

HEMATOLOGICAL EFFECTS OF TR-701, LINEZOLID AND PLACEBO ADMINISTERED FOR 21 DAYS IN HEALTHY SUBJECTS

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INTRODUCTION

TR-701 is a novel oxazolidinone prodrug of the active moiety, TR-700. Preclinical studies have shown that oral TR-701 is generally 6 times more efficacious than linezolid (LNZ) in vivo.

STUDY DESIGN

Oxazolidinones are known to induce dose- and time-dependent reversible hematologic effects. In order to maximize observable effects of TR-701 and LNZ on hematologic parameters, we conducted a 21 day Phase 1 study comparing the two drugs and placebo in healthy subjects. Each cohort (8 active and 2 placebo) received either single daily oral doses of 200, 300, or 400 mg TR-701, or 600 mg BID LNZ.

DATA

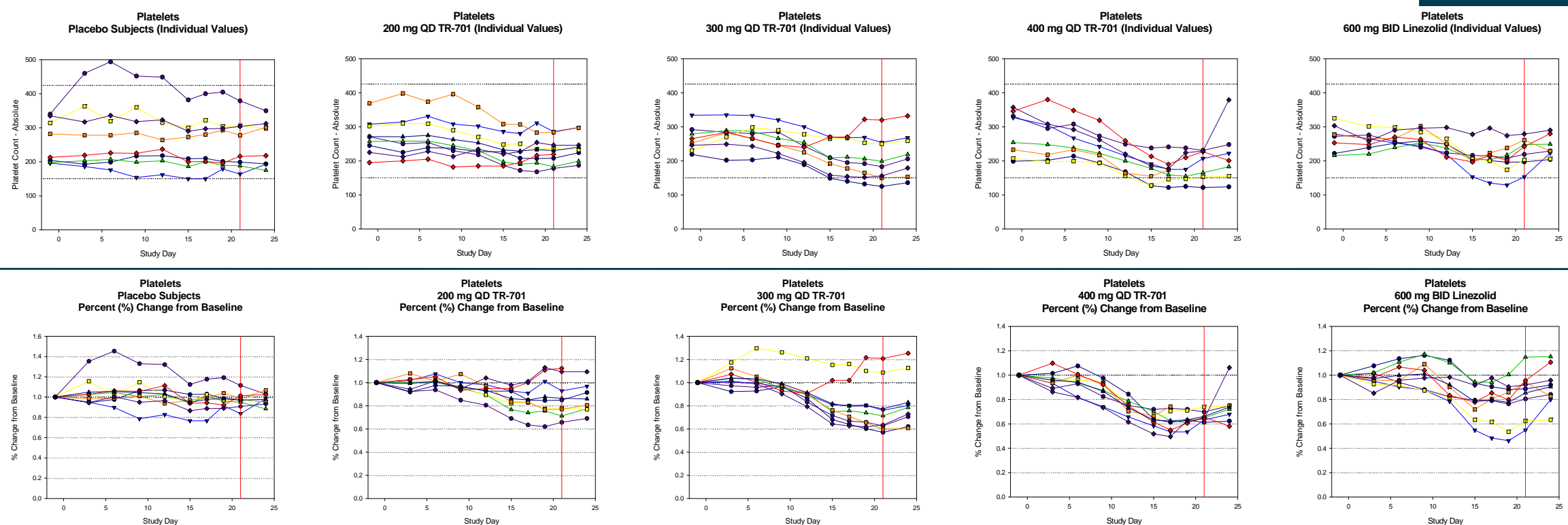
Maximum Cohort Mean Percent (%) Decrease Over 21 Days

DOSE	Platelets (%)	Neutrophils (%)	Reticulocytes (%)	RBCs (%)
PLACEBO	-5	-2	-8	-3
200 mg TR-701 QD	-15	-18	-14	-2
300 mg TR-701 QD	-23	-4	-5	-3
400 mg TR-701 QD	-38	-37	-39	-11
600 mg LNZ BID	-22	-38	-21	-7

Maximum Individual Percent (%) Decrease Over 21 Days

DOSE	Platelets (%)	Neutrophils (%)	Reticulocytes (%)	RBCs (%)
PLACEBO	-23	-57	-38	-11
200 mg TR-701 QD	-38	-51	-42	-9
300 mg TR-701 QD	-43	-44	-57	-7
400 mg TR-701 QD	-50	-66	-91	-27
600 mg LNZ BID	-54	-66	-95	-13

EFFECTS OF TR-701 AND LINEZOLID ON PLATELETS OVER 21 DAYS DOSING



RESULTS

- ◆ No significant changes in hematologic parameters were seen over the first 7 days for TR-701 or LNZ
- ◆ TR-701 200 mg QD effects on hematologic parameters over 21 days were comparable to placebo
- ◆ TR-701 300 mg QD effects on platelet counts over 21 days were minimal compared to placebo
- ◆ TR-701 400 mg QD effects on platelet counts over 21 days were comparable to LNZ 600 mg BID
- ◆ For TR-701 and LNZ, thrombocytes were the blood cell line primarily affected. Changes in platelets generally appeared by Day 9-12, stabilizing with no further decrease during the 3rd week of dosing

CONCLUSIONS

- ◆ Based on these results, the doses currently being tested in an ongoing complicated skin and skin structure Phase 2 study (200, 300, 400 mg QD; 5-7 days treatment) are not likely to produce any alterations in hematologic parameters over 7 days
- ◆ With a 6-fold increased potency over LNZ (see poster A-985), once-daily dosing and low PK variability (see poster F1-2064), and an anticipated shorter duration of therapy, TR-701 should provide an improved therapeutic alternative for the treatment of Gram-positive infections