

P CrPĩP°C,P°PrPěPS PSp°P»PµP¶PěC,CH PrPs PrCĤCřPiPsPiPs PĩPsPePsP»C-PSPSCĬ
P°PSC,PěPiC-CĬC,P°PjC-PSPSPěC... PiCĤPµPiP°CĤP°C,C-PI C- C" P°PSC,P°PiPsPSC-CĬC,Pj
PiC-CĬC,P°PjC-PSCř C,CĤPěPiP°P»PsC— PrC-C— P· PIPěP±C-CĤPePsPIPsCĤ
PiPµCĤPěC,,PµCĤPěC‡PSPsCĤ P°PSC,P°PiPsPSC-CĬC,PěC‡PSPsCĤ P°PeC,PěPiPSC-CĬC,CĤ PrPs
Pĕ,-CĤPµC†PµPiC,PsCĤC-PI. P"PµCĬPeC- P· PNePsPiPs PjPµC,P°P±PsP»C-C,C-PI
(PrPµP·P»PsCĤP°C,P°PrPěPS C- PNePsPiPs PiC-PrCĤPsPeCřPěP»CHPsPIP°PSC-
PjPµC,P°P±PsP»C-C,Pě) P·P±PµCĤC-PiP°CĤC,CH P°PSC,PěPiC-CĬC,P°PjC-PSPSCř

P°PeC, PēPIPS-ClC, CH C- PjPsP¶CfC, CH C†P°ClC, PePsPIPs C¶PsP±PēC, Pē ClPIC-PMē
PIPSµClPsPe PrPs P·P°PiP°P»CHPSPsC— PµC,, PµPeC, PēPIPSsClC, C- PīC¶PµPīP°C¶P°C, Cr.

P°PsClP»C-PrP¶PµPSPSC¶ C¶CfPīP°C, P°PrPēPSCr *in vitro* Cr PIPēClPsPeC-PMē
PePsPSC†PµPSC, C¶P°C†C-C— PīPsPeP°P·P°P»Pē PiP°P»CHPjCfPIP°PSPSC¶
PrPµPiC¶P°PSCfP»C¶C†C-C— PsPīP°ClPēClC, PēC... PeP»C-C, PēPS, ClPīC¶PēC†PēPSPµPSPµ
C-PjCfPSPsP»PsPiC-C†PSPēPjPē C- PSPµC-PjCfPSPsP»PsPiC-C†PSPēPjPē
PīPsPrC¶P°P·PSPēPeP°PjPē, P° C, P°PePsP¶ PIPēC...C-Pr C†PēC, PsPeC-PSC-PI, P·PsPeC¶PµPjP°
TNF_a, C-P· PsPīP°ClPēClC, PēC... PeP»C-C, PēPS C- PjPsPSPsC†PēC, C-PI P»CHPrPēPSPē.
PµP»C-PSC-C†PSPµ P·PSP°C†PµPSPSC¶ ClPīPsClC, PµC¶PµP¶CfPIP°PSPēC...
PµPeClPīPµC¶PjPµPSC, P°P»CHPSPēC... PrP°PSPēC... C%Pµ C, C-P»CHPePē
PSP°P»PµP¶PēC, CH PiC-PrC, PIPµC¶PrPēC, Pē.

PµC-Pr C†P°Cl PeP»C-PSC-C†PSPēC... PrPsClP»C-PrP¶PµPSC¶ P·P°ClC, PsClCfPIP°PSPSC¶
C¶CfPīP°C, P°PrPēPSCr Cr PrPsP·C- PIC-Pr 2 PjPi PrPs 100 PjPi Cr PrPsP±C¶PsPIPsP»CHC†C-PI
(n=375) C, P° PiP°C†C-C°PSC, C-PI (n=2650) P· P°P»PµC¶PiC-C†PSPēPj C¶PēPSC-C, PsPj C, P°
C...C¶PsPSC-C†PSPsC¶ C-PrC-PsPīP°C, PēC†PSPsC¶ PeC¶PsPīPēPIb¶™ ClPSPePsC¶ PSPµ
P±CfP»Ps PIPēC¶PIP»PµPSPs P·PSP°C†PSPsPiPs PIPīP»PēPICr PīC¶PµPīP°C¶P°C, Cr PSP°
C¶PµP·CfP»CHC, P°C, Pē PµP»PµPeC, C¶PsPeP°C¶PrC-PsPiC¶P°C,, C-C†PSPsPiPs
PrPsClP»C-PrP¶PµPSPSC¶.

P¶C¶PsPSC-C†PSP° C-PrC-PsPīP°C, PēC†PSP° PeC¶PsPīPēPIb¶™ ClPSPeP°
PrPsClP»C-PrP¶CfPIP°P»P°ClC¶ PI CrPjPsPIP°C... PeP»C-PSC-C†PSPsC— PjPsPrPµP»C-
P·P°C...PIPsC¶C¶PIP°PSPSC¶, PsClPeC-P»CHPePē, PSPµP·PIP°P¶P°C¶C†Pē PSP°
PµC, C-PsP»PsPiC-C¶, PīP°C, PsC,, C-P·C-PsP»PsPiC-C¶ P·P°C...PIPsC¶C¶PIP°PSPSC¶
P·P°P»PēC¶P°C°C, CHClC¶ C, P°PePsC¶ P¶, P° C, P°PePsP¶ C, PsPjCr C%Ps PI
PīPµC¶CfPīPµPeC, PēPIC- PīP°C†C-C°PSC, C-PI C-P· C...C¶PsPSC-C†PSPsC¶ C,, PsC¶PjPsC¶
P±CfPrPµ P»PµPiC¶Pµ P·P°P»CrC†PēC, Pē PrPs CrC†P°ClC, C- Cr PrPsClP»C-PrP¶PµPSPSC-.
P¶PµC¶PµP· C, Pµ C%Ps PIPēPIC-P»CHPSPµPSPSC¶ PiC-ClC, P°PjC-PSCr C°
PīC¶PēC†PēPSPSPēPj C,, P°PeC, PsC¶PsPj CrClC-C... PīC¶PsC¶PIC-PI PeC¶PsPīPēPI'ClPSPePē,
PsC†C-PeCrC°C, CHClC¶ PµC,, PµPeC, PēPIPS-ClC, CH C¶CfPīP°C, P°PrPēPSCr PīC¶Pē
PīC¶PsPIPµPrPµPSPSC- ClPēPjPiC, PsPjP°C, PēC†PSPsC— C, PµC¶P°PiC-C—
C...C¶PsPSC-C†PSPsC— C-PrC-PsPīP°C, PēC†PSPsC— PeC¶PsPīPēPI'ClPSPePē C, P° C-PSC¶PēC...
PīC¶PsC¶PIC-PI PeC¶PsPīPēPI'ClPSPePē, ClPe C†Pµ PIPeP°P·P°PSPs Cr PeP»C-PSC-C†PSPēC...
PSP°ClC, P°PSPsPIP°C....

PµC-Pr C†P°Cl PīP»P°C†PµP±Ps-PePsPSC, C¶PsP»CHPsPIP°PSPēC... PrPsClP»C-PrP¶PµPSC¶
C...C¶PsPSC-C†PSPsC— C-PrC-PsPīP°C, PēC†PSPsC— PeC¶PsPīPēPIb¶™ ClPSPePē
C¶CfPīP°C, P°PrPēPS PµC,, PµPeC, PēPIPSs P·PSPēP¶CfPIP°PI ClPµC¶PµPrPSC-PMē P±P°P»
ClPēPjPiC, PsPjC-PI (P·PSPēP¶PµPSPSC¶ PīPsC¶C-PIPSClPSPs C-P· PīPsC†P°C, PePsPIPēPjPē
PīPsPeP°P·PSPēPeP°PjPē: C¶CfPīP°C, P°PrPēPS B b¶" B 57,5 %, B PīP»P°C†PµP±Ps B b¶" B 44,8
) B C, P° B ClPµC¶PµPrPSC¶ B PeC-P»CHPeC-ClC, CH B PIPēClPēPīP°PSC¶ B (54,3 %
B PīPsC¶C-PIPSClPSPs B P·

39,7 %) C†PµC¶PµP· C†PsC, PēC¶Pē C, PēP¶PSC- P»C-PeClPIP°PSPSC¶.

P°P°C¶PjP°PePsPeC-PSPµC, PēPeP°.

P¶P±ClPsC¶P±C†C-C¶ C- P±C-PsP»PsPiC-C†PSP° PrPsClC, CrPīPSC-ClC, CH.

P CrPīP°C, P°PrPēPS C¶PIPēPrPePs PICrPjPsPeC, CrC°C, CHClC¶ PiC-ClP»C¶
PīPµC¶PsC¶P°P»CHPSPsPiPs PīC¶PēPMēPsPjCr, t_{max} ClC, P°PSPsPIPēC, CH PīC¶PēP±P»PēP·PSPs

B B B B B B B B B B B B B B B B 0,75 PiPsPrPëPSPë PïC-Cl'P»Cł PïChjPëPNëPsPjCr
C,P°P±P»PμC,PePë. PŸPμCĤjPμPrPSCł PŸ_{max} Cl'C,P°PSPsPIPëP»P° 2,6 PSPi/PjP» PïC-Cl'P»Cł
PsPrPSPsCĤjP°P·PsPIPSPiPs PïChjPëPNëPsPjCr PïPμCĤjPsCĤjP°P»CHßPSPsC— PrPsP·Pë 10 PjPi C- 4,6
PSPi/PjP» PïC-Cl'P»Cł PsPrPSPsCĤjP°P·PsPIPSPiPs PïPμCĤjPsCĤjP°P»CHßPSPsPiPs
PïChjPëPNëPsPjCr PrPsP·Pë B B B B B B B B B B B B B B 20 PjPi.
PαP°CĤjPjP°PePsPeC-PSPμC,PëPeP° CĤjCrPïP°C,P°PrPëPSCr P±CrP»P° P»C-PSC-PNëPSPsCĤ
PrP»Cł PrPsP· PIC-Pr 10 PrPs 40 PjPi. PμC-Cl'P»Cł PïChjPëPNëPsPjCr PrPsP·Pë 10 PjPi PsPrPëPS
CĤjP°P· PSP° PrPsP±Cr PïChjPsC,CłPiPsPj 7 PrPSC-PI Cl'PμCĤjPμPrPSCł PŸ_{max}
Cl'C,P°PSPsPIPëP»P° 3,8 PSPi/PjP». PñPsPSC†PμPSC,CĤjP°C†C-Cł PI PïP»P°P·PjC-
P·PSPëP¶CrPIP°P»P°CłCł P·P° P±C-PμPeCl'PiPsPSPμPSC†C-P°P»CHßPSPsCĤ PeCĤjPëPIPsCĤ P·
Cl'PμCĤjPμPrPSC-Pj PïPμCĤjC-PsPrPsPj PSP°PïC-PIIPëPIPμPrPμPSPSCł 5,9 PiPsPrPëPSPë.
PñPsPμC,,C-C†C-C"PSC, P·PI'CłP·CrPIP°PSPSCł CĤjCrPïP°C,P°PrPëPSCr P· P±C-P»PeP°PjPë
PïP»P°P·PjPë Cl'C,P°PSPsPIPëPI 98,5BĤ"99 %.

PhCfPSP±P»PëPIC- PiCfCfPiPë PiP°C+C-C"PSC,C-PI

PJ C...PsPrC- PrPsCfP»C-PrP¶PµPSPSC¶ P·P° CrC±P°CfC,Ch P·PrPsCfPSPiPëC...
PrPsP±CfPSPiPSP»ChC†C-PI PrP»C¶ PiPsCfC-PIPSC¶PSPSC¶ C¶PµP·CfP»ChC,P°C,C-PI,
PsC,C¶PëPjP°PSPëC... Cr PjPsP»PsPrPëC... PrPsCfPSPiP»PëC... PsCfC-P± C,P° PsCfC-P±
P»C-C,PSCHbPsPiPs PIC-PeCr, PiPµP»PëC±PëPSPë AUC C- PŸ_{max} C¶CfPiP°C,P°PrPëPSCr
P±CfP»Pë PiPëC%PëPjPë Cr PsCfC-P± P»C-C,PSCHbPsPiPs PIC-PeCr Cr
PiPsCfC-PIPSC¶PSPSC- P· PrP°PSPëPjPë, PsC,C¶PëPjP°PSPëPjPë Cr PjPsP»PsPrPëC...
PrPsCfPSPiP»PëC... PsCfC-P±. PTM PjPsPIC-C¶PSPs, C†Pµ PsP±CfPjPsPiP»PµPSPs
P·PSPëP¶PµPSPSC¶Pj PiPµC†C-PSPePsPiPsPjPµC,P°P±PsP»C-P·PjCr PiC¶Pë PiPµC¶C¶PsPjCr
PiC¶PSPC...PsPrP¶PµPSPSC- C†PµC¶PµP· PiPµC†C-PSPeCr Cr PsCfC-P± P»C-C,PSCHbPsPiPs
PIC-PeCr. P©PsPrPs B PjPµC,P°P±PsP»C-C,C-PI PIC-PrPjC-PSPSPsCfC,PµPNë PjC-P¶
PiPsPeP°P·PSPëPeP°PjPë AUC C- PŸ_{max} Cr PjPsP»PsPrPëC... PrPsCfPSPiP»PëC... PsCfC-P± C,P°
PsCfC-P± P»C-C,PSCHbPsPiPs PIC-PeCr PSPµ C¶PiPsCfC,PµC¶C-PiP°P»PsCfC¶.
PŸPµC¶PµPrPSC-PNë PiPµC¶C-PsPr PSP°PiC-PIPiPëPiPµPrPµPSPSC¶ C¶CfPiP°C,P°PrPëPSCr Cr
P»C-C,PSC-C... C- Cr PjPsP»PsPrPëC... PrPsP±CfPSPiPSP»ChC†C-PI CfC,P°PSPsPiPëPI 8,7
PiPsPrPëPSPë C- 5,9 PiPsPrPëPSPë PIC-PrPiPsPIC-PrPSPs. PhCfPeC-P»ChPePë
C¶PµP·CfP»ChC,P°C,Pë PrP»C¶ C¶CfPiP°C,P°PrPëPSCr C- PrP»C¶ PNëPsPiPs
PjPµC,P°P±PsP»C-C,C-PI PSPµ P±CfP»Pë PeP»C-PSC-C†PSPs P·PSP°C±CfC%PëPjPë, P±CfPI
P·C¶PSP±P»PµPSPëPNë PiPëCfPSPsPiPsPe, C%Ps PiC¶Pë PiC¶PëP·PSP°C†PµPSPSC- 10 PjPi
P»C-PeP°C¶CfChPePsPiPs P·P°CfPSP±Cf PiP°C+C-C"PSC,P°Pj P»C-C,PSCHbPsPiPs PIC-PeCr
PePsC¶PµPeC†C-C¶ PrPsP·Pë PSPµ PiPsC,C¶C-P±PSP°.

P"PsPeP»C-PSC-C†PSC- PrP°PSC- P· P±PµP·PiPµPePë

P"°PSC- PrPsPeP»C-PSC-C†PSPëC... PrPsCfP»C-PrP¶PµPSCHb PSPµ PiPeP°P·CfChC,Ch PSP°
C-CfPSCrPiP°PSPSC¶ PsCfPSP±P»PëPiPsPiPs C¶PëP·PëPeCr PrP»C¶ P»ChPrCfChPePsPiPs
PsC¶PiP°PSC-P·PjCr PSP° PiC-PrCfC,P°PIC- CfC,P°PSPrP°C¶C,PSPëC...
PrPsCfP»C-PrP¶PµPSCHb C,,P°C¶PjP°PePsP»PsPiC-C†PSPsC— C,PsPeCfPëC†PSPsCfC,C- PiC¶Pë
PiPsPIC,PsC¶PSPsPjCr P·P°CfC,PsCfCfPiP°PSPSC-, PiPµPSPsC,PsPeCfPëC†PSPsCfC,C- C,P°
PeP°PSC†PµC¶PSPiPµPSPSPsCfC,C-.

P"PsP·Pë C¶CfPiP°C,P°PrPëPSCr, C%Ps Cr 100 C¶P°P·C-PI PiPµC¶PµPiPëC%CrPiP°P»Pë
C¶PµPePsPjPµPSPrPsPiP°PSCr PeP»C-PSC-C†PSCr PrPsP·Cr (10 PjPi), PSPµ PiPiP»PëPiP°P»Pë
PSP° C-PSC,PµC¶PiP°P»Pë QTc C,P° QRS C- PSPµ C¶PiC¶PëC†PëPSC¶P»Pë C¶PëPjPiC,PsPjC-PI
P°C¶PëC,PjC-C— Cr C¶C-P·PSPëC... PiPëPrC-PI C,PIP°C¶PëPS, PSP°PiC¶PëPeP»P°Pr Cr
C%CrC¶C-PI, PjPsC¶CfChPePëC... C¶PiPëPSPsPe C,P° C¶PsP±P°Pe. P CrPiP°C,P°PrPëPS C,P°
PNëPsPiPs PsCfPSPsPiPSPëPNë PjPµC,P°P±PsP»C-C, PI PsC¶PiP°PSC-P·PjC- P»ChPrPëPSPë, 3-
PiC-PrC¶PSPeCfPëPrPµP·P»PsC¶P°C,P°PrPëPS, PSPµ PiPiP»PëPiP°ChC,Ch PSP°
PiPsC,PµPSC†C-P°P» PrC-C— C¶PµC¶C†PµPiPsPj'CiP·Cr Cr PiPsP»PsPePSP°C...
PµCrC¶PeC-PSCHb" C¶PsP±P°Pe Cr PePsPSC†PµPSC,C¶P°C†C-C¶C..., C%Ps PjC-PSC-PjCrPj Cr
2000 C¶P°P·C-PI PiPëC%C- P·P° PjP°PeCfPëPjP°P»ChbPSCr PePsPSC†PµPSC,C¶P°C†C-Ch PI
PiP»P°P·PjC- P»ChPrPëPSPë PiC¶Pë P·P°CfC,PsCfCfPiP°PSPSC- 10 PjPi PiC¶PµPiP°C¶P°C,Cr.
PµC-Pr C†P°Cf PrPsCfP»C-PrP¶PµPSPSC¶ PiPiP»PëPiCr C¶CfPiP°C,P°PrPëPSCr PSP°
PeP»PsPSPsPiP°PSPëPNë PiPµPS C¶PiPµC†PëC,,C-C†PSPsPiPs PeP°P»C-C"PiPsPiPs PeP°PSP°P»Cr
C¶PµC¶C†C¶ PIC-PS PiC¶PëPiPSC-C†CfPiP°PI C†PµPNë PeP°PSP°P» Cr
PePsPSC†PµPSC,C¶P°C†C-C—, C%Ps P±CfP»P° Cr 1685 C¶P°P·C-PI PiPëC%PsCh P·P°
PjP°PeCfPëPjP°P»ChbPSCr PePsPSC†PµPSC,C¶P°C†C-Ch PI PiP»P°P·PjC-, CiPeP°
PrPsCfC¶PiP°P»P°CfC¶ PiC¶Pë P·P°CfC,PsCfCfPiP°PSPSC- 10 PjPi PiC¶PµPiP°C¶P°C,Cr.
P"µP·P»PsC¶P°C,P°PrPëPS, PjPµC,P°P±PsP»C-C, C-P· PSP°PNëPiPëC%PsCh
P°PeC,PëPiPSC-CfC,Ch, PSPµ C†PëPSPëC,Ch P¶PsPrPSPsPiPs PiPiP»PëPiCr PiC¶Pë

PePsPSC†PμPSC, CḡP°C†C-C— 10 PjPePḡPsP»CH/P». B P"PsCÍP»C-PrP¶PμPSPSC¶
CḡPsP·PīPsPrC-P»CÍ PI C, PeP°PSPëPSP°C... C%oCÍCḡC-PI CḡP°PrC-PsP°PeC, PëPIPSPs
PjC-C†PμPSPsPiPs CḡCÍPīP°C, P°PrPëPSCÍ PīPsPeP°P·P°P»Pë, C%oPs PIC-PS PSPμ
PSP°PePsPīPëC†CÍ"C, CHCÍC¶ PI C, PeP°PSPëPSP°C... CÍPμCḡC†C¶.

PŸPīPsCÍC, PμCḡC-PiP°P»PsCÍC¶ P·PSP°C†PSPμ P·PSPëP¶PμPSPSC¶
C,, PμCḡC, PëP»CHPSPsCÍC, C- C¶Pe CÍP°PjC†C-PI, C, P°Pe C- CÍP°PjPsPe C%oCÍCḡC-PI PīCḡPë
P·P°CÍC, PsCÍCÍPīP°PSPSC-B PrPsP·Pë 120 PjPi/PePi/PrPsP±CÍ, PePsP»Pë
PjP°PeCÍPëPjP°P»CHPSP° PePsPSC†PμPSC, CḡP°C†C-C¶ CÍ 268 CḡP°P·C-PI PIPëC%oP° P·P° C_{max}
PI PsCḡPiP°PSC-P·PjC- P»CHPrPëPSPë, C¶PeP° PrPsCÍC¶PiP°C"C, CHCÍC¶ PīCḡPë
P·P°CÍC, PsCÍCÍPīP°PSPSC- C, PμCḡP°PīPμPIC, PëC†PSPsC— PrPsP·Pë (10 PjPi/PrPsP±CÍ).
PμPsPIC-PrPsPjP»C¶P»PsCÍC¶ PīCḡPs C, PsPeCÍPëC†PSPëPNë PIPīP»PëPI PSP° PīP»C-Pr
(P·P°C, CḡPëPjPeP° CḡPsP·PIPëC, PeCÍ, PSPμPīPsPIPSPμ CÍC, PIPsCḡPμPSPSC¶
PeC-CÍC, PePsPIPSC— CḡPμC†PsPIPëPSPë, PSPμP·PSP°C†PSC- PIC-PrC...PëP»PμPSPSC¶
CḡPsP·PIPëC, PeCÍ CÍPePμP»PμC, P°) CÍ C%oCÍCḡC-PI PīCḡPë C, PsPeCÍPëC†PSPëC... PrP»C¶
CÍP°PjPsPe PrPsP·P°C... (25 C, P° 120 PjPi/PePi/PrPsP±CÍ). PμC-Pr C†P°CÍ
PrPsCÍP»C-PrP¶PμPSCḡ PSP° PeCḡPsP»C¶C... C, PsPeCÍPëC†PSPëPNë PIPīP»PëPI PSP°
CḡPsP·PIPëC, PsPe CÍPīPsCÍC, PμCḡC-PiP°PICÍC¶ PīCḡPë P·P°CÍC, PsCÍCÍPīP°PSPSC- PrPsP·
PrPs 100 PjPi/PePi. P C-PIPμPSCḡ, C%oPs PSPμ PIPëPeP»PëPeP°C" C€PeC-PrP»PëPIPsC—
PrC-C—, PrP»C¶ C%oCÍCḡC-PI CÍC, P°PSPsPIPëC, CH 5 PjPi/PePi/PrPsP±CÍ, P° PrP»C¶
PeCḡPsP»C-PI Bḡ" 100 PjPi/PePi/PrPsP±CÍ, PīCḡPë C†CHPsPjCÍ C_{max} PIC-PrPīPsPIC-PrPSPs CÍ 45
C, P° 116 CḡP°P·C-PI PIPëC%oP° P·P° PePsPSC†PμPSC, CḡP°C†C-Cḡ, C%oPs
PrPsCÍC¶PiP°C"C, CHCÍC¶ PīCḡPë P·P°CÍC, PsCÍCÍPīP°PSPSC- C, PμCḡP°PīPμPIC, PëC†PSPsC—
PrPsP·Pë, CÍ P»CHPrPëPSPë (10 PjPi/PrPsP±CÍ).

РљР»С-РSC-С†РSC- С...Р°СḡР°РeС, РμСḡРëСÍС, РëРeРë.

PμPsPeP°P·P°PSPSC¶.

PŸPëPjPiC, PsPjP°C, PëC†PSPμ P»C-PeCÍPIP°PSPSC¶ P°P»PμCḡPiC-C†PSPsPiPs CḡPëPSC-C, CÍ C-
PeCḡPsPīPëPIBḡ™ C¶PSPePë CÍ PrPsCḡPsCÍP»PëC... C, P° PīC-PrP»C-C, PeC-PI PIC-PePsPj PIC-Pr
B B B B B B B B B B B B B 12 CḡPsPeC-PI.

PμCḡPsC, PëPīPsPeP°P·P°PSPSC¶.

P"C-PīPμCḡC†CÍC, P»PëPIC-CÍC, CH PrPs PrC-CHC†PsC— CḡPμC†PsPIPëPSPë P°P±Ps PrPs
P±CÍPrCH-C¶PePsPiPs C-PSC€PsPiPs PePsPjPīPsPSPμPSC, P° PīCḡPμPīP°CḡP°C, CÍ.

***P'P·P°C" PjPsPrC-C¶ P· C-PSC€PëPjPë P»C-PeP°CḡCÍCHPePëPjPë P·P°CÍPsP±P°PjPë C, P°
C-PSC€C- PIPëPrPë PIP·P°C" PjPsPrC-PNë.***

P'P·P°C" PjPsPrC-C¶ C, P°P±P»PμC, PsPe CḡCÍPīP°C, P°PrPëPSCÍ PīPs 10 PjPi C-P·
C-PSC€PëPjPë P»C-PeP°CḡCÍCHPePëPjPë P·P°CÍPsP±P°PjPë
PrPsCÍP»C-PrP¶CÍPIP°P»P°CÍCH CÍ PrPsCḡPsCÍP»PëC... C, P° PrC-C, PμPNë PIC-PePsPj
PIC-Pr 12 CḡPsPeC-PI.

P'PīP»PēPI C-PSC€Pēc... P»C-PeP°CḡCḡCHPePēc... P·P°CḡPsP±C-PI PSP° PrC-CH
CḡCḡPīP°C,P°PrPēPSCḡ

PŸP»C-Pr CrPSPēPeP°C,Pē CḡCrPīCrC,PSCHPsPiPs P·P°CḡC,PsCḡCrPIP°PSPSCḡ
PīPsC,CrPḡPSPēC... C-PSPiC-P±C-C,PsCḡC-PI CYP3A4 (PSP°PīCḡPēPeP»P°Pr
C-C,CḡP°PePsPSP°P·PsP»Cr, PePμC,PsPePsPSP°P·PsP»Cr, PIPsCḡPēPePsPSP°P·PsP»Cr,
PīPsP·P°PePsPSP°P·PsP»Cr, C-PSPiC-P±C-C,PsCḡC-PI P'P†P PīCḡPsC,PμP°P·Pē,
PeP»P°CḡPēc,CḡPsPjC-C†PēPSCr, PSPμC,,P°P·PsPrPsPSCr), P° PīPsPjC-CḡPSC-
C-PSPiC-P±C-C,PsCḡPē CYP3A4 (PμCḡPēc,CḡPsPjC-C†PēPS, C,,P»CrPePsPSP°P·PsP»,
PrPēP»C,C-P°P·PμPj) PīPsC,CḡC-P±PSPs P·P°CḡC,PsCḡPsPICrPIP°C,Pē P·
PsCḡPsP±P»PēPIPsCH PsP±PμCḡPμPḡPSC-CḡC,CH.

PŸCrPjC-CḡPSPμ PīCḡPēP·PSP°C†PμPSPSCḡ CḡCrPīP°C,P°PrPēPSCr Cr PrPsP·C- 20 PjPi
C- PePμC,PsPePsPSP°P·PsP»Cr P°P±Ps PμCḡPēc,CḡPsPjC-C†PēPSCr PīC-PrCḡPēP»CHC"
CḡPēcCḡC,PμPjPSCr PrC-CH CḡCrPīP°C,P°PrPēPSCr PI 10 CḡP°P·C-PI C- PI 2Bḡ"3
CḡP°P·Pē PIC-PrPīPsPIC-PrPSPs. P|C- PjPsPrPēc,,C-PeP°C†C-C— PSPμ
CḡCrPīCḡPsPIPsrPḡCrCHC,CHCḡCḡ P·PjC-PSP°PjPē C-PSC,PμCḡPIP°P»Cr QT P°P±Ps
P·P±C-P»CHC€PμPSPSCḡPj PīPsP±C-C†PSPēC... CḡPμP°PeC†C-PNḡ
PīPsCḡC-PIPSCḡPSPs P· PsPeCḡPμPjPēPj P·P°CḡC,PsCḡCrPIP°PSPSCḡPj
PIPeP°P·P°PSPēC... PīCḡPμPīP°CḡP°C,C-PI.

P'P·P°C" PjPsPrC-Cḡ P· PiCḡPμPNḡPīC,,CḡCḡC,PsPj

PḡPrPSPsC†P°CḡPSPēPNḡ PīCḡPēPNḡPsPj PiCḡPμPNḡPīC,,CḡCrC,PsPIPsrPiPs CḡPsPeCr PI
3,5 CḡP°P·P° PīC-PrCḡPēP»CHC" P·P°PīP°P»CHPSCr PrC-CH CḡCrPīP°C,P°PrPēPSCr.
PḡPμ CḡP»C-Pr PIPḡPēPIP°C,Pē PiCḡPμPNḡPīC,,CḡCrC,PsPIPēPNḡ CḡC-Pe
PsPrPSPsC†P°CḡPSPs P· PīCḡPēPNḡPsPjPsPj PīCḡPμPīP°CḡP°C,Cr.

P'PīP»PēPI CḡCḡPīP°C,P°PrPēPSCḡ PSP° C-PSC€C- P»C-PeP°CḡCḡCHPeC- P·P°CḡPsP±Pē

PŸP»C-Pr P· PsP±PμCḡPμPḡPSC-CḡC,CH P·P°CḡC,PsCḡPsPICrPIP°C,Pē
CḡCrPīP°C,P°PrPēPS C-P· C-PSC€PēPjPē PīCḡPμPīP°CḡP°C,P°PjPē P· PICrP·CHPePēPj
C,PμCḡP°PīPμPIC,Pēc†PSPēPj PrC-P°PīP°P·PsPSPsPj, PsCḡPeC-P»CHPePē
C-PSC,,PsCḡPjP°C†C-Cḡ PīCḡPs PNḡPsPiPs PIPīP»PēPI PSP° C†C- PīCḡPμPīP°CḡP°C,Pē
PsP±PjPμPḡPμPSP°.

P'P·P°C" PjPsPrC-Cḡ P· P°P»PePsPiPsP»PμPj

PμC-CḡP»Cḡ PīCḡPēPNḡPsPjCr P°P»PePsPiPsP»CH PrPsP·P° CḡCrPīP°C,P°PrPēPSCr 10 PjPi
PIPēCḡPIP»CḡC" PSPμP·PSP°C†PSPēPNḡ PIPīP»PēPI PSP° CḡPμP·CrP»CHC,P°C,Pē
PrPμCḡPePēc... C,PμCḡC,C-PI PSP° PīCḡPēc...PsPjPsC,PsCḡPSCr P°PeC,PēPIPSC-CḡC,CH, C%oPs
P·PSP°C†PSPs PSPμ PIC-PrCḡC-P·PSCḡC" C,CHCḡCḡ PIC-Pr PIPīP»PēPICr PīCḡPēPNḡPsPjCr
C,C-P»CHPePē PsPrPSPsPiPs P°P»PePsPiPsP»CH. P"PsP·P° 20 PjPi PīC-PrCḡPēP»CHPIP°P»P°
P·PjC-PSPē, CḡPīCḡPēc†PēPSPμPSC- PīCḡPēPNḡPsPjPsPj P°P»PePsPiPsP»CH.

P'P·P°C" PjPsPrC-Cḡ P· PrPμPīCḡPμCḡP°PSC,P°PjPē P|PḡPŸ

PīPe C- Cr CḡP°P·C- P·P°CḡC,PsCḡCrPIP°PSPSCḡ C-PSC€Pēc...
P°PSC,PēPiC-CḡC,P°PjC-PSPSPēC... PīCḡPμPīP°CḡP°C,C-PI, PSPμ PjPsPḡPSP°

PIPëPeP»CĤC±PëC,Pë PIP·P°C”PjPsPrC-C— P· PrPµPïCĤPµCĬP°PSC,P°PjPë P|PĳPŸ.

P'P·P°C”PjPsPrC-CĬ P·C- CĬC,P°C,PëPSP°PjPë

P'PµP·CĬPëPjPïC,PsPjPSPµ PïC-PrPIPëC%PµPSPSCĬ
PeCĤPµP°C,PëPSC,,PsCĬC,,PsPeC-PSP°P·Pë C-PSPsPrC- PIC-PrPjC-C±P°P»Pë PïC-Pr
C±P°CĬ PeP»C-PSC-C±PSPëC... PrPsCĬP»C-PrP¶PµPSCĤ CĤCřPïP°C,P°PrPëPSCř.
P PëP·PëPe PïCĤPë PIP·P°C”PjPsPrC-C— P·C- CĬC,P°C,PëPSP°PjPë, PrPµCĬPeC- P·
PSPëC... C,P°PePsP¶ PjPµC,P°P±PsP»C-P·CřCĤC,CHCĬCĬ C-P·PsC,,PµCĤPjPµPSC,PsPj
CYP3A4 C†PëC,PsC...CĤPsPjCř P450, PSPµPIC-PrPsPjPëPN. PŸPsPjCř
CĤCřPïP°C,P°PrPëPS CĬP»C-Pr P· PsP±PµCĤPµP¶PSC-CĬC,CĤ
P·P°CĬC,PsCĬPsPICřPIP°C,Pë PïCĤPë PsPrPSPsC±P°CĬPSPsPjCř
PïCĤPëP·PSP°C±PµPSPSC- P·C- CĬC,P°C,PëPSP°PjPë.

P'P·P°C”PjPsPrC-CĬ P· PjC-PrP°P·PsP»P°PjPsPj

PµC-CĬP»CĬ PïCĤPëPNPsPjCř PrPsP·Pë CĤCřPïP°C,P°PrPëPSCř 10 PjPi Cř
PePsPjP±C-PSP°C†C-C— P· 7,5 PjPi PjC-PrP°P·PsP»P°PjPsPj, PïC-PrPIPëC%PµPSPSCĬ
PµPeCĬPïPsP·PëC†C-C— (Cmax C,P° AUC) PjC-PrP°P·PsP»P°PjCř P±CřP»P° PrPµC%Ps
PIPëC%PsCĤ. P— C†C-C”C— PïCĤPëC±PëPSPë CĤCřPïP°C,P°PrPëPS PrC-C” CĬPe
P»PµPïPePëPN C-PSPiC-P±C-C,PsCĤ

CYP3A4.

PhCĬPsP±P»PëPIPsCĬC,C- P·P°CĬC,PsCĬC¿PIP°PSPSCĬ.

PĳPµ CĤPµPePsPjPµPSPPrCřC”C,CHCĬCĬ PsPrPSPsC±P°CĬPSPëPN PïCĤPëPNPsPj
CĤCřPïP°C,P°PrPëPSCř P· PïCĤPµPNPïC,,CĤCřC,PsPIPëPj CĬPsPePsPj (PrPëPI. CĤPsP·PrC-P»
B«P'P·P°C”PjPsPrC-CĬ P· C-PSC€PëPjPë P»C-PeP°CĤCĬCHPePëPjPë P·P°CĬPsP±P°PjPë C,P°
C-PSC€C- PIPëPrPë PIP·P°C”PjPsPrC-PNëB»).

PŸP»C-Pr CřPSPëPeP°C,Pë PsPrPSPsC±P°CĬPSPsPiPs P·P°CĬC,PsCĬCřPIP°PSPSCĬ
CĤCřPïP°C,P°PrPëPSCř C-P· PïPsC,CřP¶PSPëPjPë C-PSPiC-P±C-C,PsCĤP°PjPë CYP3A4, P° P·
PïPsPjC-CĤPSPëPjPë C-PSPiC-P±C-C,PsCĤP°PjPë CYP3A4 BĤ“ P·P°CĬC,PsCĬPsPICřPIP°C,Pë C-P·
PsCĬPsP±P»PëPIPsCĤ PsP±PµCĤPµP¶PSC-CĬC,CĤ (PrPëPI. CĤPsP·PrC-P»
B«P'P·P°C”PjPsPrC-CĬ P· C-PSC€PëPjPë P»C-PeP°CĤCĬCHPePëPjPë P·P°CĬPsP±P°PjPë C,P°
C-PSC€C- PIPëPrPë PIP·P°C”PjPsPrC-PNëB»).

PĤPsP¶Pµ PIPëPSPëPePSCřC,Pë PSPµPsP±C...C-PrPSC-CĬC,CH Cř PePsCĤPµPeC†C-C— PrPsP·Pë
C±CřC,P»PëPIPëC... CĬCřP±CĬC,CĤP°C,C-PI PrP»CĬ CYP3A4 (PSP°PïCĤPëPeP»P°Pr
CĬPëPjPIP°CĬC,P°C,PëPSCř, P»PsPIP°CĬC,P°C,PëPSCř) C,P° CĬCřP±CĬC,CĤP°C,C-PI
C,,PµCĤPjPµPSC,Cř CYP3A4 C-P· PICřP·CHPePëPj C,PµCĤP°PïPµPIC,PëC±PSPëPj
PrC-P°PïP°P·PsPSPsPj (PSP°PïCĤPëPeP»P°Pr C†PëPeP»PsCĬPïPsCĤPëPSCř,
C,P°PeCĤPsP»C-PjCřCĬCř, CĬPëCĤPsP»C-PjCřCĬCř, PµPIPµCĤPsP»C-PjCřCĬCř,
C†PëP·P°PïCĤPëPrCř), PsCĬPeC-P»CHPePë CĤCřPïP°C,P°PrPëPS PjPsP¶Pµ
PïC-PrPIPëC%CřPIP°C,Pë C—C...PSC- PïP»P°P·PjPsPIC- PePsPSC†PµPSC,CĤP°C†C-C— (PrPëPI.
CĤPsP·PrC-P» B«P'P·P°C”PjPsPrC-CĬ P· C-PSC€PëPjPë P»C-PeP°CĤCĬCHPePëPjPë
P·P°CĬPsP±P°PjPë C,P° C-PSC€C- PIPëPrPë PIP·P°C”PjPsPrC-PNëB»).

РљР°СђРrC-РsР»РsРiC-СђРSP° Р±РµР·РiРµРµР° СђСrРiР°C,Р°РrРёРSCr РiРёРiCђР°Р»Р°СђСђ РiC-Рr СђР°Сђ РrРsСђР»C-РrР¶РµРµРSPSCЦ Thorough QT/QTc. Р—Р°СђС,РsСђСrРiР°РSPSCЦ РrРsР· СђСrРiР°C,Р°РrРёРSCr, C°°Рs Сr 10 СђР°Р·C-Рi РiРёC°°C- Р·Р° C,РµСђР°РiРµРiC,РёСђРSC-, РSPµ РiРёСЦiРiР»СЦiР»Рs Р¶РsРrРSPsРiРs РiРiР»РёРiCr РSP° СђРµР·CrР»СђС,Р°C,Рё Р·РљР°-РrРsСђР»C-РrР¶РµРµРSCђ, C,РsРjСr РNёРsРiРs Р·Р°СђС,РsСђСrРiР°РSPSCЦ РSPµ РiРёРёР»РёРёР°C" РiРёC,Р°РSCђ Р· РёР°СђРrC-РsР»РsРiC-СђРSPsC— Р±РµР·РiРµРµРё. РђРrРSP°Рё СђСrРiР°C,Р°РrРёРPS СђР»C-Рr РiСђРёР·РSP°СђР°C,Рё Р· РsР±РµСђРµР¶РµР¶РSC-СђС,Сђ РiР°СђC-С"РSC,Р°Рj Р· РiРsРrРsРiР¶РµРµРSPёj C-РSC,РµСђРiР°Р»Р»РsРj QT, РiР°СђC-С"РSC,Р°Рj Р· РSPµСђРёРsСђРёРiРsРiР°РSPsСђ РiC-РiРsРёР°Р»C-С"РjC-С"Сђ, РiР°СђC-С"РSC,Р°Рj Р·C- СђС,С-РNёРёРёРjРё РiСђРsР°СђРёC,РjC-СђРSPёРjРё СђС,Р°РSP°РjРё, C,Р°РёРёРjРё СЦiРё РёР»C-РSC-СђРSPs Р·РSP°СђСrC°°Р° Р±СђР°РrРёРёР°СђРrC-СЦ, РiРsСђС,СђР° C-СёРµРµРjC-СЦ РjC-РsРёР°СђРr°.

Р СrРiР°C,Р°РrРёРPS Сr C,Р°Р±Р»РµC,РёР°C... РiРs 10 РjРi РSPµРsР±C...C-РrРSPs Р· РsР±РµСђРµР¶РµР¶РSC-СђС,Сђ РiСђРёР·РSP°СђР°C,Рё Р»C-С,РSC-Рj РiР°СђC-С"РSC,Р°Рj (РiC-РёРsРj РiC-Рr 65 СђРsРёC-Рi).B РrРsСђР° Рi C...РsРrC- РёР»C-РSC-СђРSPёC... РiРёРiСђРsР±СђРiР°РSCђ РSPµ РiC-РrРjC-СђР°Р»Рё Р·Р°РiР°Р»CђРSPёC... РiC-РrРjC-РSPSPСђС,РµРNё Рi РµC,,РµРёC,РёРiРSPsСђС,С- Р°Р±Рs Р±РµР·РiРµРµРiСђC-, РSPµ РjРsР¶РSP° РiРёРёР»CђСђРёC,Рё РjРsР¶Р»РёРiРsСђС,С- РiC-РrРiРёC°°РµРSPsC— СђСrC,Р»РёРiРsСђС,С- Сr РrРµСЦiРёРёC... РiР°СђC-С"РSC,С-Рi Р»C-С,РSCђРsРiРs РiC-РёСr, РsСђРёC-Р»СђРёРё РёC-Р»СђРёC-СђС,Сђ РiР°СђC-С"РSC,С-Рi, СЦiРёC- Р±СђР°Р»Р» РёСђСђР°СђС,Сђ Сr РiРёРiСђРsР±СђРiР°РSPSCЦC..., Р±СђР»Р°Р° РSPµР·РSP°СђРSPsСђ (РrРёРi. СђРsР·РrC-Р» B«Р°Р°СђРjР°РёРsР»РsРiC-СђРSC- РiР»Р°СђС,РёРiРsСђС,С-B»).

РµСђРs РiСђРёР·РSP°СђРµРSPSCЦ РrC-С,СЦiРj РiC-РёРsРj РiРsРSP°Рr 12 СђРsРёC-Рi C- РiР°СђC-С"РSC,Р°Рj Р· РSPёСђРёРsРiРёРjРё Р°Р±Рs РiРµСђC-РSPёРsРiРёРjРё РiРsСђСrСёРµРSPSCЦiРjРё РrРёРi. Сr СђРsР·РrC-Р»C- B«РiРiРsСђС-Р± Р·Р°СђС,РsСђСrРiР°РSPSCЦ C,Р° РrРsР·РёB».

РђСђРёC-Р»СђРёРё C,Р°Р±Р»РµC,РёРё СђСrРiР°C,Р°РrРёРSCr РjC-СђС,СЦC,Сђ Р»Р°РёC,РsР·Сr, РiСђРµРiР°СђР°C, РSPµ СђР»C-Рr РiСђРёРNёРjР°C,Рё РiР°СђC-С"РSC,Р°Рj Р· СђС-РrРёРёРjРё СђРiР°РrРёРsРiРёРjРё РiСђРsР±Р»РµРjРё РiР°Р»Р»Р°РёC,РsР·РSPsC— РSPµРiРµСђРµРSPsСђРёРjРsСђС,С-, РrРµC,,C-СђРёC,Сr Р»Р°РёC,Р°Р·Рё Р»Р°РiРiР° Р°Р±Рs РiР»СђРёРsР·Рs-РiР°Р»Р°РёC,РsР·РSPsC— РjР°Р»СђР°Р±СђРsСђР±СђC—.

Р—Р°СђС,РsСђСrРiР°РSPSCЦ Сё РiРµСђР-РsРr РiР°C-С,РSPsСђС,С- Р°Р±Рs РiРsРrCёРiР°РSPSCЦ РiСђСёРrРrСђ.

Р'Р°РiC-С,РSC-СђС,Сђ

Р†СђРSCrСђС,Сђ РsР±РjРµР¶РµРµРSC- РrР°РSC- C°°РsРrРs Р·Р°СђС,РsСђСrРiР°РSPSCЦ СђСrРiР°C,Р°РrРёРSCr РiР°РiC-С,РSPёРjРё Р¶iC-РSPёРj. Р"РsСђР»C-РrР¶РµРµРSPSCЦ РSP° C,РiР°СђРёРSP°C... РSPµ СђРiC-РrСђР°C,Сђ РiСђРs Р±РµР·РiРµРiСђРµСђРrРSC-РNё Р°Р±Рs РsРiРsСђРµСђРµРiР°РSPёРNё СёРёC-РrР»РёРiРёРNё РiРiР»РёРi РSP° РµРjР±СђС-РsРS/РiР»C-Рr, РiРµСђРё- C,Р° РiРsСђС,РSP°C,Р°Р»СђРSPёРNё СђРsР·РiРёC,РsРё (РrРёРi. СђРsР·РrC-Р» B«Р°Р°СђРjР°РёРsР»РsРiC-СђРSC- РiР»Р°СђС,РёРiРsСђС,С-B»).B РiРё Р·Р°СђС,РµСђРµР¶РµР¶РSPёРNё Р·Р°C...C-Рr СђР»C-Рr СrРSPёРёР°C,Рё РiСђРёРNёРsРjСr СђСrРiР°C,Р°РrРёРSCr РiC-Рr СђР°Сђ РiР°РiC-С,РSPsСђС,С-.

P"PsPrCžPIP°PSPSCІІ PiCṪCžPrPrCḤ

P CrPİP°C,P°PrPëPS PIPëPrC-P»CІC"°C,CHCÍCІCІ PI PjPsP»PsPePs C,PIP°CṪPëPS.
PќPµPIC-PrPsPjPs, C±Pë PiCṪPsPSPëPeP°C" CṪCrPİP°C,P°PrPëPS P· PsCṪPiP°PSC-P·PjCr
PjP°C,PµCṪC-, CІPeP° PiPsPrCÍC" PiCṪCrPrPrCḤ, Cr PjPsP»PsPePs.B PµPsC,CṪC-P±PSPs
PiCṪPëPNëPSCІCІC,Pë CṪC-CëPµPSPSCІC C°PsPrPs PiCṪPëPiPëPSPµPSPSCІC
PiPsPrCÍPIP°PSPSCІC PiCṪCrPrPrCḤ P°P±Ps PiCṪPëPiPëPSPµPSPSCІC/PIC-PrPjPsPIPë PIC-Pr
P·P°CÍC,PsCÍCrPIP°PSPSCІC CṪCrPİP°C,P°PrPëPSCÍ C-P· CrCṪP°C...CrPIP°PSPSCІCj
PePsCṪPëCÍC,C- PIC-Pr PiCṪCrPrPSPsPiPs PIPëPiPsPrPsPICÍPIP°PSPSCІC PrP»CІC PrPëC,PëPSPë
C,P° PePsCṪPëCÍC,C- PIC-Pr C,PµCṪP°PiC-C— PrP»CІC P¶C-PSPePë.

PαPµCṪC,PëP»CHPSC-CÍC,CH

PḽP»C-PSC-C±PSC- PrP°PSC- PiCṪPs PIPİP»PëPI PSP° C,,PµCṪC,PëP»CHPSC-CÍC,CH
PIC-PrCÍCrC,PSC-. P"PsCÍP»C-PrP¶PµPSPSCІC PSP° C,PIP°CṪPëPSP°C... CÍPIC-PrC±P°C,CH
PiCṪPs P·PSP°C±PSPµ P·PSPëP¶PµPSPSCІC C,,PµCṪC,PëP»CHPSPsCÍC,C- PiCṪPë
PePsPSC†PµPSC,CṪP°C†C-CІC..., PIPëC°PëC... P·P° PjP°PeCÍPëPjP°P»CHPSC-
C,PµCṪP°PiPµPIC,PëC±PSC- PePsPSC†PµPSC,CṪP°C†C-C— Cr P»CḤPrPëPSPë (PrPëPI.
CṪPsP·PrC-P» B«PαP°CṪPjP°PePsP»PsPiC-C±PSC- PIP»P°CÍC,PëPIPsCÍC,C-B»).B

P—PrP°C,PSC-CÍC,CH PIPİP»PëPIP°C,Pë PSP° CëPIPëPrPeC-CÍC,CH CṪPµP°PeC†C-C— PiCṪPë
PePµCṪCžPIP°PSPSC- P°PIC,PsC,CṪP°PSCÍPiPsCṪC,PsPj P°P±Ps C-PSCëPëPjPë
PjPµC...P°PSC-P·PjP°PjPë.

P'PiP»PëPI CṪCrPİP°C,P°PrPëPSCÍ 10 PjPi PSP° P·PrP°C,PSC-CÍC,CH PePµCṪCrPIP°C,Pë
C,CṪP°PSCÍPiPsCṪC,PSPëPjPë P·P°CÍPsP±P°PjPë C,P° PiCṪP°C†CḤPIP°C,Pë P· C-PSCëPëPjPë
PjPµC...P°PSC-P·PjP°PjPë PSPµP·PSP°C±PSPëPNë. PµCṪPsC,Pµ CÍP»C-Pr P±CÍC,Pë
PsP±PµCṪPµP¶PSPëPj PiC-Pr C±P°CÍ PePµCṪCrPIP°PSPSCІC C,CṪP°PSCÍPiPsCṪC,PSPëPjPë
P·P°CÍPsP±P°PjPë C,P° CṪPsP±PsC,Pë P· PjPµC...P°PSC-P·PjP°PjPë, PrPsPiPsPePë
CṪPµP°PeC†C-CІC PsCṪPiP°PSC-P·PjCr PSP° CṪCrPİP°C,P°PrPëPS PSPµ PIPëP·PSP°C±PµPSP°.

PŸPiPsCÍC-P± P·P°CÍC,PsCÍCžPIP°PSPSCІC C,P° PrPsP·Pë.

P"PsCṪPsCÍP»C- C- PrC-C,Pë PIC-PePsPj PIC-Pr 12 CṪPsPeC-PI

P PµPePsPjPµPSPPrPsPIP°PSP° PrPsP·P° бṪ" 10 PjPi (PsPrPSP° C,P°P±P»PµC,PeP°) PsPrPëPS
CṪP°P· PSP° PrPsP±CÍ PSPµP·P°P»PµP¶PSPs PIC-Pr PiCṪPëPNëPsPjCr C—P¶C-.

PµP°C†C-C"PSC,Pë P»C-C,PSCHPsPiPs PIC-PeCÍ

PµP°C†C-C"PSC,P°Pj P»C-C,PSCHPsPiPs PIC-PeCÍ CṪCrPİP°C,P°PrPëPS CÍP»C-Pr
P·P°CÍC,PsCÍPsPICÍPIP°C,Pë P· PsP±PµCṪPµP¶PSC-CÍC,CḤ (PrPëPI. CṪPsP·PrC-P»
B«PhCÍPsP±P»PëPIPsCÍC,C- P·P°CÍC,PsCÍCrPIP°PSPSCІC»).

PµP°C†C-C"PSC,Pë P· PSPëCṪPePsPIPsCḤ P°P±Ps PiPµC±C-PSPePsPIPsCḤ
PSPµPrPsCÍC,P°C,PSC-CÍC,CḤ

PŞPµCṪPµP· PIC-PrCÍCrC,PSC-CÍC,CH PeP»C-PSC-C±PSPsPiPs PrPsCÍPIC-PrCr
P·P°CÍC,PsCÍCrPIP°PSPSCІC PiCṪPµPiP°CṪP°C,Cr PiP°C†C-C"PSC,P°Pj P·

РiРsСҫСrС€РµPSPSCПjРё С,,СrPSPeC†C-C— PSPёСҫPsPe Р°Р±Ps РiРµC‡C-PSPeРё РrР»CП
Р»C-PeC†PIP°PSPSCП C,Р°PeРёC... РiР°C†C-C”PSC,C-PI РiСҫРµРiР°СҫР°C, PSPµ
СҫРµPePsPjРµPSPrPsPIP°PSPёPNё.

РҫСҫРёPIP°Р»C-СГC,СҪ Р»C-PeC†PIP°PSPSCП PIPёР·PSP°C‡Р°C” Р»C-PeР°Сҫ Р·Р°Р»РµPҫPSPs
PIC-Pr C,СПPҫPePsCГC,C- C,Р° РiРµСҫРµРµP±C-PiC† Р·Р°C...PIPсСҫСҫPIP°PSPSCП.
Р»C-PeC†PIP°PSPSCП СГР»C-Pr РiСҫРёРiРёPSPёC,Рё РiC-СГР»CП Р·PSPёPePSPµPSPSCП
СГРёРjРiC,PsPjC-PI C,Р° PIC-PrPSPsPIPёC,Рё РiC-СГР»CП РiPsPIC,PsСҫPSPsPiPs C—C...
PIPёPSPёPePSPµPSPSCП.

Р”C-C,Рё.

Р”Р°PSPёPNё Р»C-PeР°СҫСГCҪPeРёPNё Р·Р°СГC-P± PSPµ СҫРµPePsPjРµPSPrC†C”C,СҪСГCП
РiСҫРёР·PSP°C‡Р°C,Рё РrC-C,СПj PIC-PePsPj РrPs 12 СҫPsPeC-PI C‡РµСҫРµР·
PSPµРrPsCГC,Р°C,PSC-СГC,СҪ РrР°PSPёC... РiСҫPs Р±РµР·РiРµPeC† C,Р°
РµC,,РµPeC,РёPIPSC-СГC,СҪ.

РµРµСҫРµРrPsP·C‡PIP°PSPSCП.

РќРµ РiPsPIC-PrPsPjР»CП»PsCГCП РiСҫPs PIPёРiР°РrPeРё РiРµСҫРµРµРrPsP·C†PIP°PSPSCП
РiСҫРµРiР°СҫР°C,PsPj. Pj C...PsPrC- РrPsCГР»C-PrPҫРµPSPSCП PeР»C-PSC-C‡PSPsC—
Р±РµР·РiРµPeРё СҫСГРiР°C,Р°РrРёPS РrPsP±СҫРµ РiРµСҫРµРµPSPsCГРёPICГCП PI
РrPsP±PsPIC-PNё РrPsP·C- 100 PjPi РiСҫPsC,СПPiPsPj 6 РrPSC-PI.
РќР°PNёРiPsC€РёСҫРµPSC-C€PsCҫ РiPsP±C-C‡PSPсCҫ СҫРµР°C-C”Cҫ C”
СГPsPSP»РёPIC-СГC,СҪ. РµСҫРё PIPёРiР°РrPePsPiPsPjC† РiСҫРёPNёPsPjC-
PICГРµСҫРµРrРёPSc† РrC†Pҫ РiРёCГPsPeРёC... РrPsP· СҫРµPePsPjРµPSPrPsPIP°PSP°
СГРёРjРiC,PsPjР°C,РёC‡PSP° C,Р° РiC-PrC,СҫРёРjC†CҫР°C,РµСҫР°CҫР°C-СП.

РµPsP±C-C‡PSC- СҫРµР°PeC†C-C—.

РµC-Pr C‡Р°CГ PeР»C-PSC-C‡PSPёC... РrPsCГР»C-PrPҫРµPSCҫ СҫСГРiР°C,Р°РrРёPS,
C,Р°Р±Р»РµC,PeРё РiPs 10 PjPi, Р·Р°СГC,PsCГPsPIC†PIP°PICГCП PI Р»C-PeC†PIP°PSPSC- 2043
РrPsСҫPsCГР»РёC... C,Р° РiC-PrР»C-C,PeC-PI, 120 C-Р· СПPeРёC... РiСҫРёPNёPjР°Р»Рё
РiСҫРµРiР°СҫР°C, PjC-PSC-PjC†Pj РiСҫPsC,СПPiPsPj СҫPsPeC†.

РќР°PNёРiPsC€РёСҫРµPSC-C€РёPjРё РiPsP±C-C‡PSPёPjРё СҫРµР°C-СПPjРё РiC-Pr C‡Р°CГ
PePsPSC,СҫPsР»CҫPsPIP°PSPёC... PeР»C-PSC-C‡PSPёC... РrPsCГР»C-PrPҫРµPSCҫ Р±C†Р»Рё
СГPsPSP»РёPIC-СГC,СҪ (9,4 %), РiPsР»PsPIPSPёPNё Р±C-Р»Cҫ (6,9 %) C- PIC,PsPjР° (3,1 %),
Р°СГC,РµPSC-СП (1,5 %), СГC†C...C-СГC,СҪ C† СҫPsC,C- (1,2 %),
Р·Р°РiР°PjPsСҫPsC‡РµPSPSCП (1,03 %).

Р’C-Р»CҫC€C-СГC,СҪ РiPsP±C-C‡PSPёC... СПPIPёC%, C%Ps
СГРiPsCГC,РµСҫC-PiР°Р»РёCГCП РiC-Pr C‡Р°CГ PePsPSC,СҫPsР»CҫPsPIP°PSPёC...
PeР»C-PSC-C‡PSPёC... РrPsCГР»C-PrPҫРµPSCҫ, Р±C†Р»Рё PIC-Pr СГР»Р°Р±PePsPiPs РrPs
РiPsPjC-СҫPSPsPiPs CГC,СГРiРµPSCП C- Р·Р°Р·PIPёC‡Р°PNё PSPµ PIPёPjР°РiР°Р»Рё
РiСҫРёРiРёPSPµPSPSCП Р»C-PeC†PIP°PSPSCП.

$$P - P_{\pm} P_s P_e C \acute{z} C \acute{e} P_e C - C \bar{H} P \ddot{e} C - P \ddot{C} - P r C \acute{e} P_e C - C \bar{H} P S P s C - C, P_e P^{\circ} P S P \ddot{e} P S P \ddot{e}$$

PŷPμCḦPjC-PS PīCḦPēPṛP°C, PSPsCÍC,C-. 3 CḦPsPePē.

PJPjPsPIPë P·P±PμCḡC-PiP°PSPSCI.

P—P±PμCḡC-PiP°C,Pë PI PeP°CḡC,PsPSPSC-PNë PePsCḡPsP±C†C-B PrP»Cḡ P·P°C...PëCḡC,Cr
PIC-Pr CḡPIC-C,P»P°.

P—P±PμCḡC-PiP°C,Pë Cr PSPμPrPsCḡC,CrPiPSPsPjCr PrP»Cḡ PrC-C,PμPNë PjC-CḡC†C-.

PJPiP°PePsPIPeP°.

PμPs 10 C,P°P±P»PμC,PsPe Cr P±P»C-CḡC,PμCḡC-, PiPs 1, 3 P°P±Ps 5 P±P»C-CḡC,PμCḡC-PI Cr
PeP°CḡC,PsPSPSC-PNë PePsCḡPsP±C†C-.

PμPs 15 C,P°P±P»PμC,PsPe Cr P±P»C-CḡC,PμCḡC-, PiPs 2 P±P»C-CḡC,PμCḡP° Cr
PeP°CḡC,PsPSPSC-PNë PePsCḡPsP±C†C-.

PḡP°C,PμPiPsCḡC-Cḡ PIC-PrPiCrCḡPeCr. P—P° CḡPμC†PμPiC,PsPj.

P'PëCḡPsP±PSPëPe.

PkPsCrPePsCḡ PḡPμP»Cḡ, PŸ.Pḡ.

**PḡC-CḡC†PμP·PSP°C...PsPrPḡPμPSPSCI PIPëCḡPsP±PSPëPeP° C,P° P°PrCḡPμCḡP°
PjC-CḡC†Cḡ PiCḡPsPIP°PrPḡPμPSPSCI PNëPsPiPs PrC-CḡP»CḡPSPsCḡC,C-.**

PμCḡPsCḡPiPμPeC, P''PμP» PḡP°PjC- P PμPNëP°P», 51-57, PμP°P»P°Cr-PŸPsP»C-C,P° C-
PμP»PμPiP°PjP°PSCḡ, 08184, P†CḡPiP°PSC-Cḡ.