated CFTR
- Ivacaftor (VX-770) approved

**Correctors** restore the processing of CFTR to the surface
- Orkambi approved (Lumacaftor (VX-809)+ Ivacaftor)
- Need of type 1 (C1) corrector and type 2 (C2) corrector for maximum channel restoration
Challenges and Opportunities of Pursuing CF treatment

Ivacaftor provides significant benefits in G551D patients

Orkambi (Ivacaftor + Lumacaftor) provides meaningful but modest improvement in F508del patients

• Lumacaftor is a CYP3A4 inducer, presenting DDI perpetrator liability (Van Goor, NACFC, 2016, Orlando)
• Opportunity for better therapy exists
What’s the Strategy?
A Combination Approach

Type I Corrector-C1
- **Objective:** to rapidly identify best-in-class corrector to enable clinical study of P + C1

Type II Corrector-C2
- **Objective:** to rapidly identify C2 that can achieve highest combo efficacy with P and C1 to address the largest possible patient population

Potentiator
- **GLPG-1837**
- **Objective:** Rapidly advance to FIH

CF Patients
Objective: Identify best in class type I corrector compound to enable combination treatment of CF

- High Potency, efficacy, and suitable PK profile to enable QD or BID dosing
- Structure differentiation to address liabilities of existing therapy

Strategy: Leverage AbbVie medicinal chemistry design and synthesis expertise, and rich collection of compounds to achieve differentiation

- Large collection of proprietary monomers from legacy and ongoing programs
- Chemistry amenable to fast SAR exploration
- Optimize target potency and clearance to deliver candidate
Execution

Proprietary amines & Proprietary acids

AbbVie Collection of Fragments

Filter by MW, alerts
Enumerate virtual library
filter by calculated properties

Library Production

SWIFT Synthesis Platform

- Reactions run in Conjure flow reactor
- Fully integrated synthesis and purification, enabling rapid registration

Fully integrated synthesis and purification

Registration and dispersal

CFTR Correctors

**Assays**

### Functional Assays

**HBE-TECC (Human Bronchial Epithelial-TransEpithelial Clamp Circuit)**
- Primary human bronchial epithelial cells from CF patients
- E-Phys measurement of ion flux
- Measure (Ieq) current changes
- Gold standard for CFTR function and clinical efficacy correlation

### Localization Assays

**CSE-HRP (Cell Surface Expression)**
- CSE-HRP-tagged

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**Diagram:**

- Primary Human bronchial epithelial cells
- Co-incubate Correctors with Potentiator overnight
- Measure Ieq in TECC after Forskolin activation of CFTR
- O/N incubation with Correctors and Potentiators
Medicinal Chemistry Approach and Assay Funnel

- Compound design based on data analysis, experience, and cheminformatic tools
- Prospective property calculation
- Prioritization based on synthetic accessibility

- Data generation and analysis
- Library as well as individual compound generation
- Specialized synthetic chemists tackle novel cores and optimize routes

ABBV/GLPG Med Chem

Tier 1 ADME
- Metabolic stability
- Solubility
- Permeability

CSE- HRP

MPO score (Club \* EC50)
Efficacy ≥ 70%

RAT PK

Tier 2 ADME
- CYP inhibition/induction
- CYP phenotyping

TECC
F508del CFTR
HBE

EC50 < 300 nM
Efficacy ≥ 70% C1 Standard

Low Clp,u
Clean DDI profile

Rat CV & Higher Species PK

Candidate

MoA Studies
**CFTR C1**

*Chromane Exploration*

Chromane groups demonstrated unexpected activity

- From proprietary amine collection
- Difference in stereochemistry observed
- C-2 phenyl analogs followed up: high efficacy, tunable SAR

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSE-HRP (EC₅₀ μM, Max. Act% C1 control)</td>
<td>2.6, 99%</td>
<td>4.1, 100%</td>
<td>&gt;20, 8%</td>
<td>&gt;10, 22%</td>
<td>2.7, 110%</td>
</tr>
</tbody>
</table>
### CFTR C1

**Chromane Exploration-Contd**

![Chemical Structures](attachment:image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSE-HRP (EC\textsubscript{50} μM, Max. Act% C1 Control)</td>
<td>2.7, 110%</td>
<td>12, 33%</td>
<td>4.1, 77%</td>
<td>0.80, 92%</td>
<td>0.21, 119%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>In Vitro ADME</th>
<th>Rat/Human Clint,u (L/hr/kg)- hep</th>
<th>470/49</th>
<th>580/110</th>
<th>460/110</th>
<th>230/77</th>
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<tbody>
<tr>
<td>PAMPA Peff (x10\textsuperscript{-6} cm/s)</td>
<td>0.04</td>
<td>0.3</td>
<td>0.26</td>
<td>0.03</td>
<td>0.3</td>
</tr>
</tbody>
</table>

- C-2 phenyl potent/efficacious
- Substitution on distal phenyl important
- Compounds have high in vitro hepatocyte clearance (>>20L/hr/kg) and poor permeability (<1 x 10\textsuperscript{-6} cm/s))
**CFTR C1**

*Chromane Exploration-Confirm HBE Activity*

**Compound 10**  
(R,R)-configuration  
CSE: 0.19 μM, 121%

**Compound 9**  
CSE: 0.21 μM, 119%

**Compound 11**  
(S,S)-configuration  
CSE: 0.97 μM, 71%

Need to improve clearance

In Vivo PK

High CLp (~100% LBF)

**EC₅₀ 27 nM**

HBE-TECC Functional Testing

(corrected for vehicle ctrl)
### CFTR C1

**Chromane Exploration - Improve Clearance**

<table>
<thead>
<tr>
<th>Compound</th>
<th>In Vitro Activity</th>
<th>In Vitro ADME</th>
<th>In Vivo PK</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HBE-TECC (EC(_{50}) (\mu)M, Max. Act%)</td>
<td>Rat/Human Clint,(u) (L/hr/kg)- hep</td>
<td>Cl(_p) (%LBF) (rat)</td>
</tr>
<tr>
<td></td>
<td>0.028, 145%</td>
<td>280/106</td>
<td>~100% LBF</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Alcohol group is weaker, still high clearance
- Acid group retains activity, reduces in vitro/in vivo clearance, improves permeability
- Maintain acid group, improve potency and clearance

<table>
<thead>
<tr>
<th>Compound</th>
<th>CYP 3A4 induction</th>
<th>PAMPA Peff (x10(-6) cm/s)</th>
<th>F (PO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>18</td>
<td>3.2</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>14</td>
<td>3.3</td>
</tr>
</tbody>
</table>

- 16/5
- 18
- Negative
- Negative
- 20/14
- 14
- Negative
- Negative
- 27
- 24
Type 1 Correctors

Early View of DDI Properties (all >50% in CSE)

- No systemic CYP3A4 induction issue
- No systemic CYP inhibition issue
Type 1 Correctors

Early View of Series In Vitro-In Vivo Clearance Correlation (all >50% in CSE)

- Good correlation between in vitro clearance and in vivo hepatocyte clearance
  - Unbound in vitro hepatocyte clearance (<20 L/kg/hr) used to guide SAR progression
CFTR C1
Chromane Synthesis

- Enantio-selective boronic acid conjugated addition installs chiral center
- Platinium-catalyzed hydrogenation provides (cis)-diastereo selectivity
### C1-GS792 Series

**Chromanes LO**

<table>
<thead>
<tr>
<th>Compound</th>
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<th>15</th>
<th>16</th>
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</thead>
<tbody>
<tr>
<td><strong>In-Vitro Assay</strong></td>
<td>HBE TECC</td>
<td>HBE TECC</td>
<td>HBE TECC</td>
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<tr>
<td>EC₅₀ µM, Max %C₁ standard</td>
<td>0.238, 95%</td>
<td>0.075, 117%</td>
<td>0.087, 97%</td>
</tr>
<tr>
<td><strong>In Vitro ADME</strong></td>
<td>Rat/Human Clint,u (L/hr/kg)- hep</td>
<td>25/17</td>
<td>14/7</td>
</tr>
<tr>
<td>CYP 3A4 induction</td>
<td>Negative</td>
<td>NT</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>In Vivo PK</strong></td>
<td>Clₚ (%LBF) (rat)</td>
<td>&lt; 30%</td>
<td>&lt; 50%</td>
</tr>
<tr>
<td>T₁/₂ (hr)</td>
<td>3.3</td>
<td>2.3</td>
<td>2.53</td>
</tr>
</tbody>
</table>

- Difluoromethoxy on the chromane phenyl ring provides best potency

What about 1,4-substituted phenyl?
**CFTR Type 1 Correctors**

*Chromanes Candidate Identification*

<table>
<thead>
<tr>
<th>Compound</th>
<th>13</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-Vitro Assay</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBE TECC</td>
<td>0.238, 95%</td>
<td>0.009, 94%</td>
<td>0.005, 87%</td>
</tr>
<tr>
<td>EC50 µM, Max %C1 standard</td>
<td></td>
<td></td>
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<tr>
<td><strong>In Vitro ADME</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat/Human Clint,u (L/hr/kg)- hep</td>
<td>25/17</td>
<td>15/3</td>
<td>7/3</td>
</tr>
<tr>
<td>CYP 3A4 induction</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>In Vivo PK</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clp (%LBF) (rat)</td>
<td>&lt; 30%</td>
<td>&lt; 30%</td>
<td>&lt; 30%</td>
</tr>
<tr>
<td>T1/2 (hr);</td>
<td>3.3</td>
<td>~3</td>
<td>3~5</td>
</tr>
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</table>

- para-substituted acid **17** has improved potency, and reduced clearance
- **Compound 18** was nominated as preclinical candidate
ABBV-2222

*Increases F508del CFTR Cell Surface Expression*

**A. IB: CFTR-F508del-AVI Total Protein**

- AVI-tag labeled CFTR is a tool to assess the localization and endocytic trafficking of the channel
- ABBV-2222 increases the amount of folded protein (band C) and mature protein at the cell surface

**B. IF: Cell surface CFTR-F508del-AVI Expression**
ABBV-2222
Highly Potent in Primary Human Cells

ABBV2222 Increases Function of F508del/F508del CFTR in HBE-TECC Assay

A. Potency Comparison of ABBV2222 in HBE TECC Assay

B. Potency of ABBV2222 in Different Donors

- ABBV-2222 is highly potent (6 ± 3 nM) in multiple donors (n = 14)
Phase 1 (SAD and MAD) completed with exposure ($C_{\text{max}}$ and AUC) of ABBV-2222 increasing dose proportionally up to the 600 mg dose

No SAEs reported in any SAD or MAD dose group

Van de Steen et al, NACFC, Orlando, 2016
Status of ABBV-2222

• Urinary 6β-OH-cortisol/cortisol ratio was not impacted, confirming that ABBV-2222 is not a CYP3A4 inducer

• Currently enrolling a Phase 2 PoC study combined with Ivacaftor in CF patients with G551D gating mutation

• Q1 2017 planned Phase 2 study of ABBV-2222 alone in F508del homozygous patients

• Future studies planned, combining ABBV-2222 with other CFTR modulators (dual and triple combinations) in patients with F508del mutation
Summary

• **Potential best in class type 1 corrector rapidly identified**
  - Leveraged large collection of proprietary fragments to identify unique scaffold
    - Availability of diverse set of monomers enabled fast exploration of SAR
    - Rapid design/synthesis cycles enabled by both medicinal chemistry expertise and synthetic capability
    - Synthetic chemistry expertise enabled asymmetric synthesis of lead compounds
    - Optimization of in vitro clearance led to in vivo clearance improvement

• **Human PK profile supports clinical development**

• **Phase II study initiated**
ABBV-2222

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ABBV-2222

*Single Channel Po in combination with ABBV Potentiator*

ABBV2222 combines with ABBVPot to increase single channel Po of F508del CFTR

- F508del CFTR channel open probability (Po) was evaluated using single channel patch clamp experiments
- Po is greatly enhanced by treatment with potentiator and ABBV-2222