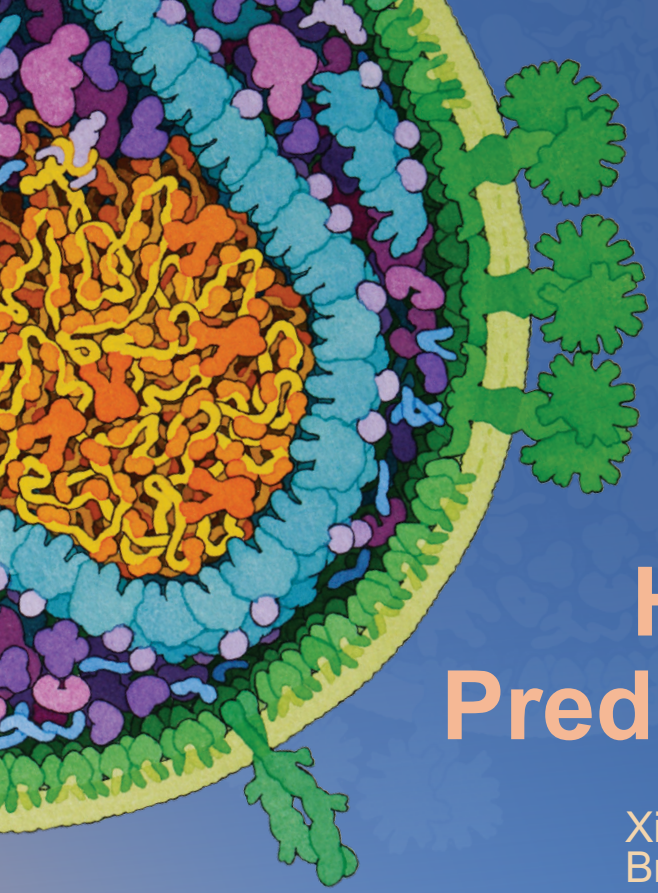

SCIENCE SPOTLIGHT™

# High Lung Levels of Active Triphosphate Predicted with Oral AT-527 in COVID Patients

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*Disclosure:* [1]Employees, [2]Contractor of Atea Pharmaceuticals, Inc.

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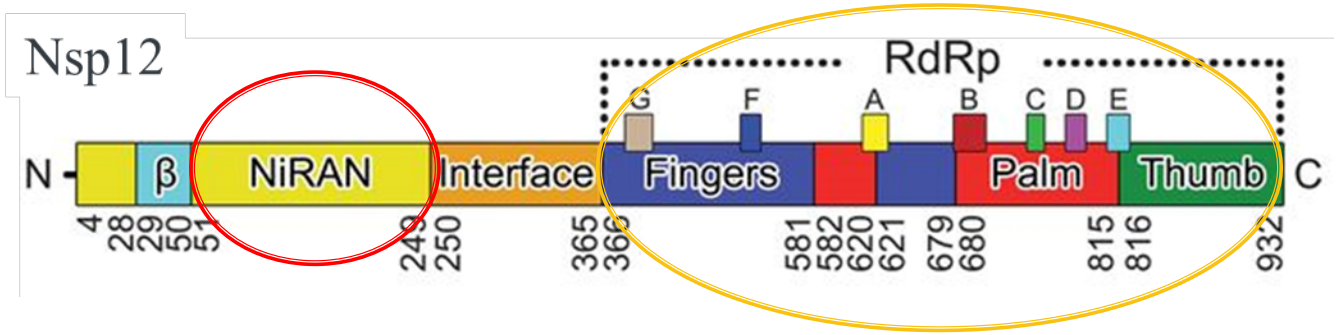
CROI 2021

*March 6th, 2021*

# AT-527, Oral Direct-Acting Antiviral, Potential Transformative Treatment for COVID-19

- Novel guanosine nucleotide prodrug; potent *in vitro* antiviral activity against SARS-CoV-2, virus of COVID-19
- Targets SARS-CoV-2 RNA polymerase (nsp12), a highly conserved gene with potential to limit Impact of naturally-evolving mutants
- Safety and efficacy demonstrated in HCV participants prompted clinical evaluation for COVID-19
- Phase 1 results show favorable PK profile, safety and confirm dosing regimen
- High lung levels of active triphosphate predicted with oral AT-527 in COVID patients; clinical dosing (550 mg BID) selected to achieve effective concentrations in lungs against SARS-CoV-2

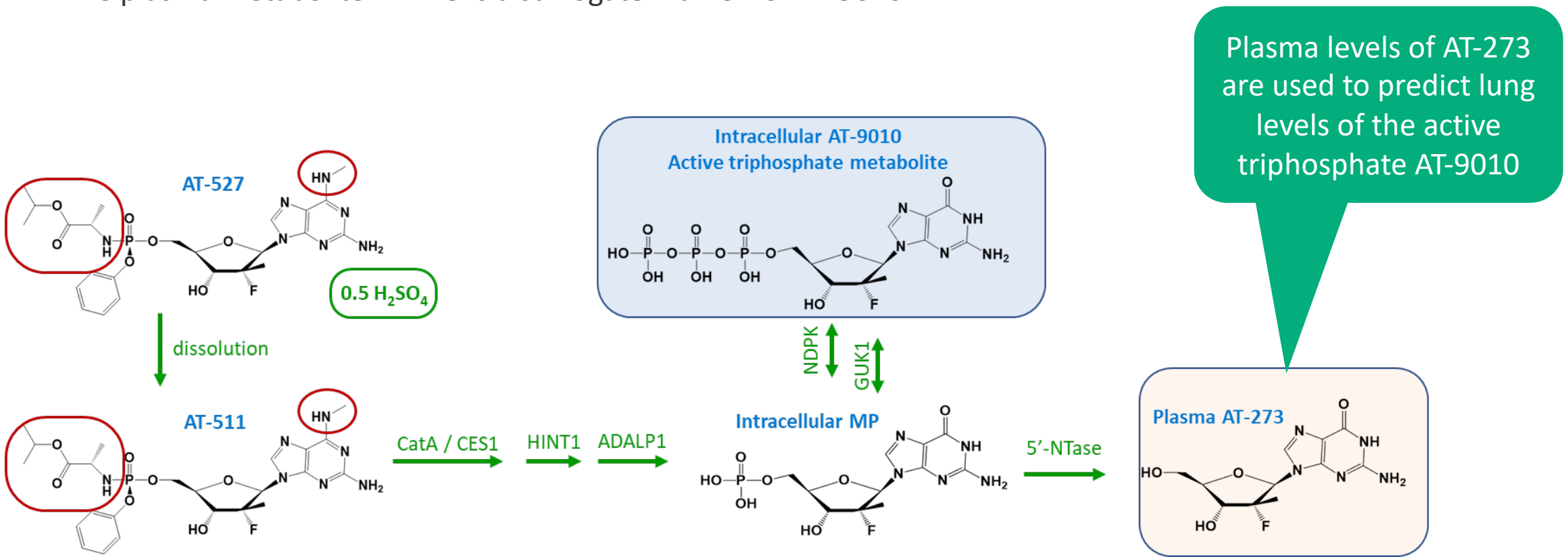
- Non-structural protein (nsp) 12/7/8 polymerase complex is responsible for both viral RNA replication and transcription
- Nsp12 has two functional domains
  - RdRp = RNA-dependent RNA polymerase
  - NiRAN = Nidovirus RdRp-Associated Nucleotidyltransferase




- Impairment of NiRAN function leads to viral growth inhibition

# Metabolism of AT-527 to Active Triphosphate

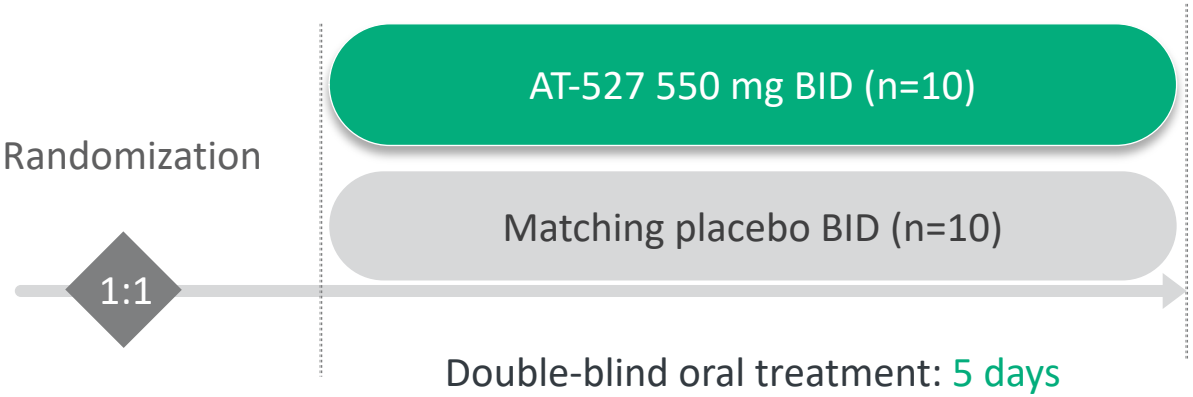
- AT-527, a hemisulfate salt with improved pharmaceutical properties, is rapidly solubilized to AT-511
- AT-511 undergoes multistep activation to the intracellular active triphosphate metabolite AT-9010, inhibiting viral RNA synthesis via the dual mechanism of action
- The plasma metabolite AT-273 is a surrogate marker for AT-9010



# AT-527 Phase 1 Results Demonstrate Favorable PK, Safety and Confirm Dosing Regimen

**Inclusion Criteria:** healthy male and female (N=20) participants 18-65 years of age

**Country:** Canada3
NCT04711187

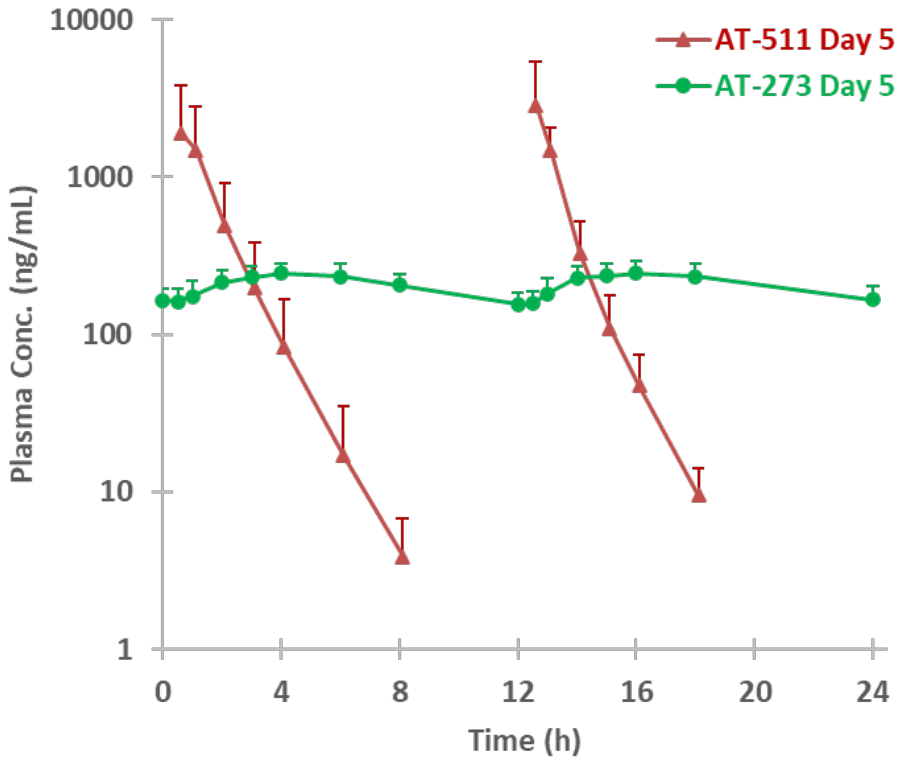


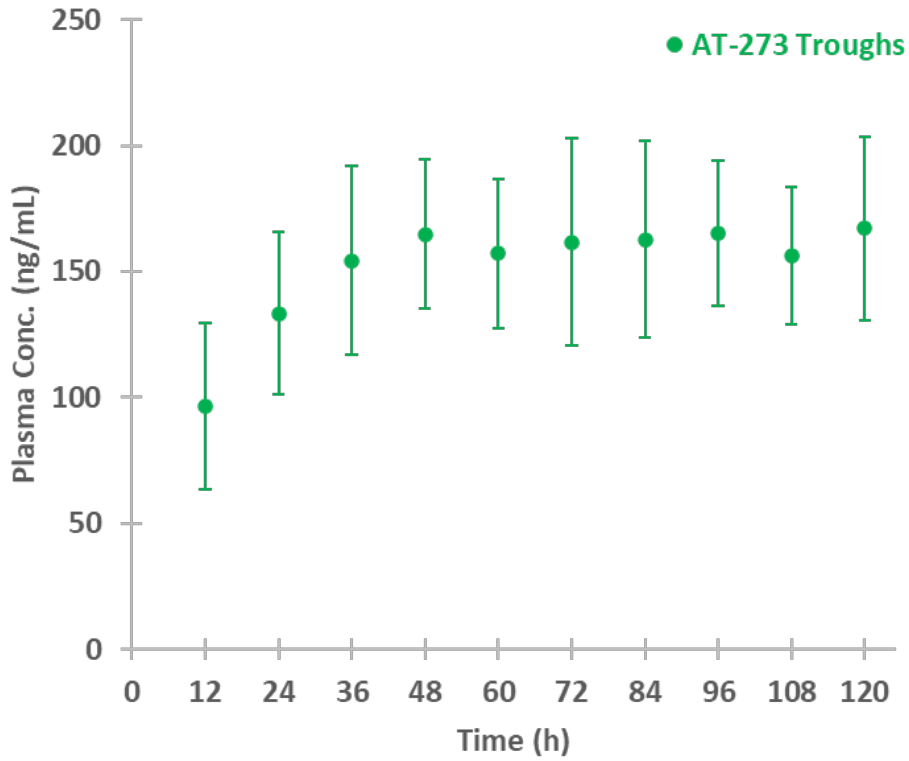

**Study objectives:** Safety and PK of 550 mg BID dosing regimen

**Population and Safety Summary**

- Healthy volunteers were mostly male (80%), white (95%), with mean age of 47.3 years old
- All participants completed study
- AT-527 was well-tolerated
- No SAEs/discontinuations
- Four participants (two in each arm) reported non-serious AEs
  - None were treatment-related; all resolved
- No clinically significant laboratory or ECG abnormalities

# Plasma Pharmacokinetics of AT-511 and AT-273, Surrogate of Intracellular TP



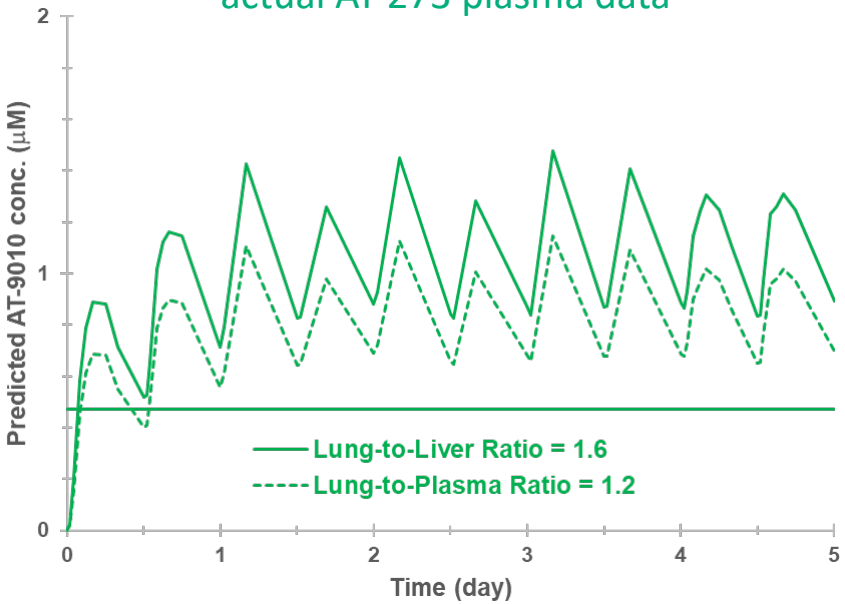

**Following Oral Dosing of AT-527 550 mg BID for 5 days in Healthy Volunteers (n=10)**

- AT-511 was rapidly absorbed and metabolized
- Plasma AT-511 levels were typically BLQ after 8 h; no accumulation following BID dosing
- Steady state reached with 4$^{th}$ dose based on trough levels of AT-273
- As expected, BID regimen quickly achieved high and sustained trough AT-273 levels

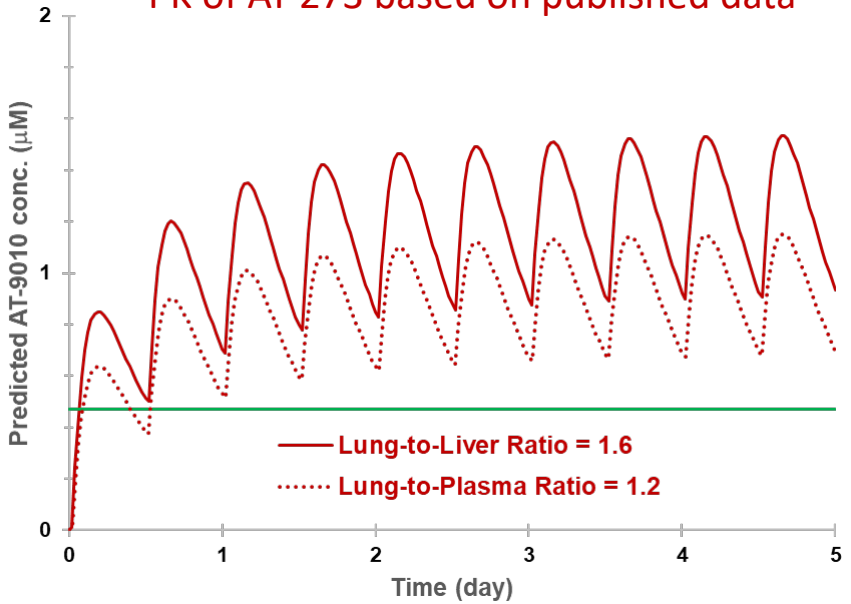
# 550 mg BID Regimen Selected to Achieve Effective Concentrations in Lungs Against SARS-CoV-2

$EC_{90}$=0.5 µM

Predicted lung AT-9010 using actual AT-273 plasma data




Predicted AT-9010 using simulated plasma PK of AT-273 based on published data [1,2]




Human plasma AT-273 PK (surrogate for active TP) was used to predict lung AT-9010 concentrations using scaling factors determined in NHP lung vs. liver (1.6x) and lung vs. plasma (1.2x) [2]

- Predicted AT-9010 lung levels consistently exceed the *in vitro* $EC_{90}$ of 0.5 µM of drug inhibiting SARS-CoV-2 replication in HAE cells
- Favorable PK with rapid steady state attainment and fast build-up of trough levels of AT-273, predicting efficacious levels of the active TP in lungs
- AT-527 550 mg BID regimen currently being evaluated in Phase 2 studies for the treatment of COVID-19 (NCT04396106, NCT04709835)

[1] https://aac.asm.org/content/63/12/e01201-19
[2] https://aac.asm.org/content/early/2021/02/02/AAC.02479-20.long