Treatment of Severe COVID-19 with Low-Dose Selinexor: Demonstration of Anti-Viral and Anti-Inflammatory Activities in a Randomized, International, Multicenter, Placebo-Controlled Phase 2 Clinical Trial

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Karyopharm® Therapeutics

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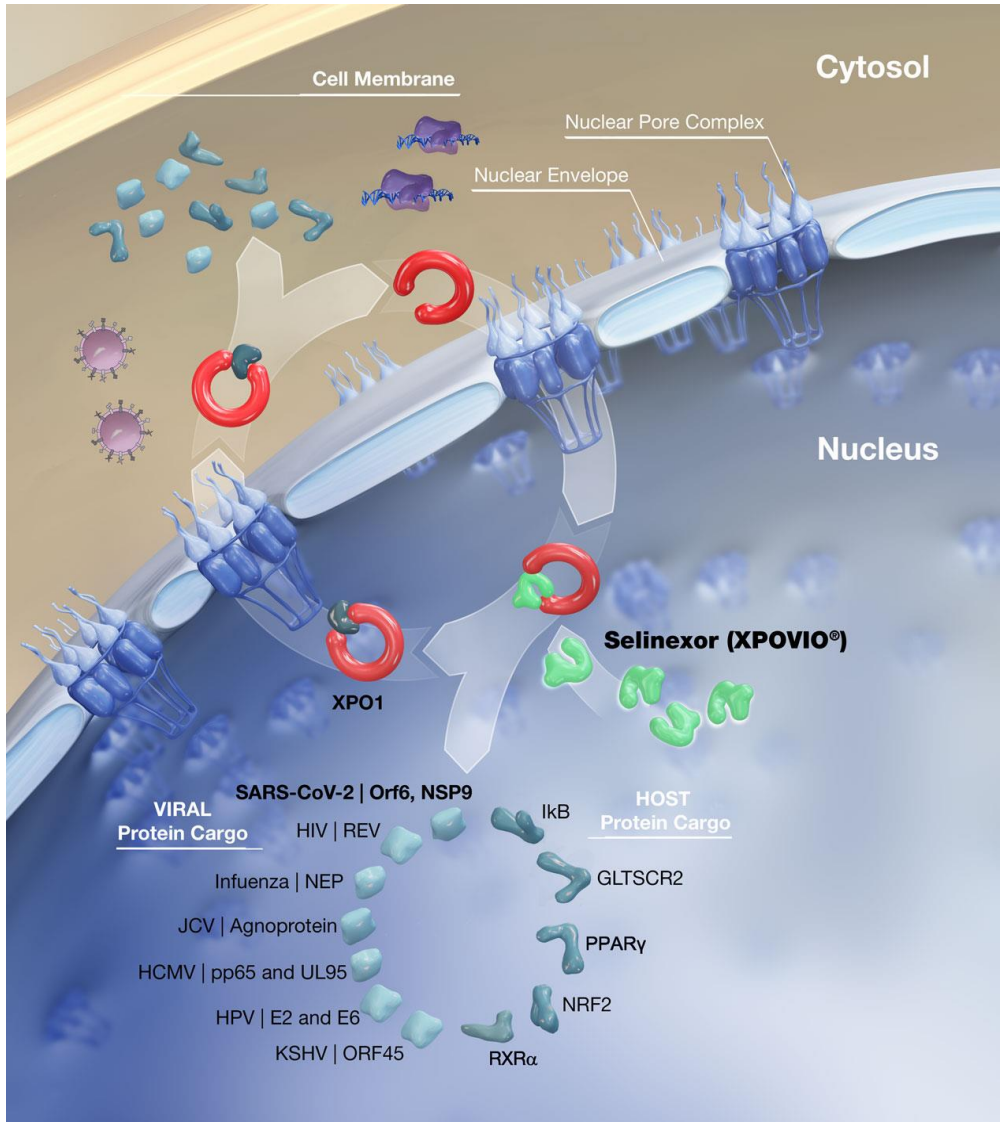
Exportin 1 (XPO1): Viral replication

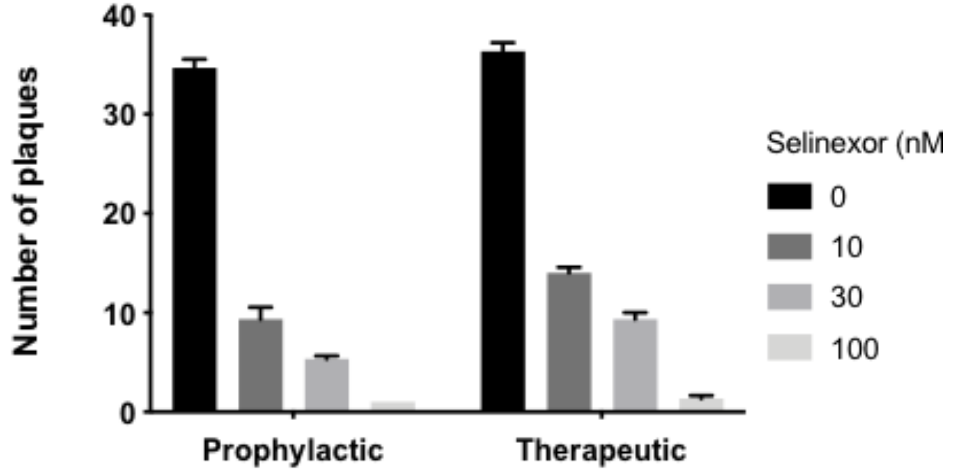
- Exportin 1 (XPO1) mediates SARS-CoV-2 lifecycle and proinflammatory transcription factors
- XPO1 has been identified as a “hub” host protein for SARS-CoV propagation.
- XPO1 plays a central role in inflammation through regulation of the NF-kB and COX-2 pathways
- XPO1 facilitates the nuclear export of the HMGB1, RXRα, COMMD1, PPARγ, and GLTSCR2, all of which augment inflammatory signaling and inhibit innate immune response to enable viral infection

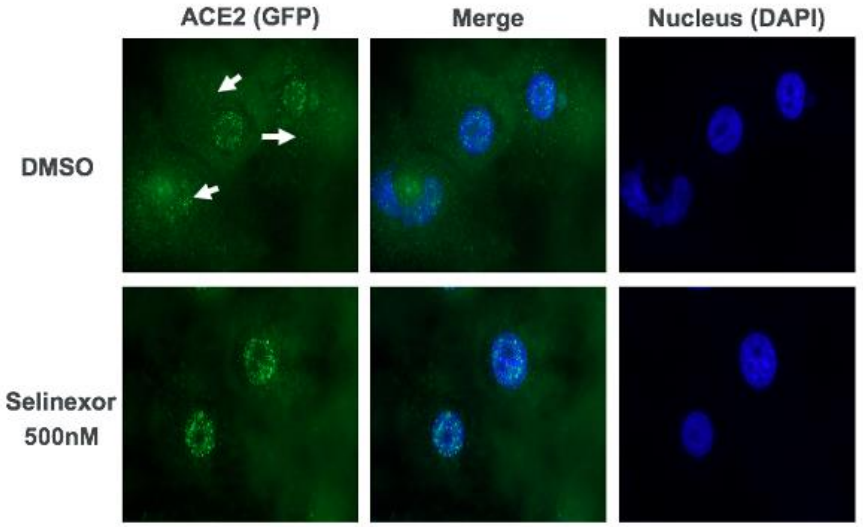
Selinexor (XPOVIO®) XPO1 Inhibition: Unique Dual Mechanism of Action with Anti-Viral and Anti-inflammatory Activities

Class	Virus / Host Cellular Pathway	XPO1 Cargo	Outcome
DIRECT - VIRAL XPO1 cargos essential for viral propagation	SARS-CoV-2	ORF3b, ORF6, 9b, spike, N-protein	↓viral replication and propagation
	HIV	Rev	↓HIV late mRNA translation ↓virus production
	Influenza	NEP	↓viral replication
	HCMV	pp65/UL95	↓viral replication
	JCV	agnoprotein	↓viral RNA processing
INDIRECT – HOST XPO1 cargos. Nuclear entrapment reduces inflammation & blocks viral propagation	Cell membrane receptor	ACE-2	↓SARS-CoV-2 viral propagation
	NF-kB	IkB, COMMD1, FoxO	↓NFkB gene expression ↑oxidative stress response
	IL1β	RXRα	↓inflammatory response
	COX2, iNOS	COX2 and iNOS mRNAs	↓inflammatory mediators
	PPARγ	PPARγ	↑anti-inflammatory and cytoprotective response
	TLR2, TLR4, RAGE	HMGB1	↓necrosis induced inflammation
	FoxO, FoxP	Forkhead Proteins	↓inflammatory response
	HIF-1	COMMD1	↓NFkB gene expression
	Nrf2	Nrf2	↑oxidative stress response
	Rig1 Innate Immunity	GLTSCR2	↑RIG-I activity ↑interferon β production
	IRF7	KSHV ORF 45	↑IFNα/β production
	p53	HPV E2 and E6	↓p53 degradation ↓apoptotic response

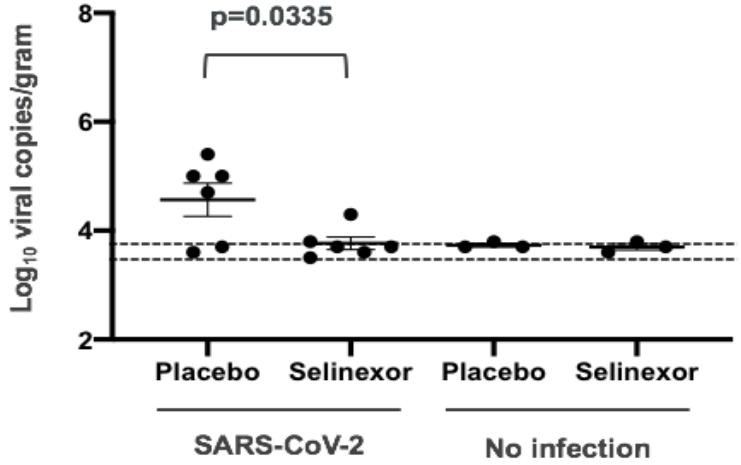


Selinexor Inhibits SARS-CoV-2 Viral Propagation and Shedding and Induces Nuclear Accumulation of ACE2 *In Vitro*

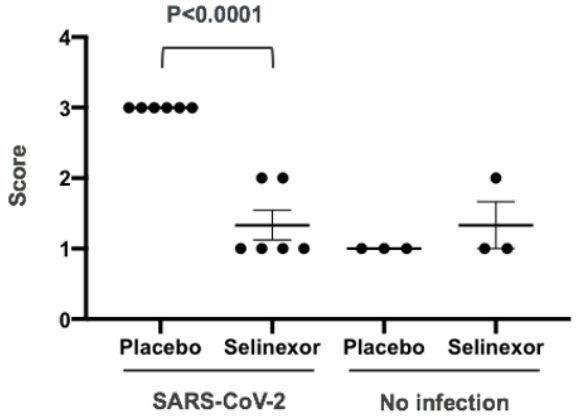




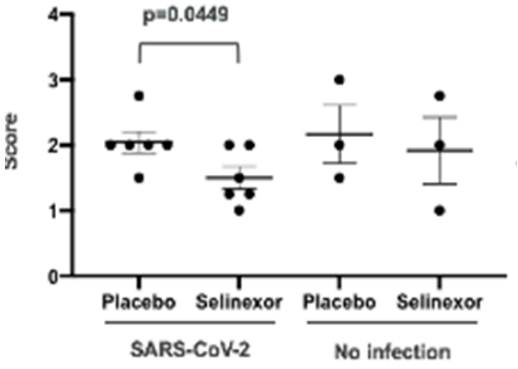
Selinexor Decreases SARS-CoV-2 Viral Load and Severity of Rhinitis and Lung Inflammation *In Vivo*



Rhinitis



Alveolitis



XPORT-CoV-1001: A Phase 2 Randomized Single-Blind Study to Evaluate the Activity and Safety of Low Dose Oral Selinexor (KPT-330) in Patients with Severe COVID-19

~70 International Study Sites, ~8 countries

2 interim analyses (~74 randomized and ~124 randomized)

2:1 ⇨ 1:1 randomization
N ~ 223

Hospitalized Patients ≥18 years old with COVID-19

Oral Selinexor
20 mg Days 1, 3, and 5 of each week for up to 2 weeks

If the patient is tolerating therapy well and clinically benefitting, dosing can continue for additional 2 weeks on Days 15, 17, 19, 22, 24, 26

Oral Placebo
Days 1, 3, and 5 of each week for up to 2 weeks

Primary endpoints:

Day 14 Ordinal Scale Improvement (OSI) -

Proportion of patients with at least a 2-point improvement in the Ordinal Scale from baseline to Day 14

Key Secondary endpoint

- Overall death rate on Day 28
- Rate of mechanical ventilation
- Time to mechanical ventilation
- Time to an improvement of 2 points using Ordinal Scale Improvement (TTCI-2)

XPORT-CoV-1001: Inclusion Criteria

Eligible patients had symptoms of severe COVID-19 as demonstrated by:

At least 1 of the following:

- Fever
- Cough
- Sore throat
- Malaise
- Headache
- Muscle pain
- Shortness of breath at rest or with exertion
- Confusion
- Symptoms of severe lower respiratory symptoms including dyspnea at rest or respiratory distress

AND

Clinical signs indicative of lower respiratory infection with COVID-19, with at least 1 of the following:

- SpO2 ≤92% or requires ≥4 LPM oxygen by nasal canula, or
- Non-rebreather/Ventimask (or similar device) or
- High-flow nasal canula in order to maintain SpO2 ≥92%.

  Patients with COPD or chronic lung disease must demonstrate evidence of increased oxygen needs above baseline

XPORT-CoV-1001: Patient Characteristics (ITT)

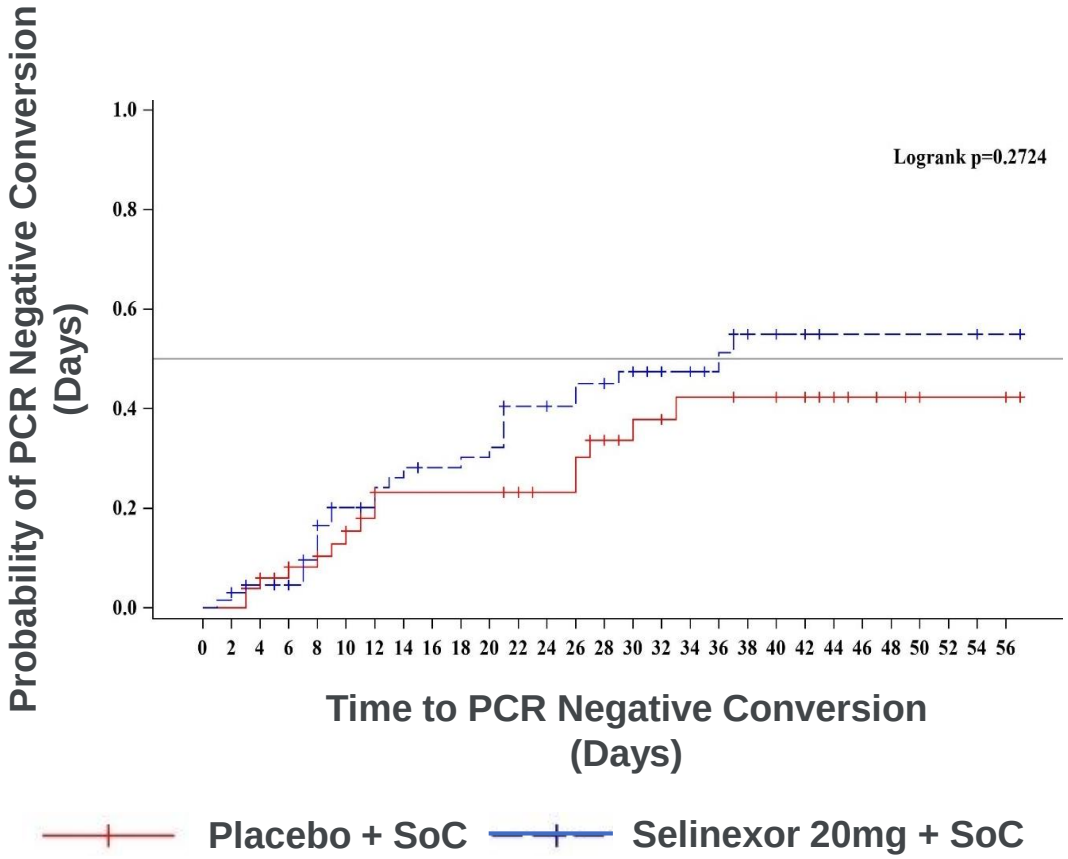
CHARACTERISTIC	N = 117
Age, years	
Median, (range)	55.0 (25-98)
Sex, n (%)	
Male	68 (58.1)
Concomitant Therapies, n (%)	
Remdesivir	59 (50.4)
Hydroxychloroquine	1 (0.9)
Systemic corticosteroid	54 (46.2)
IL-6 inhibitor*	10 (8.6)
No. of High-Risk Comorbidities, n (%)	
≥2	43 (36.8)
1	26 (22.2)
None	46 (39.3)
Comorbidities, n (%)	
Hypertension	44 (37.6)
Metabolic	87 (74.4)
Cancer	13 (11.1)
Diabetes	44 (37.6)
Cardiac	26 (22.2)
Renal	22 (18.8)

XPORT-CoV-1001: Treatment-Related Adverse Events (ITT)

n, (%)	Selinexor N=65				Placebo N=50			
	Grade 1/2	Grade 3	Grade 4	Total	Grade 1/2	Grade 3	Grade 4	Total
Any Treatment-Related Adverse Event	14 (21.5)	4 (6.2)	1 (1.5)	19 (29.2)	8 (16.0)	2 (4.0)	0 (0)	10 (20.0)
Hematological								
Hyponatremia	**3 (4.6)**	**1 (1.5)**	**0 (0)**	**4 (6.2)**	**3 (6.0)**	**0 (0)**	**0 (0)**	**3 (6.0)**
Neutropenia	1 (1.5)	0 (0)	0 (0)	1 (1.5)	0 (0)	0 (0)	1 (2.0)	1 (2.0)
Non-Hematological								
Nausea	5 (7.7)	0 (0)	0 (0)	5 (7.7)	4 (8.0)	0 (0)	0 (0)	4 (8.0)
Constipation	1 (1.5)	0 (0)	0 (0)	1 (1.5)	2 (4.0)	0 (0)	0 (0)	2 (4.0)
Cough	2 (3.1)	0 (0)	0 (0)	2 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.0)	0 (0)	0 (0)	2 (4.0)
Vomiting	1 (1.5)	0 (0)	0 (0)	1 (1.5)	1 (2.0)	0 (0)	0 (0)	1 (2.0)
Serious TRAEs				**2 (3.1)**				**0 (0)**

XPORT-CoV-1001: Efficacy (ITT)

Parameter	Selinexor N=66 n (%)	Placebo N=51 n (%)
Clinical improvement Day 14 (2-point improvement in ordinal scale), n (%)	35 (53.0)	28 (54.9)
Time to clinical improvement (2 points), median days (range)	11.0 (9.0, 16.0)	9.0 (8.0, 16.0)
Overall Mortality at Day 28	10 (15.2)	2 (3.9)
Mechanical ventilation required, n (%)	9 (13.6)	5 (9.8)
Admission to ICU, n (%)	33 (50.0)	23 (45.1)
Length of hospitalization, days, median (range)	9.0 (2-39)	8.0 (3-42)
Hospital discharge, n (%)	48 (72.7)	39 (76.5)
Conversion to negative SARS-CoV-2 PCR, n (%)	24 (36.4)	10 (19.6)



XPORT-CoV-1001: Safety Outcomes (Low LDH/DD)

Parameter	Low LDH/DD*		High LDH/DD*	
	Selinexor N=38 n (%)	Placebo N=27 n (%)	Selinexor N=27 n (%)	Placebo N=23 n (%)
Patients with at least 1 AE	24 (63.2)	14 (51.9)	21 (77.8)	12 (52.2)
Patients with at least 1 Grade 3/4 AE	3 (7.9)	1 (3.7)	6 (22.2)	7 (30.4)
SAEs	5 (13.2)	1 (3.7)	11 (40.7)	5 (21.7)
Non-fatal SAEs	3 (7.9)	0 (0)	2 (7.4)	3 (13)
Invasive MV or ECMO	3 (7.9)	3 (11.1)	6 (22.2)	3 (13.0)
Death within 30 days of last dose	2 (5.3)	1 (3.7)	9 (33.3)	2 (8.7)

* The Low LDH/DD subgroup was comprised of patients with LDH ≤370 U/L or D-dimer ≤600 mcg/L FEU. The High LDH/DD subgroup was comprised of patients with LDH >370 U/L and D-dimer >600 mcg/L FEU.

- No related Grade 5 AEs were reported in the mITT population
- Side effects were generally reversible and managed with dose modifications and/or standard supportive care

XPORT-CoV-1001: Efficacy – Selinexor improved clinical status as compared with placebo (Low LDH/DD)

Parameter	Low LDH/DD*		High LDH/DD*	
	Selinexor N=38 n (%)	Placebo N=28 n (%)	Selinexor N=28 n (%)	Placebo N=23 n (%)
Hospital Discharged by Day 14	30 (78.9)	16 (57.1)	13 (46.4)	14 (60.9)
OSI-2 by Day 14	30 (78.9)	18 (64.3)	12 (42.9)	15 (65.2)

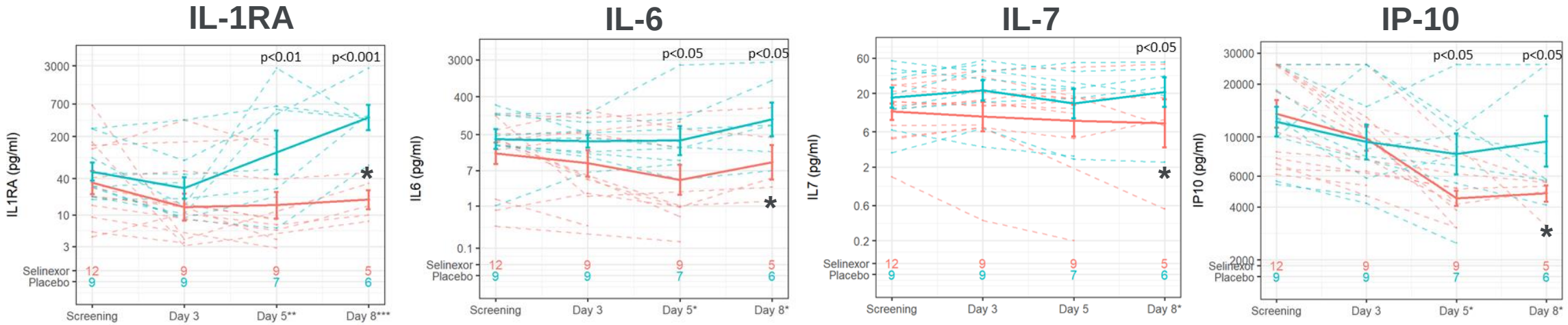
* The Low LDH/DD subgroup was comprised of patients with LDH ≤370 U/L or D-dimer ≤600 mcg/L FEU. The High LDH/DD subgroup was comprised of patients with LDH >370 U/L and D-dimer >600 mcg/L FEU.

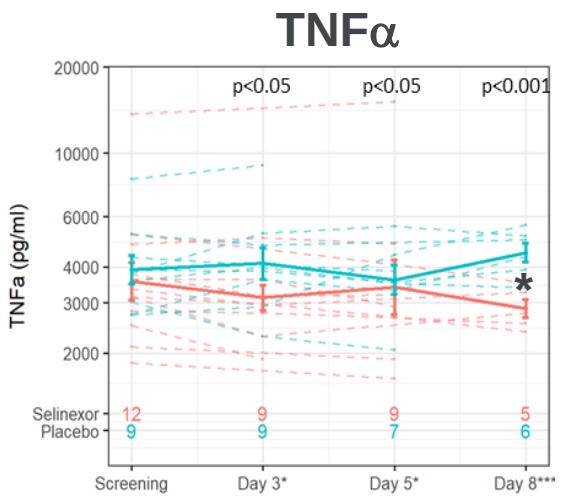
XPORT-CoV-1001: Efficacy – Selinexor improved PCR negative conversion rate and time to PCR negative as compared with placebo (Low LDH/DD)

Parameter	Low LDH/DD*		High LDH/DD*	
	Selinexor N=38 n (%)	Placebo N=28 n (%)	Selinexor N=28 n (%)	Placebo N=23 n (%)
Converted to PCR negative status	16 (42.1)	8 (28.6)	11 (39.3)	7 (30.4)

* The Low LDH/DD subgroup was comprised of patients with LDH ≤370 U/L or D-dimer ≤600 mcg/L FEU. The High LDH/DD subgroup was comprised of patients with LDH >370 U/L and D-dimer >600 mcg/L FEU.

XPORT-CoV-1001: Selinexor reduces cytokines associated with COVID-19 (Low LDH/DD)





ARM
- Selinexor
- Placebo

Parameter	Selinexor N=38 n (%)	Placebo N=28 n (%)
LDH	11/34 (32)	3/24 (13)
D-dimer	21/34 (62)	13/25 (52)
CRP	19/38 (50)	12/25 (48)

XPORT-CoV-1001: Summary and Conclusions

- XPO1 is an important target with and critical role in viral replication cycle
- Selinexor has demonstrated anti-viral activity in vitro and in vivo
  - Selinexor protects healthy cells from infection via reduction in ACE receptor expression on cell surface
- Oral selinexor has a dual role in COVID-19, with both an anti-viral and anti-inflammatory
  - ITT: Improvement in converted to PCR negative status: from 19.6% to 36.4%
- Clinical Benefit in subset of patients with normal LDH or < 2ULN of D Dimer
  - Improvement in Hospital Discharge by Day 14: 57.1% to 78.9%
  - Improvement in OSI-2 by Day 14: 64.3% to 78.9%
  - Converted to PCR negative status: 28.6% to 42.1%
- Future studies to evaluate the safety and efficacy of oral selinexor in hospitalized patients with confirmed severe COVID-19 and Low LDH/DD as well as in patients with mild/moderate COVID-19 and Outpatient COVID are warranted

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Thank You