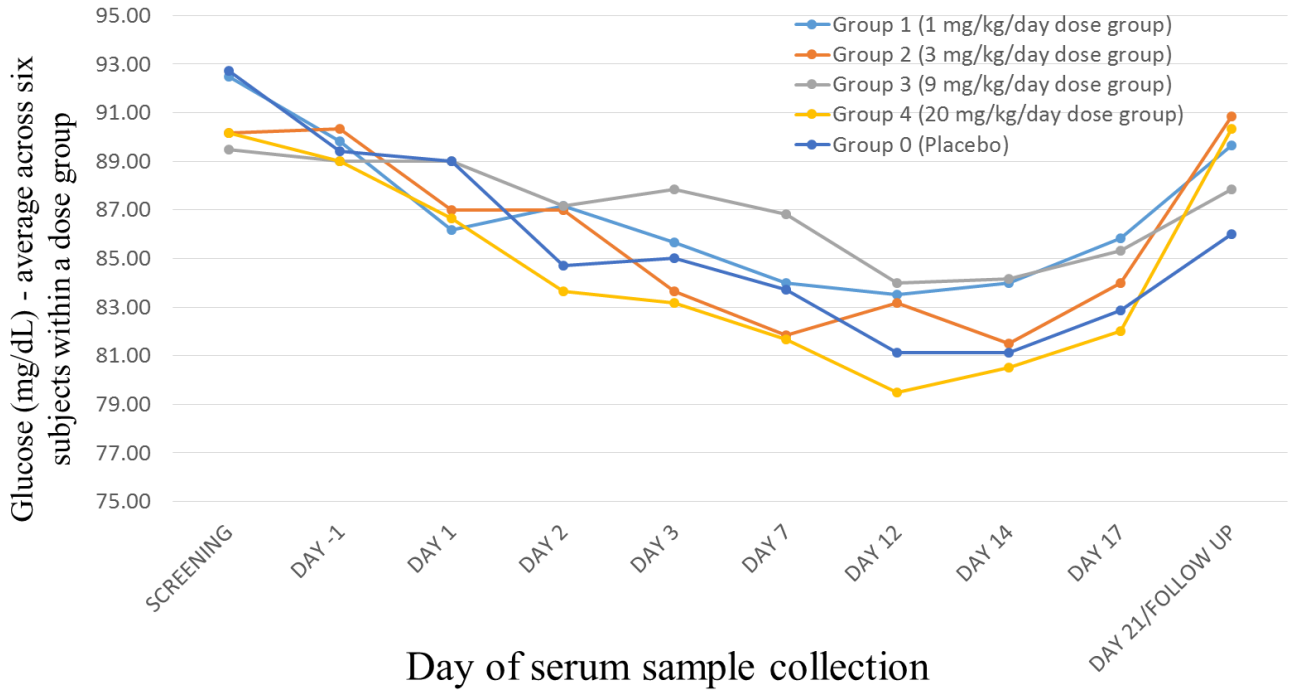
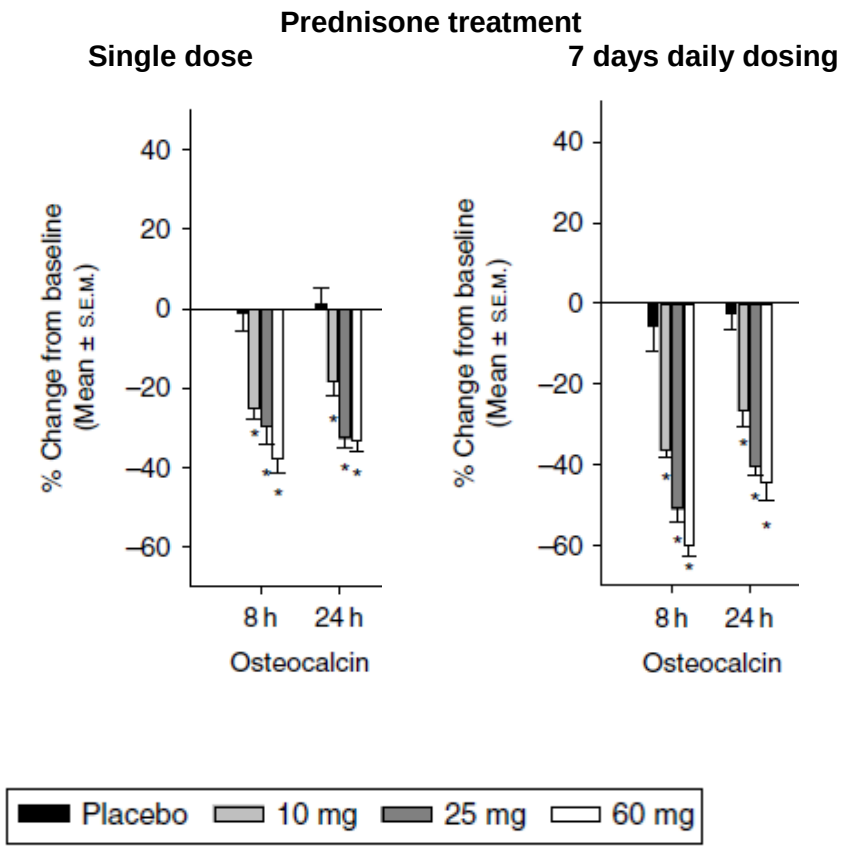
Supplementary Materials:

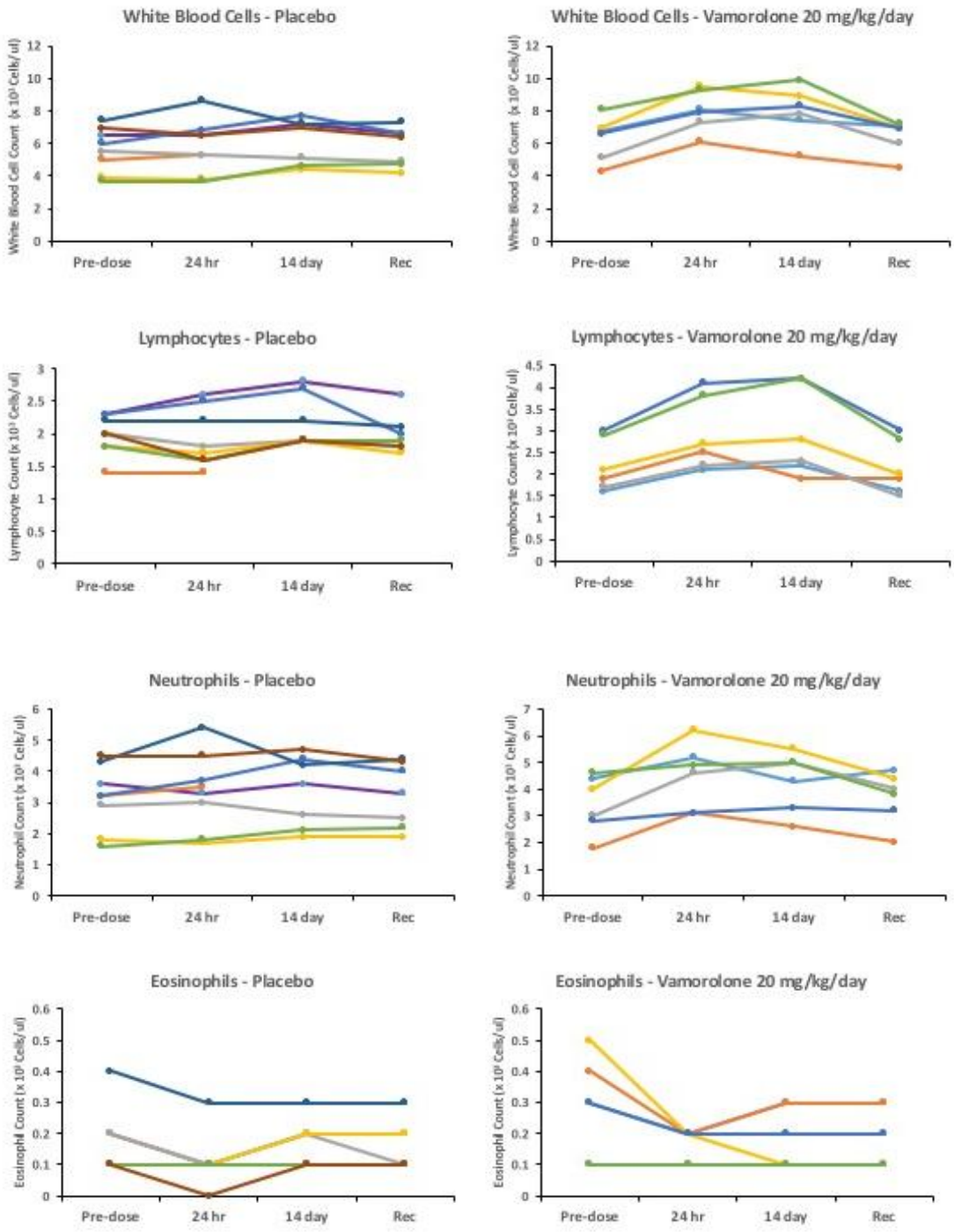


Supplemental Figure 1. Glucose measures of vamorolone-treated adult volunteers are not significantly different from placebo. Fasting blood glucose levels were measured on the mornings of the indicated days, with vamorolone or placebo treatment on days 1 – 14. Days 14-21 are recovery time points. Placebo subjects showed a decline over time in the Phase 1 in-patient unit, possibly due to diet, but these differences were similar to all vamorolone-treated groups. This data shows that vamorolone does not cause insulin resistance as seen with glucocorticoids.



Equivalencies **0.125 mg/kg** **0.31 mg/kg** **0.75 mg/kg**

Supplemental Figure 2. Serum levels of a biomarker of bone formation, osteocalcin, are significantly decreased by 0.125 mg/kg of prednisone (taken from Kauh et al. 2013) (*Error! Bookmark not defined.***).** A 10 mg dose (equivalent to ~0.125 mg/kg) of prednisone shows significant declines in blood levels of osteocalcin both 8 hours after a single dose, and after 7 days of daily dosing. In contrast, vamorolone showed no declines through 20 mg/kg/day. Each prednisone dosed group was compared to placebo using a non-parametric test and reported p-values are adjusted for multiple comparisons; * indicates a statistically significant difference from placebo at the p≤0.05 level.



Supplemental Figure 3. Differential blood counts are not significantly different from placebo. White blood cells and subsets (lymphocytes, neutrophils, eosinophils) were measured at screening, day -1, pre-dose on days 1-14, day 17, and at follow-up (recovery). Day 1 (pre-dose), Day 2 (24 hr after first dose), Day 14 and follow-up (recovery) time points are graphed

below. Dosing was halted on Day 9 for one patient in the 20 mg/kg/day cohort (orange line) and one patient in the placebo cohort (purple line).

Supplemental Tables:

All data shown mean ± SEM

Supplemental Table 1. Blood glucose measures: Single ascending dose study.

Dose	Time Point (mg/dL)						
	Screening[a]	Day -1[b]	<2 hours predose	24 Hours Post Dose	48 Hours Post Dose	72 Hours Post Dose	Follow-up Visit
Placebo	97 ± 2	92 ± 1	95 ± 1	91 ± 2	89 ± 2	90 ± 1	94 ± 2
0.1 mg/kg	94 ± 4	99 ± 3	95 ± 3	95 ± 4	95 ± 3	94 ± 4	98 ± 4
0.3 mg/kg	93 ± 2	91 ± 2	93 ± 2	91 ± 2	90 ± 2	91 ± 1	88 ± 4
1.0 mg/kg	92 ± 3	92 ± 3	93 ± 3	86 ± 3	88 ± 3	86 ± 3	93 ± 2
3.0 mg/kg	96 ± 5	89 ± 3	92 ± 4	93 ± 3	89 ± 4	88 ± 3	91 ± 5
8.0 mg/kg	89 ± 4	90 ± 5	86 ± 3	91 ± 4	87 ± 3	89 ± 4	94 ± 4
20.0 mg/kg	93 ± 3	94 ± 3	97 ± 4	91 ± 2	86 ± 2	88 ± 2	89 ± 3

Supplemental Table 2. Blood glucose measures: Multiple ascending dose study.

Dose	Time Point (md/dL)									
	Screening[a]	Day -1[b]	Day 1[c]	Day 2[c]	Day 3[c]	Day 7[c]	Day 12[c]	Day 14[c]	Day 17[d]	Day 21[e]
Placebo	93 ± 2	90 ± 1	90 ± 2	85 ± 1	85 ± 1	85 ± 1	85 ± 4	81 ± 1	83 ± 1	86 ± 2
1.0 mg/kg	92 ± 1	90 ± 2	86 ± 1	87 ± 2	86 ± 2	84 ± 2	83 ± 1	84 ± 1	86 ± 1	90 ± 3
3.0 mg/kg	90.1 ± 1.5	90 ± 1	87 ± 1	87 ± 1	84 ± 2	82 ± 1	83.1 ± 1.4	81 ± 2	84 ± 1	91 ± 2
9.0 mg/kg	89 ± 3	89 ± 1	89 ± 2	87 ± 1	88 ± 2	87 ± 2	84 ± 2	84 ± 2	85 ± 2	88 ± 2
20.0 mg/kg	90 ± 3	89 ± 1	87 ± 1	84 ± 1	83 ± 1	82 ± 1	80 ± 2	80 ± 2	81 ± 2	91 ± 3

[a] Up to 30 days prior to randomization (day 1)
[b] Up to 24 hours prior to first dose
[c] Predose (within 2 hours prior to dosing)
[d] 3 days after last dose (Day 14)
[e] Follow-up visit

Supplemental Table 3. Osteocalcin: Multiple ascending dose

Dose	Osteocalcin: Time Point (ng/ml)					
	Day 1 (predose)[a]	Day 1[b]	Day 14 (predose)[a]	Day 14[b]	Day 15[c]	Day 17[d]
Placebo	46.3 ± 9.7	40.1 ± 7.4	42.7 ± 8.8	34.0 ± 6.7	40.8 ± 7.9	38.8 ± 6.2
1.0 mg/kg	33.2 ± 11.5	27.4 ± 9.3	30.3 ± 9.7	21.0 ± 7.8	28.8 ± 9.3	25.9 ± 8.0
3.0 mg/kg	13.7 ± 11.6	13.6 ± 11.5	17.1 ± 13.3	13.0 ± 11.0	16.1 ± 12.5	13.9 ± 9.5
9.0 mg/kg	32.9 ± 8.6	20.4 ± 4.7	24.0 ± 6.4	18.7 ± 4.3	26.7 ± 5.2	33.5 ± 7.2
20.0 mg/kg	31.5 ± 6.7	20.2 ± 4.6	32.8 ± 7.6	17.0 ± 3.7	27.8 ± 5.9	34.6 ± 6.1

Supplemental Table 4. CTX1: Multiple ascending dose

Dose	CTX1: Time Point (ng/ml)					
	Day 1 (predose)[a]	Day 1[b]	Day 14 (predose)[a]	Day 14[b]	Day 15[c]	Day 17[d]
Placebo	0.66 ± 0.12	0.28 ± 0.05	0.81 ± 0.21	0.30 ± 0.07	0.88 ± 0.22	0.84 ± 0.22
1.0 mg/kg	0.50 ± 0.11	0.22 ± 0.02	0.58 ± 0.12	0.22 ± 0.01	0.68 ± 0.16	0.55 ± 0.09
3.0 mg/kg	0.31 ± 0.05	0.18 ± 0.00	0.48 ± 0.13	0.18 ± 0.00	0.48 ± 0.10	0.46 ± 0.12
9.0 mg/kg	0.59 ± 0.11	0.19 ± 0.006	0.73 ± 0.14	0.23 ± 0.03	0.77 ± 0.13	0.60 ± 0.10
20.0 mg/kg	0.70 ± 0.14	0.22 ± 0.02	0.88 ± 0.12	0.29 ± 0.06	0.92 ± 0.14	0.76 ± 0.10

[a] Up to 30 days prior to randomization (day 1)
[b] Up to 24 hours prior to first dose
[c] Predose (within 2 hours prior to dosing)
[d] 3 days after last dose (Day 14)
[e] Follow-up visit

Supplemental Table 5. White blood cells counts: Multiple ascending dose study

Dose	Time Point									
	Screening[a]	Day -1[b]	Day 1[c]	Day 2[c]	Day 3[c]	Day 7[c]	Day 12[c]	Day 14[c]	Day 17[d]	Day 21[e]
Placebo	5.8 ± 1.6	6.0 ± 1.2	5.6 ± 1.4	5.8 ± 1.6	6.2 ± 1.6	5.8 ± 1.2	6.4 ± 1.6	6.2 ± 1.4	5.8 ± 1.2	6.9 ± 2.9
1.0 mg/kg	5.9 ± 2.2	5.5 ± 0.8	5.2 ± 1.0	5.3 ± 0.9	5.4 ± 0.8	5.9 ± 0.7	6.1 ± 0.9	5.9 ± 0.9	5.7 ± 0.6	5.5 ± 0.7
3.0 mg/kg	6.2 ± 2.9	6.1 ± 1.9	5.8 ± 2.0	5.9 ± 1.5	6.1 ± 2.2	6.3 ± 2.0	6.0 ± 2.0	5.8 ± 1.8	6.6 ± 1.6	6.3 ± 1.6
9.0 mg/kg	5.2 ± 1.3	5.5 ± 1.1	5.2 ± 1.1	6.7 ± 1.2	6.8 ± 1.0	6.6 ± 1.3	6.8 ± 0.9	6.8 ± 1.3	5.5 ± 0.7	5.2 ± 1.1
20.0 mg/kg	6.1 ± 1.1	7.3 ± 1.1	6.3 ± 1.4	8.0 ± 1.3	7.9 ± 0.7	8.2 ± 1.0	8.3 ± 0.5	8.5 ± 0.4	6.8 ± 0.2	6.8 ± 0.4

Supplemental Table 6. Neutrophil cell counts: Multiple ascending dose

Dose	Time Point									
	Screening[a]	Day -1[b]	Day 1[c]	Day 2[c]	Day 3[c]	Day 7[c]	Day 12[c]	Day 14[c]	Day 17[d]	Day 21[e]
Placebo	3.5 ± 1.3	3.3 ± 0.8	3.1 ± 1.0	3.4 ± 1.2	3.6 ± 1.2	3.4 ± 1.0	3.5 ± 1.1	3.4 ± 1.2	3.2 ± 1.0	4.2 ± 2.7
1.0 mg/kg	3.6 ± 2.0	2.8 ± 0.9	2.8 ± 1.0	3.0 ± 0.9	2.8 ± 0.8	3.1 ± 0.9	3.2 ± 1.0	3.0 ± 1.0	3.0 ± 0.8	3.0 ± 0.6
3.0 mg/kg	3.5 ± 1.8	3.5 ± 1.4	3.4 ± 1.3	3.4 ± 1.2	3.4 ± 1.4	3.3 ± 0.9	3.2 ± 1.1	3.0 ± 1.1	4.0 ± 1.1	3.9 ± 1.4
9.0 mg/kg	3.0 ± 1.0	2.9 ± 0.6	2.9 ± 0.9	3.7 ± 1.1	3.6 ± 0.7	3.4 ± 1.0	3.5 ± 0.9	3.6 ± 1.0	3.1 ± 0.7	2.9 ± 1.0
20.0 mg/kg	3.5 ± 1.2	3.9 ± 1.1	3.4 ± 1.1	4.5 ± 1.2	4.3 ± 1.2	4.4 ± 0.7	4.4 ± 0.4	4.6 ± 0.4	4.0 ± 0.3	4.0 ± 0.3

Supplemental Table 7. Lymphocytes: Multiple ascending dose

Dose	Time Point									
	Screening[a]	Day -1[b]	Day 1[c]	Day 2[c]	Day 3[c]	Day 7[c]	Day 12[c]	Day 14[c]	Day 17[d]	Day 21[e]
Placebo	1.8 ± 0.4	2.1 ± 0.5	2.0 ± 0.3	1.9 ± 0.4	2.0 ± 0.5	1.9 ± 0.3	2.3 ± 0.6	2.2 ± 0.4	2.0 ± 0.3	2.0 ± 0.5
1.0 mg/kg	1.8 ± 0.5	2.1 ± 0.5	1.9 ± 0.4	1.8 ± 0.3	2.1 ± 0.2	2.1 ± 0.3	2.3 ± 0.3	2.3 ± 0.2	2.1 ± 0.4	2.0 ± 0.2
3.0 mg/kg	2.0 ± 1.0	1.9 ± 0.6	1.8 ± 0.6	2.0 ± 0.4	2.1 ± 0.7	2.4 ± 0.8	2.1 ± 0.7	2.2 ± 0.6	2.0 ± 0.5	1.8 ± 0.6
9.0 mg/kg	1.7 ± 0.5	2.1 ± 0.7	1.8 ± 0.4	2.5 ± 0.7	2.7 ± 0.7	2.6 ± 0.6	2.8 ± 0.6	2.6 ± 0.6	1.9 ± 0.5	1.8 ± 0.7
20.0 mg/kg	2.0 ± 0.5	2.6 ± 0.5	2.2 ± 0.6	2.9 ± 0.8	2.9 ± 0.7	3.2 ± 0.9	3.2 ± 0.4	3.1 ± 0.4	2.2 ± 0.3	2.2 ± 0.3

Supplemental Table 8. Eosinophils: Multiple ascending dose

Dose	Time Point									
	Screening[a]	Day -1[b]	Day 1[c]	Day 2[c]	Day 3[c]	Day 7[c]	Day 12[c]	Day 14[c]	Day 17[d]	Day 21[e]
Placebo	0.15 ± 0.08	0.20 ± 0.13	0.18 ± 0.10	0.11 ± 0.08	0.13 ± 0.07	0.14 ± 0.07	0.16 ± 0.05	0.17 ± 0.08	0.16 ± 0.08	0.16 ± 0.11
1.0 mg/kg	0.13 ± 0.08	0.18 ± 0.10	0.17 ± 0.08	0.17 ± 0.08	0.17 ± 0.08	0.20 ± 0.14	0.20 ± 0.09	0.18 ± 0.08	0.17 ± 0.08	0.15 ± 0.10
3.0 mg/kg	0.18 ± 0.08	0.20 ± 0.06	0.23 ± 0.08	0.23 ± 0.08	0.20 ± 0.06	0.18 ± 0.08	0.18 ± 0.04	0.20 ± 0.06	0.17 ± 0.05	0.18 ± 0.04
9.0 mg/kg	0.10 ± 0.00	0.12 ± 0.04	0.10 ± 0.00	0.13 ± 0.05	0.10 ± 0.00	0.10 ±0.00	0.12 ± 0.04	0.13 ± 0.05	0.08 ± 0.04	0.12 ± 0.04
20.0 mg/kg	0.25 ± 0.14	0.32 ± 0.16	0.28 ± 0.16	0.17 ± 0.05	0.15 ± 0.08	0.15 ± 0.08	0.12 ± 0.02	0.16 ± 0.04	0.16 ± 0.04	0.26 ± 0.02

Supplemental Table 9. Crystallographic data of vamorolone

	Vamorolone
Crystal data	
Chemical formula	$C_{22}H_{28}O_4$
M_r	356.44
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	110
a, *b*, *c* (Å)	8.18746 (9), 18.0748 (2), 37.5595 (4)
V (Å^3)	5558.31 (10)
Z	12
Radiation type	Cu *Kα*
□ (mm^{-1})	0.69
Crystal size (mm)	0.51 × 0.38 × 0.31
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, Atlas
Absorption correction	Analytical *CrysAlis PRO*, Agilent Technologies, Version 1.171.36.32 (release 02-08-2013 CrysAlis171 .NET) (compiled Aug 2 2013,16:46:58). Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by R.C. Clark & J.S. Reid. (Clark, R. C. & Reid, J. S. (1995). Acta Cryst. A51, 887-897)
T_{min}, T_{max}	0.774, 0.844
No. of measured, independent and observed [$I > 2\sigma(I)$]	36042, 10890, 10330

reflections	
R_{int}	0.017
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.616
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.030, 0.089, 1.06
No. of reflections	10890
No. of parameters	719
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.24, -0.13
Absolute structure	Flack x determined using 4305 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.02 (3)