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Nuovi modulatori di CFTR all'orizzonte

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Genova

XXVII Congresso Italiano della Fibrosi Cistica

XVII Congresso Nazionale della Società Italiana per lo studio della Fibrosi Cistica

Napoli, 20-23 ottobre 2021

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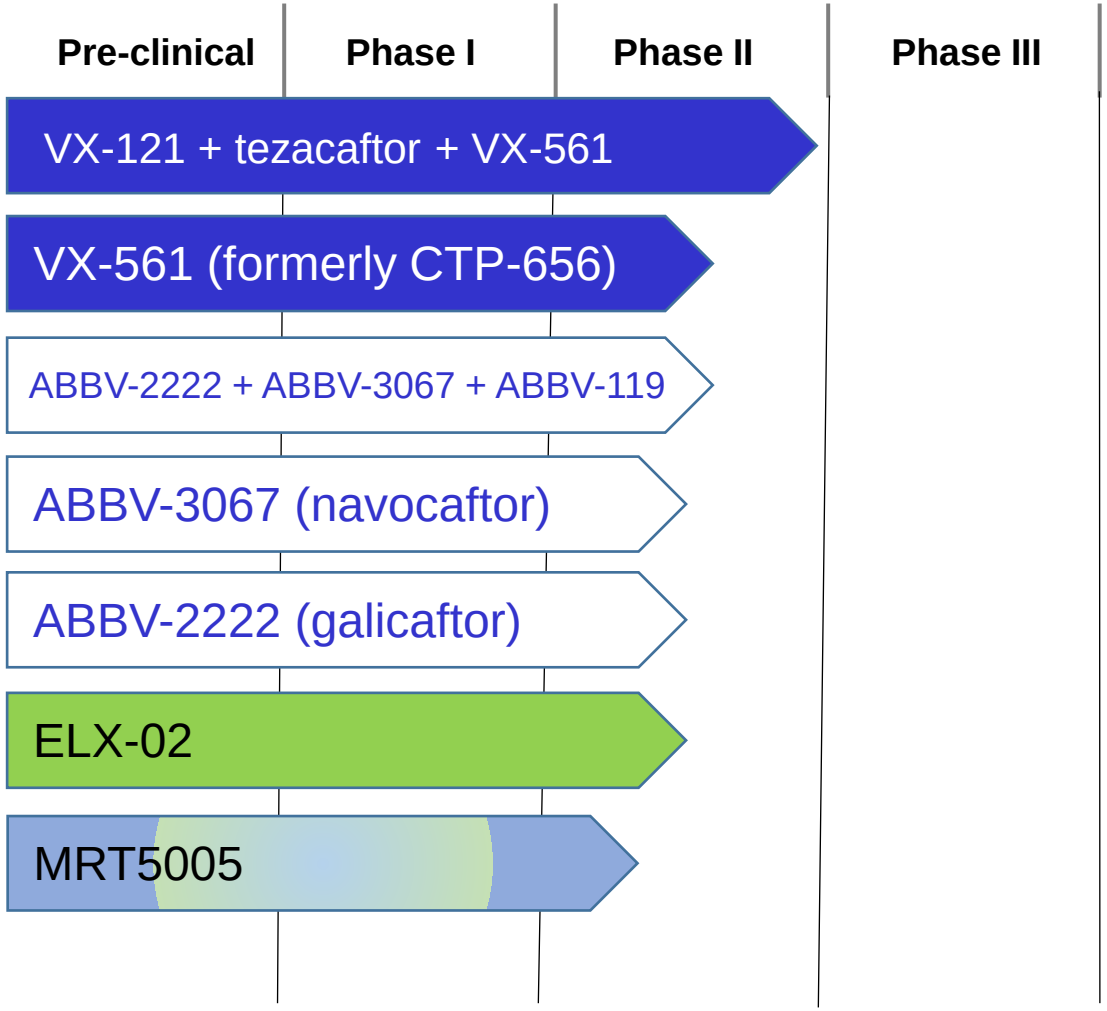
Nuovi modulatori di CFTR all’orizzonte

Search for new modulators of mutant CFTR

We are here!

Discovery → Preclinical Development → Phase I → Phase II → Phase III → NDA → Marketing Authorization

New CFTR modulators in clinical development

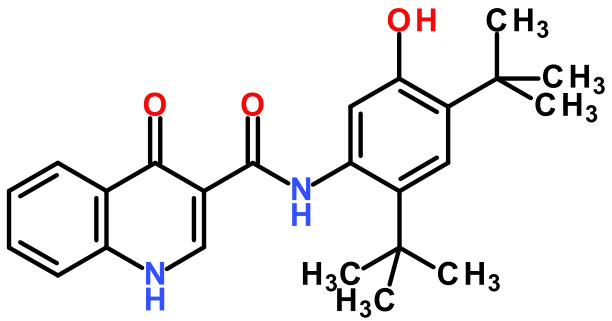


Modified from: *Cystic Fibrosis Foundation* - https://www.cff.org/trials/pipeline

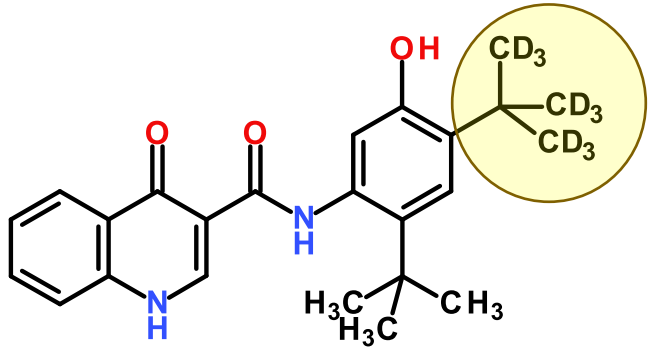
VX-121 + tezacaftor + VX-561

VX-121: Most likely, a «next generation» corrector. The structure has not been disclosed.

VX-561: deutivacaftor. Deuterated derivative of ivacaftor, previously known as CPT-656 (Concert Pharmaceuticals, Inc.).



ivacaftor



deutivacaftor

- Deuterium substitution does not alter the pharmacology of ivacaftor and its major metabolites.
- CPT-656 has increased metabolic stability in *in vitro* assays.
- When dosed in healthy volunteers at 150 mg, CPT-656 average half-life was ~15 hrs, 40% longer than that of ivacaftor, ~ 11 hrs.

Harbeson et al., *JPET* 2017, 362, 359-367

Phase 2 study of VX-121 + tezacaftor + VX-561

Results from Phase 2 study of VX-121/ tezacaftor/ VX-561 in adults with one *F508del* and one *minimal function* mutation (F/MF).

	ppFEV$_1$ (Percentage Points)	**Sweat Chloride** (mmol/L)
F/MF Treatment Group		
Placebo n=10	**+1.9** (p=0.5214)	**+2.3** (p=0.6198)
VX-121 (5 mg qd)/ **tezacaftor** (100 mg qd)/ **VX-561** (150 mg qd) Triple Combination Regimen n=9	**+4.6** (p=0.1253)	**-42.8** (p<0.0001)
VX-121 (10 mg qd)/ **tezacaftor** (100 mg qd)/ **VX-56**1 (150 mg qd) Triple Combination Regimen n=19	**+14.2** (p<0.0001)	**-45.8** (p<0.0001)
VX-121 (20 mg qd)/ **tezacaftor** (100 mg qd)/ **VX-561** (150 mg qd) Triple Combination Regimen n=20	**+9.8** (p<0.0001)	**-49.5** (p<0.0001)

Source: Vertex Press Release, July 28, 2021

Phase 2 study of VX-121 + tezacaftor + VX-561

Results from Phase 2 study of VX-121/ tezacaftor/ VX-561 in adults with one *F508del* and one *minimal function* mutation (F/MF).

	ppFEV$_1$ (Percentage Points)	**Sweat Chloride** (mmol/L)
F/MF Treatment Group		
Placebo n=10	**+1.9** (p=0.5214)	**+2.3** (p=0.6198)
VX-121 (5 mg qd)/ **tezacaftor** (100 mg qd)/ **VX-561** (150 mg qd) Triple Combination Regimen n=9	**+4.6** (p=0.1253)	**-42.8** (p<0.0001)
VX-121 (10 mg qd)/ **tezacaftor** (100 mg qd)/ **VX-561** (150 mg qd) Triple Combination Regimen n=19	**+14.2** (p<0.0001)	**-45.8** (p<0.0001)
VX-121 (20 mg qd)/ **tezacaftor** (100 mg qd)/ **VX-561** (150 mg qd) Triple Combination Regimen n=20	**+9.8** (p<0.0001)	**-49.5** (p<0.0001)

Results from Phase 2 study of VX-121/ tezacaftor/ VX-561 in adults with two *F508del* mutations (F/F).

	ppFEV$_1$ (Percentage Points)	**Sweat Chloride** (mmol/L)
F/F Treatment Group		
Tezacaftor (100 mg qd)/ **ivacaftor** (150 mg q12h) (active control) n=10	**-0.1** (p=0.9635)	**-2.6** (p=0.3633)
VX-121 (20 mg qd)/ **tezacaftor** (100 mg qd)/ **VX-561** (150 mg qd) Triple Combination Regimen n=18	**+15.9** (p<0.0001)	**-45.5** (p<0.0001)

Source: Vertex Press Release, July 28, 2021

Phase 3 study of VX-121 + tezacaftor + VX-561

Objective

Evaluation of efficacy and safety in CF patients who are heterozygous for F508del and a minimal function mutation.

Start date: September 14, 2021

Estimated Primary Completion Date: June 2023

Primary Outcome: Absolute change from baseline in ppFEV$_1$ through week 24

Secondary Outcome: Absolute change from baseline in sweat chloride (SwCl) through week 24

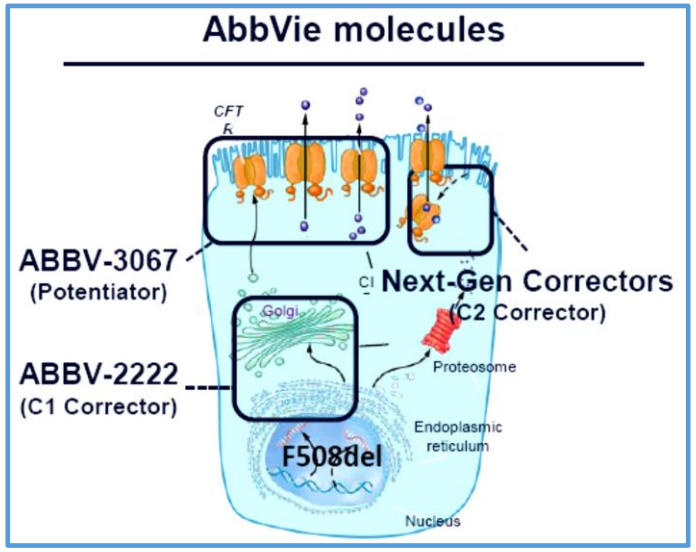
- Proportion of participants with SwCl <60 mmol/L through week 24
- Proportion of participants with SwCl <30 mmol/L through week 24

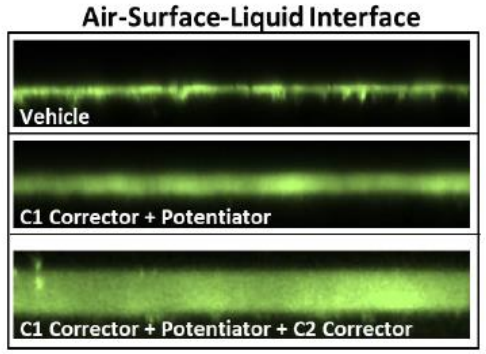
Source: www.clinicaltrials.gov

AbbVie CF pipeline

AbbVie has multiple compounds under clinical development.

- C1 Corrector: **ABBV-2222**
- Two potentiators: ABBV-3067 (navocaftor) and ABBV-191
- C2 Corrector: **ABBV-119**, IND submission Q2 2020
- ABBV-2222+ ABBV-3067 doublet in Phase 2



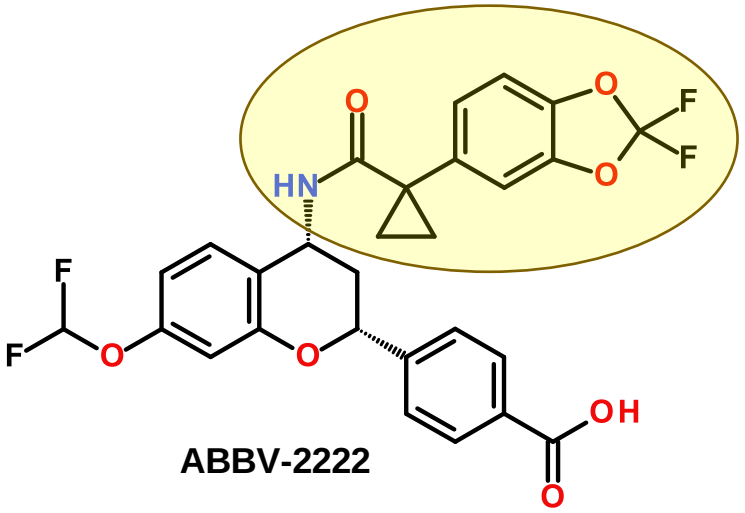


AbbVie triplets show full restoration of fluid homeostasis.

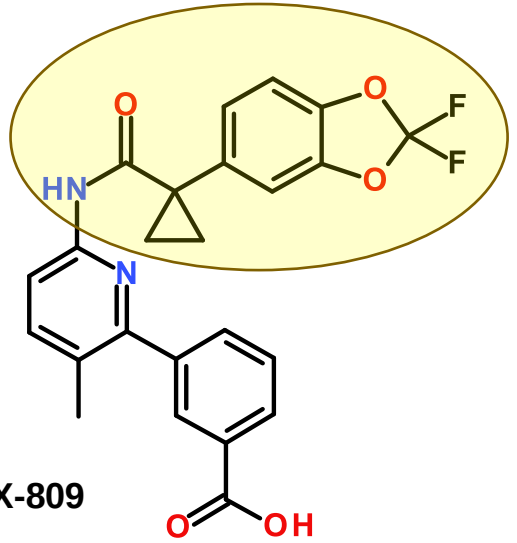
Source: AbbVie Sell-Side R&D Deep Dive - March 10, 2020

ABBV-2222 (formerly GLPG2222)

ABBV-2222, **galicaftor,** is an analog of lumacaftor (VX-809).



ABBV-2222



VX-809

ABBV-2222 is a type I corrector, over 25-fold more potent than lumacaftor (XV-809).

In phase 1 studies, single-dose pharmacokinetics were similar in healthy subjects and CF patients.

ABBV-2222 phase 2a studies

Two phase 2a studies were conducted in:

- patients homozygous for the F508del mutation;
- patients with one F508del mutation and a gating mutation (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1225P, S549N, and S549R), who were receiving ivacaftor.

Sweat chloride decreased from baseline, with biggest effect observed in F508del homozygous patients.

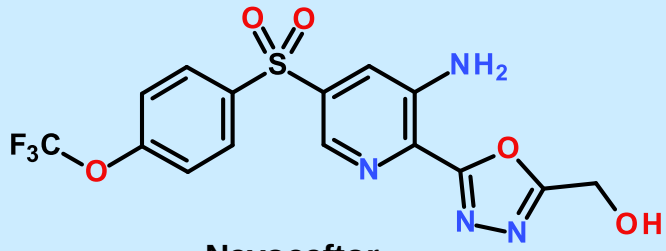
The greatest increase in $ppFEV_1$ was 2.6% points versus placebo in F508del heterozygous subject, but was not statistically significant.

Multiple oral doses of ABBV-2222 had no effect on ivacaftor exposure.

Bell et al., *J. Cystic Fibrosis* 2019, 18, 700-707

Phase 2 study of Galicaftor + Navocaftor + ABBV-119

Study of combination therapy in CF patients homozygous or heterozygous for the F508del mutation.



Navocaftor
ABBV-3067

ABBV-119: C2 corrector
structure not disclosed.

Start date: September 13, 2021

Estimated Completion Date: December 2022

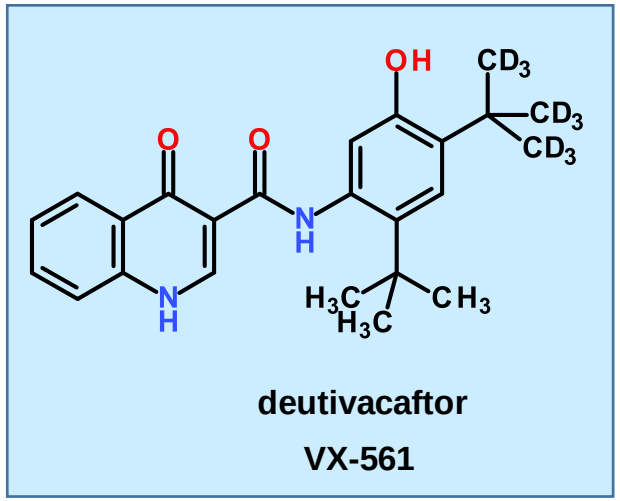
Primary Outcome: Absolute change from baseline in ppFEV$_1$ up to 29 days

Secondary Outcome Measures:

- Absolute change from baseline in sweat chloride (SwCl) up to 29 days
- Other additional 7 outcomes.

Source: www.clinicaltrials.gov

Phase 2 study of potentiator VX-561



deutivacaftor

VX-561

The study evaluated efficacy and safety of VX-561 in subjects aged 18 years and older with cystic fibrosis.

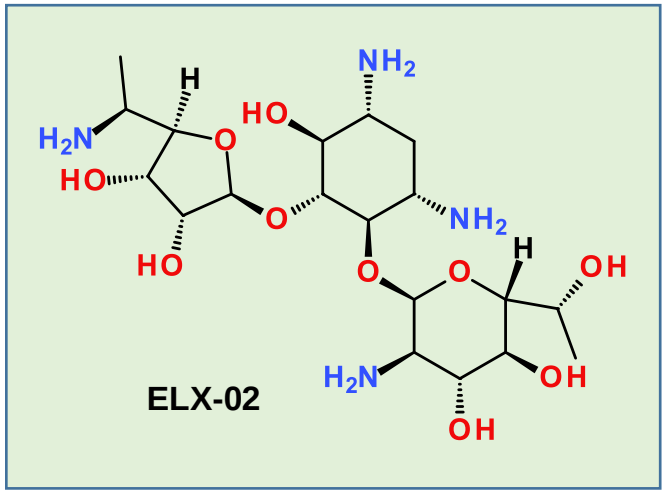
Actual Study Completion Date: August 20, 2020

Active comparator: ivacaftor, 150-mg film-coated tablet for oral administration.

No Results Disclosed

Source: www.clinicaltrials.gov

ELX-02, a read-through agent



A non-antibiotic, aminoglycoside analog under developed for the treatment of genetic diseases caused by nonsense mutations.

Dose-dependent read-through of nonsense mutations in either *CFTR* or *CTNS* to generate full-length, functional protein, demonstrated in preclinical studies.

Generally well tolerated in Phase 1 clinical studies, with more than 100 volunteers exposed, no reported drug-related serious adverse events or renal findings and limited, reversible, auditory findings.

Phase 2 start date: November 2019

CF patients with at least one G542X allele.
ELX-02 given SC

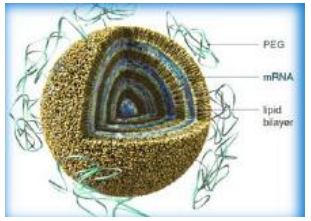
Designated an orphan drug by the FDA, and an orphan medicinal product by the EMA.

E. Kerem *Expert Opinion on Investigational Drugs*, 2020, 29, 1347-1354

MRT5005: phase 1/2 study

First clinical-stage **mRNA** product candidate designed to deliver mRNA encoding fully functional CFTR protein to the lung epithelial cells through nebulization.

mRNA of CFTR encapsulated in lipid nanoparticles.



Repeat dosing of MRT5005 was generally safe and well tolerated with no serious adverse events.

- single-ascending dose (SAD) data (8, 16 and 24 mg dose groups);
- multiple-ascending dose (MAD) groups (five once-weekly doses of 8, 12 and 16 mg);

one month follow-up post treatment.

No pattern of increases in $ppFEV_1$ was observed

Source: Translate Bio's press release, March 17, 2021

Navigating www.clinicaltrials.gov

Personalized Theratyping Trial

Explore the use of off-label CFTR modulators (Symdeko) that may affect CFTR function in patients with CFTR mutations that are not currently approved for these drugs.

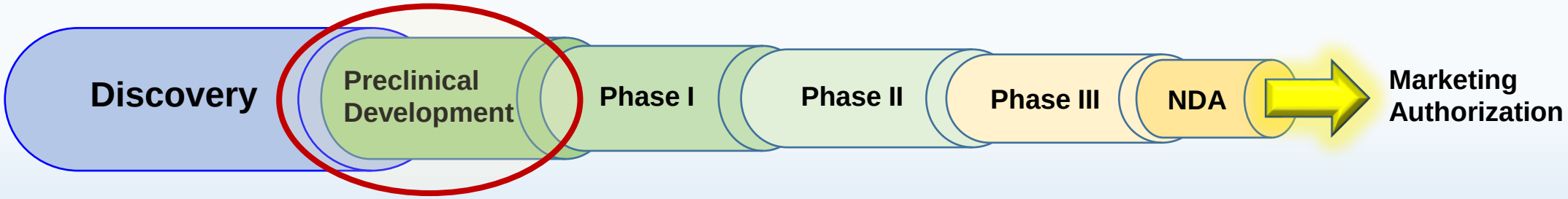
Sponsor: University of Alabama at Birmingham (USA)

Improvement of mucociliary dysfunction by anti-inflammatory therapy.

Test the hypothesis that losartan provides a safe and effective anti-inflammatory therapy in CF patients.

Sponsor: University of Kansas Medical Center (USA)

Preclinical Development



Compounds in Preclinical Development

ARCT-032: mRNA of CFTR

This is being developed by **Arcturus Therapeutics**, and is partially funded by Cystic Fibrosis Foundation. CTA is expected in 1H2022.

ReCode Therapeutics

RCT223: CFTR tRNA agent.

RCT223 was shown to restore CFTR function for at least 72 hours in patient-derived hBE cells after a single administration.

RTX0001: mRNA of CFTR.

In CF hBE cells, RTX0001 significantly restored CFTR function after a single, low dose. Additionally, CFTR activity was maintained for at least 72 hours after twice-weekly administration.

ReCode plans to apply to the U.S. FDA in 2022 to start clinical trials of these therapies in the U.S.

Compounds in Preclinical Development

Spirovant Sciences

SP-101: AAV-CFTR for gene therapy, single dose administration.

SP-102: LVV-CFTR for gene therapy, one-time curative dose.

SP-101 and SP-102 are administered by inhalation.

4D Molecular Therapeutics

4D-710: a customized adeno-associated virus (AAV) vector designed to deliver a CFTR gene specifically to cells in the lungs.

Compounds in Preclinical Development

SpliSense's CF Pipeline

SPL84-23, an Anti Sense Oligonucleotide (ASO) designed to treat the 3849+10kb C->T CFTR mutation.

SPL84-23 demonstrated to completely restore CFTR channel function in patient-derived cell cultures.

SpliSence plans to initiate a Phase 1/2a trial in 2022.

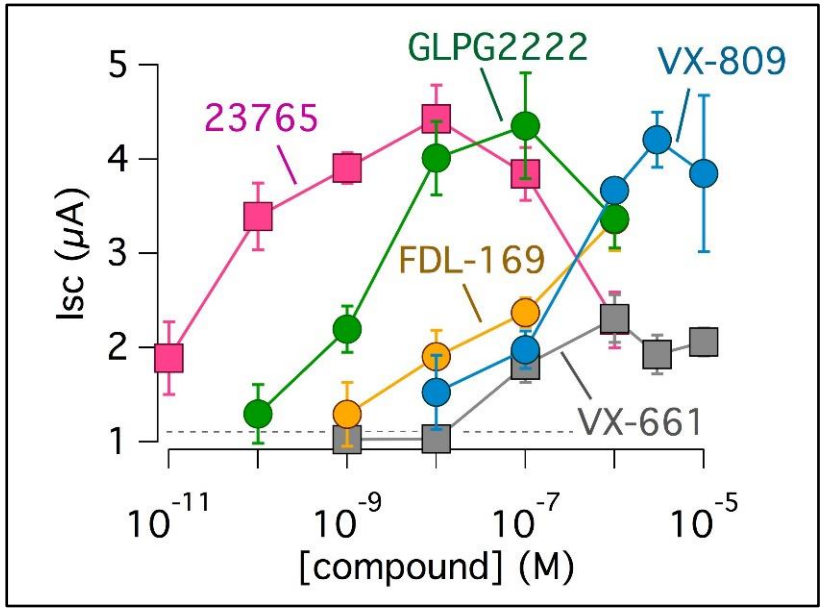
Source: SpliSense website

Compounds in Preclinical Development

The C1 corrector ARN23765 was developed by the Task Force for Cystic Fibrosis.

ARN23765 has higher potency than:

- the drugs VX-809 (lumacaftor) and VX-661 (tezacaftor),
- the corrector GLPG-2222 under clinical development.



Dose-response study in primary human bronchial epithelial cells from CF patient homozygous for the F508del CFTR mutation (Ussing chamber).

ARN23765 EC_{50} : **0.038** nM
VX-809 EC_{50} : ~**200** nM

Task Force for Cystic Fibrosis (TFCF) Project funded by

Pedemonte,..., Bandiera & Galietta, *Science Advances* 2020; **6**: eaay9669

Compounds in Preclinical Development

KIT-2014: a small peptide.

KIT-2014 is being developed by **Kither Biotech** in combination with standard of care compounds and as monotherapy.

KIT-2014 received Orphan Drug designation from the EMA.

Source: Kither Biotech website

Conclusions

A few small molecules modulating the activity of mutant CFTR are undergoing Phase 1-3 clinical trials.

Two new triple combinations of 2 correctors plus 1 potentiator are under clinical investigation by Vertex and AbbVie.

A read-through agent for treating patients with CFTR gene with class I mutations is in Phase 2 clinical trials.

Several candidate drugs are undergoing Preclinical Development and are expected to start clinical trials in 2022.

mRNAs, ASOs, and CFTR gene (gene therapy) represent most of the disclosed candidate drugs currently in Preclinical Development.

New drugs for disease-modifying therapy of CF are expected most likely in 2-4 years.

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THANK YOU!

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