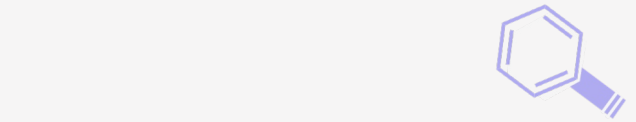
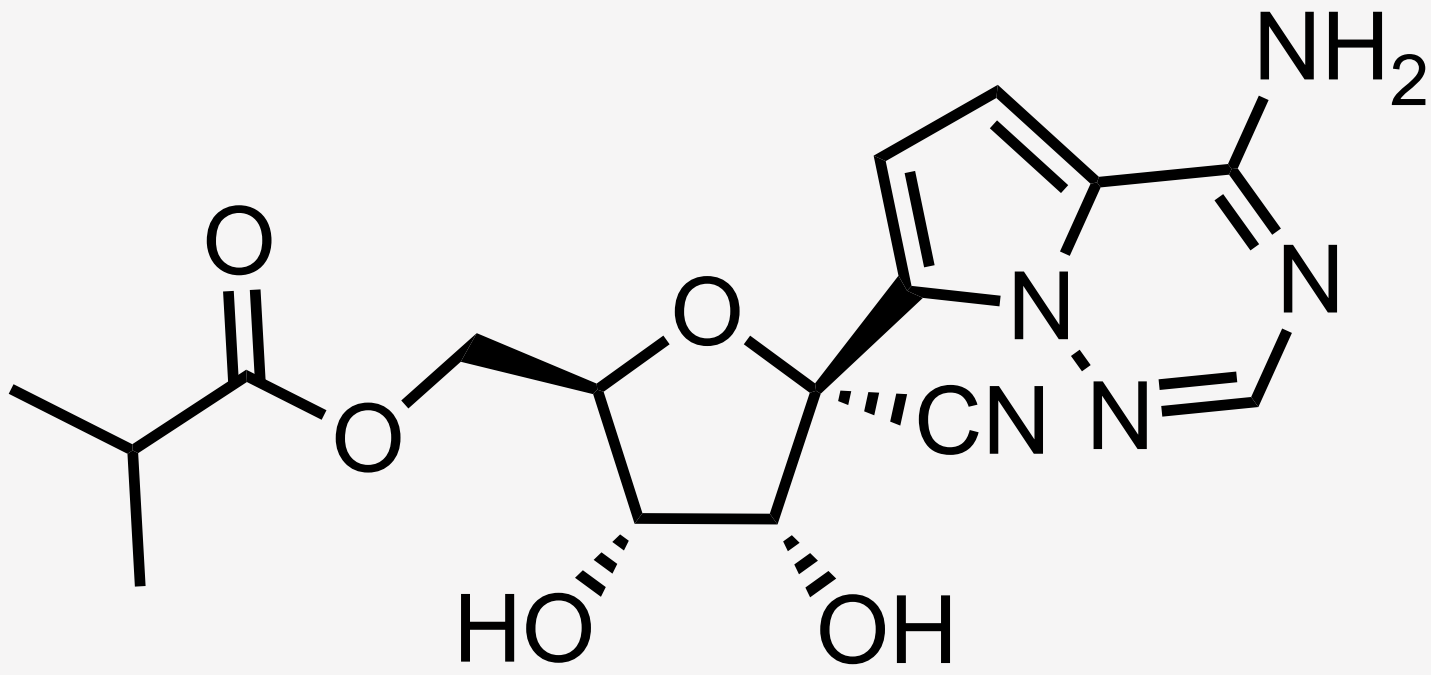
GS-5245 (RdRp inhibitor)

Gilead Sciences

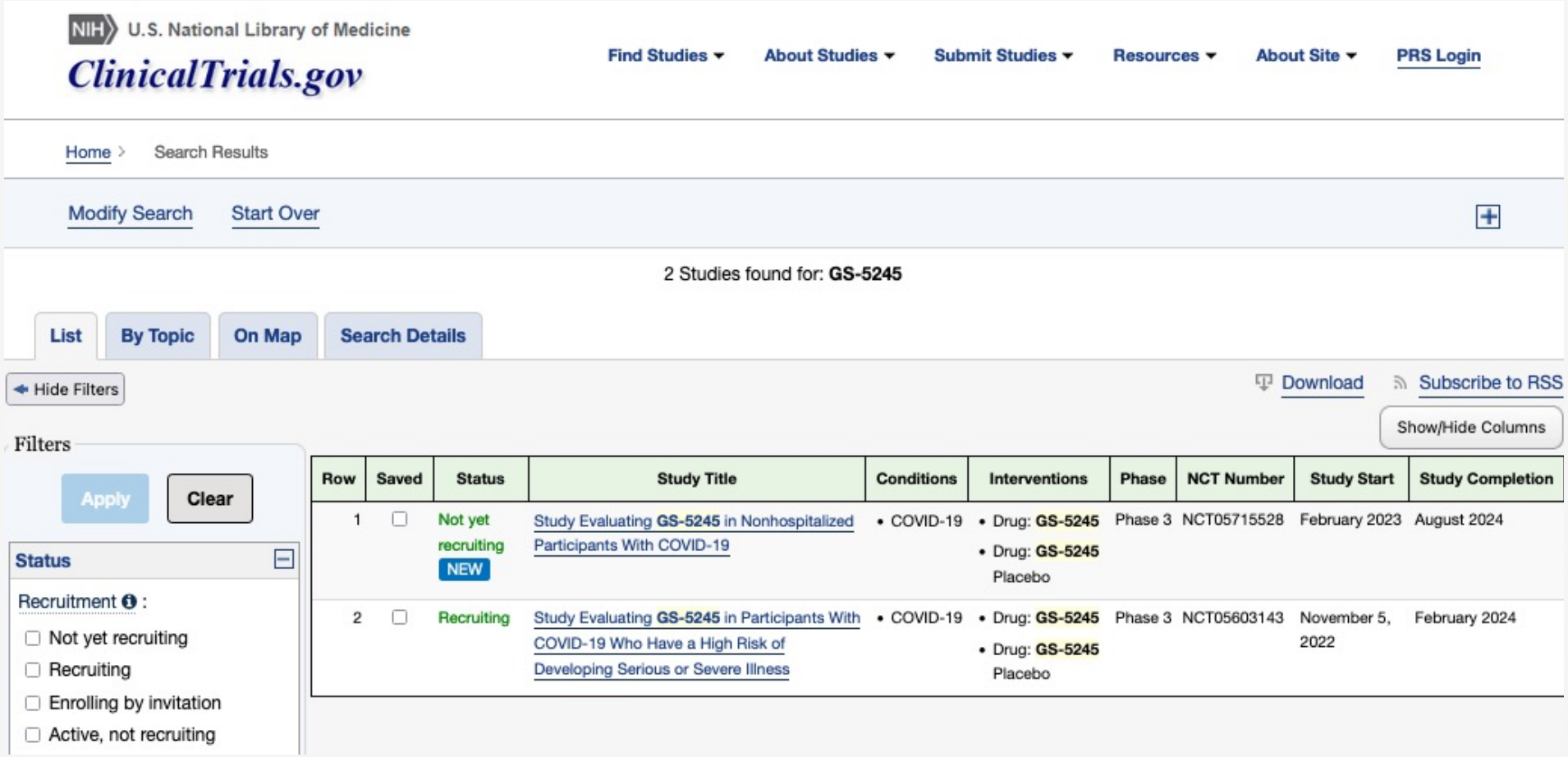




GS-5245 (obeldesivir)

GS-5245 is currently in phase 3 trials for the outpatient treatment of COVID-19

NCT05715528, NCT05603143



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2 Studies found for: **GS-5245**

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Status

Recruitment :

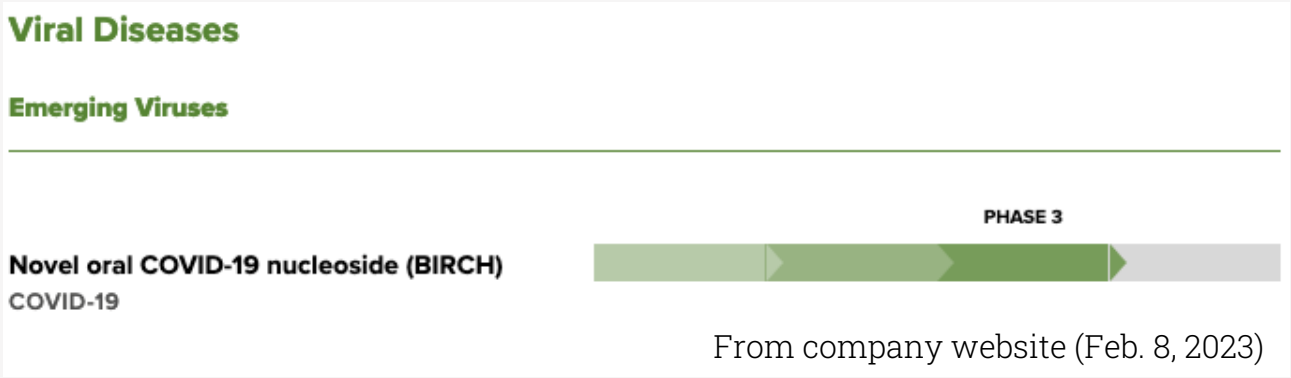
- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting

Row	Saved	Status	Study Title	Conditions	Interventions	Phase	NCT Number	Study Start	Study Completion
1	☐	Not yet recruiting NEW	Study Evaluating **GS-5245** in Nonhospitalized Participants With COVID-19	• COVID-19	• Drug: **GS-5245** • Drug: **GS-5245** Placebo	Phase 3	NCT05715528	February 2023	August 2024
2	☐	Recruiting	Study Evaluating **GS-5245** in Participants With COVID-19 Who Have a High Risk of Developing Serious or Severe Illness	• COVID-19	• Drug: **GS-5245** • Drug: **GS-5245** Placebo	Phase 3	NCT05603143	November 5, 2022	February 2024

What's in a name?

GS-5245 is often dubbed "oral remdesivir".

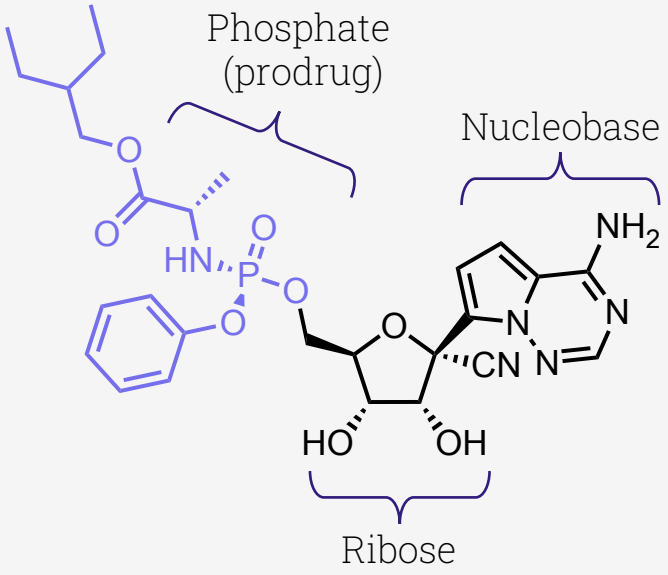
But it is more cryptically called "novel oral COVID-19 nucleoside" on the company site.



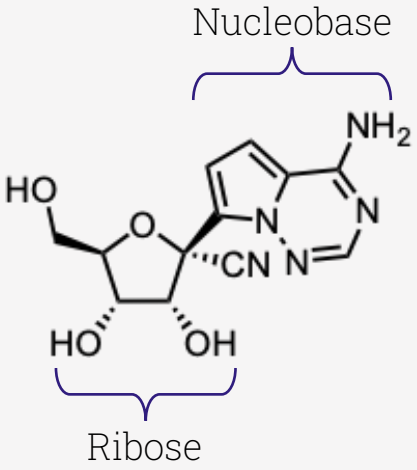
From company website (Feb. 8, 2023)

Why is this semantic detail important?

- Remdesivir is nucleo**tide**, not a nucleo**side**
- The parent nucleo**side** of remdesivir is called GS-441524
- This detail is a key step in discerning the structure of GS-5245

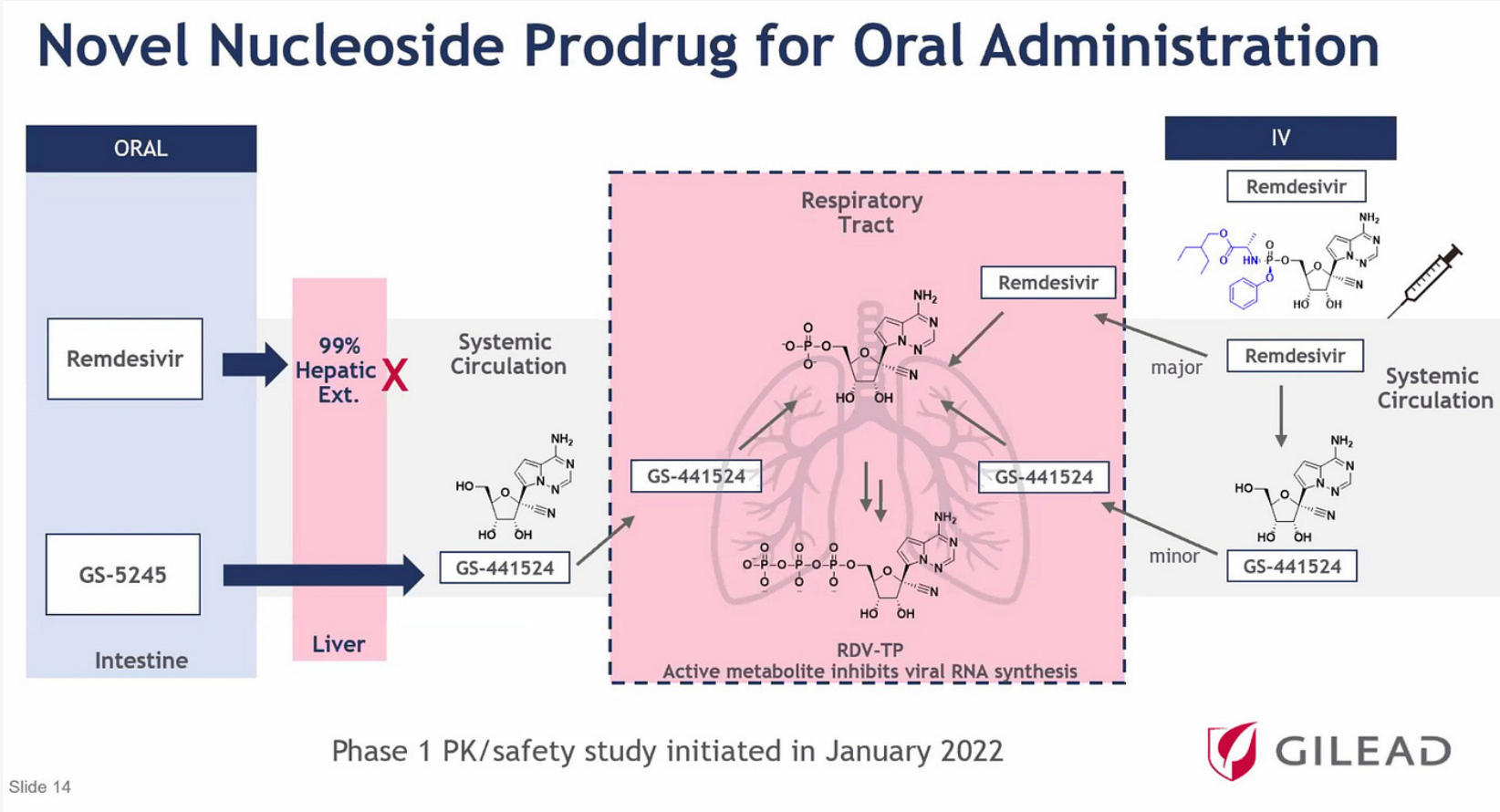


Remdesivir
(nucleo**tide**)



GS-441524
(nucleo**side**)

Big break: NIH Filovirus Workshop



GS-5245 is a prodrug designed to deliver GS-441524 into circulation. This is clear by the fact that intact GS-5245 is designed to be hydrolyzed by the liver upon first pass.

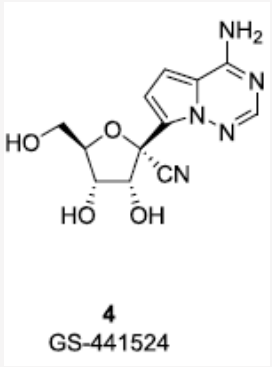
GS-5245 is a prodrug that improves the bioavailability of GS-441524 in humans

GS-441524 suffers from low bioavailability in (non-human) primates

GS-441524: PK Property Summary NCATS OpenData Portal

	IV*		PO**				
	CL_p (mL/min/kg)	Vd_{ss} (L/kg)	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng.hr/mL)	$t_{1/2}$ (hr)	F (%)
Mouse	26	2.4	582	1.5	2540	3.9	39
Rat	25	2.2	193	3.8	2170	3.4	33
Dog	4.1	0.92	6010	0.28	19000	4.1	85
Cyno	9.5	1.1	59.4	2.0	734	7.7	8.3

* IV dose: 5 mg/kg from mouse/rat; 2 mg/kg from dog/cyno
** PO dose: 10 mg/kg from mouse/rat; 5 mg/kg from dog/cyno



4
GS-441524

Table 2. In Vitro and In Vivo Profiles of Esters 11–14

cpd.	5′-ester	2′, 3′-esters	RSV HEp-2 EC_{50}/CC_{50} (μM)	log *D*	Caco-2 AB/BA (10×10^{-6} cm^{-1})	F%[a] rat/dog/cyno
4	H	H	0.53/>100	<0.3	0.17/2.1	12/89/3.4
11	acetyl	acetyl	0.82/>100	1.7	0.9/1.9	
12	propionyl	propionyl	0.43/>100	2.7	<0.1/0.26[b]	
13	*iso*-butyryl	*iso*-butyryl	0.26/81	3.6	2.1/1.5	57[c]/-/28[c]
14	valine	H	1.11/>100	0.5	0.55/0.45	

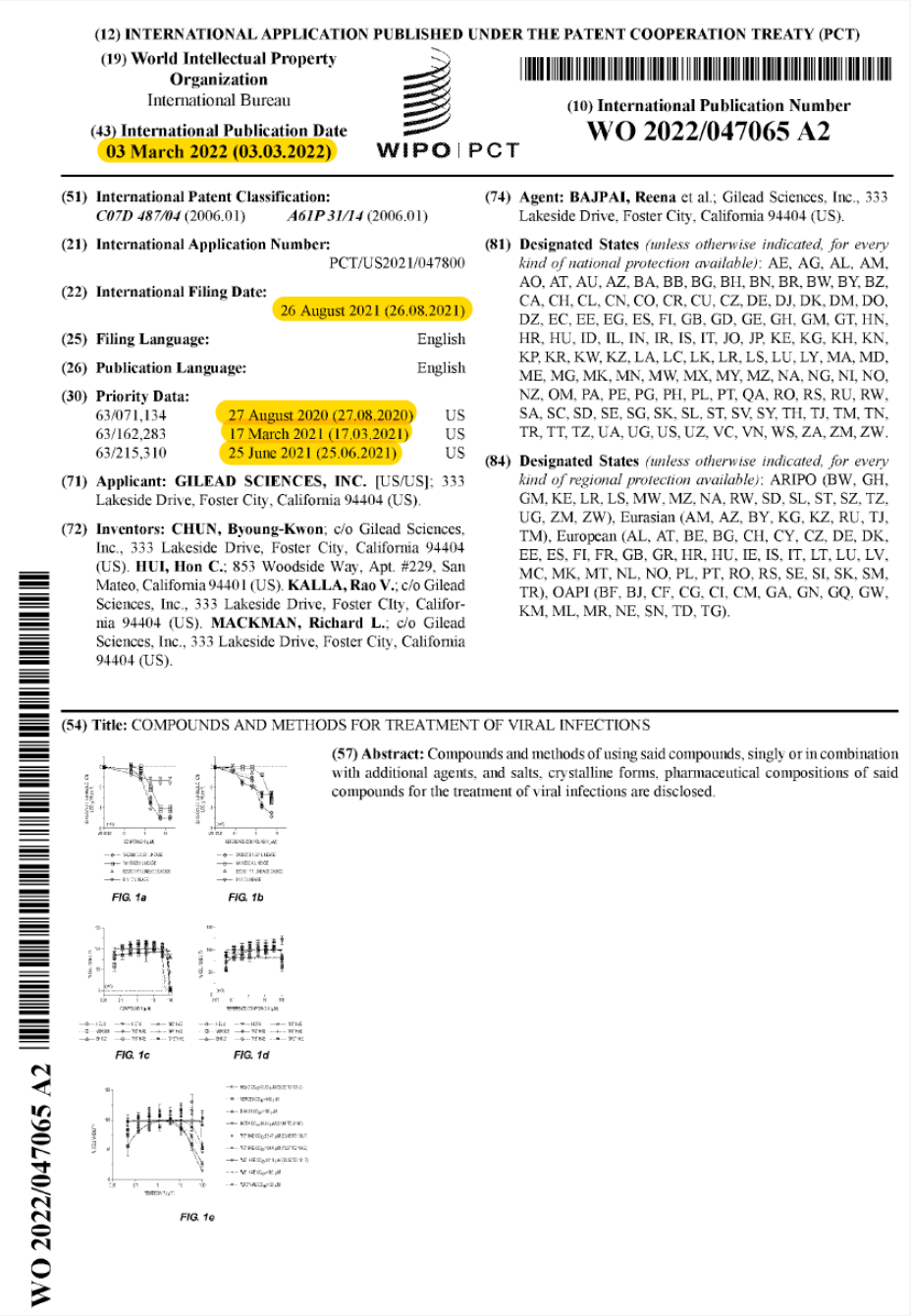
[a] $n = 3$ animals. [b] Caco-2 compound recovery is low. [c] F% of compound 4 based on the mg equivalent of 4 administered as the prodrug, standard deviation ±3% for rat and ±9% for cyno. All in vitro data are $n \geq 2$ replicates unless noted.

Mackman et al. J. Med. Chem. (2021); Gilead study

But what could the prodrug be?

Patent on GS-441524 ester prodrugs has significant in vivo characterization for 2 compounds

WO 2022/047065



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(74) Agent: **BAJPAI, Reena** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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(54) Title: COMPOUNDS AND METHODS FOR TREATMENT OF VIRAL INFECTIONS

FIG. 1a FIG. 1b

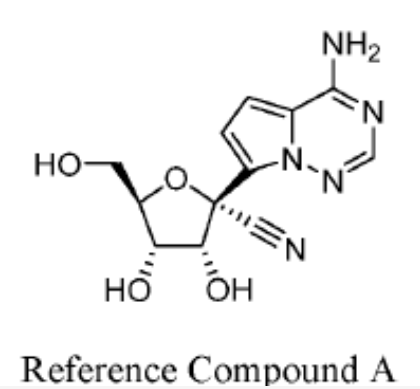
FIG. 1c FIG. 1d

FIG. 1e

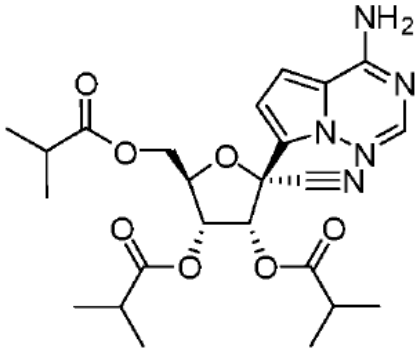
(57) Abstract: Compounds and methods of using said compounds, singly or in combination with additional agents, and salts, crystalline forms, pharmaceutical compositions of said compounds for the treatment of viral infections are disclosed.

WO 2022/047065 A2

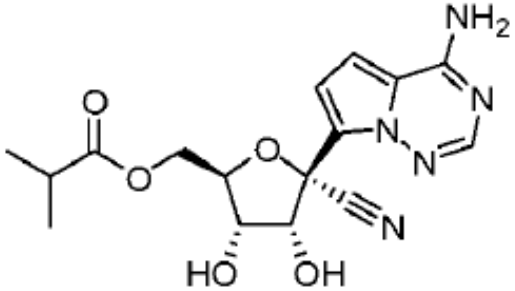
Summary PK of the 2 extensively characterized examples



Reference Compound A



Compound 1



Compound 15

% Oral bioavailability of GS-441524 after administration of prodrug					
	Mouse	S-D rat	Ferret	Dog	Cyno
GS-441524 (ref cmpd A)	33	21.6	87	89	3.4
Cmpd 1 (tri-ester)	49	117	114	68	48
Cmpd 15 (GS-5245)	41	63.9	154	94	38

Compound 1 has much more in vivo efficacy characterization in ferrets compared to Compound 15

Some examples

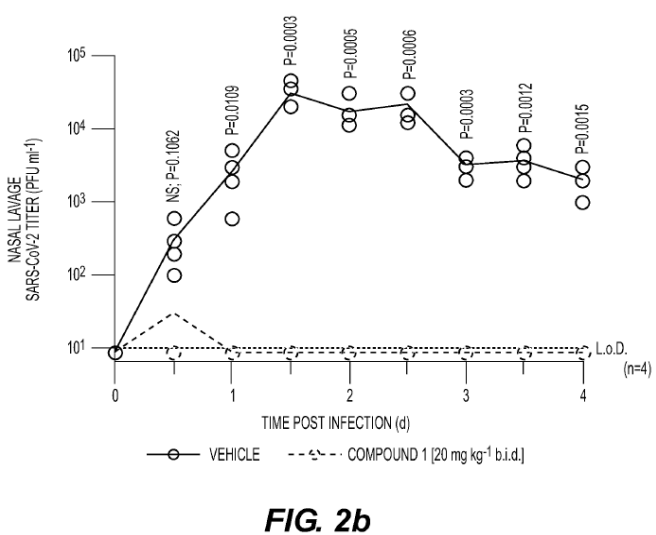


FIG. 2b

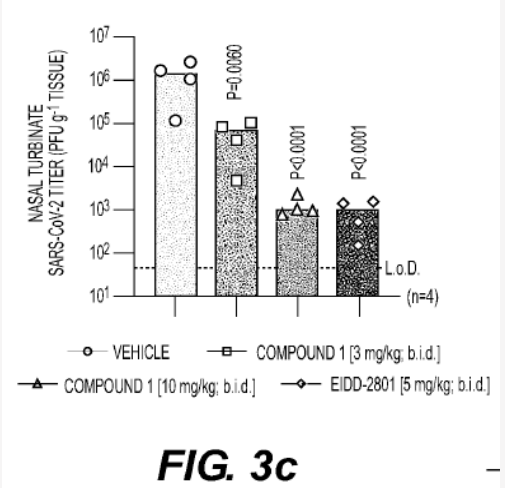


FIG. 3c

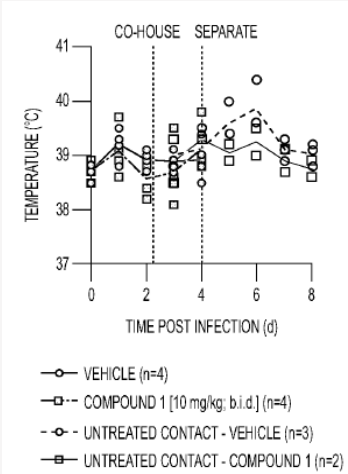


FIG. 5a

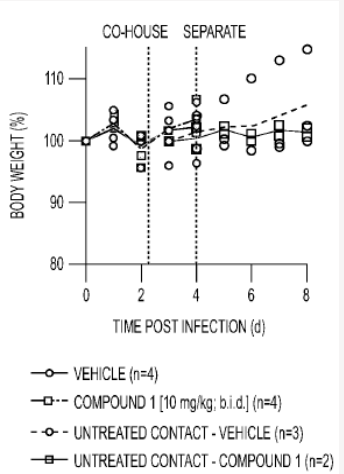


FIG. 5b

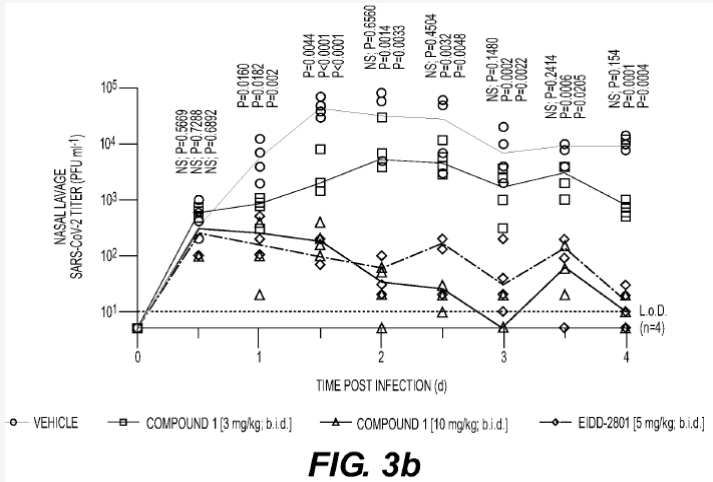


FIG. 3b

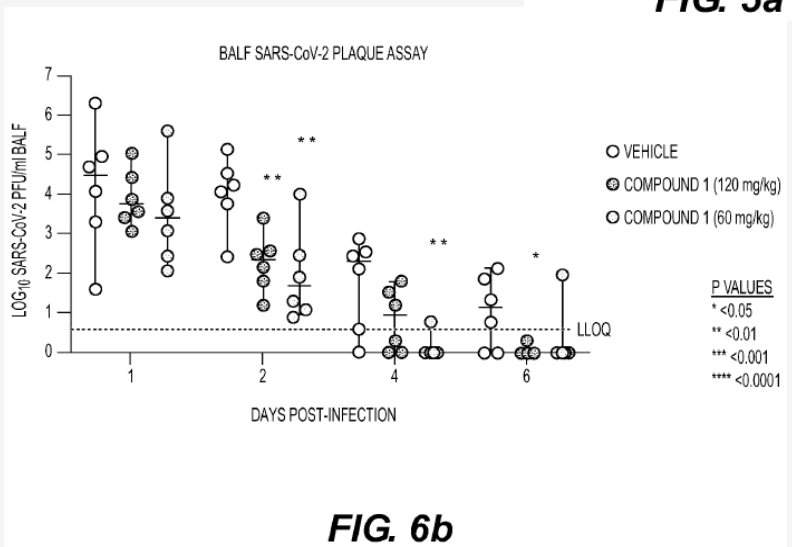


FIG. 6b

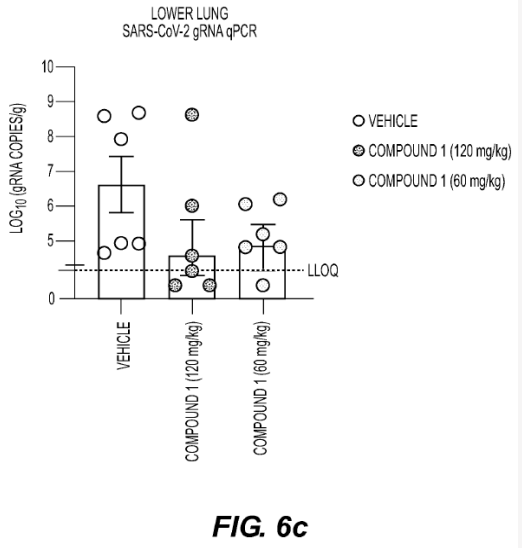


FIG. 6c

These data on Compound 1 were later published in high-profile papers

Compound 1 = GS-621763

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-26760-4 OPEN

Check for updates

Oral prodrug of remdesivir parent GS-441524 is efficacious against SARS-CoV-2 in ferrets

Robert M. Cox[1], Josef D. Wolf[1], Carolin M. Lieber[1], Julien Sourimant[1], Michelle J. Lin[2], Darius Babusis[3], Venice DuPont[3], Julie Chan[3], Kim T. Barrett[3], Diane Lye[3], Rao Kalla[3], Kwon Chun[3], Richard L. Mackman[3], Chengjin Ye[4], Tomas Cihlar[3], Luis Martinez-Sobrido[4], Alexander L. Greninger[2], John P. Bilello[3] & Richard K. Plemper[1✉]

Science Translational Medicine

RESEARCH ARTICLES

Cite as: A. Schäfer *et al.*, *Sci. Transl. Med.* 10.1126/scitranslmed.abm3410 (2022).

CORONAVIRUS

Therapeutic treatment with an oral prodrug of the remdesivir parental nucleoside is protective against SARS-CoV-2 pathogenesis in mice

Alexandra Schäfer[1†], David R. Martinez[1†], John J. Won[1], Rita M. Meganck[1], Fernando R. Moreira[1], Ariane J. Brown[1], Kendra L. Gully[1], Mark R. Zweigart[1], William S. Conrad[1], Samantha R. May[1], Stephanie Dong[1], Rao Kalla[2], Kwon Chun[2], Venice Du Pont[2], Darius Babusis[2], Jennifer Tang[2], Eisuke Murakami[2], Raju Subramanian[2], Kimberly T. Barrett[2], Blake J. Bleier[2], Roy Bannister[2], Joy Y. Feng[2], John P. Bilello[2], Tomas Cihlar[2], Richard L. Mackman[2], Stephanie A. Montgomery[3,4], Ralph S. Baric[1], Timothy P. Sheahan[1*]

But is the tri-ester prodrug actually the structure of GS-5245?

Reason for skepticism: Gilead stated it was not interested in further development

Remdesivir maker Gilead is partnering with the GSU researchers as they work to create an oral version of the drug. So far, it's only been tested on animals and the company said it had no immediate plans to study the drug in clinical trials.

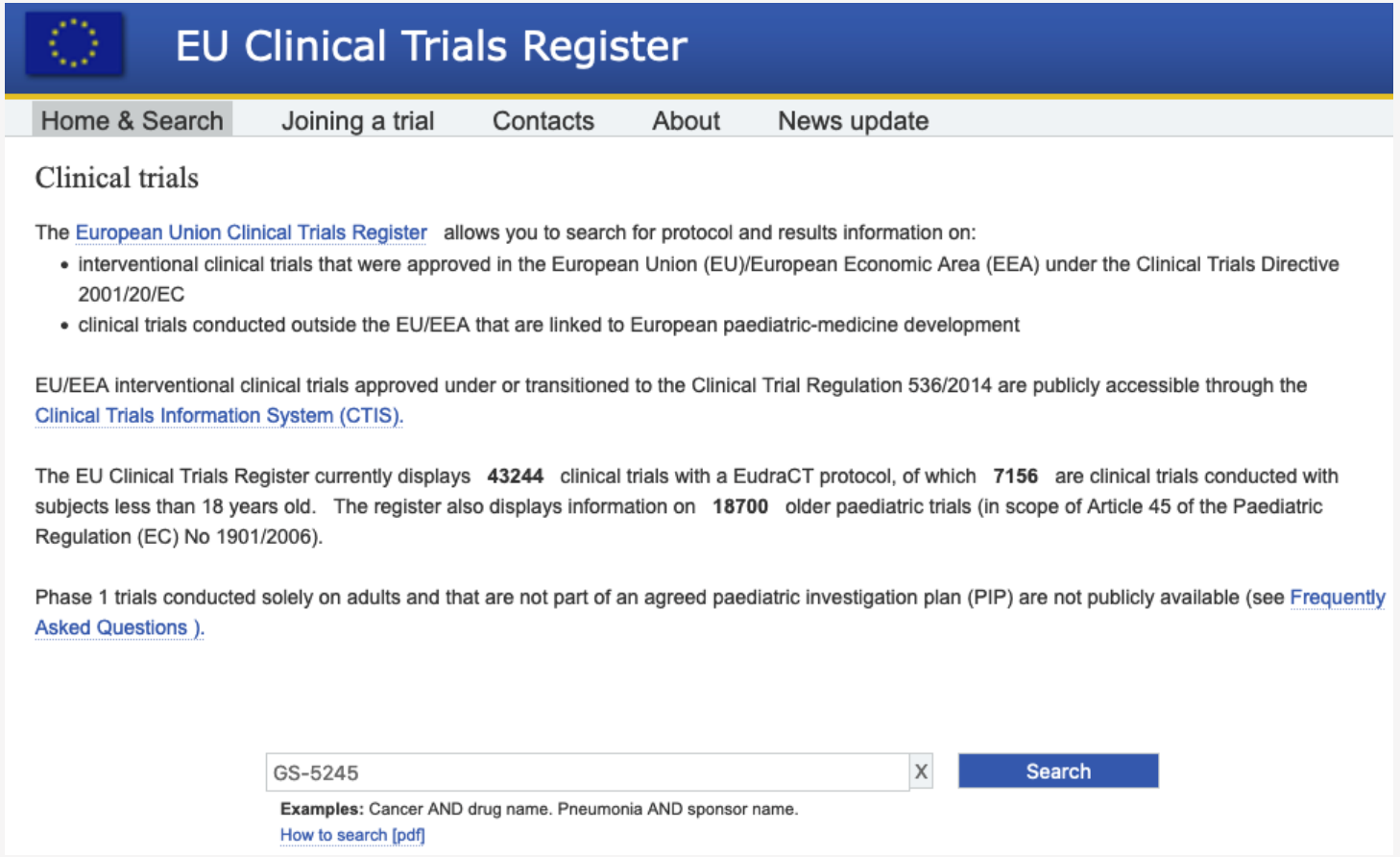
"Gilead is working with Georgia State because of their extensive expertise in animal models for SARS-CoV-2 infection that are suitable for testing the preclinical efficacy of new investigational antiviral agents," the company said in a statement. "There are currently no immediate plans to study GS-621763 in clinical trials; the compound has been used in the preclinical studies as a tool to validate specific strategy for the design of oral antivirals for COVID-19."

Plemper said the effectiveness of the medicine depends on the time the treatment is initiated, the earlier the better.

WSB-TV (Nov. 15, 2021)

So then what could GS-5245 be?

EU Clinical Trials Register holds the key!



EU Clinical Trials Register shows the CAS number for GS-5245

2647441-36-7

D.3.8 to D.3.10 IMP Identification Details (Active Substances)		
D.3.8	INN - Proposed INN	Not available
D.3.9.1	CAS number	2647441-36-7
D.3.9.2	Current sponsor code	GS-5245
D.3.9.3	Other descriptive name	GS-5245
D.3.9.4	EV Substance Code	SUB268881
D.3.10	Strength	
D.3.10.1	Concentration unit	mg milligram(s)
D.3.10.2	Concentration type	equal
D.3.10.3	Concentration number	350

Looking up the CAS number reveals the structure of GS-5245

A 5’ mono-isobutyric rdyrt prodrug of GS-441524!

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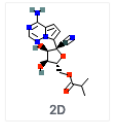
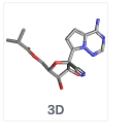
COMPOUND SUMMARY

Obeldesivir

PubChem CID	162513664
Structure	 2D  3D Find Similar Structures
Molecular Formula	$C_{16}H_{19}N_5O_5$
Synonyms	Obeldesivir Obeldesivir [INN] Q55KCM7PXB ATV006 2647441-36-7 More...
Molecular Weight	361.35
Dates	Modify 2023-02-04 Create 2022-02-06

1.1 2D Structure

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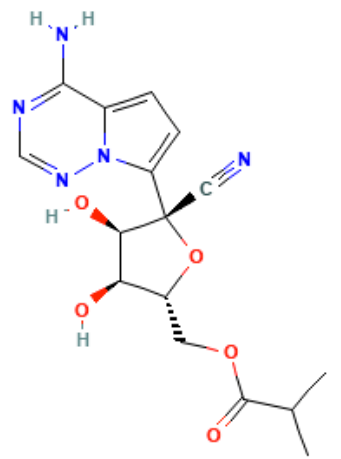
Chemical Structure Depiction



Questions?

Email: victoriacyanide@gmail.com

Twitter: @victoriacyanide