A phase I study to explore the activity and safety of SCH 532706, a small molecule chemokine receptor-5 (CCR5) antagonist in HIV-1 infected subjects

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background

- SCH 532706 is a small molecule CCR5-receptor antagonist

- SCH 532706 in vitro data:
  - high affinity for CCR5 receptor - Kd = 0.36 ± 0.09 nM
  - inhibits replication of HIV-1 primary isolates in PBMCs: IC_{50} and IC_{90} 0.2 and 1.8 nM, respectively
  - long dissociation half life of 78 ± 24 hours
  - resistance has been difficult to generate

- pre-clinical pharmacokinetic characteristics:
  - good bioavailability in animal models
  - moderate protein binding (80%)
  - metabolism via CYP3A4; without potent inhibition/induction
  - not a P-glycoprotein (P-gp) efflux substrate
  - eliminated by urinary and biliary routes
  - weak inhibition of hERG current (- 8% in 5 µM solution)

SCH 532706 PK characteristics: healthy volunteers

- in a prior rising multiple-dose study in healthy volunteers SCH 532706 was safe and well tolerated

- the effects of administration with a potent CYP3A4 inhibitor were to:
  - increase AUC 11 fold
  - increase Cmin 18 fold
  - prolong $t_{1/2}$ from 12 to 26 hours
  - reduce PK variability from 30 to 10%

objectives

primary objective:

- to examine the antiviral activity of SCH 532706 in untreated, R5-tropic HIV-1-infected individuals about to begin or resume cART

secondary objectives:

- to determine the PK profile of SCH 532706 in HIV-1-infected individuals;
- to explore the relationship between plasma drug exposure and virological response;
- to further document safety and tolerability of SCH 532706

endpoints and analysis

Primary endpoint:

- change from baseline to Day 10 plasma HIV RNA (log_{10} copies/mL)

Secondary endpoints:

- proportion of patients with Day 10 plasma HIV RNA <50 copies/mL
- proportion of patients with ≥1 log_{10} copies/mL decline at Day 10
- standard PK assessments after single and multiple doses
- changes in immunological parameters and tropism
- adverse events: clinical and laboratory
- ECG changes

Analyses

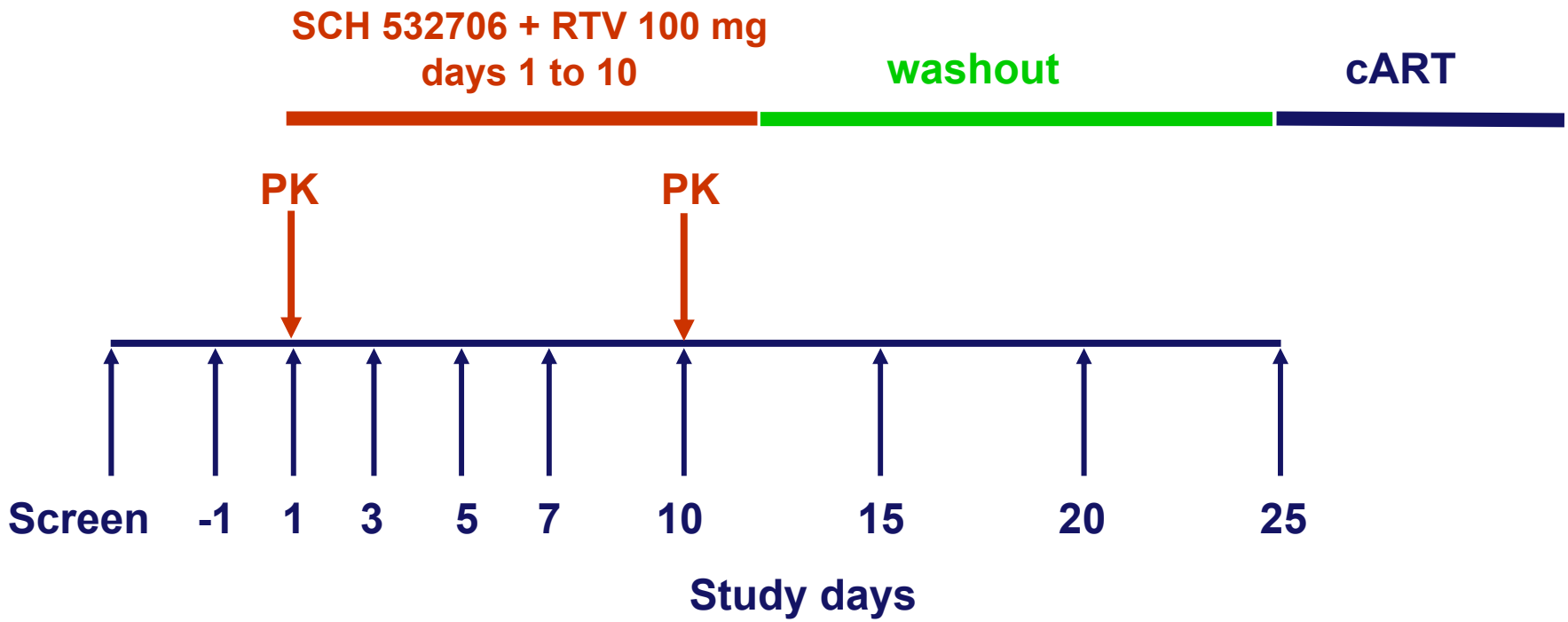
- ITT
- ANOVA model for the primary efficacy parameter i.e. log_{10} change in HIV RNA from baseline to day 10
- Summary statistics for concentration data at each sampling time and the derived PK parameters
- safety parameters summarised

materials and methods

Design: single site, fixed sequence

patient population (n=12): HIV-1-infected: cART naïve/ART-experienced off cART for >3 mths; CD4+ T-cell count >100 cells/μL; plasma HIV RNA >5000 copies/mL; R5-tropic*

Study Schema

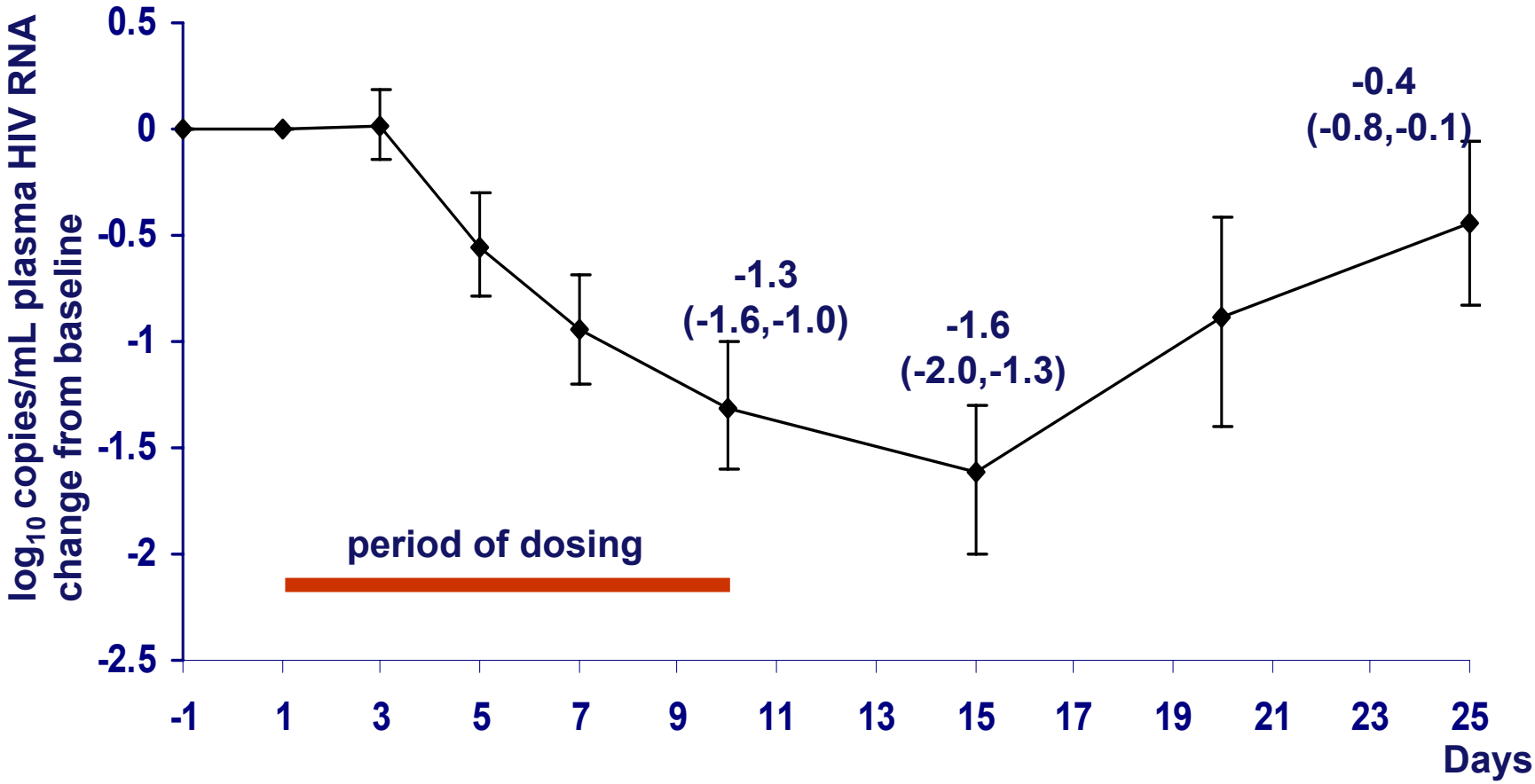


*performed at Invirion Diagnostics using the ViroTect tropism assay

baseline characteristics

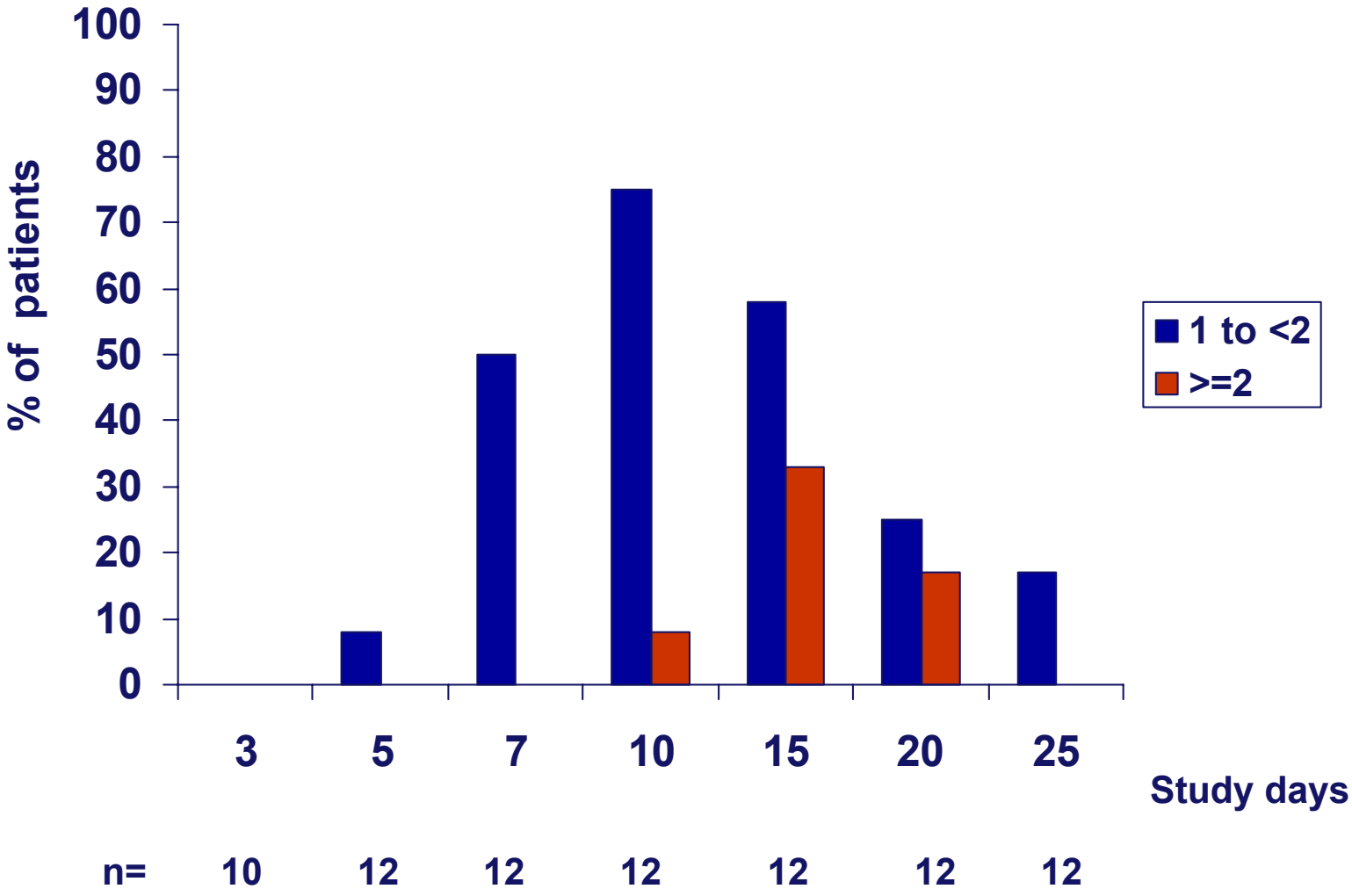
characteristic	N=12
median (range) age years	36 (30-52)
male (%)	12 (100%)
ethnicity	
White (%)	11 (92%)
Non-White (%)	1 (8%)
median baseline $CD4^+$ cell count cells/μL (range)	327 (117-1008)
median log_{10}HIV RNA copies/mL (range)	4.6 (3.8-5.5)
cART naïve (%)	4 (33%)
cART experienced (%)	8 (67%)
median time off cART (months) (n=8)	32 (range 3-71)

mean HIV-1 RNA log10 cp/mL (95%CI) change from baseline



N=	12	12	10	12	12	12		12		12		12
VL<50cp/mL		0	0	0	0	0		0		0		0

virological efficacy: percentage of patients with ≥1 $\log_{10}$ copies/mL plasma HIV decline by time interval



pharmacokinetic parameters

mean (%CV) PK parameters SCH 532706 on days 1 and 10*

Day	Cmin (ng/mL)	Cmax (ng/mL)	AUC(0-12hr) (ng/hr*mL)	t1/2 (h)
Day 1	**35.6** (26)	**80.7** (37)	**586** (27)	NA
Day 10	**178** (19)	**295** (15)	**2780** (16)	**39.4** (37)

*one patient excluded from Day 10 results due to missed am dose on Day 10

other secondary endpoints

- Immunological parameters: mean changes in CD4+ and CD8+ T-cell count at day 10 were +59 cells/μL and +114 cells/μL respectively
- HIV tropism: no X4-tropism detection
- ECG: no prolongation of QTc interval to >500 ms or change from baseline of >60 ms

safety profile

adverse events – clinical

- 92% at least 1 treatment-emergent AE
- 75% mild; 58% unlikely related to SCH 532706
- GI upset was the commonest AE reported in 67% of patients
  - diarrhoea (33%)
  - abdominal pain (25%)
  - GI disorder reported in <10%: abdominal distension, nausea, abdominal pain (upper/lower), frequent bowel movement
- one SAE: pericarditis (grade 2) reported 13 days after last receipt of SCH 532706, resolved with no sequelae after 4 days

adverse events – laboratory

- no laboratory AEs considered clinically significant
- 25% grade 1 ALT elevation

conclusion

- SCH 532706, in the presence of ritonavir, at a dose of 60mg bid was safe and well tolerated
- the drug was biologically active against HIV-1
- SCH 532706 is suitable for once daily dosing in a ritonavir-containing regimen

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