INTREPID ALLIANCE

INTERNATIONAL READINESS FOR PREVENTING INFECTIOUS VIRAL DISEASE

APRIL 29, 2024

Antiviral Clinical Development Landscape and Promising Clinical Compounds

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INTREPID Alliance: Antiviral Clinical Development Landscape - Second Edition. 29 April 2024. Available at intrepidalliance.org.

INTREPID Alliance Pandemic Preparedness

- **INTREPID Alliance Landscaping Activities**
  - Highlight strengths and weaknesses of the antiviral drug development pipeline for potential pandemic viral pathogens
  - Support the 100 Days Mission (100DM) which seeks to identify two 'Phase 2 ready' therapeutic candidates against each of the identified viral pathogen families of greatest pandemic potential
- **Landscape Analysis**
  - A living analysis of the antiviral landscape that will be updated based on emerging data
  - Derived from Airfinity database information on diverse compounds against 12 viral families (See Slide 3)
  - Focused on direct acting small molecule antivirals
- **Timing and Publication on Website**
  - **First Edition:** Initial triage and selection of clinical compounds with favorable properties and antiviral mechanism of action – January 2024
  - **Second Edition:** Detailed review and identification of most Promising Clinical and Approved-Indication Expansion Compounds – April 2024
  - Antiviral Preclinical Development Landscape release – June 2024
  - Quarterly Updates – Ongoing

Landscape Analysis Components

Airfinity monitors 12 viral families that pose the greatest risk of pandemic potential.

With thanks to Airfinity for its contributions to the presentation.

Baseline Information Identified:

- Diverse Compound/Indications by Viral Family and Disease
- Phase of Development (e.g., Preclinical through Phase 4, Approved)
- MOA/Target
- Route of Administration
- Developer or Sponsor (Type, Location)
- Clinical Trials (Links, Status, Trial Site Locations)

Figures & Tables:

- 12 Viral Families of Interest for Pandemic Preparedness
- Total Pipeline by Viral Family
- Promising Clinical & Indication-Expansion Compounds
- Compounds by Viral Family and Phase of Development
- Compounds by MOA/Target and Viral Family
- Phase of development vs viral disease for each MOA
- Developer or Sponsor

- Emerging information is reviewed on a monthly basis.
- Antiviral Landscape updated on the INTREPID Alliance website on a quarterly basis.

INTREPID Alliance Clinical Antiviral Landscape: Clinical Antiviral Compounds Analysis (January 2024)*

- Initial analysis of the clinical antiviral landscape data as of November 16, 2023 was posted on the INTREPID website on **January 24, 2024**.
  - Two rounds of rigorous scientific triage on 300 clinical phase entries reduced the number to 61 distinct compounds associated with 80 compound/indication pairings.

Initial Analysis

Exclusion Criteria:

- Antibodies
- Antibiotics & Anti-infectives
- Cell-based Therapy
- HIV or HCV-specific
- Host Targets (incl. Imm. Mod.)
- Natural Products/ Nutraceuticals/Herbals
- Vaccines

Inclusion Criteria:

- Known Antiviral MOA
- *In Vitro/In Vivo* Activity
- Small Molecules
- Peptides
- RNA-based
- SAD/MAD Data
- FIH Completed
- No Major Safety Signals

*As of November 16, 2023

INTREPID Alliance Clinical Antiviral Landscape: Clinical Antiviral Compounds Analysis (March 2024)*

- Further analysis investigated the clinical landscape with data updates from March 2024:
  - Novel Clinical Phase Antiviral Compounds (e.g., not yet approved for a virus disease indication)
  - Approved-Indication Expansion Antiviral Compounds (e.g., initial approval for one viral indication and under evaluation for other viral indication(s))
- Additional scientific analysis** of only the novel compounds categorized them as follows:
  - **Promising**
  - **Watch & Wait**
  - **Archived**
- Based on these analyses of the March 2024 data, there are 60 distinct antiviral compounds in the antiviral clinical development landscape.

*As of March 8, 2024; **See criteria and references on slide 6

Criteria* for Promising Clinical Antiviral Compound Analysis (March 2024)**

- FIH trial completed & data at adequate doses and dosing duration available
- POC study ongoing *or* completed & data available
  - POC demonstration via viral endpoint, symptom alleviation, etc.
  - POC in animal model may be applicable for certain viral diseases where clinical POC is not feasible
- Adequate PK/PD to support Phase 2/3 dose selection and route of administration
- Safety and tolerability consistent with the target dose/exposure and no difficult-to-manage clinical safety signals
- Other criteria such as chemical structure, synthesis, scalability, etc. are taken into account where data are available.

*In addition to the collective antiviral drug development experience of INTREPID member companies, guidance documents from Regulatory Authorities such as the US FDA routinely used by drug developers, and publicly available Target Product Profiles such as the NIH/NIAID Target Product Profiles for Antivirals, were used to inform the clinical phase triage.

**As of March 8, 2024; FIH: first-in-human; POC: proof-of-concept; PK/PD: pharmacokinetic/pharmacodynamic; CMC: chemistry, manufacturing, and controls

Categories for Clinical Antiviral Compound Analysis (March 2024)*

- **Promising** (e.g., meets "Promising Criteria")
  - 100DM Ready
  - Registration & Approval for established viral diseases
- **Watch & Wait**
  - FIH or POC Study just starting/ongoing or data are unavailable for a completed study
  - Unable to make a data-driven evaluation
- **Archived**
  - Development paused, no recent information >5 years
- **Exclude**
  - Known disqualifying data related to safety and tolerability, efficacy, developability, chemical structure, etc.

*As of March 8, 2024; FIH: first-in-human; POC: proof-of-concept

Summary of Updated Antiviral Clinical Development Landscape with Promising Clinical Compounds (March 2024)*

- Identified **60** distinct antiviral clinical compounds
  - **19** Approved for COVID-19 and/or Influenza; 0 for other viral diseases
    - 11 by Stringent Authority (S.A.)
    - 7 by Other National Authority (O.N.A.)
    - 1 by S.A. and O.N.A. (favipiravir)
  - **41** Novel compounds
- There are **78** indications being studied from the 60 distinct antiviral compounds**
  - **23** Approvals for COVID-19 and/or Influenza
    - 11 approved for COVID-19
    - 8 for Influenza
    - 4 approved for COVID-19 and Influenza
  - 7 of the 19 distinct Approved antiviral compounds are being evaluated for **13** other viral indications
  - **42** indications for Novel compounds; 1 compound being evaluated for two indications
- Novel Promising and Watch & Wait compounds target protease (**16**), entry (**12**), replication (**9**), and assembly-release (**1**).

*As of March 8, 2024; **Some compounds are being evaluated for more than 1 viral indication

INTREPID Alliance Antiviral Clinical Development Landscape: Overview of Priority Viral Families*

As of March 8, 2024, the 60 clinical phase and approved antiviral compounds fall into 8 of 12 viral families with greatest risk of pandemic potential.

Viral Family	Adenoviridae	Arenaviridae	Coronaviridae	Filoviridae	Flaviviridae	Hantaviridae
Indication	Human Adenovirus A-G	Lassa fever Chapare hemorrhagic fever	COVID-19	Ebola	Dengue Japanese encephalitis	X

Viral Family	Nairoviridae	Orthomyxoviridae	Paramyxoviridae	Peribunyaviridae	Picornaviridae	Togaviridae
Indication	Crimean Congo hemorrhagic fever	Influenza	X	X	Rhinovirus Polio	X

X = absence of clinical phase or approved antivirals

*As of March 8, 2024

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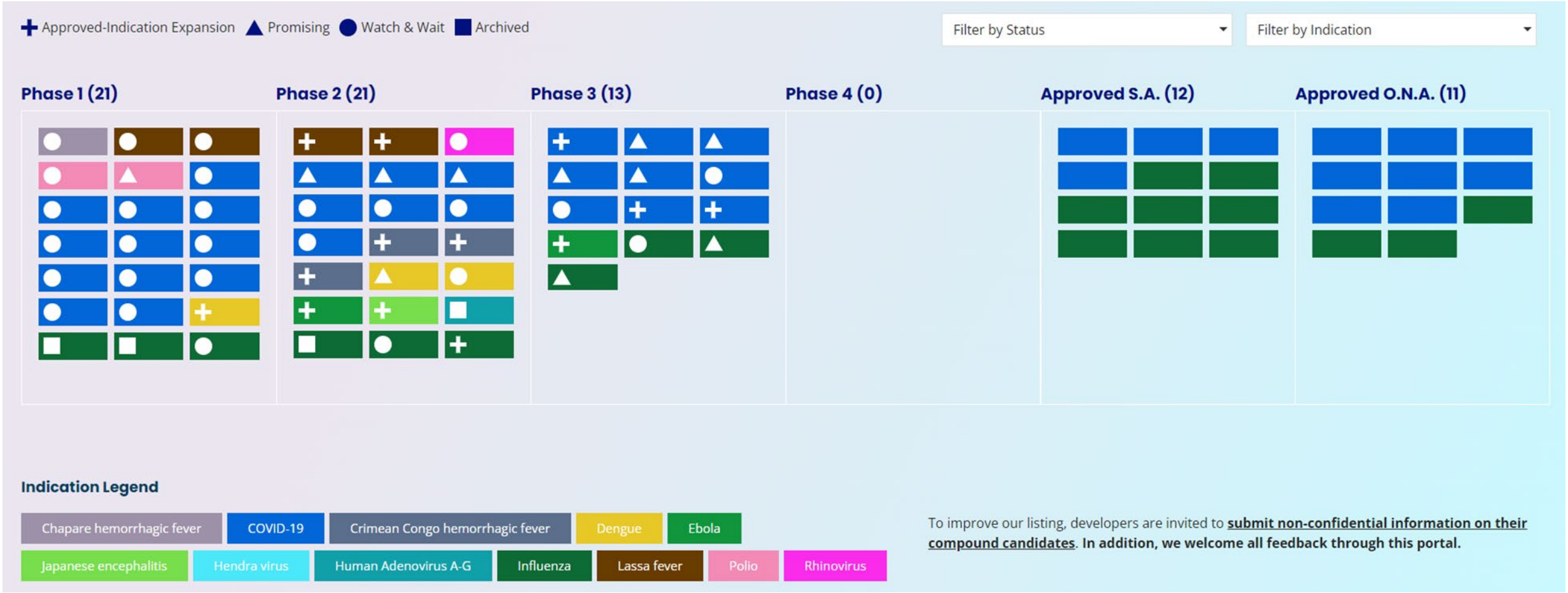
Static View of Interactive Antiviral Clinical Development Pipeline: INTREPID Alliance Analysis (March 2024)*



*As of March 8, 2024; WHO-defined Other National Authority (https://www.who.int/publications/m/item/list-of-transitional-wlas)
Favipiravir also has S.A. approval

Approved-Indication Expansion Clinical Antivirals (Previous Approval for COVID-19 and/or Influenza) (N=13)

INTREPID Alliance Analysis (March 2024)*

Phase of Development

Phase 1 (n=1)	Phase 2 (n=8)	Phase 3 (n=4)	Phase 4 (n=0)
Zanamivir	Favipiravir	Amantadine	
	Ribavirin	Remdesivir	
	Favipiravir+Ribavirin	Ribavirin	
	Favipiravir	Oseltamivir	
	Ribavirin		
	Molnupiravir		
	Favipiravir		
	Ribavirin		

Viral Disease (N)

- Chapare hemorrhagic fever (-)
- COVID-19 (3)
- Crimean Congo hemorrhagic fever (3)
- Dengue (1)
- Ebola (2)
- Hendra virus (-)
- Human Adenovirus A-G (-)
- Influenza (1)
- Japanese encephalitis (1)
- Lassa fever (2)
- Polio (-)
- Rhinovirus (-)

These Approved-Indication Expansion antiviral compounds which have already demonstrated an acceptable safety and tolerability profile, will be evaluated against the Promising compounds criteria.

*March 8, 2024 data with “Promising” Analysis March 2024

Novel Clinical Antivirals (Promising, Watch & Wait, Archived) (N=41)

INTREPID Alliance Analysis (March 2024)*

▲ Promising ● Watch & Wait ■ Archived ** New; Change in Status

Phase 1 (n=21)

V-7404 ▲	RQ-01** ●	YKYY017 ●
S-892216 ●	WPV01/rtv** ●	CC-42344 ●
ISM3312 ●	ABBV 903 ●	ARN-75039 ●
ALG-097558 ●	ASC11/rtv ●	LHF 535 ●
CDI-988 ●	Delcetravir ●	LHF 535 ●
IPD-52520** ●	NV-CoV-2 ●	Radavirsen ■
Pocapavir** ●	HY3000 ●	AL-794 ■

Phase 2 (n=12)

EDP-235 ▲	Vapendavir ●
Ibuzatrelvir (PF-07817883) ▲	WPV01 ●
SHEN26 ▲	P315V3 ●
Mosnodenvir (JNJ-1802) ▲	HNC042 ●
HS 10517/rtv ●	Brincidofovir ■
EYU688 ●	Flufirvitide-3 ■

Phase 3 (n=9)

GST-HG171 ▲	Bemnifosbuvir ●
QLS1128 ▲	FB2001 ●
STI-1558 ▲	ZX-7101A ●
Obeldesivir ▲	
GP681 ▲	
Onradivir** (ZSP1273) ▲	

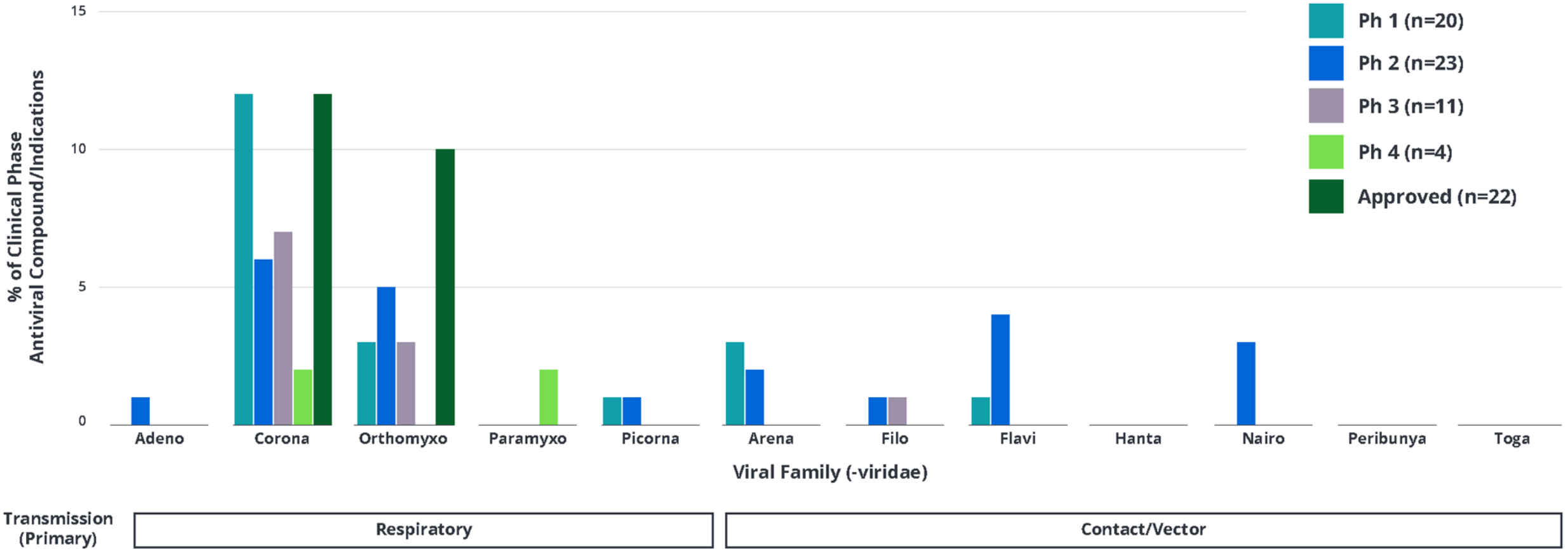
Viral Disease (N)

Chapare hemorrhagic fever (1)	COVID-19 (25)	Crimean Congo hemorrhagic fever (-)	Dengue (2)	Ebola (0)			
Japanese encephalitis (-)	Hendra virus (-)	Human Adenovirus A-G (1)	Influenza (8)	Lassa fever (2)	Polio (2)	Rhinovirus (1)	

*March 8, 2024 data with “Promising” Analysis March 2024

The Majority of Clinical Phase Antiviral Compound/Indications Are Targeting Coronaviruses and Orthomyxoviruses*

% Clinical Phase Antiviral Compound/Indications by Virus Family (N=80)



*As of November 16, 2023; March 2024 data are forthcoming

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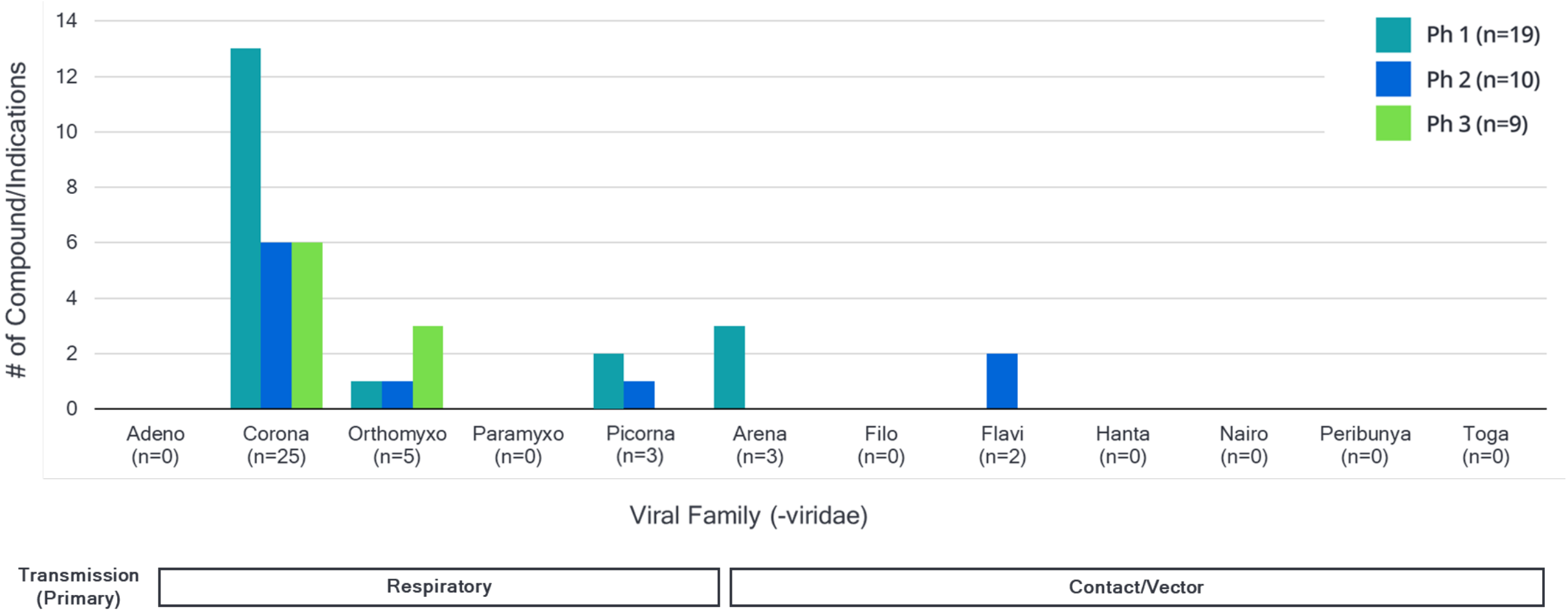
“Promising” Compounds Analysis (March 2024)*

Novel Compounds (Promising and Watch & Wait) by Virus Family (N=38)



Transmission (Primary)	Respiratory	Contact/Vector

*As of March 8, 2024

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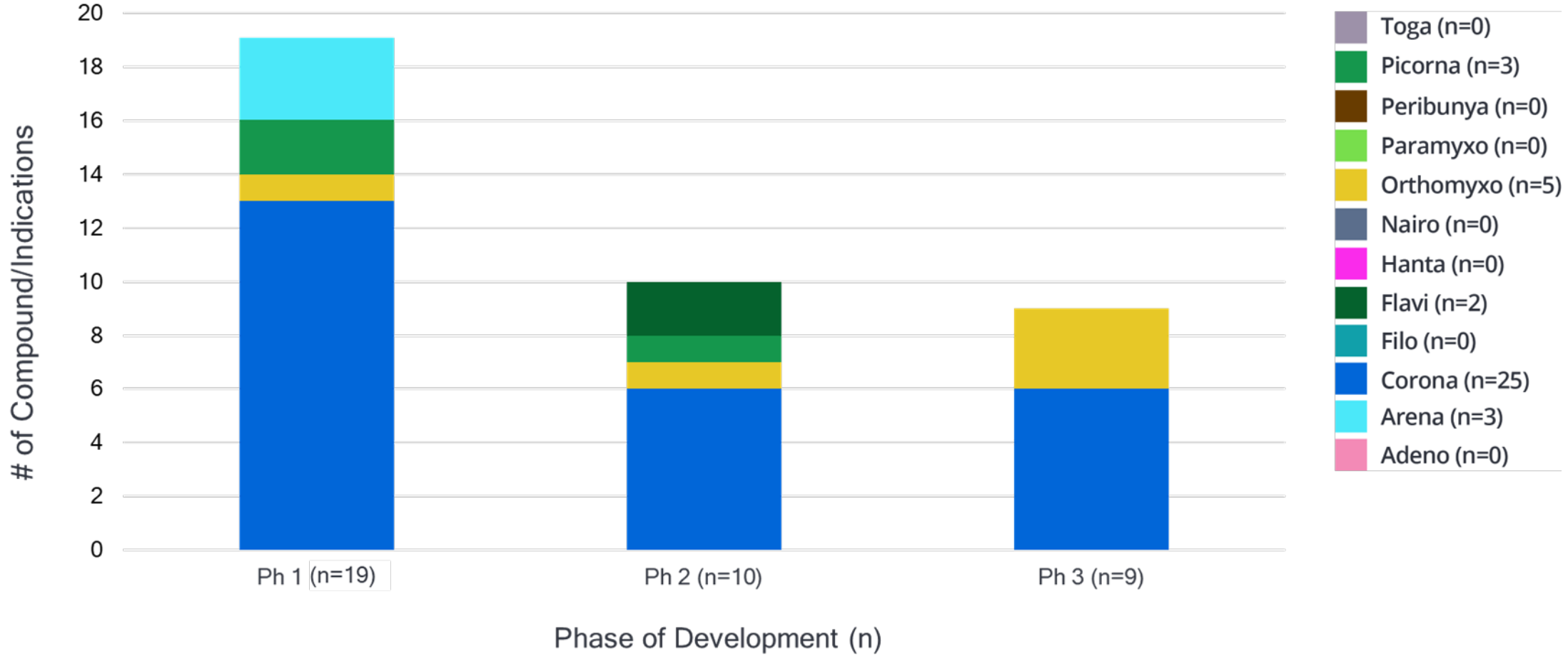
“Promising” Compounds Analysis (March 2024)*

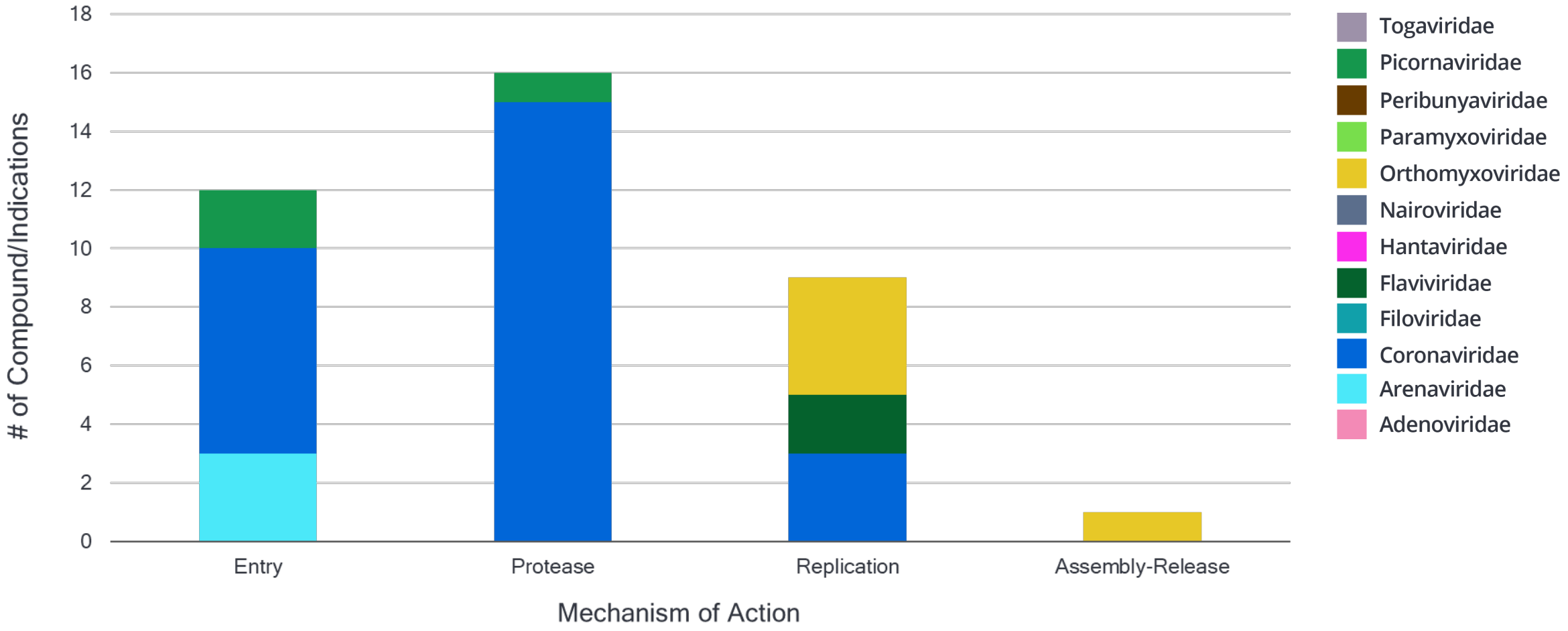
Novel Compound/Indications (Promising and Watch & Wait) by Phase of Development (N=38)



*As of March 8, 2024

“Promising” Compounds Analysis (March 2024)*

Novel Compound/Indications (Promising and Watch & Wait) by MOA and Viral Family (N=38)



*As of March 8, 2024

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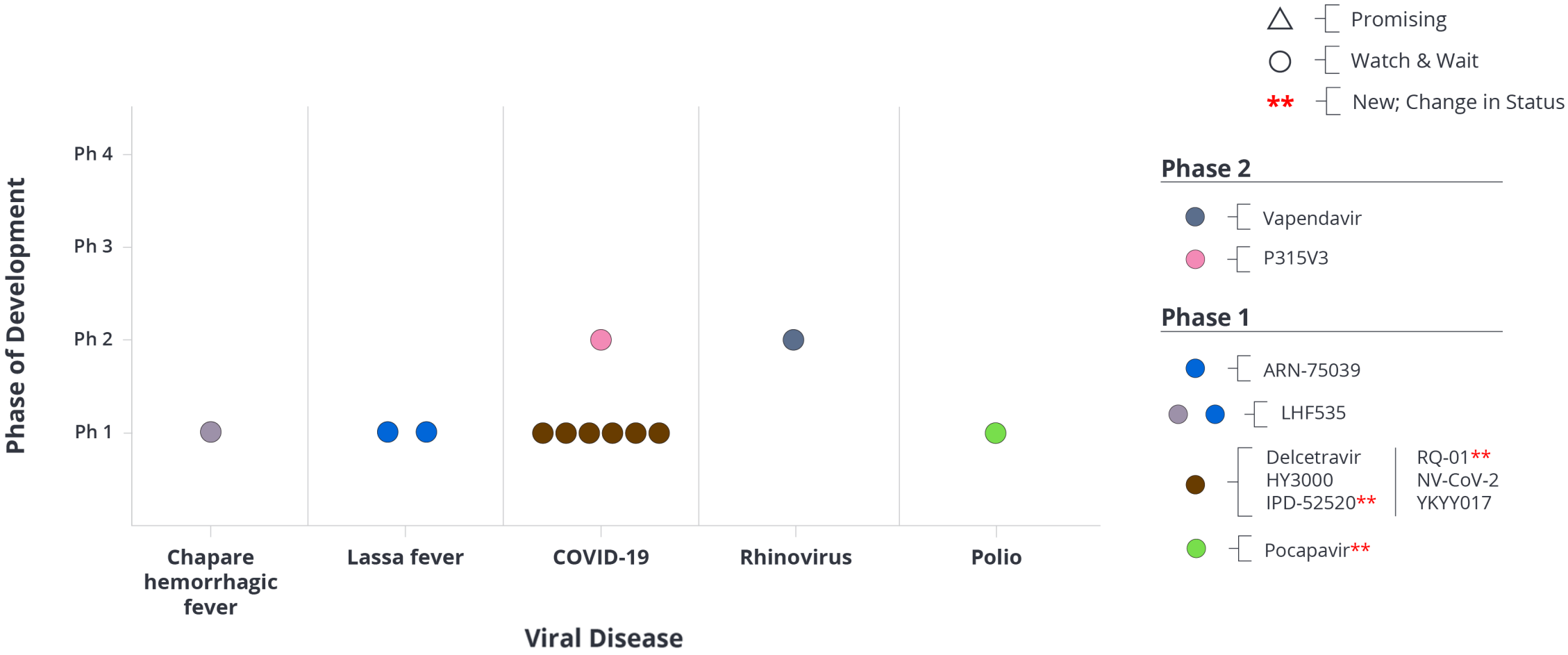
Novel Clinical Antiviral Entry Inhibitors*

Novel Compound/Indications (Promising, Watch & Wait (N=12))



*As of March 8, 2024; Attachment, Capsid (Rhinovirus), Fusion

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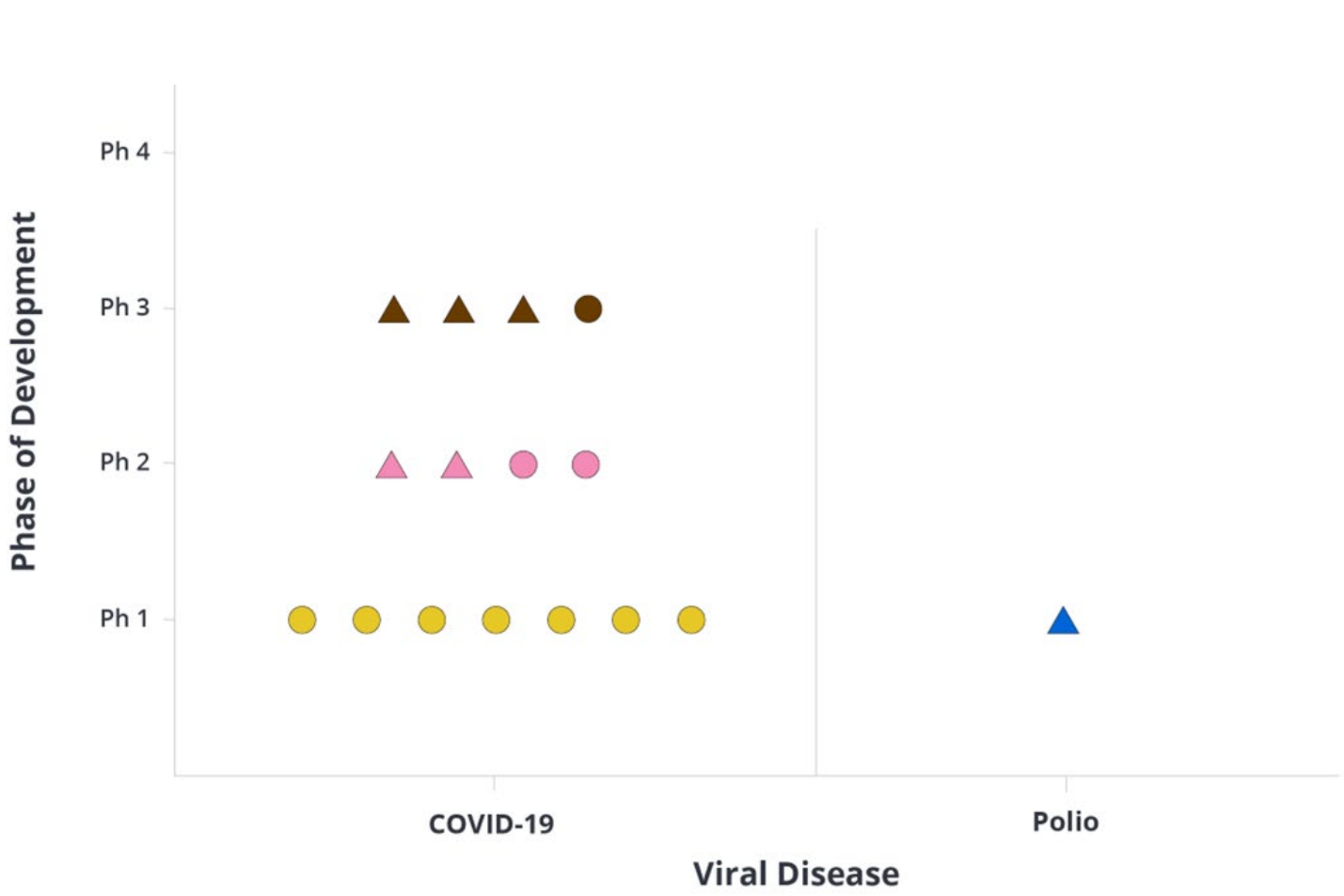
Novel Clinical Antiviral Protease Inhibitors*

Novel Compound/Indications (Promising, Watch & Wait, Archived (N=16))



△ Promising

○ Watch & Wait

** New; Change in Status

Phase 3

▲ GST-HG171
QLS1128
STI-1558

● FB2001

Phase 2

▲ EDP-235
Ibuzatrelvir (PF-07817883)

● HS 10517/Ritonavir
WPV01

Phase 1

▲ V-7404

● ABBV 903
ALG-097558
ASC11/Ritonavir
CDI-988
ISM3312
S-892216
WPV01/rtv**

*As of March 8, 2024; Mpro (Coronavirus and Enterovirus)

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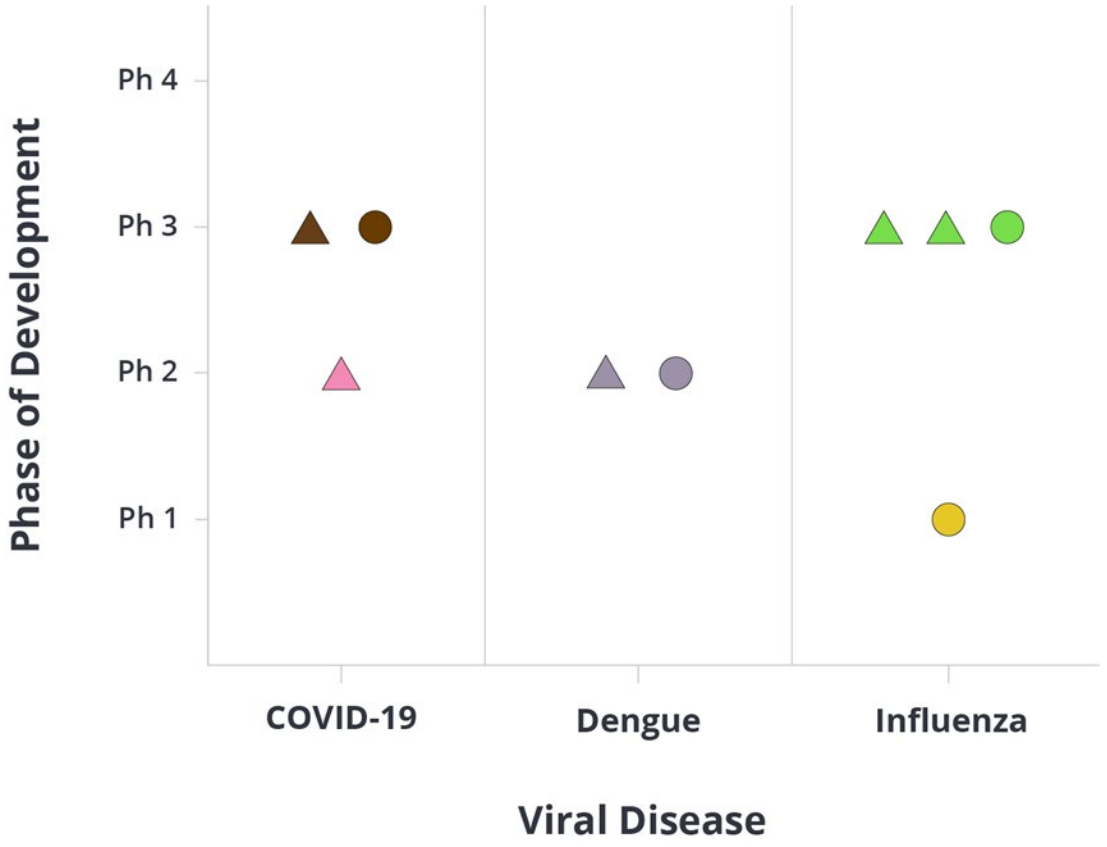
Novel Clinical Antiviral Replication Inhibitors*

Novel Compound/Indications (Promising, Watch & Wait (N=9))



△ Promising

○ Watch & Wait

** New; Change in Status

Phase 3

- Obeldesivir (GS-5245)
- Bemnifosbuvir
- Onradivir (ZSP1273)** GP681
- ZX-7101A

Phase 2

- SHEN26
- Mosnodenvir (JNJ-1802)
- EYU688 (NITD-688)

Phase 1

- CC-42344

*As of March 8, 2024; Polymerase, Endonuclease, Replicase, DENV NS4B

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Novel Clinical Antiviral Assembly-Release Inhibitors*

Novel Compound/Indications (Promising, Watch & Wait, Archived (N=1))

*As of March 8, 2024; Neuraminidase

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Summary of Updated Antiviral Clinical Development Landscape with Promising Clinical Compounds (March 2024)*

- Identified 60 distinct antiviral clinical compounds
  - 19 Approved for COVID-19 and/or Influenza; 0 for other viral diseases
    - 11 by Stringent Authority (S.A.)
    - 7 by Other National Authority (O.N.A.)
    - 1 by S.A. and O.N.A. (favipiravir)
  - 41 Novel compounds
- There are 78 indications being studied from the 60 distinct antiviral compounds**
  - 23 Approvals for COVID-19 and/or Influenza
    - 11 approved for COVID-19
    - 8 for Influenza
    - 4 approved for COVID-19 and Influenza
  - 7 of the 19 distinct Approved antiviral compounds are being evaluated for 13 other viral indications
  - 42 indications for Novel compounds; 1 compound being evaluated for two indications
- Novel Promising and Watch & Wait compounds target protease (16), entry (12), replication (9), and assembly-release (1).

*As of March 8, 2024; **Some compounds are being evaluated for more than 1 viral indication

Supplemental Information

12 Compounds Approved by a Stringent Regulatory Authority (S.A.)*

COVID-19 (n=4), Influenza (n=8)

Compound	Developer/Sponsor	Mechanism/Target
COVID-19		
Ensitrelvir (S-217622)	Shionogi	Protease – Mpro
Molnupiravir (MK-4482)	Merck & Co./Merck Sharp & Dohme (MSD), Ridgeback Biotherapeutics	Replication – RdRp
Nirmatrelvir/Ritonavir	Pfizer	Protease – Mpro
Remdesivir	Gilead Sciences	Replication – RdRp
INFLUENZA		
Amantadine	Novartis	Entry – Proton Channel M2
Baloxavir Marboxil	Shionogi, Roche	Replication – Endonuclease
Favipiravir**	FUJIFILM Toyama Chemical	Replication – RdRp
Laninamivir	Daiichi Sankyo, Biota Pharmaceuticals	Assembly/Release – NA
Oseltamivir	Roche	Assembly/Release – NA
Peramivir	BioCryst Pharmaceuticals	Assembly/Release – NA
Rimantadine	Allergan	Entry – Proton Channel M2
Zanamivir***	GlaxoSmithKline (GSK)	Assembly/Release – NA

*As of March 8, 2024; WHO defined Stringent Authority (https://www.who.int/publications/m/item/list-of-transitional-wlas);
**Favipiravir also has O.N.A. approval; ***Zanamivir also has Dengue study via Investigator Sponsored Study

8 Compounds Approved by Other National Authority (O.N.A.)*

COVID-19 (n=5), Influenza (n=0), COVID-19 & Influenza (n=3)

Compound	Developer/Sponsor	Mechanism/Target
COVID-19		
Azvudine	HeNan Sincere Biotech, Zhengzhou Granlen PharmaTech, Genuine Biotech, Fosun Pharma	Replication – RdRp
Favipiravir**	Promomed, R-Pharm	Replication – RdRp
Leritrelvir (RAY1216)	Guangdong Zhongsheng Pharmaceutical	Protease – Mpro
Simnotrelvir/Ritonavir	Simcere Pharmaceutical, Shanghai Institute of Materia Medica (SIMM), Jiangsu Simcere Pharmaceutical	Protease – Mpro
Mindeudesivir (VV116)	Shanghai Junshi Biosciences	Replication – RdRp
INFLUENZA		
–	–	–
COVID-19 & INFLUENZA		
Enisamium (VR17-04)	Farmak	Replication – RdRp
Triazavirin	Medsintez Pharmaceutical	Replication – RdRp
Umifenovir	Pharmstandard	Entry – Fusion

*As of March 8, 2024; WHO defined Other National Authority (https://www.who.int/publications/m/item/list-of-transitional-wlas);
**Favipiravir also has S.A. approval

11 “Promising” Novel Clinical Antiviral Compounds*

COVID-19 (n=7), Influenza (n=2), Dengue (n=1), Polio (n=1)

Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development	Viral Disease
EDP-235	Enanta Pharmaceuticals	U.S.	Protease - Mpro	2	COVID-19
GST-HG171	Fujian Cosunter Pharmaceutical	China	Protease - Mpro	3	COVID-19
Obeldesivir (GS-5245)	Gilead Sciences	U.S.	Replication - RdRp	3	COVID-19
Ibuzatrelvir (PF-07817883)	Pfizer	U.S.	Protease - Mpro	2	COVID-19
QLS1128	Qilu Pharmaceutical	China	Protease - Mpro	3	COVID-19
SHEN26	Kexing Biopharm	China	Replication - RdRp	2	COVID-19
STI-1558	Sorrento Therapeutics	U.S.	Protease - Mpro	3	COVID-19
Mosnodenvir (JNJ-1802)	Janssen Pharmaceuticals	Belgium	Replication –DENV NS4B	2	Dengue
GP681	Jiangxi Qingfeng Pharmaceutical	China	Replication - Endonuclease	3	Influenza
Onradivir (ZSP1273)	Raynovent	China	Replication - DdRp	2	Influenza
V-7404	ViroDefense, Pfizer	U.S.	Protease - EV 3C pro	1	Polio

*As of March 8, 2024

“Watch & Wait” Novel Clinical Antiviral Compounds (N=13 of 27)*

COVID-19 (n=9), Influenza (n=1), Dengue (n=1), Rhinovirus (n=1), Polio (n=1)

Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development	Viral Disease
ALG-097558	Aligos Therapeutics	U.S.	Protease - Mpro	1	COVID-19
Bemnifosbuvir	Atea Pharmaceuticals	U.S.	Replication - RdRp	3	COVID-19
CDI-988	CoCrystal Pharma	U.S.	Protease - Mpro	1	COVID-19
HS 10517/Ritonavir	Abbott Laboratories, AbbVie, Gilead Sciences, Jiangsu Hansoh Pharmaceutical	U.S., U.S., China	Protease - Mpro	2	COVID-19
IPD-52520**	IAVI	U.S.	Entry	1	COVID-19
ISM3312	Insilico Medicine	Hong Kong	Protease - Mpro	1	COVID-19
RQ-01**	Red Queen Therapeutics	U.S.	Entry	1	COVID-19
S-892216	Shionogi	Japan	Protease - Mpro	1	COVID-19
WPV01/rtv**	Westlake University	China	Protease - Mpro	1	COVID-19
EYU688 (NITD-688)	Novartis	Switzerland	Replication - NS4B	2	Dengue
CC-42344	CoCrystal Pharma	U.S.	Replication - Flu A Pol	1	Influenza
Vapendavir	Vaxart, Altesa Biosciences	U.S., U.S.	Entry - Capsid	2	Rhinovirus
Pocapavir**	ViroDefense	U.S.	Entry - Capsid	1	Polio

*As of March 8, 2024; **New Addition

“Watch & Wait” Novel Clinical Antiviral Compounds (N=14 of 27)*

COVID-19 (n=9), Influenza (n=2), Lassa fever (n=2), Chapare hemorrhagic fever (n=1)

Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development	Viral Disease
LHF 535**	Kineta	U.S.	Entry - Fusion	1, 1	Chapare hemorrhagic fever; Lassa fever
ABBV 903	AbbVie	U.S.	Protease - Mpro	1	COVID-19
ASC11/Ritonavir	Ascletis Pharma	China	Protease - Mpro	1	COVID-19
Delcetravir	Esfam Biotech	Australia	Entry - Attachment	1	COVID-19
FB2001	Frontier Biotechnologies	China	Protease - Mpro	3	COVID-19
HY3000	Hybio Pharmaceutical	China	Entry - Fusion	1	COVID-19
NV-CoV-2	NanoViricides	U.S.	Entry - Attachment	1	COVID-19
P315V3	Institute of Microbiology of the Chinese Academy of Sciences	China	Entry - Fusion	2	COVID-19
WPV01	Westlake University	China	Protease - Mpro	2	COVID-19
YKYY017	Yuekang Pharmaceutical	China	Entry - Fusion	1	COVID-19
HNC042	Guangzhou Henovcom Bioscience Co. Ltd.	China	Assembly/Release - NA	2	Influenza
ZX-7101A	Nanjing Zenshine Pharmaceuticals	China	Replication - Endonuclease	3	Influenza
ARN-75039	Arisan Therapeutics	U.S.	Entry - Fusion	1	Lassa fever

*As of March 8, 2024; **LHF535 under evaluation for two Viral Diseases

4 “Archived” Novel Clinical Antiviral Compounds*

Influenza (n=3), Human Adenovirus A-G (n=1)

Compound	Developer/Sponsor	Country	Mechanism/Target	Phase of Development	Viral Disease
Brincidofovir	Chimerix	U.S	Replication - DdDp	2	Human Adenovirus A-G
AL-794	Janssen Pharmaceuticals	Belgium	Replication - Endonuclease	1	Influenza
Flufirvitide-3	Autoimmune Technologies	U.S.	Entry - Flu HA	2	Influenza
Radavirsen	Sarepta Therapeutics	U.S.	Replication - translation	1	Influenza

*As of March 8, 2024

Select References for "Promising" Novel Clinical Antiviral Compounds*

These were cited in addition to information provided by Airfinity.

Compound	Selected References
EDP-235	• Encanta Pharmaceuticals. Enanta Pharmaceuticals Announces Positive Data from a Phase 1 Clinical Study of EDP-235, its Oral 3CL Protease Inhibitor Designed for the Treatment of COVID-19. Accessed: July 29, 2022. • Encanta Pharmaceuticals. Molecular Basis for the Antiviral Action of EDP-235: A Potent and Selective SARS-CoV-2 3CLpro Inhibitor. Accessed: April 4, 2022. • Encanta Pharmaceuticals. Enanta Pharmaceuticals Reports Positive Topline Results from Phase 2 SPRINT Trial Evaluating EDP-235 in Standard Risk Patients with COVID-19. Accessed: May 8, 2023.
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Obeldesivir (GS-5245)	• Anoshchenko O., et al. 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); Copenhagen, Denmark. Poster 2620. https://shorturl.at/bHJMP. Accessed: April 13-18, 2023. • Pitts J., et al. IDWeek; Boston, MA, USA. Poster 539. Efficacy in Multiple SARS-CoV-2 Animal Models Supports Phase 3 Dose Selection for Obeldesivir. https://doi.org/10.1093/ofid/ofad500.608. Accessed: November 23, 2023. • Mackman R, et al. J Med Chem. Discovery of GS-5245 (Obeldesivir), an Oral Prodrug of Nucleoside GS-441524 That Exhibits Antiviral Efficacy in SARS-CoV-2-Infected African Green Monkeys. https://doi.org/10.1021/acs.jmedchem.3c00750. Accessed: August 19, 2023. • Martinez D., et al. BioRxiv. Efficacy of the oral nucleoside prodrug GS-5245 (Obeldesivir) against SARS-CoV-2 and coronaviruses with pandemic potential. https://doi.org/10.1101/2023.06.27.546784. Accessed: June 28, 2023.
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