

Potent Antiretroviral Activity of the Once-Daily CCR5 Antagonist INCB009471 Over 14 Days of Monotherapy

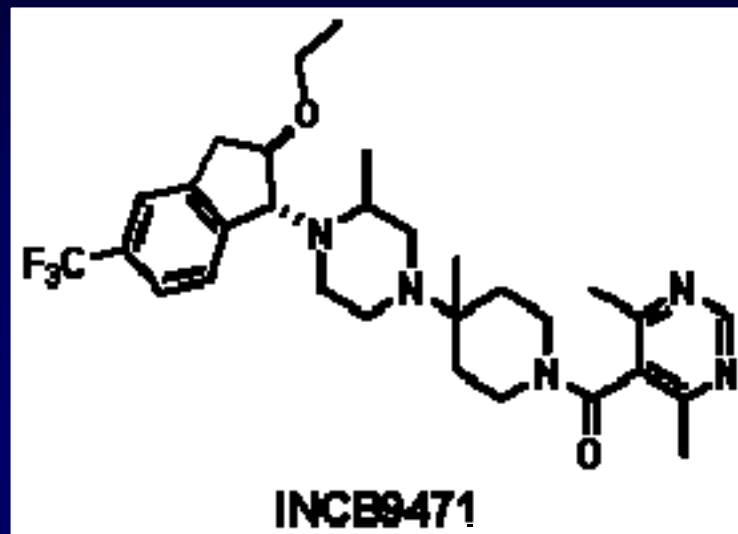
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Background Information: INCB9471

- ◆ Preclinical studies demonstrate:
 - ◆ Selective for CCR5 receptor
 - ◆ 90% IC for R5-tropic viruses = 8-10 nM
 - ◆ Moderate plasma protein binding
 - ◆ free fraction = 16%
 - ◆ **Protein-binding adjusted IC₉₀ = 50-60 nM**
 - ◆ Additive/synergistic *in vitro* for other ARVs
- ◆ Single and multiple dose Phase 1 studies demonstrate:
 - ◆ Rapid absorption
 - ◆ Long plasma half-life ~ 60 h;
 - ◆ Low peak-to-trough ratio
 - ◆ Predicted C_{min} levels with 200 mg QD dosing of ~ 400 nM



5-[(4-[(3S)-4-[(1R,2R)-2-ethoxy-5-(trifluoromethyl)-2,3-dihydro-1H-inden-1-yl]-3-methylpiperazin-1-yl]-4-methylpiperidin-1-yl)carbonyl]-4,6-dimethylpyrimidine dihydrochloride

Baseline Characteristics

- ◆ Patient Population: HIV+ adults; naive or experienced (no antiretroviral treatment for > 3 months)
- ◆ Screening viral load ≥ 4.0 log
- ◆ 14 day dosing period

Parameter	Placebo (mean \pm SEM, N = 4)	200 mg INCB009471 (mean \pm SEM, N = 19)
Mean baseline VL (log)	4.43 \pm 0.17	4.76 \pm 0.12
# with VL > 100,000 copies/mL	0	5
Mean CD4+ Cell count	639 \pm 124	521 \pm 72
# treatment-naïve	2	10
# treatment-experienced	2	9

Demographics

Parameter

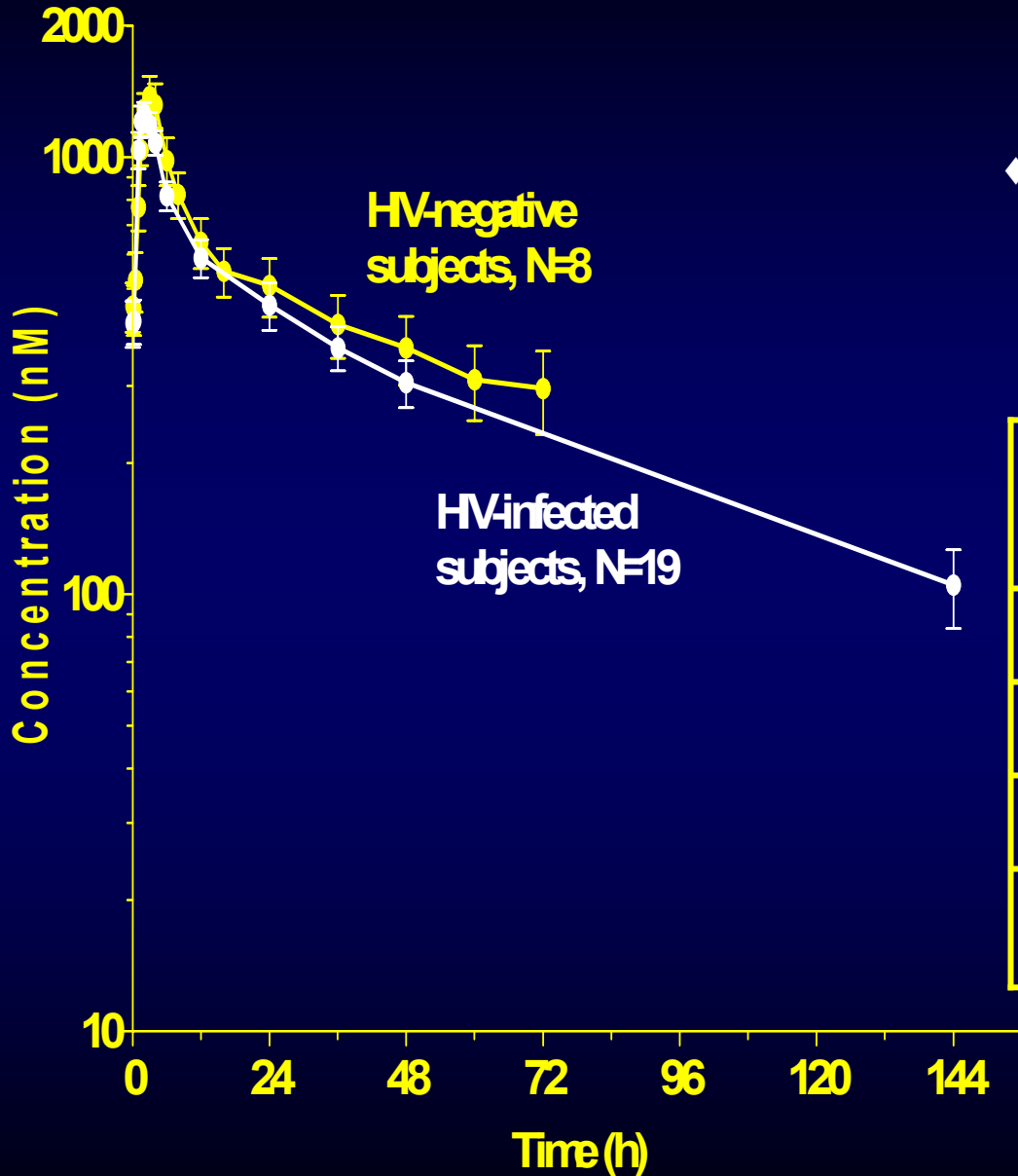
N

N enrolled	23
N completing study	23
Mean Age	37 yrs
% African American	17%
% Latino	22%
% Female	4 %

Endpoints

- ◆ Primary:
 - ◆ Mean / median change in viral load
 - ◆ Adverse events
- ◆ Secondary:
 - ◆ % > 1 log, > 1.5 log and > 2.0 log decline from BL
 - ◆ % < 400 and < 50 c/mL

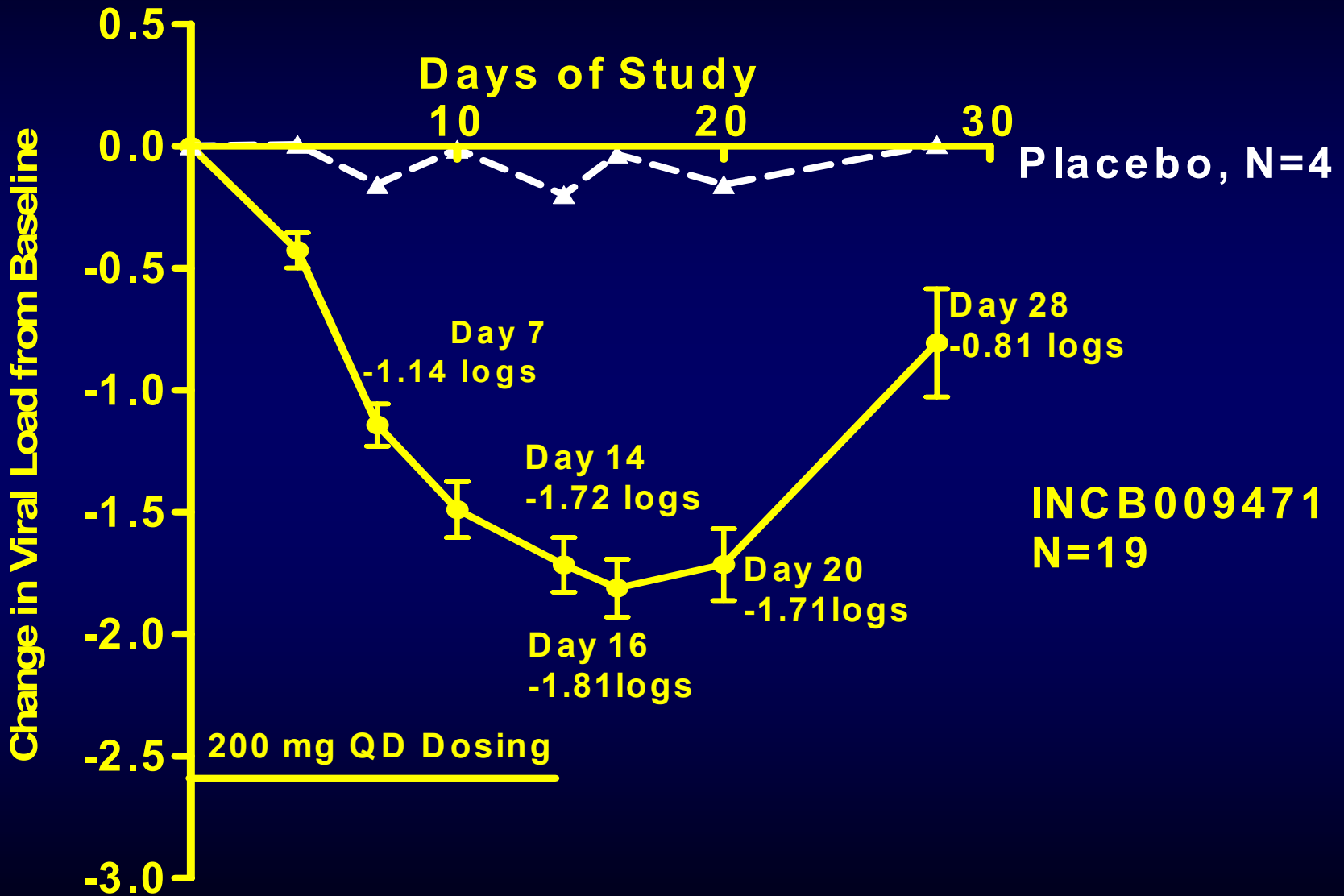
Pharmacokinetic Results



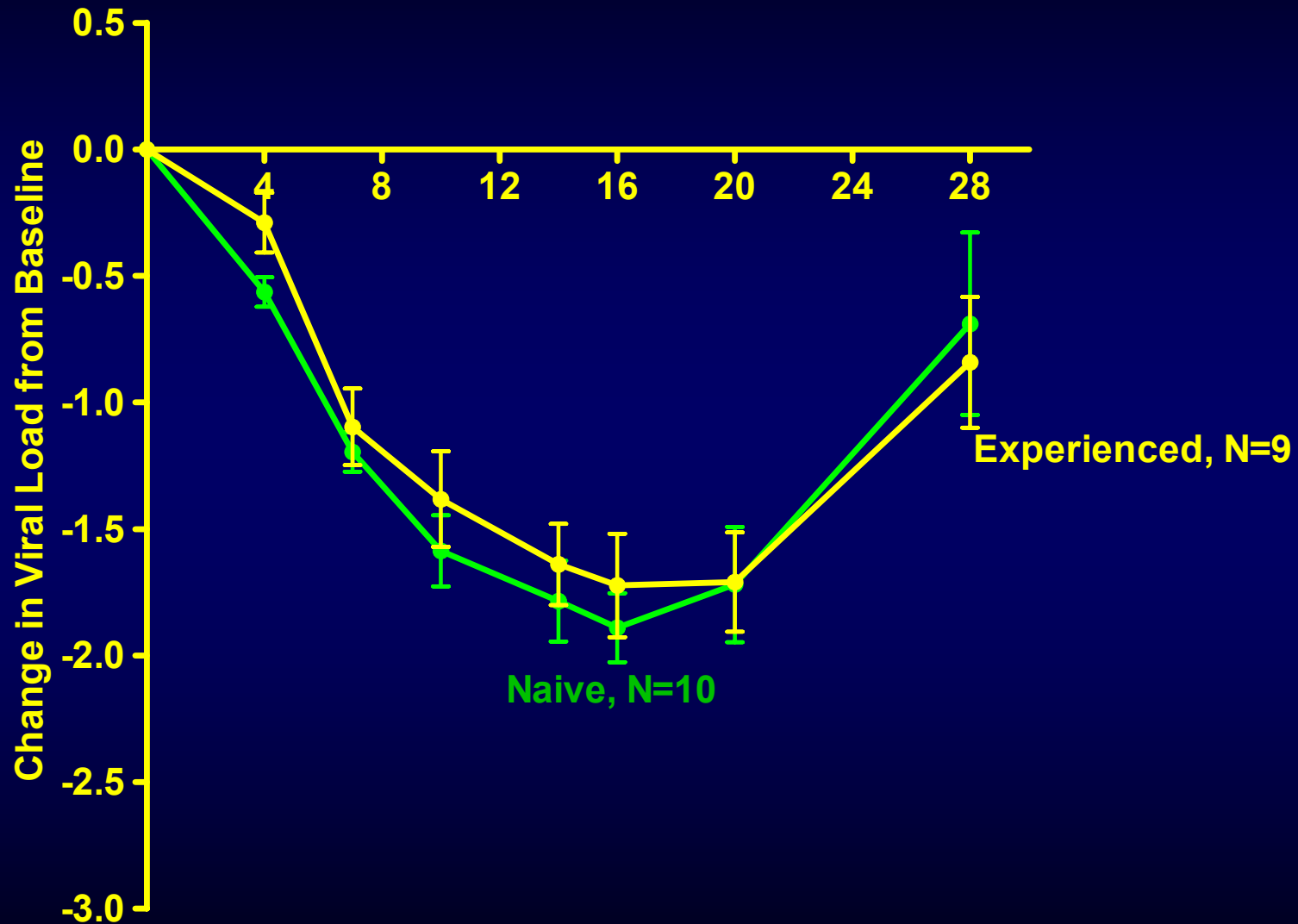
- ◆ Similar PK seen with HIV-infected subjects in this study and prior HIV-negative study

Parameter	HIV-infected subjects	HIV-negative subjects
N	19	8
C _{max} , nM	1378 ± 325	1417 ± 394
C _{min} , nM	394 ± 210	446 ± 164
AUC, nM*h	16458 ± 6037	17787 ± 6021

Antiviral Activity (Mean \pm SEM)



Impact of Prior ARV Therapy on Antiviral Activity (mean \pm SEM)



Tropism Findings

- Tropism determined at:
 - Screening, BL (pre-dose), day 7 or 14, day 28 and f/up
- N = 2 / 19 on drug showed tropism change
 - Both treatment experienced
- #1: R5 at Screen, d-1; Dual/Mixed d7 and d28
 - Preliminary clonal sequencing:
 - D/M virus at day -1 at low levels
- #2: R5 at Screen, d-1; Dual/Mixed d14; R5 d28
 - Preliminary clonal sequencing
 - D/M virus from unidentified ancestral virus
- Both pts. show reversion to R5 after d28
 - Similar to other CCR5 antagonists as monotherapy

Antiviral Response Rates at Nadir

- ◆ Mean Nadir at 16.8 days
- ◆ Range: Day 7 (n=1), Day 14 (n=4), Day 16 (n=6); Day 20 (n=8)

Parameter	Placebo	200 mg INCB009471	
		All Subjects	Subjects who Remained R5
N	4	19	17
> 1.0 log drop	0	18/19 (95%)	17/17 (100%)
> 1.5 log drop	0	16/19 (84%)	16/17 (94%)
> 2.0 log drop	0	8/19 (42%)	8/17 (47%)
< 400 copies/mL	0	8/19 (42%)	8/17 (47%)
< 50 copies/mL	0	1/19 (5%)	1/17 (6%)

Safety Results (1)

- ◆ No serious adverse events
- ◆ No discontinuations for any reason

Number of Subjects Reporting Adverse Events Assessed as at Least Possibly Related

MedDRA Term	200 mg INCB009471 N=19
Any AE	4 (21.1%)
Mild Constipation	1 (5.3%)
Mild Diarrhea	1 (5.3%)
Mild Nausea	1 (5.3%)
Mild Headache	1 (5.3%)
Mild Hiccoughs	1 (5.3%)
Mild Rash	1 (5.3%)

Safety Results (2)

Effect on QTcF:

Parameter	Placebo, N=3*	INCB009471, N=19
Mean Δ from Baseline	-2.5 msec	-1.8 msec
N / % subjects with ≥ 30 msec Δ from BL	1 (33%)	3 (16 %)
N / % subjects with ≥ 60 msec Δ from BL	0	0

LFT (ALT, AST) changes during study

*One pt with missing data

Parameter	Placebo, N=4	INCB009471, N=19
N with Grade 1 abnormalities	1 (25%)	4 (21%)
N with Grade 2 abnormalities	0	0

No change to chemistry and hematology parameters

Conclusions: INCB009471 (1)

- 200 mg once daily for 14 days was well tolerated
 - No clinically significant chemistry, hematology, ECG changes observed
- Rapid virologic response
 - Mean maximal viral load decline -1.81 log on Day 16
- 16 / 19 demonstrate VL decline > 1.5 log
 - 16 / 17 remaining R5-tropic had >1.5 log decline
- Viral load suppressed beyond dosing interval
 - Consistent with prolonged plasma half-life
 - Day 28 (two wks post dosing) VL -0.81 log from BL

Conclusions (2): INCB009471

- N = 2 had unmasking of X4-using virus populations
 - Preliminary analysis: X4-using virus from pre-existing variants
- 200 mg once daily warrants longer-term Phase 2b studies in R-5 screened HIV-infected patients
 - The safety/activity of other once-daily doses of INCB009471 is under investigation
 - Phase 2b studies are planned of one (or more) doses

Acknowledgements

Participating subjects

Investigators

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