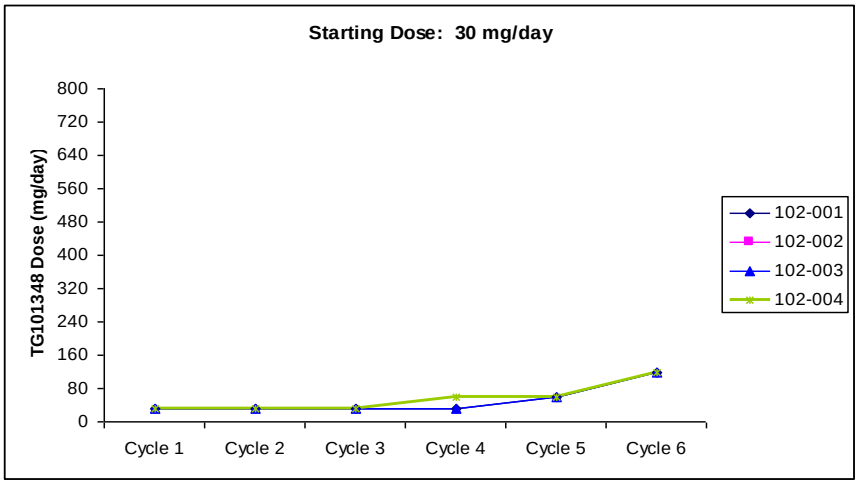
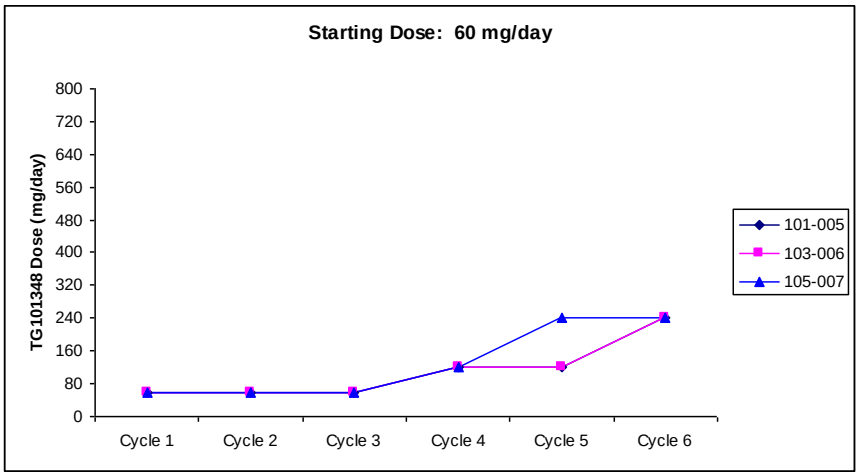
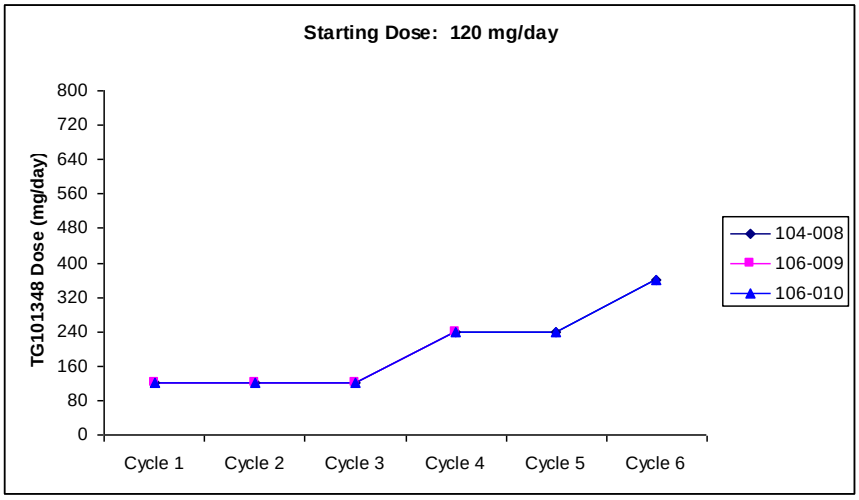
# Safety and Efficacy of TG101348, a Selective JAK2 Inhibitor, in Myelofibrosis

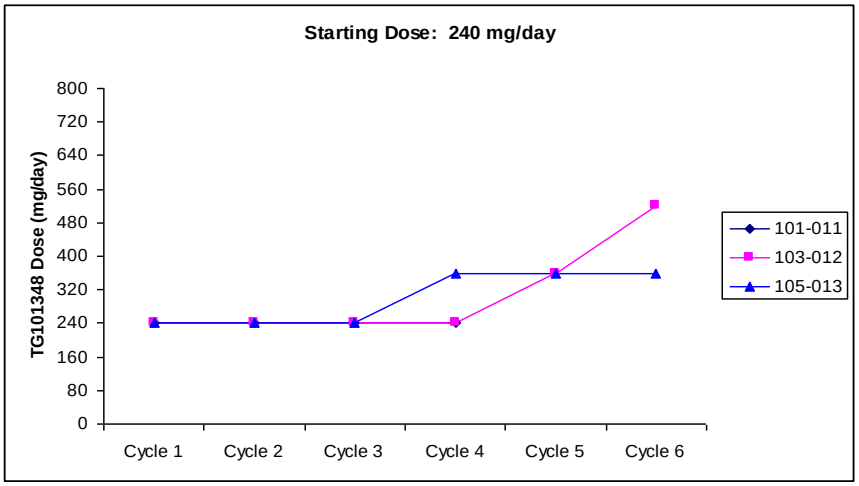
Pardanani et al

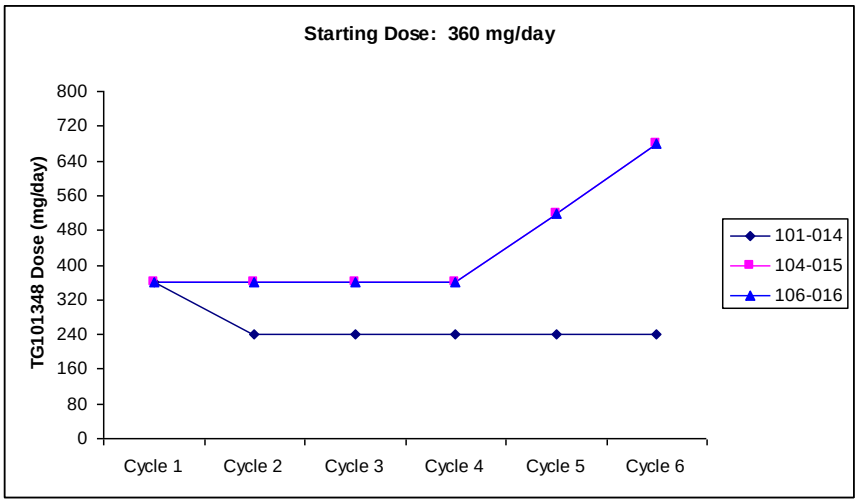
**Supplemental Figure 1A. Distribution of TG101348 doses at the end of each cycle for subjects who initiated dosing at 30-520 mg/day and 800 mg/day (n = 25)**

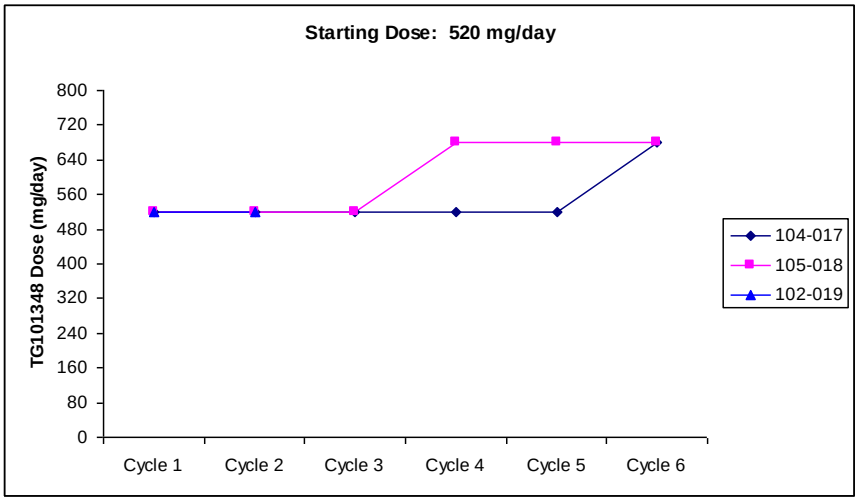


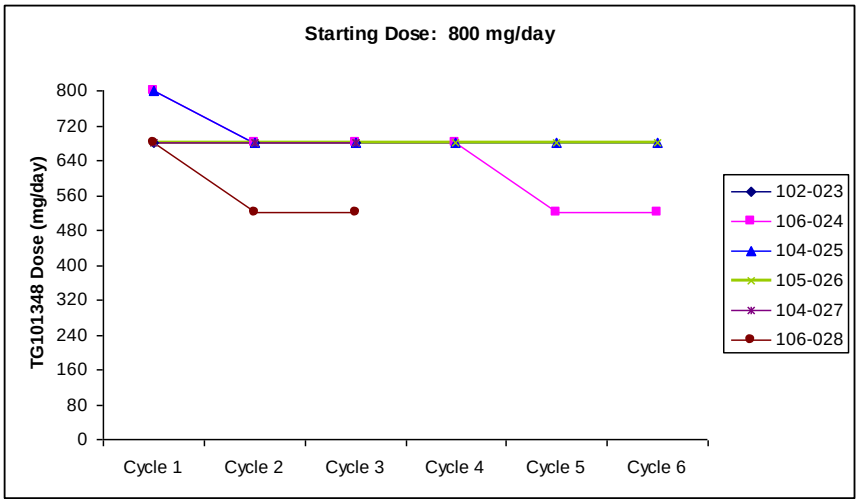



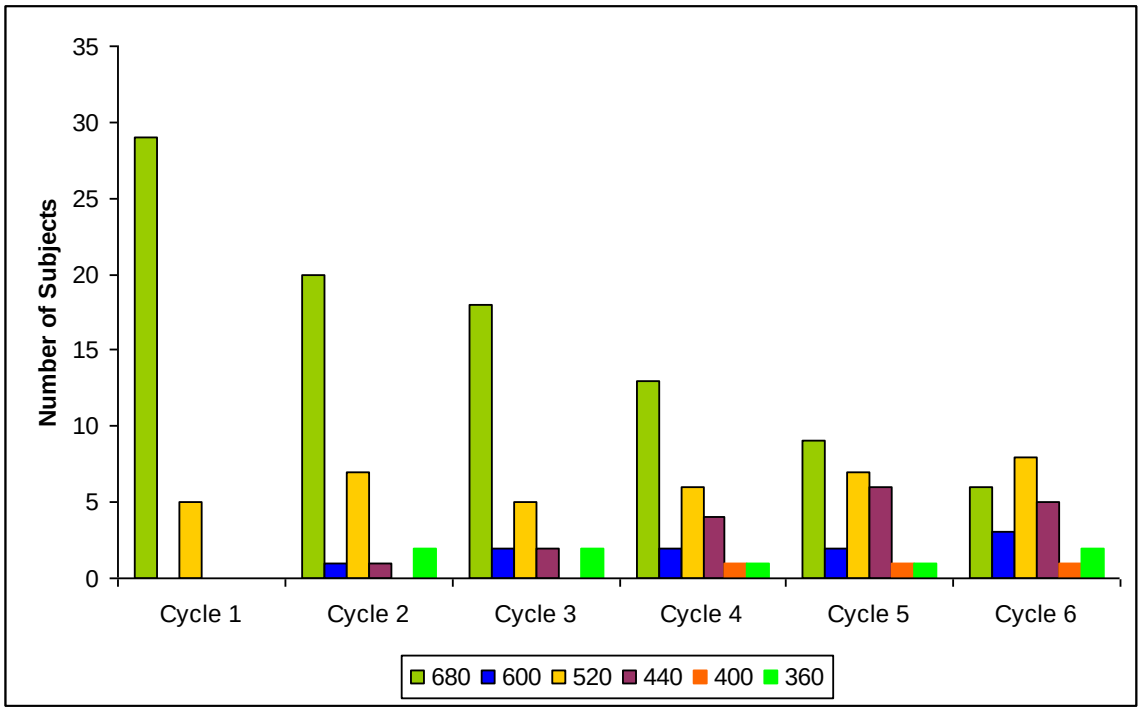

Starting Dose: 240 mg/day
TG101348 Dose (mg/day)
800
720
640
560
480
400
320
240
160
80
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
101-011
103-012
105-013


Starting Dose: 360 mg/day
TG101348 Dose (mg/day)
800
720
640
560
480
400
320
240
160
80
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
101-014
104-015
106-016

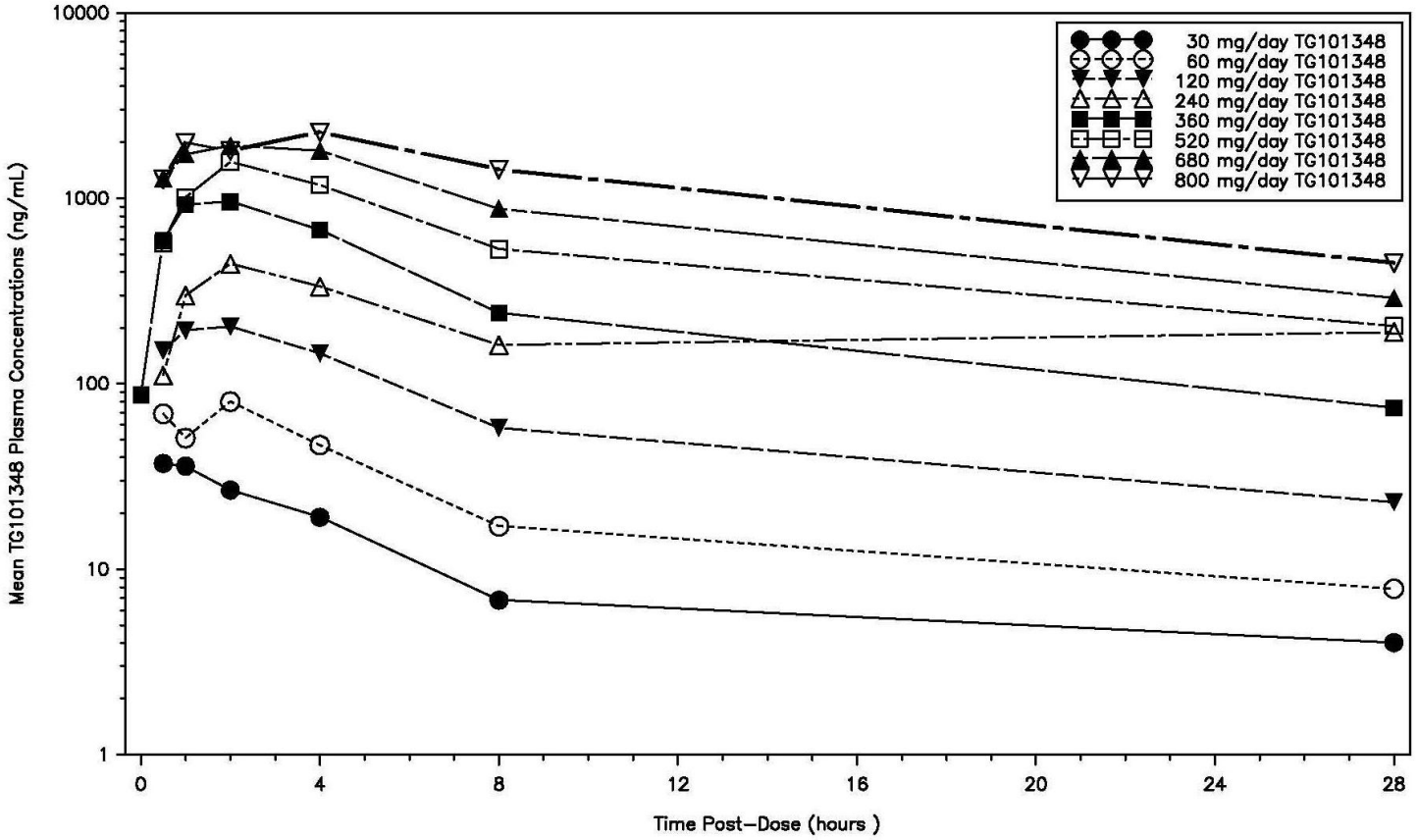

Starting Dose: 520 mg/day
TG101348 Dose (mg/day)
800
720
640
560
480
400
320
240
160
80
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
104-017
105-018
102-019



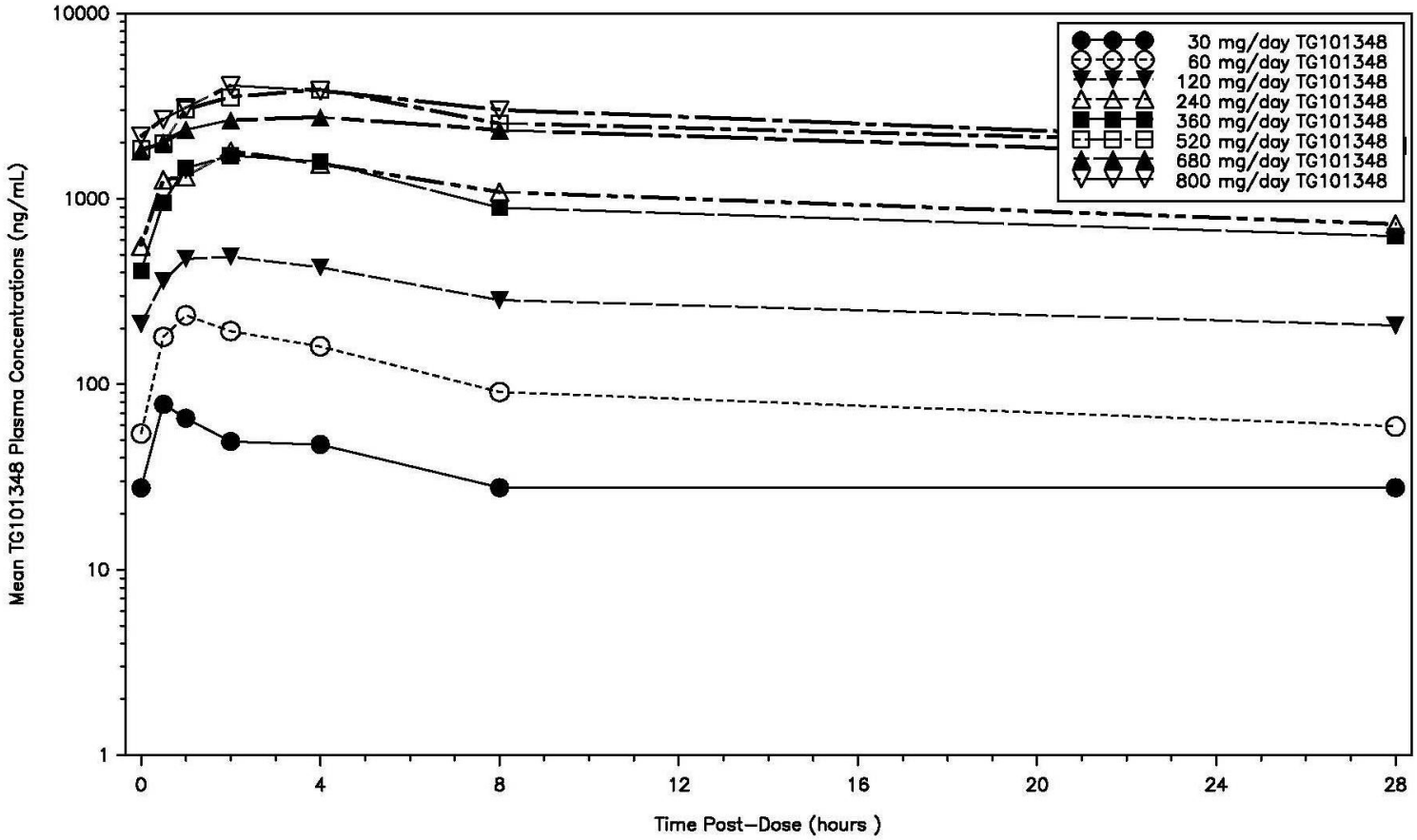

**Supplemental Figure 1B. Distribution of TG101348 doses at the end of each cycle for subjects who initiated dosing at 680 mg/day (n = 34)**



**Supplemental Figure 2A. Plot of mean plasma TG101348 plasma concentrations versus time on a semi-log scale (Cycle 1, Day 1)**

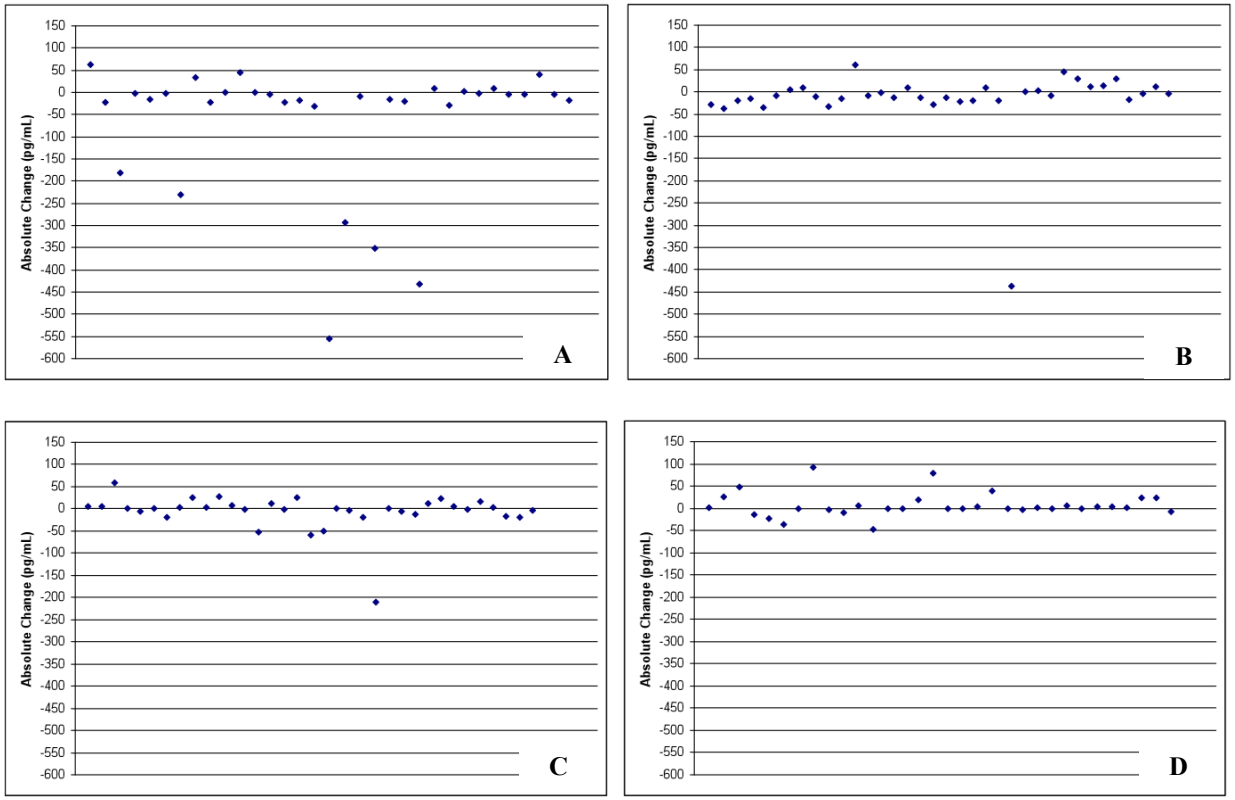


**Supplemental Figure 2B. Plot of mean plasma TG101348 plasma concentrations versus time on a semi-log scale (Cycle 1, Day 28)**



**Supplemental Figure 3. Absolute changes in pro-inflammatory cytokine levels from baseline at Cycle 6:**

**IL-6 (A), TNF-α (B), IL-8 (C), and IL-2 (D)**




Absolute differences in IL-6 (-4719 pg/mL) and IL-2 (-1827 pg/mL) are omitted from panels A and D, respectively, for 1 subject (101-039) because they skewed presentation of data for other subjects.

**Supplemental Table 1. Detailed enrollment criteria for MF-TG101348-001**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 1. Diagnosis of MF (PMF, post-PV MF, or post-ET MF) according to the revised WHO criteria.* | 1. Any chemotherapy, immunomodulatory drug therapy, immunosuppressive therapy, corticosteroids > 10 mg/day prednisone or equivalent, or growth factor treatment within 14 days (28 days in the case of darbepoetin) prior to initiation of TG101348. |
| 2. High-risk MF (defined by Mayo PSS), or Mayo PSS intermediate-risk MF** accompanied by symptomatic splenomegaly and/or unresponsive to available therapy. | 2. Major surgery or radiation therapy within 28 days prior to initiation of TG101348. |
| 3. At least 18 years of age. | 3. Concomitant treatment with agents known to inhibit or induce CYP3A4, unless approved by the sponsor. |
| 4. Body weight $\geq$ 50 kg. | 4. Known hypersensitivity to any ingredients in the study drug formulation. |
| 5. ECOG performance status $\leq$ 2. | 5. Active infection requiring antibiotics. |
| 6. Within 4 days prior to initiation of TG101348:<br>• ANC $\geq 1 \times 10^9$/L<br>• Platelet count $\geq 50 \times 10^9$/L<br>• Serum creatinine $\leq$ 2.0 mg/dL<br>• Total bilirubin $\leq$ 2.0 mg/dL<br>• AST or ALT $\leq$ 3 times the ULN (unless clinically compatible with hepatic EMH) | 6. Uncontrolled CHF (NYHA Classification 3 or 4), angina, MI, CVA, coronary/peripheral artery bypass graft surgery, TIA, or pulmonary embolism within 3 months prior to initiation of study drug. |
| 7. Life expectancy $\geq$ 12 weeks. | 7. Cardiac dysrhythmias requiring ongoing treatment, bundle branch block on ECG or QRS duration > 120 ms, or prolongation of the QTc (Fridericia) interval to > 450 ms for males or > 470 ms for females. |
| 8. Negative serum pregnancy test result for women of childbearing potential. | 8. Pregnant or lactating females. |
| 9. Absence of active malignancy other than MF, with the exception of adequately treated basal cell carcinoma and squamous cell carcinoma of the skin. | 9. Women of childbearing potential, unless surgically sterile for at least 3 months (i.e., hysterectomy), postmenopausal for at least 12 months (FSH > 30 U/mL), unless they agree to use effective, dual contraceptive methods (i.e., oral, injectable, or barrier method with male partner using a condom) while on study drug. |
| 10. Provide written informed consent to participate. | 10. Men who partner with a woman of childbearing potential, unless they agree to use effective, dual contraceptive methods (i.e., a condom, with female |

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| | partner using oral, injectable, or barrier method) while on study drug. |
| 11. Willing to comply with scheduled visits, treatment plans, laboratory assessments, and other study-related procedures. | 11. Known HIV- or AIDS-related illness. |
| | 12. Clinically active hepatitis B or C. |
| | 13. Any severe, acute or chronic medical, neurological, or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, may interfere with the informed consent process and/or with compliance with the requirements of the study, or may interfere with the interpretation of study results and, in the investigator's opinion, would make the patient inappropriate for entry into this study. |

The study was conducted at six U.S. locations (UCSD Moores Cancer Center, Stanford Comprehensive Cancer Center, Dana Farber Cancer Institute, University of Michigan Comprehensive Cancer Center, Mayo Clinic, Rochester, and MD Anderson Cancer Center.

Abbreviations: AIDS = acquired immunodeficiency syndrome; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CHF = congestive heart failure; CVA = cerebrovascular accident; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMH = extramedullary hematopoiesis;.FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; MF = myelofibrosis; MI = myocardial infarction; NYHA = New York Heart Association; PSS = prognostic scoring system; TIA = transient ischemic attack; WBC = white blood cell.

*Tefferi and Vardiman. Leukemia. 2008 Jan;22(1):14-22

**High-risk disease requires two and intermediate-risk disease requires one of the following prognostic factors: hemoglobin < 10 g/dL, WBC count < 4 or > $30 \times 10^9$/L, platelet count < $100 \times 10^9$/L, absolute monocyte count $\geq 1 \times 10^9$/L.

**Supplemental Table 2. Mean (SD) plasma pharmacokinetic parameters following multiple daily doses of TG101348 (Cycle 1, Day 28) in MF-TG101348-001**

| | Dose/Day | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **30 mg (n = 3)** | **60 mg (n = 3)** | **120 mg (n = 3)** | **240 mg (n = 3)** | **360 mg (n = 3)** | **520 mg (n = 3)** | **680 mg (n = 27)** | **800 mg (n = 5)** |
| **$C_{max}$ (ng/mL)** | 81.85 (95.630) | 257.33 (121.138) | 556.67 (135.500) | 1796.67 (648.254) | 1717.33 (1558.705) | 3886.67 (3560.707) | 3064.07 (1129.671) | 4380.00 (1764.809) |
| **$T_{max}$* (hr)** | 2.00 (0.5, 4.0) | 1.00 (1.0, 4.0) | 2.00 (0.5, 4.0) | 2.00 (2.0, 2.1) | 2.00 (2.0, 4.0) | 4.00 (4.0, 4.0) | 4.00 (0.0, 8.3) | 2.25 (2.0, 4.0) |
| **$AUC_{(0-t)}$ (hr*ng/mL)** | 806.76 (806.973) | 2426.53 (1048.264) | 7645.69 (2810.740) | 26193.40 (11767.460) | 23879.05 (16898.162) | 61749.22 (57240.295) | 55111.68 (25702.038) | 70840.97 (32668.886) |
| **$T_{1/2}$ (hr)** | 20.94 (7.039) | 15.68 (3.464) | 24.42 (8.434) | 20.77 (6.238) | 21.39 (7.090) | 20.94 (5.006) | 33.71 (33.674) | 23.99 (9.674) |
| **λz (1/hr)** | 0.0354 (0.01016) | 0.0456 (0.00918) | 0.0305 (0.00932) | 0.0352 (0.00903) | 0.0353 (0.01309) | 0.0343 (0.00723) | 0.0301 (0.01421) | 0.0331 (0.01321) |

*$T_{max}$ is presented as median (min, max)

SD indicates standard deviation; $C_{max}$, peak plasma concentration; $T_{max}$, the time to the maximal concentration; $AUC_{(0-t)}$, area under the concentration–time curve from time zero to the last measurable concentration; $T_{1/2}$, terminal half-life; and λz, the elimination rate constant.

**Supplemental Table 3. Serious Adverse Events Assessed by Investigators as at Least Possibly Related to Therapy (MF-TG101348-001 and MF-TG101348-002)**

| Subject # | Event | Starting Dose/Dose at Event (mg/day) | Onset From Start of Dosing (days) | CTCAE Severity Grade | Action Taken With Study Drug | Outcome |
|---|---|---|---|---|---|---|
| 105-013 | Thrombocytopenia | 240/360 | 215 | 4 | None | Recovered/resolved |
| | Thrombocytopenia | 240/360 | 247 | 4 | Permanently discontinued | Not recovered/not resolved |
| | Hyperlipasemia | 240/0 | 356 | 4 | None | Recovered/resolved |
| 104-015 | Depression | 360/520 | 256 | 3* | Permanently discontinued | Not recovered/not resolved |
| 106-024 | Nausea | 800/680 | 87 | 2 | Stopped temporarily | Recovered/resolved |
| | Vomiting | 800/680 | 87 | 2 | Stopped temporarily | Recovered/resolved |
| | Diarrhea | 800/680 | 87 | 3 | Stopped temporarily | Recovered/resolved |
| | Dehydration | 800/680 | 87 | 2 | Stopped temporarily | Recovered/resolved |
| | Tumor lysis syndrome | 800/440 | 366 | 3 | Stopped temporarily | Recovered/resolved |
| | Dehydration | 800/400 | 474 | 3 | None | Recovered/resolved |
| 106-033 | Pleuritic pain | 680/680 | 8 | 2 | Stopped temporarily | Recovered/resolved |
| 106-045 | Dehydration | 680/440 | 170 | 3 | Stopped temporarily | Recovered/resolved |
| 101-047 | Neutropenia | 680/680 | 52 | 2 | Stopped temporarily | Recovered/resolved |
| 105-056 | Cerebrovascular accident | 680/680 | 22 | 4 | Stopped temporarily | Recovered/resolved |
| | Gallbladder pain | 680/520 | 95 | 3 | Stopped temporarily | Recovered/resolved with sequelae |
| 105-059 | Hyperlipasemia | 680/680 | 8 | 3 | Stopped temporarily | Recovered/resolved |
| | Hyperlipasemia | 680/520 | 28 | 3 | Stopped temporarily | Recovered/resolved |
| | Cardiac arrest | 680/360 | 42 | 5 | Permanently discontinued | Fatal |

*Subject died (suicide) approximately 12 weeks after discontinuation of study drug.
One subject presented with severe pulmonary hypertension and right heart failure during cycle 4 (at 240 mg/day); the event was considered unrelated to TG101348 per the investigator.

**Supplemental Table 4. Subjects discontinuing study due to death, toxicity, withdrawal of consent, or intercurrent illness**

**MF-TG101348-001 Reasons for Discontinuation**

| Subject | Starting Dose (mg/day) | Dose at Termination (mg/day) | Duration of Treatment (days) | Reason |
|---|---|---|---|---|
| 102-002 | 30 | 30 | 2 | Investigator discretion – previously undiagnosed cardiac condition with long $QT_c$ interval |
| 106-009 | 120 | 240 | 109 | Patient withdrew consent |
| 101-011 | 240 | 240 | 100 | Patient withdrew consent |
| 102-019 | 520 | 520 | 42 | Adverse event – neutropenia (grade 3; probably related) |
| 102-023 | 800 | 680 | 70 | Investigator discretion – recurrent Waldenstrom's macroglobulinemia |
| 104-027 | 800 | 680 | 77 | Adverse event – thrombocytopenia (grade 4; possibly related) |
| 106-028 | 800 | 520 | 44 | Adverse event – thrombocytopenia (grade 4; possibly related) |
| 104-029 | 680 | 680 | 44 | Adverse event – endocarditis (grade 3; not related), embolic stroke (grade 3; not related) |
| 101-032 | 680 | 680 | 8 | Investigator discretion – Acquired factor VIII inhibitor |
| 101-040 | 680 | 520 | 24 | Adverse events – diarrhea (grade 3; possibly related) |
| 103-043 | 680 | 360 | 68 | Patient withdrew consent |
| 103-046 | 680 | 680 | 26 | Patient withdrew consent |
| 102-051 | 680 | 600 | 108 | Patient withdrew consent |
| 102-054 | 680 | 680 | 75 | Patient withdrew consent |
| 105-059 | 680 | 360 | 27 | Adverse event – cardiac arrest (grade 5; possibly related) |

**MF-TG101348-002 Reasons for Discontinuation**

| Subject | Starting Dose (mg/day) | Dose at Termination (mg/day) | Cumulative Duration of Treatment (days) | Reason |
|---|---|---|---|---|
| 101-005 | 60 | 360 | 196 | Investigator discretion – lack of response to treatment |
| 106-010 | 120 | 520 | 185 | Investigator discretion |
| 105-013 | 240 | 360 | 321 | Adverse event – thrombocytopenia (grade 4; possibly related) |
| 104-015 | 360 | 520 | 257 | Adverse event – depression (grade 3; possibly related) |
| 106-016 | 360 | 680 | 527 | Investigator discretion – lack of response to treatment |
| 104-017 | 520 | 200 | 309 | Investigator discretion – disease progression |
| 105-021 | 680 | 520 | 357 | Patient withdrew consent |
| 101-047 | 680 | 320 | 233 | Adverse event – elevated creatinine (grade 2; possibly related) |

**Supplemental Table 5. Change in weight during study treatment**

| Weight (kg) | Baseline | | 6 Cycles | | 12 Cycles | |
|---|---|---|---|---|---|---|
| | **Overall (n=57)** | **MTD Cohort (n=38)** | **Overall (n=43)** | **MTD Cohort (n=28)** | **Overall (n=36)** | **MTD Cohort (n=26)** |
| **Median (range)** | 75.6 (48.2-105.2) | 77.7 (48.2-96.1) | 76.9 (51.4-105.8) | 77.7 (51.4-97.6) | 76.1 (49.8-106.8) | 76.5 (49.8-99.5) |
| **Change from baseline Median (range)** | n/a | n/a | 0.4 (-11.7-8.9) | 0.6 (-9.2-8.9) | 0.7 (-10.7-13.7) | 0.35 (-10.7-13.7) |

kg indicates kilograms; n, number, and MTD, maximum tolerated dose