FIG. 1

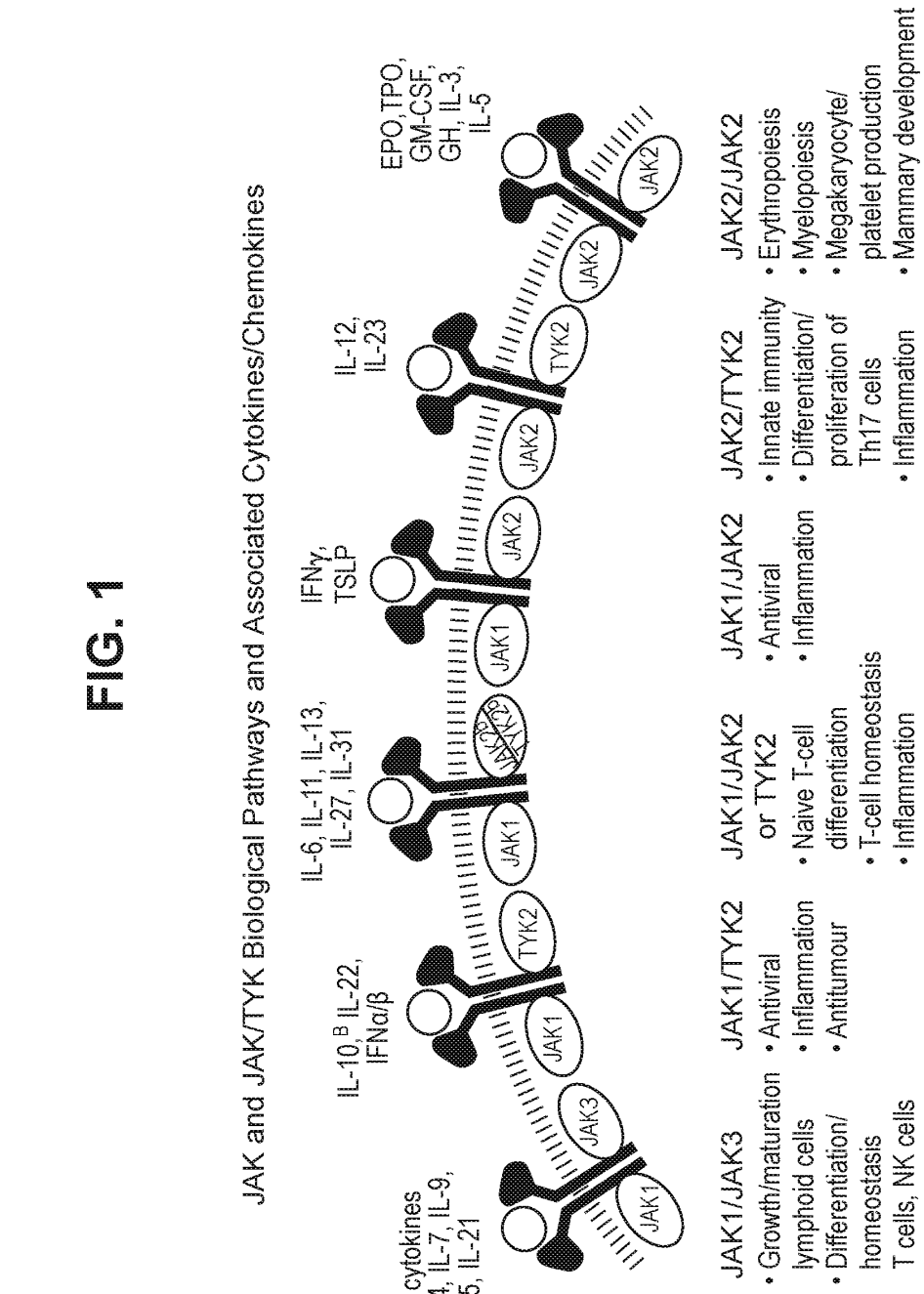

JAK and JAK/TYK Biological Pathways and Associated Cytokines/Chemokines
γ-chain cytokines
IL-2, IL-4, IL-7, IL-9,
IL-15, IL-21
IL-10, B IL-22,
IFNα/β
IL-6, IL-11, IL-13,
IL-27, IL-31
IFNγ,
TSLP
IL-12,
IL-23
EPO,TPO,
GM-CSF,
GH, IL-3,
IL-5
JAK1
JAK3
TYK2
JAK2
Function
JAK1/JAK3
• Growth/maturation lymphoid cells
• Differentiation/ homeostasis T cells, NK cells
• B-cell class switching
• Inflammation
JAK1/TYK2
• Antiviral
• Inflammation
• Antitumour
JAK1/JAK2 or TYK2
• Naive T-cell differentiation
• T-cell homeostasis
• Inflammation
• Granulopoiesis
JAK1/JAK2
• Antiviral
• Inflammation
JAK2/TYK2
• Innate immunity
• Differentiation/ proliferation of Th17 cells
• Inflammation
JAK2/JAK2
• Erythropoiesis
• Myelopoiesis
• Megakaryocyte/ platelet production
• Mammary development

FIG. 2

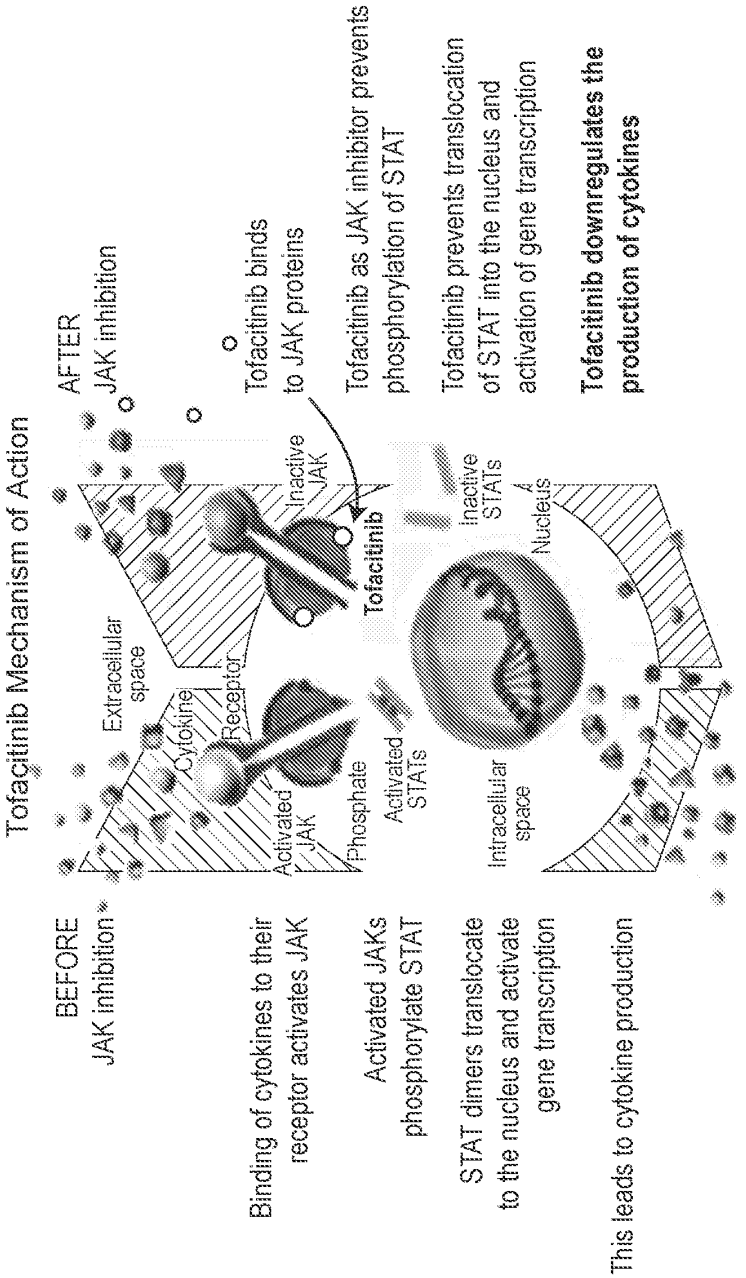

Tofacitinib Mechanism of Action
BEFORE JAK inhibition
AFTER JAK inhibition
Extracellular space
Cytokine
Receptor
Activated JAK
Phosphate
Inactive JAK
Tofacitinib
Activated STATs
Inactive STATs
Nucleus
Intracellular space
Tofacitinib binds to JAK proteins
Tofacitinib as JAK inhibitor prevents phosphorylation of STAT
Tofacitinib prevents translocation of STAT into the nucleus and activation of gene transcription
Tofacitinib downregulates the production of cytokines
Binding of cytokines to their receptor activates JAK
Activated JAKs phosphorylate STAT
STAT dimers translocate to the nucleus and activate gene transcription
This leads to cytokine production

FIG. 3

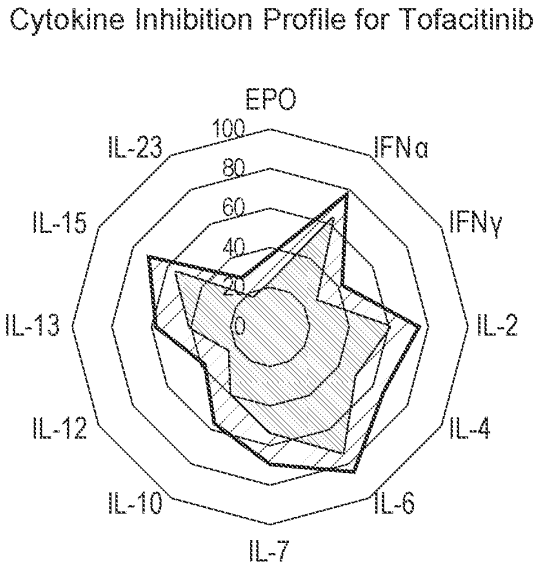

Cytokine Inhibition Profile for Tofacitinib
EPO
IFNα
IFNγ
IL-2
IL-4
IL-6
IL-7
IL-10
IL-12
IL-13
IL-15
IL-23
100
80
60
40
20
0

FIG. 4

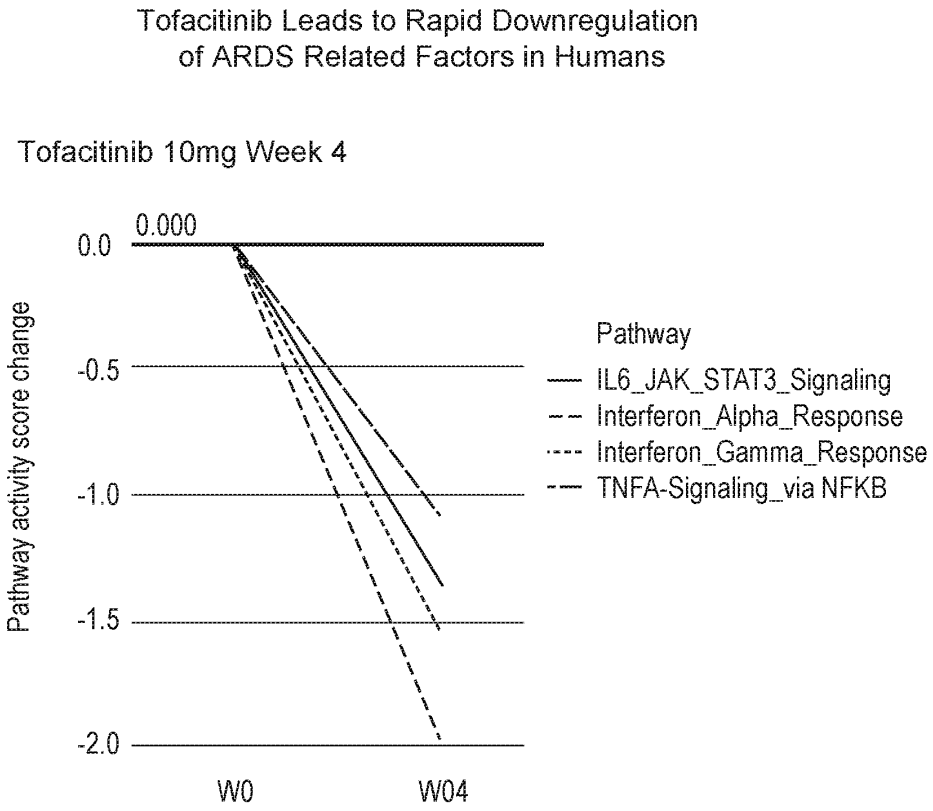

Tofacitinib Leads to Rapid Downregulation
of ARDS Related Factors in Humans
Tofacitinib 10mg Week 4
0.000
0.0
-0.5
-1.0
-1.5
-2.0
Pathway activity score change
W0
W04
Pathway
IL6_JAK_STAT3_Signaling
Interferon_Alpha_Response
Interferon_Gamma_Response
TNFA-Signaling_via NFKB

FIG. 5A

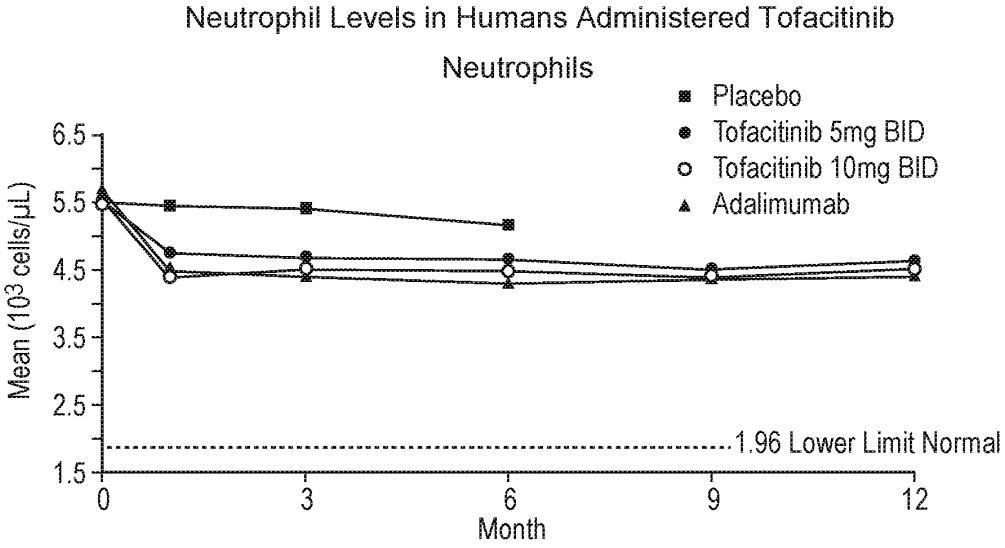

Neutrophil Levels in Humans Administered Tofacitinib
Neutrophils
Placebo
Tofacitinib 5mg BID
Tofacitinib 10mg BID
Adalimumab
Mean (10^3 cells/µL)
6.5
5.5
4.5
3.5
2.5
1.5
1.96 Lower Limit Normal
0
3
6
9
12
Month

FIG. 5B

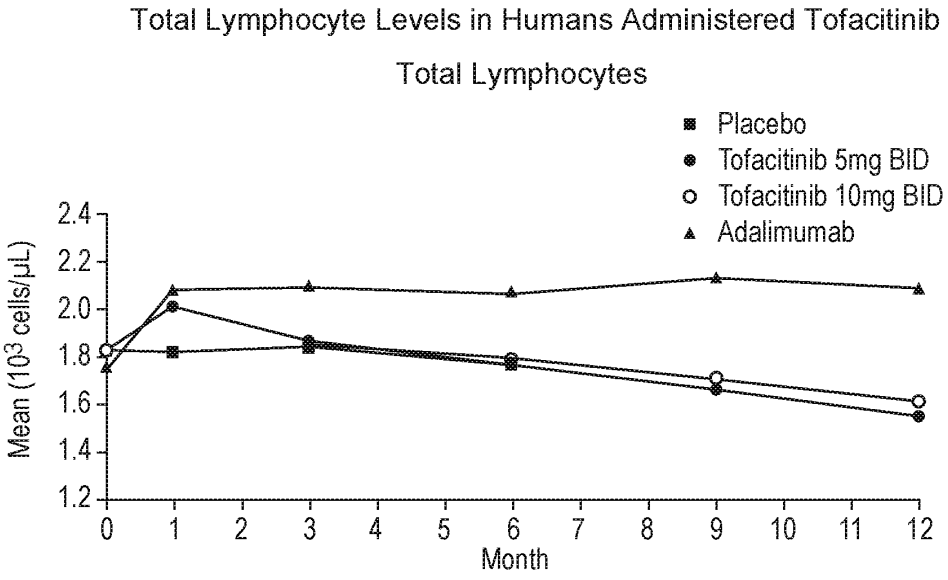

Total Lymphocyte Levels in Humans Administered Tofacitinib
Total Lymphocytes
Placebo
Tofacitinib 5mg BID
Tofacitinib 10mg BID
Adalimumab
Mean (10^3 cells/µL)
2.4
2.2
2.0
1.8
1.6
1.4
1.2
0
1
2
3
4
5
6
7
8
9
10
11
12
Month

FIG. 6

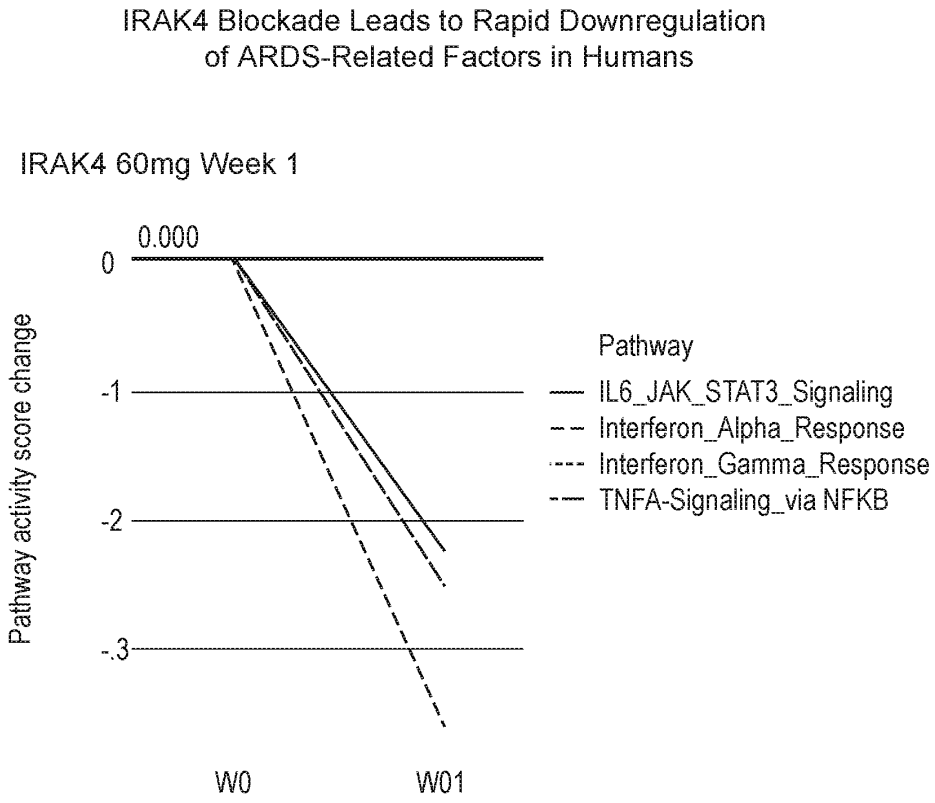

IRAK4 Blockade Leads to Rapid Downregulation
of ARDS-Related Factors in Humans
IRAK4 60mg Week 1
0.000
0
-1
-2
-.3
Pathway activity score change
W0
W01
Pathway
IL6_JAK_STAT3_Signaling
Interferon_Alpha_Response
Interferon_Gamma_Response
TNFA-Signaling_via NFKB

FIG. 7A

Proposed 10 mg Tofacitinib
Phase 2 Clinical Study Design for Treating COVID-19

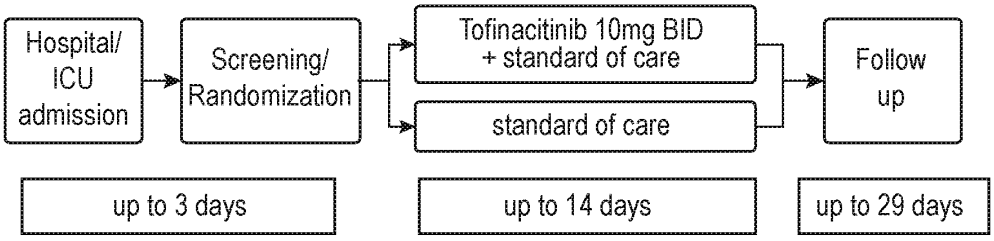


FIG. 7B

Proposed 400 mgs PF-06650833
Phase 2 Clinical Study Design for Treating COVID-19

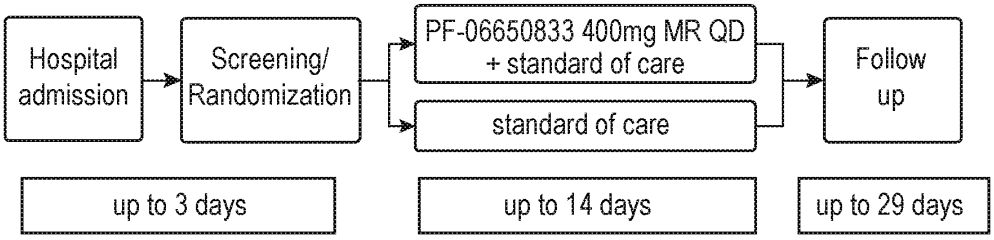


FIG. 7C

Proposed 200 mgs PF-06650833
Phase 2 Clinical Study Design for Treating COVID-19

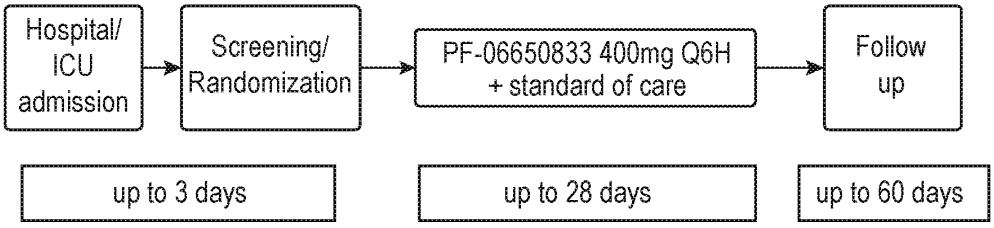


FIG. 8

Proposed 400 mgs PF-06650833
Phase 2 Clinical Study Design for Treating COVID-19
(Example 4)

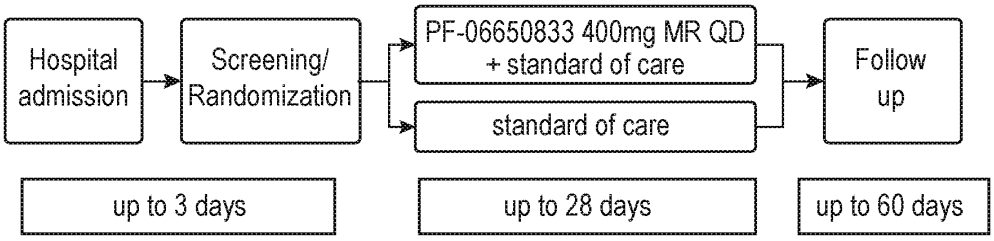


FIG. 9

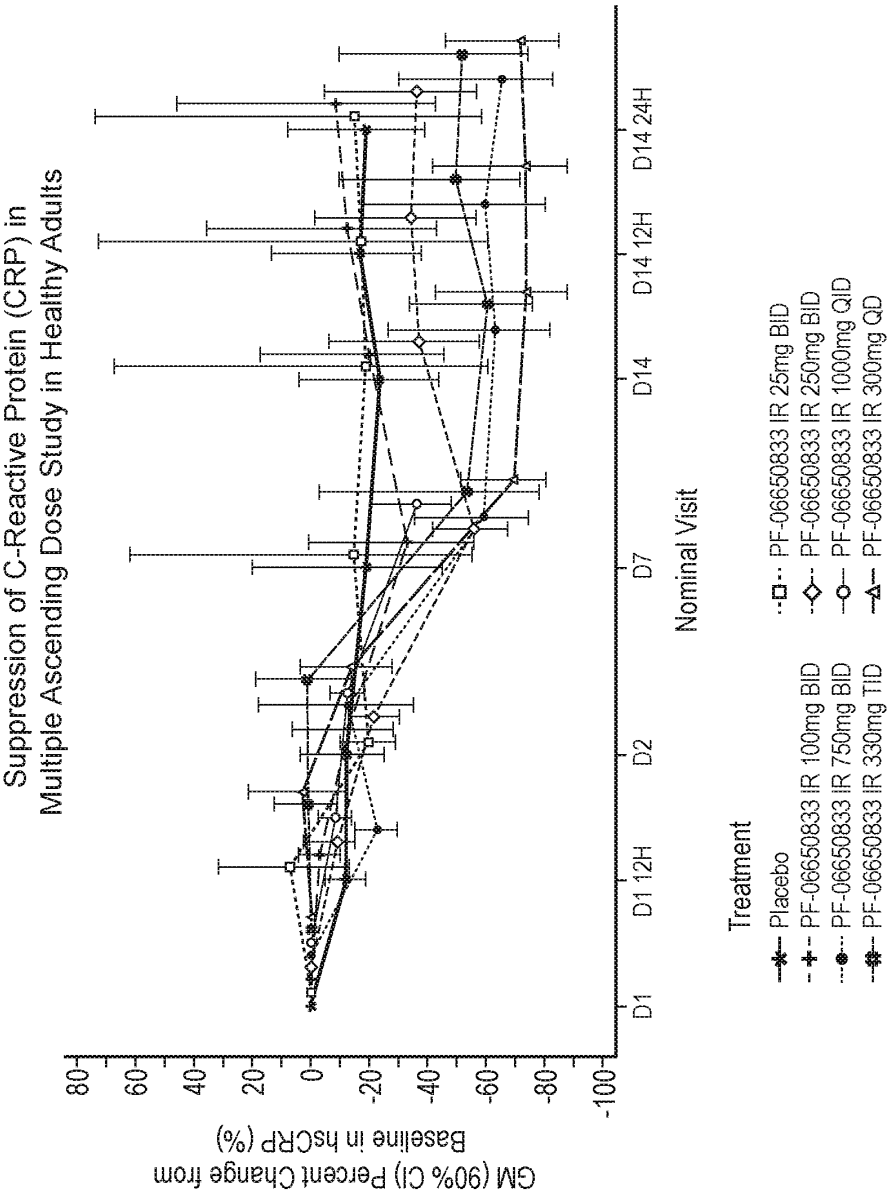

Suppression of C-Reactive Protein (CRP) in
Multiple Ascending Dose Study in Healthy Adults
GM (90% CI) Percent Change from
Baseline in hsCRP (%)
80
60
40
20
0
-20
-40
-60
-80
-100
D1
D1 12H
D2
D7
D14
D14 12H
D14 24H
Nominal Visit
Treatment
Placebo
PF-06650833 IR 100mg BID
PF-06650833 IR 750mg BID
PF-06650833 IR 330mg TID
PF-06650833 IR 25mg BID
PF-06650833 IR 250mg BID
PF-06650833 IR 1000mg QID
PF-06650833 IR 300mg QD

FIG. 10

IRAK Mechanism of Action

