

!" #&/
4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC

!"®
(GRASTIM™)

!;:04:

4VNG0 @5G>28=0: filgrastim;
1 <; @>7G8=C 3> 3@0=C;>F8B0@=>3> :>;>=VTAB83> D0:B>@0 (G-CSF) 0,3 <3 (30 <;= 01> 300);
4>?>28=8: A>@1VB (E420), ?>;VA>@10B 80, =0B@VN 0F5B0B B@83V4@0B, :8A;>B0 >FB>20
;L>4O=0, 2>40 4;O V=T:FV9.

V:0@AL:0 D>@<0. >7G8= 4;O V=□T:FV9.

\$0@<0:>B5@0?52B8G=0 3@C?0. &8B>:V=8 B0 V<>4C;OB>@8. □>;>=VTAB8@8. >4 " ! L03A02.

;V=VG=V E0@0:B5@8AB8:8.

>:070==O.

!:>@>G5==O B@820;>ABV B0 7=865==O G0AB>B8 28=8:=5==O =59B@>?5=VW B0 D51@8;L=>W
=59B@>?5=VW C E2>@8E, O:V >B@8B>:A8G=C EVB5@0?VN 7 ?@82>4C 7;>O:VA=8E 70E2>@N20=L
(70 28=OB:>< E@>=VG=>3> ;59:>7C B0 48A?;0AB8G=>3> A8=4@>
A:>@>G5==O B@820;>ABV =59B@>?5=VW B0 WW ;:V=VG=8E =0A;V4:V2 C E2>@8E, O:V >B@8
01;0B82=C B5@0?VN 7 ?>40;LH>N 0;>35==>N 01> 0CB>;>3VG=>N B@0=A?;0=B0FVTN :VAB:>2>3>
<>7:C;
<>1V;V70FVO ?5@8D5@8G=8E AB>21C@>28E ;:VB8= :@>2V (!), C B>AC?@5A82=>W B5@0?VW;
4>23>B@820;0 B5@0?VO 4;O 71V;LH5==O :V;L:>ABV =59B@>DV;V2 V 7<5=H5==O G0AB>B8 B0
B@820;>ABV V=D5:FV9=8E CA::04=5=L C 4VB59 B0 4>@>A;8E 7 B06:>N A?04:>2>N, ?5@V>48G=>N
01> V4V>?0B8G=>N =59B@>?5=VTN B0 01A>;NB=>N :V;L:VABN =59B@>DV;V2 ≤ 0,5 E 10%; B0 B06:8
<8 01> @5F8482CNG8<8 V=D5:FVO<8 2 0=0<=57V;
7=865==O @878:C 10:B5@V0;L=8E V=D5:FV9 B0 ;V:C20==O ABV9:>W =59B@>?5=VW (01A>;NB=0
:V;L:VABL =59B@>DV;V2 ≤ 1 E 10%); C ?0FVT=BV2 7 @>73>@=CB>N AB04VTN -V=D5:FVW ?@8
=55D5:B82=>ABV V=H8E 70A>1V2 :=B@>;N =59B@>?5=VW;
<>1V;V70FVO ?5@8D5@8G=8E AB>21C@>28E ;:VB8= :@>2V (!) C 74>@>28E 4>=>@V2 4;O
0;>35==>W B@0=A?;0=B0FVW !.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> DV;3@0AB8>=VTAB8@V2, *Escherichia coli* 01> 4> 1C4L-O:8E 4>?>28=
"O6:0 A?04:>20 =59B@>?5=VO (A8=4@><>AB<0=0) 7 F8B>35=5B8G=8<8 ?>@CH5==O<8 B0 0CB>V
?5=VO.

"5@

%@>=VG=89 ;59:>7 B0 48A?;0AB8G=89 A8=4@><.

!?:>AV1 70AB>AC20==O B0 4>78. "5@0?VN ?@5?0@0B>< @0AB8<® <>6=0 ?@>2>48B8 C ;V:C20;L=8E
70::040E, 45 T =5>1EV4=5 4V03=>AB8G=5 >1;04=0==O. V:0@V ?>28==V<0B8 4>A2V4 70AB>AC20==O
;V:0@AL:8E 70A>1V2, I> F8B0@=89 :>;>=VTAB8@ (G-CSF) B0 ;V:C20==O E2>@8E 7 35<0B>;>3VG=8
<8 70E2>@N20==O<8.

@>F54C@8 <>1V;V70FVW B0 0D5@57C A;V4 ?@>2>48B8 ?@8 270T<>4VW 7 ;V:0@O<8, O:V <0NBL
2V4?>2V4=89 4>A2V4 V <>6;82VABL =5>1EV4=>3><>=VB>@8=3C ;:VB8=-?>?5@54=8:V2 35<>?>57C.
59B@>?5=VO C E2>@8E, O:V >B@8B>:A8G=C EVB5@0?VN 7 ?@82>4C 7;>O:VA=8E 70E2>@N20=L.
5:><5=4>20=0 4>1>20 4>70 ?@5?0@0BC AB0=>28BL 0,5 <;= /:3 (5 B5@0?VW. @5?0@0B
70AB>A>2C20B8, ?>:8 7030;L=0 :V;L:VABL =59B@>DV;V2 C ;:V=VG=2V =5 ?5@528I8BL >GV:C20=89
@V25=L V =5 4>AO3=5 =>@<8. VA;O EVB5@0?VW 7 ?@82>4C A>;V4=8E ?CE;8=, ;V< V ;V;59:>7C
B@820;VABL ;V:C20==O 4> 4>AO3=5==O 2:070=8E 7=0G5=L AB0=>28BL 4> 14 4=V2. VA;O
V=4C:FV9=>W V :=A>;V40FV9=>W B5@0?VW 3>AB@>3> W4=>3> ;59:>7C B@820;VABL ;V:C20==O
<>65 1CB8 7=0G=> 71V;LH5=0 (4> 38 4=V2) 70;56=> 2V4 284C, 4>78 B0 AE5<8 70AB>A>20=>W
F8B>B>:A8G=>W EVB5@0?VW.

?0FVT=BV2, O:V >B@8B>:A8G=C EVB5@0?VN, <8=CI5 71V;LH5==O :V;L:>ABV =59B@>DV;V2
70728G09 A?>AB5@V30TBLAO G5@57 1-2 4>18 ?VA;O ?>G0B:C ;V:C20==O ?@5?0@0B<® @0AB8<®. ;5
4;O 4>AO3=5==O AB01V;L=>3> B5@0?52B8G=>3> 5D5:BC =5>1EV4=> ?@>4>26C20B8 B5@0?VN, ?>:8
:V;L:VABL =59B@>DV;V2 =5 ?5@528I8BL >GV:C20=89< 4> ?5@5E>4C :V;L:>ABV =59B@>DV;V2
G5@57 >GV:C20=89

!>AV1 22545==O.

@5?0@0B @0AB8<® 70AB>A>2C20B8 C 283;O4V ?V4H:V@=8E V=T:FV9 01> 2=CB@VH=L>25==8E
V=DC7V9 ?@>BO3<< 30 E28;8= 1 @07 =0 4>1C. # 1V;LH>ABV 28?04:V2 ?5@52060T ?V4H:V@=89 H;OE
22545==O. @8 2=CB@VH=L>25==>4=>@07>2>W 4>78 B@820;VABL 5D5:BC ?@5?0@0BC<<65
A:>@>GC20B8AL. ;V=VG=0 7=0GCIVABL F8E 40=8E I>4> 70AB>AC20==O 1030B>@07>28E 4>7
?@5?0@0BC =5 2AB0=>2;5=0. 81V@ A?>A>1C 22545==O 70;568BL 2V4 >A>1;82>AB59 :>=:@5B=>W
;V=VG=>W A8BC0FVW V 287=0G0TBLAO 4;O :>6=>3> E2>@>3> >:@5<>.

%2>@V, O:V >B@80I;0B82=C B5@0?VN 7 ?>40;LH>N B@0=A?;0=B0FVTN :VAB:>2>3> <<>7:C.

5:><5=4>20=0 ?>G0B:>20 4>70 ?@5?0@0BC @0AB8<® 1 <;= /:3 (10/:3) <0A8 BV;0 =0 4>1C. 5@HC 4>7C
A;V4 22>48B8 =5 @0=VH5 =V6 G5@57 24 3>48=8 ?VA;O ?@>2545==O F8B>B>:A8G=>W EVB5@0?VW,
V =5 ?V7=VH5 =V6 G5@57 24 3>48=8 ?VA;O B@0=A?;0=B0FVW :VAB:>2>3><<>7:C.

>@5:FVO 4>78: ?VA;O<0:A8<0;L=>3> 7=865==O :V;L:>ABV =59B@>DV;V2 (=048@0) 4>1>2C 4>7C
?@5?0@0BC =5>1EV4=> A:>@53C20B8 70;56=> 2V4 7ABV =59B@>DV;V2 (482. B01;8FN).

V41V@ 4>78 ?@5?0@0BC □@0AB8<® C 2V4?>2V4L =0 4>AO3=5==O =048@0.

1A>;NB=0 :V;L:VABL=59B@>DV;V2 ()	>@53C20==O 4>78 ?@5?0@0BC □@0AB8<®
> 1 x 10 ⁹ ; ?@>BO3<< 3 4V1 ?>A?V;L	=865==O 4>78 4> 0,5 <;= /:3 (5 8 BV;0 =0 4>1C
> 1 x 10 ⁹ ; ?@>BO3<< =0ABC?=8E 3 4V1 ?>A?V;L	V4 ?@5?0@0BC
/:I> ?V4 G0A ;V:C20==O 7=86CTBLAO 4> @V2=O <1 x 10 ⁹ ; , 4>7C ?@5?0@0BC 71V;LHC20B8 2V4?>2V4=> 4> 28I5707=0G5=>W AE5<8.	

!>AV1 22545==O.

@5?0@0B @>7G8=OB8 C 20 <; 5 % @>7G8=C 3;N:>78 V 70AB>A>2C20B8 C 283;O4V =5B@820;>W
2=CB@VH=L>25==>W V=DC7VW ?@>BO3<< 30 E28;8= 01> B@820;>W ?V4H:V@=>W G8
2=CB@VH=L>25==>W V=DC7VW ?@>BO3<< 24 3>48=.

>1V;V70FVO ?5@8D5@8G=8E AB>21C@>28E ;;VB8=:@>2V (!) C ?0FVT=BV2, O:V >45@6CNBL
AC?@5A82=C 01> 01;0B82=C B5@0?VN 7 ?>40;LH>N 0CB>;>3VG=>N B@0=ADC7VTN !.

%2>@V, O:V >B@8AC?@5A82=C 01> 01;0B82=C B5@0?VN 7 ?>40;LH>N 0CB>;>3VG=>N
B@0=A?;0=B0FVTN !.

;O <>1V;V70FVW !?@8 70AB>AC20==V ?@5?0@0BC @0AB8<® O: <<=>B5@0?VW @5:><5=4>20=0
4>70 AB0=>28BL 1 <;= /:3 (10 7C ?@5?0@0BC 4> 7025@H0;L=>3> ;59:0D5@57C.

;O <>1V;V70FVW !?VA;OAC?@5A82=>W EVB5@0?VW @5:><5=4>20=0 4>70 ?@5?0@0BC @0AB8<®
AB0=>28BL 0,5 <;= /:3 (5 B5@0?VW V ?>:8 :V;L:VABL =59B@>DV;V2 =5 ?5@5945 >GV:C20=89<0,5 E 10
9/; 4> >5 E 10⁹; . %2>@8<, O:V =5 >B@8W EVB5@0?VW, A;V4 ?@>2>48B8 1 A50=A ;59:0D5@57C. >:@5
<8E 28?04:0E @5:><5=4CTBLAO ?@>2>48B8 4>40B:>2V A50=A8 ;59:0D5@57C.

>1V;V70FVO !C 74>@>28E 4>=>@V2 ?5@54 0;>35==>N B@0=A?;0=B0FVTN !.

;O <>1V;V70FVW !?5@54 0;>35==>N B@0=A?;0=B0FVTN !4;O 74>@>28E 4>=>@V2 @5:><5=4>20=0
4>70 ?@5?0@0BC @0AB8<® AB0=>28BL 1 <;= /:3 (10 4 x 10⁶ CD34+ ;;VB8=/:3 <0A8 BV;0 @5F8?VT=B0.

!>AV1 22545==O.

5@54 V=DC7VTN ?@5?0@0B @>7G8=OB8 C 20 <; 5 % @>7G8=C 45:AB@>78.

>23>B@820;0 B5@0?VO 4;O 71V;LH5==O :V;L:>ABV =59B@>DV;V2 V 7<5=H5==O G0AB>B8 V
B@820;>ABV V=D5:FV9=8E CA.:04=5=L C 4VB59 B0 4>@>A;8E 7 BO6:>N A?04:>2>N, ?5@V>48G=>N
01> V4V>?0B8G=>N =59B@>?5=VTN ("%)

!>04:>20 =59B@>?5=VO.

5:><5=4>20=0 ?>G0B:>20 4>70 1,2 <;= /:3 (12
4V>?0B8G=0 V ?5@V>48G=0 =59B@>?5=VO.

5:><5=4>20=0 ?>G0B:>20 4>70 0,5 <;= /:3 (5

V41V@ 4>78.

@5?0@0B □@0AB8<® 22>48B8 I>45==> 4> 4>AO3=5==O V AB01V;L=>3> ?5@528I5==O ?>:07=8:0
:V;L:>ABV =59B@>DV;V2 1,5 E 10%;. VA;O 4>AO3=5==O B5@0?52B8G=>3> 5D5:BC 287=0G0B89%; 4>
10 E 10%;. %2>@8< V7 BO6:8<8 V=D5:FVO<8 <>6=0 70AB>AC20B8 AE5@8E 4>70<8, 28I8<8 70 2,4 <=;
(24 /:3) =0 4>1C, =5 2AB0=>2;5=0.

=865==O @878:C 10:B5@V0;L=8E V=D5:FV9 B0 ;V:C20==O ABV9:>W =59B@>?5=VW C ?0FVT=BV2 7
@>73>@=CB>N AB04VTN -V=D5:FVW.
V4=>2;5==O :V;L:>ABV =59B@>DV;V2.

5:><5=4>20=0 ?>G0B:>20 4>70 ?@5?0@0BC 0,1 <= /:3 (1 x 109%;). >@<0;V70FVO :V;L:>ABV
=59B@>DV;V2 70728G09 =0AB0T G5@57 2 4>18. # @V4:VA=8E 28?04:0E (<1 % ?0FVT=BV2) 4;O
2V4=>2;5==O :V;L:>ABV =59B@>DV;V2 4>70 ?@5?0@0BC <>65 1CB8 71V;LH5=0 4> 1 <= /:3 (10
V4B@8<0==O =>@<0;L=>W :V;L:>ABV =59B@>DV;V2.

VA;O 4>AO3=5==O B5@0?52B8G=>3> 5D5:BC ?V4B@870 AB0=>28BL 300 1C 2-3 @078 =0 B8645=L 70
0;LB5@=0B82=>N AE5<N (G5@57 4>1C). 040;V <>65 1CB8 =5>1EV4=0 V=482V4C0;L=0 :>@5:FVO
4>78 V B@820;5 70AB>AC20==O ?@5?0@0BC 4;O ?V4B@8<0==O A5@54=L>W :V;L:>ABV
=59B@>DV;V2 > 2 E 10%;.

A>1;82V :0B53>@VW E2>@8E.

>@5:FVO 4>78 =5 ?>B@V1=0 ?0FVT=B0< V7 BO6:>N ?5GV=>2>N 01> =8@:>2>N =54>AB0B=VABN,
B> WE D0@<0>:V=5B8G=V B0 D0@<0>:48=0:07=8:8 28O28;8AL ?>4V1=8<8 4> B0:8E C 74>@>28E
4>1@>2>;LFV2.

A>1;828E @5:><5=40FV9 I>4> 70AB>AC20==O ?@5?0@0BC ?0FVT=B0< ;VB=L>3> 2V:C =5<0T.

5:><5=40FVW ?5@54 70AB>AC20==O

5@54 70AB>AC20==O< ?@5?0@0BC ?@>2>4OBL 2V7C0;L=89 :>=B@>;L 2=0 01> ?>?5@54=L>
=0?>2=5=>3> H?@8F0. >7G8= ?>28=5= 1CB8 ?@>7>@8<, 157 G0AB8=>:. >@>B:>G0A=89 2?;82 =87L:8E
B5 =0 AB01V;L=VABL ?@5?0@0BC.

>72545=V @>7G8=8 ?@5?0@0BC A;V4 3>BC20B8 =5 @0=VH5 =V6 70 24 3>48=8 4> 70AB>AC20==O V
715@V30B8 2 E>;>48;L=8:C ?@8 B5>!. \$;0:>=8 B0 ?>?5@54=L> =0?>2=5=V H?@8F8 7 ?@5?0@0B<<
?@87=0G5=V ;8H5 4;O >4=>@07>2>3> 70AB>AC20==O.

5:><5=40FVW I>4> @>72545==O ?@5?0@0BC.

@5?0@0B □@0AB8<® <>6=0 22>48B8 C @>72545=>7G8=V 3;N:>78. >72545==O 4> :>=F5=B@0FVW
<5=H5 0,2 <= /<; (2 =5 @5:><5=4CTBLAO. @8 @>72545==V C :>=F5=B@0FVW

1,5 <= /<; (15 4>AO3=5==O :>=F5=B@0FVW 2 <3/<.; 0?@8;:04, ?@8 :V=F52>1 □T7G8=C 20 <; V
7030;L=>W 4>78 DV;3@0AB830 <= (300 1EV4=5 4>40B:>25 22545==O 0,2 <; 20 % (200 <3/<.) @>7G8=C
0;L1C >72545=89 ?@5?0@0B <>65 04A>@1C20B8AO A;:< B0 V=H8<8 <0B5@V0;0<8, I>
28:>@8AB>2CNBLAO 4;O V=DC7V9=>3> 22545==O.

0I>@>=5=> 28:>@8AB>2C20B8 @>7G8= E;>@84C =0B@VN 4;O @>72545==O ?@5?0@0BC.

5@5206=V 4V;O=:8 BV;0 4;O ?V4H:V@=>3> 22545==O ?@5?0@0BC ?>:070=V =0<0;N=:C:

>IVG=V @50:FVW. 09G0ABVH8<8 ?>1VG=8<8 O28I0<8 =0 B;V B5@0?VW V7 70AB>AC20==O<
DV;3@0AB8;N20;L=8E 70A>1V2.

;5@3VG=V @50:FVW C ?0FVT=BV2 A?>AB5@V30NBLAO G0ABVH5 ?@8 2=CB@VH=L>25==>
?0FVT=BC 70AB>A>2C20B8 =5 A;V4.

>IVG=V @50:FVW, I> A?>AB5@V30;8AL C ?0FVT=BV2 7>=>:>3VG=8<8 70E2>@N20==O<8.

I>:C VW A8AB5<8: 0;5@3VG=V @50:FVW, C B>?82O=:0, 0=3V>=52@>B8G=89 =01@O;: 7048H:0 B0
0@B5@V0;L=0 3V?>B5=7VO.

I>:C AC48==>W A8AB5<8: 0@B5@V0;L=0 3V?>B5=7VO (B820); ?>@CH5==O AC48=, C B>@N20==O,
A?@8G8=5=V >;N7VTN 25=, B0 ?>@CH5==O 10;0=AC @V48=8 2 >@30=V7

I>:C H:V@8 B0 ?V4H:V@=8E B:0=8=: A8=4@< !2VB0, H:V@=89 20A:C;VB.

I>:C @5A?V@0B>@=>W A8AB5<8, >@30=V2 3@C4=>3> B0 <54V0AB8=0;L=>3> 2V44V;V2: =01@O:
;535=V2, V=B5@AB8FV0;L=0 ?=52<=>VO, ;535=5289 V=DV;LB@0B.

I>:C :VAB:>2>-<O7>2>W A8AB5<8 B0 A?>;CG=8E B:0=8=: 1V;L C<O70E B0 :VAB:0E (2V4 =87L:>3>
4> A5@54=L>3> ABC?5=O BO6:>ABV), 1V;L C<O70E B0 :VAB:0E (28A:>3> ABC?5=O BO6:>ABV),
703>AB@5==O @52<0B>W4=>3> 0@B@8BC.

I>:C =8@>: B0 A5G>282V4=8E H;OEV2: ?>@CH5==O A5G>28?CA:0==O (?5@5206=> 487C@VO).

>@CH5==O >128=: :0;LFVT20 ?>403@0.

01>@0B>@=V?>:07=8:8: ?V428I5==O :>=F5=B@0FVW 2 :@>2V ;C6=>W D>AD0B078,
;0:B0B453V4@>35=078 (), 30<<0-3;CB02>W :8A;>B8 (>1>@>B=5, 4>7>70;56=5, =87L:>W 01>
A5@54=L>W BO6:>ABV).
?0FVT=BV2, O:8< ?@>2>48;8 EVB5@0?VN V7 22545==O< 28A>:8E 4>7 ?@>5?0@0BV2 7 ?>40;LH>N
B@0=A?;0=B0FVTN 0CB>;>3VG=>3> :VAB:>2>3> <>7:C, A?>AB5@V30;8AO ?>@CH5==O 7 1>:C
AC48==>W A8AB5<8. @8G8==>=-0A;V4:>2>3> 72O7:C @50:FVW V7 70AB>AC20==O< DV;3@0AB8
2;5=> =5 1C;>. ?>2V4><;5==O ?@> >:@5AB@89 30@OG:>289 =5?@>DV;L=89 45@<0B>7) C ?0FVT=BV2
7 >=:>;>3VG=8<8 70E2>@N20==O<8. 4=0: 7 C@0EC20==O< B>3>, I> 1V;LHVABL V7 F8E ?0FVT=BV2
AB@0640;8 =0 ;59:5@N20==O, O:5 G0AB> ?@872>48BL 4> A8=4@>=-0A;V4:>2>3> 72O7:C V7
70AB>AC20==O< DV;3@0AB8 =5 1C;>.
>1VG=V @50:FVW, I> A?>AB5@V30;8AL C ?0FVT=BV2 7 "%.
I>:C A8AB5<8 :@>2>B2>@5==O B0 ;VW A8AB5<8: 0=5<530;VO, O:0 2 >:@5<8E 28?04:0E
?@>3@5ACT, B@<1>F8B>?5=VO, ?>@CH5==O DC=:FV9 A5;57V=:8.
I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L.
I>:C @5A?V@0B>@=>W A8AB5<8: =>A>2V :@>2>B5GV.
I>:C B@02=>3> B@0:BC: 4V0@5O.
I>:C 35?0B>1V;V0@=>W A8AB5<8: 35?0B><530;VO.
I>:C H:V@8 B0 ?V4H:V@=8E B:0=8=: H:V@=89 20A:C;VB (?@8 B@820;>AC20==V), 0;>?5FVO,
28A8?0==O.
I>:C :VAB:>2>-<O7>2>W A8AB5<8 B0 A?>;CG=8E B:0=8=: >AB5>?>@>7, 0@B@0;3VO.
I>:C =8@>: B0 A5G>282V4=8E H;OEV2: 35<0BC@VO, ?@>B5W=C@VO.
030;L=V ?>@CH5==O B0 ?>@CH5==O C 1V;L C
01>@0B>@=V?>:07=8:8: ?V428I5==O :>=F5=B@0FVW C :@>2V ;C6=>W D>AD0B078, , A5G>2>W
:8A;>B8, 7<5=H5==O @V2=O 3;N:>78 :@>2V (B825, A5@54=L>W BO6:>ABV).
>1VG=V @50:FVW, I> A?>AB5@V30;8AL C 74>@>28E 4>=>@V2, O:8< ?@>2>48;8 <>1V;V70FVN !.
I>:C VW A8AB5<8: 0;5@3VG=V @50:FVW 28A>:>3> ABC?5=O BO6:>ABV (0=0DV;0:B8G=V @50:FVW,
0=3V>=52@>B8G=89 =01@O.: @>?82O=:0, 28A8?0==O =0 H:V@V).
I>:C A8AB5<8 :@>2>B2>@5==O B0 ;VW A8AB5<8: ;59:>F8B>7 (:>=F5=B@0FVO ;59:>F8BV2 >50 E 109/
;), B@<1>F8B>?5=VO (:>=F5=B@0FVO B@<1>F8BV2 <100 E 109/;, B820), A?;5=>530;VO (O:
?@028;>, 157A8<=0, A?>AB5@V30TBLAO B0:>6 V C ?0FVT=BV2 7 >=:>;>3VG=8<8 70E2>@N20==O<8),
?>@CH5==O DC=:FVW A5;57V=:8, @>7@82 A5;57V=:8.
I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L.
I>:C 48E0;L=>W A8AB5<8: :@>2>E0@:0==O, ;535=52V :@>2>B5GV, ;535=5289 V=DV;LB@0B, 7048H:0,
:8A=520 =54>AB0B=VABL.
I>:C :VAB:>2>-<O7>2>W A8AB5<8 B0 A?>;CG=8E B:0=8=: 1V;L C <O70E B0 :VAB:0E (2V4 =87L:>3>
4> A5@54=L>3> ABC?5=O BO6:>ABV, B829), 703>AB@5==O @52<0B>W4=>3> 0@B@8BC B0 A8
01>@0B>@=V?>:07=8:8: ?V428I5==O :>=F5=B@0FVW 2 :@>2V ;C6=>W D>AD0B078 B0
;0:B0B453V4@>35=078 () (B825, =57=0G=5), ?V428I5==O :>=F5=B@0FVW 2 :@>2V 0A?0@B0B0
B@0=AD5@078 (!") B0 A5G>2>W :8A;>B8 (B825, =57=0G=5).
450:8E 28?04:0E A?>AB5@V30;8AL ?>1VG=V O28I0 7 1>:C ;535=V2, I> ?@872>48;> 4> 48E0;L=>W
=54>AB0B=>ABV 01> @5A?V@0B>@=>3> 48AB@5A-A8=4@>@>A;8E (!), V=:>;8 ;5B0;L=8E. 04E>48;8
?>2V4><;5==O ?@> 4C65 @V4:VA=V 28?04:8 ?>1VG=8E O28I 7 1>:C ;535=V2 (:@>2>E0@:0==O,
;535=52V :@>2>B5GV, V=DV;LB@0FVO ;535=V2, 7048H:0 B0 :8A=520 =54>AB0B=VABL) C 74>@>28E
4>=>@V2.
>1VG=V @50:FVW, I> A?>AB5@V30;8AL C ?0FVT=BV2 7 -V=D5:FVO<8.
I>:C A8AB5<8 :@>2>B2>@5==O B0 ;VW A8AB5<8: ?>@CH5==O DC=:FVW A5;57V=:8, A?;5=>
<530;VO.
I>:C :VAB:>2>-<O7>2>W A8AB5<8 B0 A?>;CG=8E B:0=8=: 1V;L C <O70E B0 :VAB:0E (2V4 =87L:>3>
4> A5@54=L>3> ABC?5=O BO6:>ABV).
0 @57C;LB0B0<8 ;V:0@AL:>3> >1AB565==O, 2 CAVE 28?04:0E ABC?V=L 71V;LH5==O A5;57V=:8 C
?0FVT=BV2 7 -V=D5:FVTN 1C2 2V4 =87L:>3> 4> A5@54=L>3>, ;V=VG=89 ?5@51V3 ?>@CH5==O <02
4>1@>O:VA=89 E0@0:B5@; C 6>4=>3> 7 ?0FVT=BV2 =5 1C;> 4V03=>AB>20=> 3V?5@A?;5=V7<, 6>4=>
2545=> A?;5=5:B>20=8

5@54>7C20==O. !8<8 ?5@54>7C20==O =52V4>< :V;L:VABL F8@:C;NNG8E =59B@>DV;L=8E
3@0=C;>F8BV2 70728G09 7=86CTBLAO =0 50 %, 0 G5@57 1-7 4=V2 ?>25@B0TBLAO 4> =>@<8.

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N. 57?5:0 70AB>AC20==O ?@5?0@0BC
C ?5@V>4 203VB=>ABV =5 2AB0=>2;5=0. @8 ?@87=0G5==V ?@5?0@0BC 203VB=8< A;V4
A?V2AB028B8 >GV:C20=89 B5@0?52B8G=89 5D5:B 7 <>6;828< @878:>< 4;O ?;>40. 52V4><>, G8
?@>=8:0T DV;3@0AB8< C 3@C4=5 <>;>;, B>A>2C20B8 9>3> C ?5@V>4 3>4C20==O 3@C44N =5 @5:>
<5=4CTBLAO.

VB8. 57?5:0 B0 5D5:B82=VABL 70AB>AC20==O ?@5?0@0BC =>2>=0@>465=8< =5 2AB0=>2;5=V. 5:>
<5=40FVW I>4> 4>7C20==O 4;O E2>@8E 48BOG>3> 2V:C B0:V 6 A0@>A;8E, O:V >B@8AC?@5A82=C
F8B>B>:A8G=C EVB5@0?VN.

A>1;82>ABV 70AB>AC20==O.

59B@>?5=VO C E2>@8E, O:V >B@8B>:A8G=C EVB5@0?VN 7 ?@82>4C 7;>O:VA=8E 70E2>@N20=L.
A:V;L:8 2V4><>, I> :>;=>VTAB8@8 3@0=C;>F8BV2 (G-CSF) A?@8ONBL @>ABC W4=8E ;;VB8= *in vitro*
0=0;>3VG=V 5D5:B8 <>6CBL A?>AB5@V30B8AO *in vivo*.
57?5:0 B0 5D5:B82=VABL 70AB>AC20==O DV;3@0AB8@8< 7 48A?;07VTN V E@>=VG=8< ;59:>7<< =5
2AB0=>2;5=V. '5@57 <>6;825 ?>B5=FVN20==O @>ABC ?CE;8=8 =5 A;V4 70AB>A>2C20B8 DV;3@0AB8
< ?@8 7;>O:VA=8E 70E2>@N20==OE W4=>3> E0@0:B5@C B0 ?@8 1C4L-O:>?@>;VD5@0B82=>
@N20==V. A>1;82>W C2038 ?>B@51CT ?@>2545==O 48D5@5=FV0;L=>3> 4V03=>7C@<0FVTN
E@>=VG=>3> ;59:>7C V 3>AB@8< ;59:>7>4> 157?5:8 B0 5D5:B82=>ABV ?@5?0@0BC 4;O E2>@8E V7
2B>@8==8< 3>AB@8< F8B0@=8< ;59:>7<< () >1<565=V, ?@5?0@0B A;V4 ?@87=0G0B8 7
>15@56=VABN.

59:>F8B>7.

V;L:VABL ;59:>F8BV2 C :@>2V 4>AO30T 01> ?5@528ICT100 x 109%; <5=H5 =V6 C 5 % E2>@8E, O:V
>B@81>2C 4>7C ?@5?0@0BC 1V;LH5 0,3 <;= /:3 (3 x 109%; ?VA;O 4>AO3=5==O >GV:C20=>3> @V2=O,
A;V4 =5309=> 2V4AC20==O ?@5?0@0BC 4;O <>1V;V70FVW !9>3> =5>1EV4=> 2V4 7@>18B8
:>@5:FVN 4>78 ?@8 71V;LH5==V :V;L:>ABV ;59:>F8BV2 4>>70 x 109%;
878.; ?>2O70=89 7 ?V428I5==O< 4>78 EVB5@0?VW.

!;V4 4>B@8A>1;82>W >15@56=>ABV ?@8 ;V:C20==V E2>@8E 7V 7;>O:VA=8=8 =>2>CB2>@5==O<8,
O:V >B@8:V 4>78 F8B>AB0B8:V2, >A:V;L:8 2 F8E 28?04:0E @57C;LB0B82=VABL ;V:C20==O =5
2AB0=>2;5=0. V4><>, I> ?V428I5=V 4>78 EV?@5?0@0BV2 28O2;O;8 1V;LH 28@065=C B>:A8G=VABL,
?@872>4OG8 4> @>728B:C A5@F52>-AC48==8E, ;535=528E, =52@>;>3VG=8E V 45@<0B>;>3VG=8E
?>1VG=8E @50:FV9.

>=>B5@0?VO ?@5?0@0B>< =5 70?>1V30T @>728B:C B@><1>F8B>?5=VW B0 0=5AC?@5A82=>N EV
B5@0?VTN. # 28?04:C 70AB>AC20==O 1V;LH 28A>:8E 4>7 EV?@5?0@0BV2 (=0?@8:;04 ?>2=V 4>78
2V4?>2V4=> 4> ?@87=0G5=8E AE5<) @878: BO6:>W B@><1>F8B>?5=VW B0 0=5

5:><5=4CTBLAO @53C;O@=> :>=B@>;N20B8 B0:V ?>:07=8:8 ;;V=VG=>3> 0=0;V7C :@>2V O: 35
<0B>:@8B V :V;L:VABL B@>1>F8BV2. !;V4 4>B@8A>1;82>W >15@56=>ABV ?@8 70AB>AC20==V
>4=>:>=5=B=8E 01> :><1V=>20=8E EVB5@0?52B8G=8E ?@5?0@0BV2, O:V <>6CBL A?@8G8=8B8
BO6:C B@><1>F8B>?5=VN.

@8 70AB>AC20==V ?@5?0@0BC 4;O <>1V;V70FVW !1C;> 28O2;5=> 7<5=H5==O ABC?5=O BO6:>ABV
V B@820;>ABV B@><1>F8B>?5=VW, 7C<>2;5=>W AC?@5A82=>N 01> 01;0B82=>N EVB5@0?VTN.
=HV 70E>48 157?5:8.

D5:B82=VABL ?@5?0@0BC 4;O E2>@8E 7V 7=0G=> 7=865=>N :V;L:VABNW4=8E ;;VB8=-
?>?5@54=8:V2 =5 282G0;0AO. \$V;3@0AB8< ?V428ICT :V;L:VABL =59B@>DV;V2 H;OE x 2?;82C, ?5@H
70 2A5 =0 ;;VB8=8-?>?5@54=8:8 =59B@>DV;V2. ">@8E 7V 7=865=>N :V;L:VABN ;;VB8=-?>?5@54=8:V2
(=0?@8:;04 C @57C;LB0BV ;V:C20==O V=B5=A82=>N ?@>5=52>N B5@0?VTN 01> EVB5@0?VTN,
01> 2=0A;V4>: V=DV;LB@0FVW :VAB:>2>3><>7:C ?CE;8==8<8 ;;VB8=0<8) :V;L:VABL CB2>@N20=8E
=59B@>DV;V2 <>65 1CB8 7=865=0.

A=CNBL 40=V I>4> @>728B:C @50:FVW «B@0=A?;0=B0B ?@>B8 E07OW=0» V ;5B0;L=8E 28?04:V2 C
E2>@8E, O:V >B@835==>W B@0=A?;0=B0FVW :VAB:>2>3><>7:C.

>1V;V70FVO ?5@8D5@8G=8E AB>21C@>28E ;;VB8= :@>2V (!).

>?5@54=T ;V:C20==O F8B>B>:A8G=8<8 70A>10<8.

E2>@8E, O:8< @0=VH5 ?@>2>48;8 V=B5=A82=C AC?@5A82=C B5@0?VN, =0 B;V 70AB>AC20==O
DV;3@0AB8< CD34+ ;;VB8=/:3) 01> ?V428I5==O H284:>ABV 2V4=>2;5==O B@><1>F8BV2.

5O:V F8B>B>:A8G=V 70A>18 ?@>O2;ONBL >A>1;82C B>:A8G=VABL 2V4=>A=> ;;VB8=-

?>?5@54=8:V2 35<>?>57C B0 =530B82=> 2?:820NBL =0 WE <>1V;V70FVN. "@820;5 70AB>AC20==O
?@5?0@0BV2 <5;D0;0=, :0@1>?;0B8= 01> :0@BCNU) ?5@54 <>1V;V70FVTN ;;VB8=-?>?5@54=8:V2
<>65 ?@8725AB8 4> ?>3V@H5==O @57C;LB0BV2. 4=0: >4=>G0A=5 70AB>AC20==O <5;D0;0=C,
:0@1>?;0B8=C 01> BCNU 7 DV;3@0AB8<< 5D5:B82=5 ?@8 <>1V;V70FVW !. /:I> ?;0=CTBLAO
B@0=A?;0=B0FVO !, @5:><5=4CTBLAO ?@>25AB8 <>1V;V70FVN AB>21C@>28E ;;VB8= =0 @0==V9
AB04VW ;V:C20==O E2>@>3>. A>1;82C C203C A;V4 725@=CB8 =0 :V;L:VABL ;;VB8=-?>?5@54=8:V2,
0:B82>20=8E C B0:8E E2>@8E 4> 70AB>AC20==O ?@5?0@0BV2 EVB5@0?VW C 28A>:8E 4>70E. /:I>
@57C;LB0B8 <>1V;V70FVW 2V4?>2V4=> 4> 28I5=02545=8E :@8B5@VW2 =54>AB0B=V, A;V4
@>73;O=CB8 70AB>AC20==O 0;LB5@=0B82=8E <5B>4V2 ;V:C20==O, O:V =5 ?>B@51CNBL
28:>@8AB0==O ;;VB8=-?>?5@54=8:V2.

FV=:0 :V;L:>ABV <>1V;V7>20=8E ?5@8D5@8G=8E AB>21C@>28E ;;VB8= :@>2V.
@8 ?@>2545==V >FV=:8 :V;L:>ABV !, <>1V;V7>20=8E C E2>@8E, O:V >B@8<0;8 B5@0?VN V7
70AB>AC20==O< DV;3@0AB8A>1;82C C203C A;V4 ?@84V;OB8 <5B>4C :V;L:VA=>3> 287=0G5==O.
57C;LB0B8 ?@>B>G=>3> F8B><5B@8G=>3> 0=0;V7C :V;L:>ABV CD34+--;VB8= 7=0G=>
2V4@V7=ONBLAO 70;56=> 2V4 70AB>A>20=>W <5B>4>;>3VW 287=0G5==O, >B65, A;V4 7
>15@56=VABN AB028B8AL 4> @57C;LB0BV2 287=0G5==O WE :V;L:>ABV, >B@8<0=8E 2 V=H8E
;01>@0B>@VOE.

57C;LB0B8 AB0B8AB8G=>3> 0=0;V7C 270T<>7207:C :V;L:>ABV 22545=8E CD34+--;VB8= B0
H284:>ABV =>@<0;V70FVW :V;L:>ABV B@<1>F8BV2 ?VA;O ?@>2545==O EVB5@0?VW V7
70AB>AC20==O< 28A>:8E 4>7 EV?@5?0@0BV2 A2V4G0BL ?@> A:;04=C, 0;5 ?>ABV9=C 70;56=VABL.
5:><5=40FVW AB>A>2=> =5>1EV4=>ABV 70157?5G5==O 6 CD34+ ;;VB8=/:3 '@C=BCNBLAO =0
>?C1;V:>20=8E 40=8E ?@> 4>A2V4 045:20B=>3> 2V4=>2;5==O 35<0B>;>3VG=8E ?>:07=8:V2. @8
@V2=V, I> ?5@528ICT<5=4>20=89, B@820;VH0.

A>1;82V 70E>48 157?5:8 4;O 74>@>28E 4>=>@V2, O:V ?@>E>4OBL <>1V;V70FVN !.
>1V;V70FVO !74>@>28E 4>=>@V2 2?:820T =0 AB0= WE=L>3> 74>@>2O V 70AB>A>2CTBLAO
28=OB:>2> 4;O >B@8<0==O 0;>35==8E AB>21C@>28E ;;VB8= 4;O B@0=A?;0=B0FVW.
>=>@8, O:8< ?@>2>4OBL <>1V;V70FVN !4;O B@0=A?;0=B0FVW, ?>28==V 2V4?>2V40B8 AB0=40@B=8
< 28<>30< 70 ;;V=VG=8<8 ?>:07=8:0<8 B0 @57C;LB0B0<8 ;01>@0B>@=8E 0=0;V7V2, I> 28AC20NBLAO
4> 4>=>@V2 AB>21C@>28E ;;VB8=. A>1;82C C203C A;V4 725@B0B8 =0 ?>:07=8:8 0=0;V7V2 :@>2V B0
=0O2=VABL V=D5:FV9=8E 70E2>@N20=L. 57?5:0 B0 5D5:B82=VABL 22545==O DV;3@0AB8@>28<
4>=>@0< 2V:<< 4> 16 B0 2V4 60 @>:V2 =5 >FV=N20;8AL.

@8 =5>1EV4=>ABV ?@>2545==O 1V;LH =V6 >4=VTW ?@>F54C@8 ;59:0D5@57C >A>1;82C C203C
A;V4 ?@84V;OB8 4>=>@0<, 2<1>F8BV2 C :@>2V O:8E 4> ?>G0B:C ;59:0D5@57C AB0=>28BL
< 100 E 10%;; O: ?@028;>, ?@>2545==O ;59:0D5@57C =5 @5:><5=4>20=> ?@8 2<1>F8BV2 <
75 E 10%;

59:0D5@57 =5 ?@>2>48BLAO 4>=>@0<, O:V ?>B@51CNBL 0=B8:>03C;O=B=>W B5@0?VW 01> C O:8E
T ?>@CH5==O 35<>AB07C.

>40;LH5 22545==O DV;3@0AB8 7<5=H8B8 9>3> 4>7C C 28?04:0E 7@>AB0==O ;59:>F8BV2 4> @V2=O,
I> ?5@528ICT 70 E 10%;

>=VB>@8=3 AB0=C 4>=>@V2, O:V >B@8
74>@>28E 4>=>@V2 ?VA;O 22545==O G-CSF A?>AB5@V30;8AL B8V F8B>35==V 7

87=0G5==O 4>23>B@820;>W 157?5:8 ?@5?0@0BC ?@8 22545==V 4>=>@0< B@820T. 878: A?@80==O
CB2>@5==N 7;>O:VA=8E ;;>=V2 W4=8E ;;VB8= =5 28;;NG5=89. &5=B@0< 0D5@57C @5:><5=4>20=>
?@>2>48B8 A8AB5<0B8G=V >1AB565==O 4>=>@V2 AB>21C@>28E ;;VB8= C ?5@V>4 I>=09<5=H5 10
@>:V2 4;O 70157?5G5==O <=>VB>@8=3C ?>:07=8:V2 4>23>B@820;>W 157?5:8.

'0AB8<8 T 28?04:8 157A8<=>W A?;5=><530;VW. 8?04:8 @>7@82C A5;57V=:8 C 74>@>28E 4>=>@V2 B0
?0FVT=BV2 2=0A;V4>: 22545==O G-CSF A?>AB5@V30;8AO 4C65 @V4>: 0DV:A>20=> :V;L:0 28?04:V2
;5B0;L=>3> @>7@82C A5;57V=:8. B65, =5>1EV4=8< T @5B5;L=89 <=>VB>@8=3 @>725 >1AB565==O).
!;V4 28;;NG8B8 4V03=>7 @>7@82C A5;57V=:8 C 4>=>@V2 B0/01> ?0FVT=BV2, O:V A:0@60BLAO =0
1V;L C ;V2V9 25@E=V9 G0AB8=V 682>B0 01> C ;V2>

28?04:C ?V4>7@8 01> ?V4B25@465==O ?>1VG=>3> O28I0 7 1>:C ;535=V2 ?>40;LH5 70AB>AC20==O
DV;3@0AB82V4=C <548G=C 4>?><>3C.

"@0=A?;0=B0FVO 0;>35==8E !, <>1V;V7>20=8E 22545==O< DV;3@0AB8

0=V A2V4G0BL ?@> B5, I> V;>3VG=V9 270T<>4VW 0;>35==8E !V @5F8?VT=B0 2;0AB8289 1V;LH89 ABC?V=L @878:C @>728B:C 3>AB@>W @50:FVW B@0=A?;0=B0B0 ?@>B8 E07OW=0 ?>@V2=O=> 7 B@0=A?;0=B0FVTN :VAB:>2>3> <>7:C.

A>1;82V 70E>48 157?5:8 4;O ?0FVT=BV2 7 ""%.

>A;V465==O A.:04C :@>2V.

5>1EV4=8< T @5B5;L=89 <=>VB>@8=3 :V;L:>ABV B@<1>F8BV2, >A>1;82> ?@>BO3<< ?5@H8E B86=V2 B5@0?VW V7 70AB>AC20==O< DV;3@0AB8728B:C B@<1>F8B>?5=VW C ?0FVT=BV2, B>1B> ABV9:>3> 7=865==O 2<1>F8BV2 4> @V2=O < 100 000/<<3, ?>40;LHC B5@0?VN V7 70AB>AC20==O< DV;3@0AB82> 2V4 7<5=H8B8 9>3> 4>7C.

>6;82V 9 V=HV 7@2V, 2 B>25 ?V428I5==O 2W4=8E ;;VB8--?>?5@54=8:V2; =5>1EV4=89 @5B5;L=89 <=>VB>@8=3 D>@2V.

"@0=AD>@<0FVO 2 ;59:>7 01> ?5@54;59:>7.

A>1;820 >15@56=VABL =5>1EV4=0 ?@8 4V03=>AB8FV BO6:>W E@>=VG=>W =59B@>?5=VW, I>1 48D5@5=FVN20B8 WE 2V4 V=H8E 35<0B>;>3VG=8E 70E2>@N20=L, B0:8E O: 0?;0AB8G=0 0=5 48A?;07VO B0 ;59:>7. > ?>G0B:C ;V:C20==O A;V4 ?@>25AB8 @>73>@=CB89 0=0;V7 :@>2V 7 287=0G5==O< ;59:>F8B0@=>W D>@ABV B@<1>F8BV2, 0 B0:>6 287=0G8B8 <>@D>;>3VG=C :0@B8=C :VAB:>2>3> <>7:C 9 :0@V>B8?.

28?04:0E 28=8:=5==O C ?0FVT=B0 7 BO6:>N E@>=VG=>N =59B@>?5=VTN F8B>35=5B8G=8E ?>@CH5=L A;V4 C206=> 72068B8 A?V22V4=>H5==O :>@8ABV B0 @878:C ?>40;LH>3> 70AB>AC20==O DV;3@0AB840;LH5 22545==O DV;3@0AB848A?;0AB8G=>3> A8=4@> ;59:5<>, G8 ?V428ICT 4>23>B@820;0 B5@0?VO V7 70AB>AC20==O< DV;3@0AB8N E@>=VG=>N =59B@>?5=VTN @878: F8B>35=5B8G=8E ?>@CH5=L, ! 01> B@0=AD>@<0FVW 70E2>@N20==O =0 ;59:5@D>;>3VG=5 B0 F8B>35=5B8G=5 >1AB565==O :VAB:>2>3> <>7:C ?0FVT=BV2 A;V4 ?@>2>48B8 @53C;O@=>, 7 V=B5@20;< ?@81;87=> :>6=V 12

=HV 70E>48 157?5:8.

!;V4 28;;NG8B8 V=HV ?@8G8=8 28=8:=5==O =59B@>?5=VW, =0?@8;;04 2V@CA=V V=D5:FVW. 1V;LH5==O A5;57V=:8 T 157?>A5@54=V< =0A;V4:< 22545==O DV;3@0AB872>48B8 @53C;O@=>.

0;L?0FVO 682>B0 T 4>AB0B=V< <5B>4<< 4;O 287=0G5==O 0=><0;L=>3> 71V;LH5==O >1T 5<0BC@VO/?@>B5W=C@VO A?>AB5@V30;0AL C =525;8:>W :V;L:>ABV ?0FVT=BV2. ;O A2>TG0A=>3> 287=0G5==O F8E O28I =5>1EV4=5 @53C;O@=5 ?@>2545==O 0=0;V7C A5GV.

>:07=8:8 157?5:8 B0 5D5:B82=>ABV ?@8 70AB>AC20==V =>2>=0@>465=8< B0 ?0FVT=B0< 7 0CB>VN =59B@>?5=VTN =5 287=0G5=>.

-V=D5:FVO.

\$>@2V.

5>1EV4=89 @5B5;L=89 <=>VB>@8=3 7=0G5==O, >A>1;82> C ?5@V>4 ?5@H8E B86=V2 B5@0?VW V7 70AB>AC20==O< DV;3@0AB8AB5@V30TBLAO 4C65 H284:0 @50:FVO 7V 7=0G=8< ?V428I5==O< :V;L:>ABV =59B@>DV;V2 C 2V4?>2V4L =0 ?5@HC 4>7C DV;3@0AB8<5=4CTBLAO I>45==5 287=0G5==O ?@>BO3<< ?5@H8E 2-3 4=V2 22545==O DV;3@0AB840;LH>BO3<< ?5@H8E 2 B86=V2, 287=0G5==O @5:><5=4>20=> ?@>2>48B8 I>=09<5=H5 2 @078 =0 B8645=L, =040;V 1 @07 =0 B8645=L B0 G5@57 :>6=V 2 B86=V C ?5@V>4 ?@>2545==O ?V4B@8W B5@0?VW. # ?5@V>4 G5@3>2>3> 22545==O DV;3@0AB8 287=0G5=>N 4>7>N B0 4>7>N 30 4/4>1C (300 1C) <>6;82V 1V;LHV :>;820==O 7=0G5==O ?0FVT=B0. ;O 287=0G5==O 2V ?0FVT=B0 4;O 0=0;V7C 2A5@54=L> ?5@54 ?;0=>28< 22545==O< DV;3@0AB8

878.; 7C<>2;5=89 70AB>AC20==O< ;V:0@AL:8E ?@5?0@0BV2 AC?@5A82=>W 4VW ?V428I5=8<8 4>70 <8.

2545==O DV;3@0AB8;L>20=> =5 28;;NG0T <>6;82>ABV 28=8:=5==O B@<1>F8B>?5=VW B0 0=5 AC?@5A82=>N EVB5@0?VTN. #=0A;V4>: >B@8<0==O EV?@5?0@0BV2 C 1V;LH8E 4>70E 01> 70AB>AC20==O 1V;LH>W :V;L:>ABV B0:8E ?@5?0@0BV2 C :<1V=0FVW 7 DV;30AB@8<< @878: @>728B:C B@<1>F8B>?5=VW B0 0=52V.

=D5:FV9=V B0 7;>O:VA=V 70E2>@N20==O, I> A?@8G8=ONBLAC?@5AVN.

>728B>: =59B@>?5=VW <>65 1CB8 =0A;V4:< V=DV;LB@0FVW C :VAB:>289<>7>: 71C4=8:V2 >?>@BC=VAB8G=8E V=D5:FV9, B0:8E O: ?@54AB02=8:8 10:B5@V9 *Mycobacterium avium*, 01> C@065==O 9>3> 7;>O:VA=8<8 =>2>CB2>@5==O<8, =0?@8;;04, ;V<>N. # 28?04:C =0O2=>ABV C

?0FVT=B0 V=D5:FV9=8E 70E2>@N20=L 01> 7;>O:VA=8E =>2>CB2>@5=L, I> 2@060NBL :VAB:>289 <>7>;, 4;O CAC=5==O =59B@>?5=VW, :@V< 22545==O DV;3@0AB81EV4=> ?@>25AB8 2V4?>2V4=C B5@0?VN 4;O ;V:C20==O 70E2>@N20==O. ?;82 DV;3@0AB8?5=VW, A?@8G8=5=>W V=D5:FV9=8-8 70E2>@N20==O<8 01> 7;>O:VA=8<8 =>2>CB2>@5==O<8, I> C@060NBL :VAB:>289<>7>;, =5 287=0G02AO.

=HV 70E>48 157?5:8.

5>1EV4=> 28;;NG8B8 B0:V ?@8G8=8 B@0=78B>@=>W =59B@>?5=VW O: 2V@CA=V V=D5:FVW. 1V;LH5==O A5;57V=:8 T 2V@>3V4=8< 5D5:B><, ?>2 O70=8< 7 ;V:C20==O< DV;3@0AB8<>1EV4=> @53C;O@=> :>=B@>;N20B8 @>73;O4V.

=525;8:>W :V;L:>ABV E2>@8E A?>AB5@V30;8AO 35<0BC@VO/?@>B5W=C@VO. ;O 28;;NG5==O F8E ?@>O2V2 A;V4 @53C;O@=> ?@>2>48B8 :>=B@>;L 7030;L=>3> 0=0;V7C A5GV.

57?5:0 V 5D5:B82=VABL 70AB>AC20==O ?@5?0@0BC =>2>=0@>465=8< V E2>@8< 7 0CB>VN =59B@>?5=VTN =5 2AB0=>2;5=V.

=865==O @878:C 10:B5@V0;L=8E V=D5:FV9 B0 ;V:C20==O ABV9:>W =59B@>?5=VW C ?0FVT=BV2 7 @>73>@=CB>N AB04VTN -V=D5:FVW.

V;L:VABL ;VB8= :@>2V.

5>1EV4=> @5B5;L=> :>=B@>;N20B8 01A>;NB=C :V;L:VABL =59B@>DV;V2 (), >A>1;82> ?@>BO3< ?5@H8E B86=V2 B5@0?VW ?@5?0@0B>@8E <>65 2V47=0G0B8AO 4C65 H284:5 V 7=0G=5

71V;LH5==O ?@8 ?>G0B:>2V9 4>7V. @>BO3< ?5@H8E 2-3 4V1 70AB>AC20==O ?@5?0@0BC @5:> <5=4CTBLAO I>4=O 287=0G0B8 . # ?>40;LH>W B5@0?VW. # @07V ?5@5@28 C 70AB>AC20==V

?@5?0@0BC 2 4>7V 30 <;= /4>1C (300 1C) C E2>@8E ?V4 G0A ;V:C20==O<>65 A?>AB5@V30B8AO 7=0G=5 :>;820==O . <5B>N 287=0G5==O

878.; 7C<>2;5=89 70AB>AC20==O< 28A>:8E 4>7 AC?@5A82=8E ;V:0@AL:8E 70A>1V2.

>=>B5@0?VN ?@5?0@0B>< @0AB8<®=5 70AB>A>2C20B8 4;O 70?>1V30==O @>728B:C B@> <1>F8B>?5=VW V 0=5AC?@5A82=8E ?@5?0@0BV2. # 28?04:C 70AB>AC20==O 1V;LH 28A>:8E 4>7 01>

>4=>G0A=> :V;L:>E AC?@5A82=8E ;V:0@AL:8E 70A>1V2 C ?>T4=0==V 7 B5@0?VTN ?@5?0@0B< @0AB8<® @878: @>728B:C B@><1>F8B>?5=VW V 0=5<5=4CTBLAO @53C;O@=89 :>=B@>;L

7030;L=>3> 0=0;V7C :@>2V.

>728B>: AC?@5AVW 2=0A;V4>: V=D5:FV9 01> ?CE;8==8E =>2>CB2>@5=L.

59B@>?5=VO <>65 1CB8 7C<>2;5=0 C@065==O< :VAB:>2>3><>7:C ?@8 ?>@BC=VAB8G=8E

V=D5:FVOE, A?@8G8=5=8E 71C4=8:0<8 Mycobacterium avium complex 01> 7;>O:VA=8<8

=>2>CB2>@5==O<8, =0?@8;;04, ;V<N. @8 28O2;5==V V=DV;LB@0B82=>3> C@065==O :VAB:>2>3> <>7:C 70?0;L=>3> ?>E>465==O 01> 7;>O:VA=>3> =>2>CB2>@5==O >4=>G0A=> V7 70AB>AC20==O<

?@5?0@0BC □@0AB8<® 4;O ;V:C20==O =59B@>?5=VW =5>1EV4=> ?@87=0G8B8 2V4?>2V4=C B5@0?VN 4V03=>AB>20=8E 70E2>@N20=L. D5:B82=VABL 70AB>AC20==ODV;3@0AB8?@8

;V:C20==V =59B@>?5=VW, 7C<>2;5=>W C@065==O< :VAB:>2>3><>7:C V=D5:FV9=>3> 35=57C 01> ?CE;8==8<8 =>2>CB2>@5==O<8, =5 2AB0=>2;5=0.

=HV 70AB5@56=V 70E>48.

40=V I>4> @V4:VA=8E 28?04:V2 =51060=>3> 2?;82C =0 >@30=8 48E0==O, 7>:@5<0 I>4> @>728B:C V=B5@AB8FV0;L=>W ?=52<>=VW =0 B;V 70AB>AC20==O G-CSF. %2>@V, O:V =5I>402=> ?5@5=5A;8

V=DV;LB@0B82=5 70E2>@N20==O ;535=V2 01> ?=52<>=VN, <>6CBL <0B8 28A>:89 @878.. >O20 B0:8E A8A;V465==V B0 >7=0:0<8 ?@>3@5ACNG>W 48E0;L=>W =54>AB0B=>ABV 40NBL 7<>3C

?@8?CAB8B8 =0O2=VABL @5A?V@0B>@=>3> 48AB@5A-A8=4@>@>A;8E (!). # 28?04:C 28O2;5==O !70AB>AC20==O ?@5?0@0BC □@0AB8<® A;V4 ?@8?8=8B8 V ?@87=0G8B8 2V4?>2V4=5 ;V:C20==O.

%2>@8< V7 AC?CB=L>N :VAB:>2>N ?0B>;>3VTN B0 >AB5>?>@>7<, ?@8 B@820;>AC20==V ?@5?0@0BC @5:><5=4CTBLAO @53C;O@=> :>=B@>;N20B8 IV;L=VABL :VAB:>2>W B:0=8=8.

>15@56=VABN A;V4 ?@87=0G0B8 ?@5?0@0B ?0FVT=B0< V7 A5@?>284=>.;VB8==>N 0=5A:V;L:8 2V= <>65 ?@>2>:C20B8 @>728B>: A5@?>284=>.;VB8==>3> :@87C, V=:>; 8 ;5B0;L=>3>. "0:8< E2>@8<

=5>1EV4=> C E>4V B5@0?VW ?8;L=> :>=B@>;N20B8 2V4?>2V4=V ;V=VG=V V ;01>@0B>@=V ?>:07=8:8, 725@B0NG8 >A>1;82C C203C =0 <>6;825 71V;LH5==O A5;57V=:8 B0 @>728B>: B@><1>7C

:@>2>=>A=8E AC48=.

@8 @5=B35=>3@0DVW :VAB:>2>W B:0=8=8 2 48=0?V428I5==O 35<>?>5B8G=>W 0:B82=>ABV

:VAB:>2>3><>7:C C 2V4?>2V4L =0 B5@0?VN D0:B>@> @>ABC. &V 40=V A;V4 2@0E>2C20B8 ?@8 0=0;V7V @57C;LB0BV2 @5=B35=>3@0DVW :VAB>..

@5?0@0B @1VB, B>

40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> @>I>BV 7
V=H8<8 <5E0=V7<0<8. 5 ?>2V4><;O;>AO ?@> 28?04:8 =51060=>3> 2?;82C ?@5?0@0BC @0AB8<®=0
H284:VABL ?A8E<>B>@=8E @50:FV9. 5 2AB0=>2;5=> 2?;82C ?@5?0@0BC =0 740B=VABL :5@C20B8
02B>B@0=A?>@B< 01> ?@0FN20B8 7 V=H8<8 <5E0=V7<0<8.

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9. 5 2AB0=>2;5=V 157?5:0 B0
5D5:B82=VABL 22545==O ?@5?0@0BC 2 >48= 45=L 7AC?@5A82=8<8 F8B>B>:A8G=8<8 EV?@5?0@0B0
<8. '5@57 GCB;82VABL W4=8E ;;VB8=, I> H284:> 4V;OBLAO, ?@87=0G0B8 @0AB8<® 2 V=B5@20;V 24
3>48=8 4> 01> ?VA;O 22545==O ?@5?0@0BV2 4;O AC?@5A82=>W F8B>B>:A8G=>W EVB5@0?VW =5
@5:><5=4CTBLAO.

@8 >4=>G0A=> V 5-DB>@C@0F8;C BO6:VABL =59B@>?5=VW <>65 ?>A8;8B8AL. 70T<>4VO 7 V=H8
<8 35<>?>5B8G=8<8 D0:B>@0<8 @>ABC V F8B>:V=0<8 =52V4><0.

A:V;L:8 ;V BV9 AB8DV;V2, <>6;825 ?>A8;5==O 4VW ?@5?0@0BC ?@8 :<<1V=>20=>
>3;O4C =0 D0@<0F52B8G=C =5AC7G8=>< =0B@VN E;>@84C.

\$0@<0:>;>3VG=V 2;0AB82>ABV.

\$0@<0:>48=0.

:B82=>N @5G>28=>N ?@5?0@0BC T DV;3@0AB8< @5:><1V=0=B=89 ;N4AL:89 3@0=C;>F8B0@=89
:>;>=VTAB8@ (G-CSF). \$V;3@0AB8< <0T B0:C A0;>3VG=C 0:B82=VABL, O: V 5=4>35==89 ;N4AL:89 G-
CSF, V 2V4 >AB0==L>3> 2V4@V7=OTBLAO ;8H5 B8<, I> O2;OT A>1>N =53;V:>78;L>20=89 1V;>; 7
4>40B:>28< N:-V=F528< 70;8H:>< <5BV>=V=C. \$V;3@0AB8<, O:89 >45@6CNBL 70 B5E=>;>3VTN @5:>
<1V=0=B=>W , 284V;ONBL V7 ;;VB8= 10:B5@VW *Esherichia coli*, 4> A;;04C 35=5B8G=>3> 0?0@0BC
O:8E 22545=> 35=, I> :>4CT 1V;>; G-CSF.

N4AL:89 3@0=C;>F8B0@=89 :>;>=VTAB8@ 3;V:>?@>B5W= @53C;NT AB2>@5==O
DC=:FV>=0;L=> 0:B82=8E =59B@>DV;L=8E 3@0=C;>F8BV2 B0 WE 28EV4 C :@>2 7 :VAB:>2>3>
<>7:C. \$V;3@0AB8< 7=0G=> 71V;LHCT :V;L:VABL =59B@>DV;L=8E 3@0=C;>F8BV2 C
?5@8D5@8G=V9 :@>2V 265 ?@>BO3< ?5@H8E 24 3>48= ?VA;O 22545==O B0 >4=>G0A=>
?@872>48BL 4> 45O:>3> 71V;LH5==O :V;L:>ABV<=>F8BV2. 1V;LH5==O :V;L:>ABV
=59B@>DV;L=8E 3@0=C;>F8BV2 ?@8 70AB>AC20==V ?@5?0@0BC 2 4V0?07>=V @5:><5=4>20=8E
4>7 70;568BL 2V4 25;8G8=8 4>78. E DC=:FV>=0;L=V 2;0AB82>ABV =>@<0;L=V 01> ?>A8;5=V, ?@> I>
A2V4G0BL @57C;LB0B8 4>A;V465==O E5<>B0:A8AC V D03>F8B>7C. VA;O 70:V=G5==O ;V:C20==O
?@5?0@0B>< :V;L:VABL =59B@>DV;L=8E 3@0=C;>F8BV2 C ?5@8D5@8G=V9 :@>2V
7=86CTBLAO =0 50 % ?@>BO3< 1-2 4=V2 V 4> =>@<0;L=>3> @V2=O ?@>BO3< 1-7 4=V2.
0AB>AC20==O DV;3@0AB8 7<5=HCT G0AB>BC, BO6:VABL B0 B@820;VABL =59B@>?5=VW C
E2>@8E ?VA;O EVB5@0?VW F8B>AB0B8:0<8 01> 01;0B82=>W B5@0?VW 7 ?>40;LH>N
?5@5A04:>N :VAB:>2>3> <>7:C. 0AB>AC20==O DV;3@0AB8B5@0?VW, 0:B82CT ;;VB8=8-
?>?5@54=8:8 35<>F8BV2 ?5@8D5@8G=>W :@>2V (). &V 0CB>;>3VG=V<>6=0 7018@0B8 C
E2>@>3> V 22>48B8 9>AB0B8:0<8 C 28A>:8E 4>70E 01> 702>3> <>7:C, 01> O: 4>?>2=5==O 4>
=5W. 2545==O ?@8A:>@NT 2V4=>2;5==O :@>2>B2>@5==O, 75=HCT =5157?5:C 35<>@03VG=8E
CA;;04=5=L V ?>B@51C C ?5@5;820==V B@<1>F8B0@=>W <0A8.

4VB59 B0 4>@>A;8E V7 BO6:>N E@>=VG=>N =59B@>?5=VTN DV;3@0AB8< AB01V;L=> 71V;LHCT
:V;L:VABL =59B@>DV;L=8E 3@0=C;>F8BV2 C ?5@8D5@8G=V9 :@>2V B0 7=86CT G0AB>BC
V=D5:FV9=8E CA;;04=5=L.

\$0@<0:>:V=5B8:0.

/: ?@8 2=CB@VH=L>25==>AB5@V30TBLAO ?>78B82=0 ;V=V9=0 70;56=VABL 9>3> :>=F5=B@0FVWC
?;072V 2V4 4>78. VA;O ?V4H:V@=>3> 22545==O @5:><5=4>20=8E 4>7 ?@5?0@0BC :>=F5=B@0FVO C
A82>@>BFV :@>2V ?5@528ICT 10 =3/<; ?@>BO3<< 8-16 3>48=; >1□T< @>7?>4V;C2 :@>2V
AB0=>28BL 1;87L:> 150 <;/3. /: ?VA;O ?V4H:V@=>3>, B0: V ?VA;O 2=CB@VH=L>25==>3> 22545==O
5;V@30=V72V40T :V=5B8FV 1-3> ?>@O4:C. !5@54=T 7=0G5==O ?5@V>4C =0?V2282545==O
DV;3@0AB820B:8 :@>2V AB0=>28BL 1;87L:> 3,5 3>48=8, 0 H284:VABL::V@5=AC ?@81;87=>

0,6 <;/E2/:3. 57?5@5@2=5 22545==O H;OE<< V=DC7VW ?@>BO3<< 28 4=V2 E2>@8<, O:V
>4C6CNBL ?VA;O 0CB>;>3VG=>W ?5@5A04:8 :VAB:>2>3><>7:C, =5 AC?@>2>46C20;>AO >7=0:0<8 :C
4C =0?V2282545==O ?@5?0@0BC.

\$0@<0F52B8G=V E0@0:B5@8AB8:8.

A=>2=V DV78:>-EVABV: ?@>7>@89 15710@2=89 @>7G8=, 2V;L=89 2V4 2848<8E G0AB>: B0
AB>@>==VE 2;:NG5=L.

"5@ABV.2 @>:8.

#<>28 715@V30==O. 15@V30B8 2 =54>ABC?=>□.
5 70<>@>6C20B8.

#?0:>2:0.> 1 <; C D;0:>=V, ?> 1 D;0:>=C 2 :0@B>==V9 :>@>1FV.
> 1 <; C ?>?5@54=L> =0?>2=5=> 1 H?@8FC 2 :0@B>==V9 :>@>1FV.

0B53>@VO 2V4?CA:C. 0 @5F5?B>

8@>1=8:.-@ 544VA 01>@0B>@VA B4, =4VO.

VAF57=0E>465==O.V;L=8FO 47, A. 0GC?0;V, CB1C;0?C@ 0=40;, >:@C3 0=30 544V, =4@0 @045H, =4VO.