

!" #&/
4;O <548G=>3> 70AB>AC20==O ;V:0@AL:>3> 70A>1C

!"® 30
(MIXTARD® 30)

!,:04:
4VNG0 @5G>28=0: V=AC;V= ;N4AL:89 (@);
1 <; ACA?5=7VW 4;O V=T:FV9 100 (3,5 <3) V=AC;V=C ;N4AL:>3> 1V>A8=B5B8G=>3>, 30 %
@>7G8==>3> V=AC;V=C, 70 % :@8AB0;V2 V7>D0=-V=AC;V=C, 28@>1;5=>3> 70 B5E=>;>3VTN @2
Saccharomyces cerevisiae,
1 D;0:>=
1 (V6=0@>4=0 48=8FO) AB0=>28BL 0,035 <3 1572>4=>3> ;N4AL:>3> V=AC;V=C;
4>?>28=8: F8=:C E;>@84, 3;VF5@8=, <5B0:@57>;, D5=>;, =0B@VN 3V4@>D>AD0B 483V4@0B,
=0B@VN 3V4@>:A84, :8A;>B0 E;>@8AB>2>4=520 @>72545=0, ?@>B040 4;O V='T:FV9.

V:0@AL:0 D>@<0. !CA?5=7VO 4;O V=T:FV9.
A=>2=V DV78:>-EVABV: =59B@0;L=0 :0;03> :>;L>@C 2>4=0 ACA?5=7VO ;N4AL:>3> V=AC;V=C.

\$0@<0:>B5@0?52B8G=0 3@C?0. =B84V015B8G=V ?@5?0@0B8. <1V=0FVW V=AC;V=V2 :>@>B:>W
B0 A5@54=L>W B@820;>ABV 4VW. >4 ""% 10D01.

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

\$0@<0:>48=0
?L=89 5D5:B V=AC;V=C ?>;O30T C A?@8O==V ?>3;8=0==N 3;N:>78 B:0=8=0<8 ?VA;O 72O7C20==O
V=AC;V=C 7 @5F5?B>@0<8 <O7>28E V 68@>28E ;;VB8=, 0 B0:>6 2 >4=>G0A=>78 7 ?5GV=:8.
V:AB0@4® 30 T V=AC;V=<;, I> A:;040TBLAO 7 42>E G0AB8=
A5@54=L>DV;L 4VW ?VA;O ?V4H:V@=>W V=T:FVW B0:89:
?>G0B>: 4VW ?@>B03<< 0,5 3>48=8;
<0:A8<0;L=89 5D5:B 2V4 2 4> 8 3>48=;
B@820;VABL 4VW ?@81;87=> 24 3>48=8.
\$0@<0:>:V=5B8:0.
5@V>4 =0?V2282545==O V=AC;V=C 7 :@>2V AB0=>28BL :V;L:0 E28;8=, B>DV;L 4VW ?@5?0@0BC
V=AC;V=C 7C<>2;5=89 28=OB:>2> E0@0:B5@8AB8:0<8 9>3> 01A>@1FVW. &59 ?@>F5A 70;568BL 2V4
@O4C D0:B>@V2 (=0?@8:;04 2V4 4>78 V=AC;V=C, A?>A>1C V
IA>@1FVO. @>DV;L 2A<:BC20==O 287=0G0TBLAO B8<, I> F59 V=AC;V= T AC
E0@0:B5@87CNBLAO H284:8< B0 ?>4>265=8< 2A<:BC20==O=F5=B@0FVW C ?;07@>B:>W 4VW
=0AB0T ?@>B03<< 1,5-2,5 3>48=8 ?VA;O ?V4H:V@=>W V=T:FVW.
>7?>4V;.: =0G=>3> 72'O7C20==O V=AC;V=C 7 1V;:0<8 ?;07<8 :@>2V, 70 28=OB:< F8@:C;NNG8E
0=B8BV; 4> =L>3> (?@8 WE=V9 =0O2=>ABV), 28O2;5=> =5 1C;>.
5B0I>;V7 N4AL:89 V=AC;V= @>7I5?;NTBLAO V=AC;V=>28<8 ?@>B5070<8 G8
V=AC;V=453@04CNG8<8 D5@<5=B0<8 V, <>6;82>, ?@>B5W=48AC;LDV4V7><5@07>N. 8O2;5=> @O4
4V;O=>.: =0 O:8E 2V41C20NBLAO @>7@828 (3V4@>;V7)<>;5:C;8 ;N4AL:>3> V=AC;V=C. >45= 7
<5B01>;VBV2, I> CB2>@8;8AO ?VA;O 3V4@>;V7C, =5<0T 1V>;>3VG=>W 0:B82=>ABV.
;V"@820;VABL =0?V2282545==O V=AC;V=C 287=0G0TBLAO H284:VABN 9>3> 2A<:BC20==O 7
?V4H:V@=>W ;;VB:>28=8. B G>W) V=AC;V=C 7 ?;07<8 :@>2V (t½V=AC;V=C 7 :@>2>B>:C
AB0=>28BL CAL>3> :V;L:0 E28;8=). 0 40=8<8 ?@>2545=8E 4>A;V465=L, t½AB0=>28BL
10 3>48=.

>;V=VG=V E0@0:B5@8AB8:8.
>:070==O.

V:C20==O FC:@>2>3> 4V015BC.

@>B8?>:070==O.

V?>3;V:5 ;N4AL:>3> V=AC;V=C 01> 4> 1C4L-O:>3> V=3@54VT=B0 ?@5?0@0BC.

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.

/: 2V4<>, @O4 ;V:0@AL:8E 70A>1V2 2?;820T =0 >178.

V:0@AL:V 70A>18, O:V<>6CBL 7=86C20B8 ?>B@51C 2 V=AC;V=V

5@>@0;L=V FC:@>7=86C20;L=V 70A>18 (&), V=3V1VB>@8 <=>0:A84078 (), =5A5;5:B82=V □-04@5=>1;>:0B>@8, V=3V1VB>@8 0=3V>B5=78=?5@5B2>@N20;L=>3> D5@<5=BC (\$), A0;VF8;0B8, 0=01>;VG=V AB5@>W48 B0 AC;LD0=V;0

V:0@AL:V 70A>18, O:V<>6CBL ?V428IC20B8 ?>B@51C 2 V=AC;V=V

5@>@0;L=V :=B@0F5?B828, BV07848, 3;N:>:@B8:>W48, B8@5>W4=V 3>@<=>8, A8

□-04@5=>1;>:0B>@8 <>6CBL <0A:C20B8 A8<8 3V?>3;V:52V;L=N20B8 2V4=>2;5==O ?VA;O 3V?>3;V:5 :B@5>B84/;0=@5>B84 <>65 O: 7=86C20B8, B0: V ?V428IC20B8 ?>B@51C 2 V=AC;V=V.

;:>3>;L<>65 ?>A8;N20B8 01> 7<5=HC20B8 3V?>3;V:5

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

5045:20B=5 4>7C20==O 01> ?@8?8=5==O ;V:C20==O (>A>1;82> ?@8 4V015BV B8?C)<>6CBL

?@8725AB8 4> 3V?5@3;V:5B0 4V015B8G=>3> :5B>0F84>7C. 0728G09 ?5@HV A8<8 3V?5@3;V:5

72820NBLAO ?>ABC?>2>, ?@>BO3<:V;L:>E 3>48= 01> 4V1. >=8 2;;NG0NBL 2V4GCBBO A?@038, G0AB5 A5G>28?CA:0==O, =C4>BC, 1;N20==O, A>=:82VABL, ?>G5@2>=V==O V ACEVABL H:V@8, ACEVABL C @>BV, 2B@0BC 0?5B8BC, 0 B0:>6 70?0E 0F5B>=C C ?>2VB@V, I> 2848E0TBLAO.

@8 4V015BV B8?C 3V?5@3;V:5=5 ;V:CTBLAO, ?@872>48BL 4> 4V015B8G=>3> :5B>0F84>7C, O:89 ?>B5=FBV9=> T ;5B0;L=> =5157?5G=8

V?>3;V:5 <>65 28=8:=CB8, O:I> 4>70 V=AC;V=C 70=04B> 28A>:0 ?> 2V4=>H5==N 4> ?>B@518 2

V=AC;V=V. # @07V 3V?>3;V:5O:I> 3V?>3;V:57@NTBLAO, ?@5?0@0B =5 22>48B8.

@>?CA: ?@89> =5?5@5410G5=5 ?V428I5=5 DV78G=5 =020=B065==O <>6CBL ?@8725AB8 4> ?>O28 3V?>3;V:5

%2>@V, C O:8E VAB>B=> ?>;V?H82AO :=B@>;L @V2=O 3;N:>78 2 :@>2V 7024O:8 V=B5=A82=V9 V=AC;V=>B5@0?VW, <>6CBL 2V47=0G8B8 72VA=8:V2 3V?>3;V:5I> WE A;V4 702G0A=> ?>?5@548B8. 28G09=V A8<8-?@>2VA=8:8 <>6CBL 7=8:=CB8 C ?0FVT=BV2 7 4>23>B@820;8< 4V015B>

!C?CB=V 70E2>@N20==O, >A>1;82> V=D5:FVW B0 30@OG:>2V AB0=8, 71V;LHCNBL ?>B@51C 2 V=AC;V=V. !C?CB=V 70E2>@N20==O =8@>;, ?5GV=:8, =04=8@=8:V2, 3V?>DV70, I8B>284=>W 70;>78 <>6CBL A?@8G8=8B8 ?>B@51C C 77 V=AC;V=C. >;8 ?0FVT=B0 ?5@52>4OBL =0 V=H89 B8?

V=AC;V=C, A8<8 3V?>3;V:5 AB0NBL <5=H 28@065=8<8.

5@52545==O E2>@>3> =0 V=H89 B8? 01> 284 V=AC;V=C 2V41C20TBLAO ?V4 AC2>@8< <548G=8< :=B@>;5=F5=B@0FVW, 284C (28@>1=8:0), B8?C, ?>E>465==O V=AC;V=C (;N4AL:89 01> 0=0;>3

;N4AL:>3> V=AC;V=C) B0/01> <5B>4C 28@>1=8FB20 <>65 7C<>28B8 =5>1EV4=VABL :>@5:FVW 4>78 V=AC;V=C. 0FVT=B8, O:8E ?5@52>4OBL =0 V:AB0@4® 30 7 V=H>3> B8?C V=AC;V=C, <>6CBL

?>B@51C20B8 ?V428I5==O :V;L:>ABV 45==8E V=T:FV9 01> 77C20==O ?>@V2=O=> 7 V=AC;V=<, O:89 2>=8 70728G09 70AB>A>2C20;8. 5>1EV4=VABL ?V41>@C 4>78 <>65 28=8:=CB8 O: ?@8 ?5@H>2>3>

?@5?0@0BC, B0: V ?@>BO3< ?5@H8E :V;L:>E B86=V2 01> 3> 70AB>AC20==O.

@8 70AB>AC20==V 1C4L-O:>W V=AC;V=>B5@0?VW <>6CBL 28=8:=CB8 @50:FVW C ® 30 . 5@54 ?>4>@>6C20==O< 7V 7N G0A>28E ?>OAV2 E2>@8< A;V4 >B@8<0B8 :=AC;LB0FVN ;V:0@O,

>A:V;L:8 ?@8 FL>

!CA?5=7VW V=AC;V=C =5 A;V4 70AB>A>2C20B8 2 V=AC;V=>28E =0A>A0E 4;O B@820;>3>

?V4H:V@=>3> 22545==O V=AC;V=C.

<<1V=0FVO BV07>;V48=4V>=V2 B0 ?@>4C:BV2 V=AC;V=C

@8 70AB>AC20==V BV07>;V48=4V>=V2 C :<1V=0FVW 7 V=AC;V=< ?>2V4<>;O;>AO ?@> 28?04:8

@>728B:C 70ABV9=>W A5@F52>W =54>AB0B=>ABV, >A>1;82> C E2>@8E 7 D0:B>@0<8 @878:C

@>728B:C 70ABV9=>W A5@F52>W =54>AB0B=>ABV. &5 20@B> 2@0E>2C20B8 ?@8 ?@87=0G5==V

;V:C20==O :<1V=0FVTN BV07>;V48=4V>=V2 7 V=AC;V=<1V=>20=>AC20==V F8E ?@5?0@0BV2

?0FVT=B8 ?>28==V ?5@51C20B8 ?V4 =03;O4<;V:0@O I>4> @>728B:C >7=0: B0 A8W A5@F52>W

=54>AB0B=>ABV, 71V;LH5==O<0A8 BV;0 B0 28=8:=5==O =01@O:V2. # 28?04:C 1C4L-O:>3>

?>3V@H5==O DC=:FVW A5@FO ;V:C20==O BV07>;V48=4V>=0<8 A;V4 ?@8?8=8B8.

A>1;82V ?>?C;OFVW

0FVT=B8 ;VB=L>3> 2V:C (>65 @>:V2).

@5?0@0B V:AB0@4® 30 <>6=0 70AB>A>2C20B8 ?0FVT=B0< ;VB=L>3> 2V:C.

?0FVT=BV2 ;VB=L>3> 2V:C A;V4 ?>A8;8B8 <=>VB>@8=3 3;N:>78 B0 V=482V4C0;L=>

2V4:>@83C20B8 4>7C V=AC;V=C.

8@:>20 B0 ?5GV=:>20 =54>AB0B=VABL.

8@:>20 B0 ?5GV=:>20 =54>AB0B=VABL<>65 7=878B8 ?>B@51C 2 V=AC;V=V. # ?0FVT=BV2 7

=8@:>2>N B0 ?5GV=:>2>N =54>AB0B=VABN A;V4 ?>A8;8B8 <=>VB>@8=3 3;N:>78 B0 V=482V4C0;L=> 2V4:>@83C20B8 4>7C V=AC;V=C.

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

A;V;L:8 V=AC;V= =5 ?@>=8:0T G5@57 ?;0F5=B0@=89 10@'T@, =5<0T >1<565=L ;V:C20==O 4V015BC

V=AC;V=>< C ?5@V>4 203VB=>ABV. 5:<5=4CTBLAO ?>A8;8B8 :>=B@>;L @V2=O 3;N78 2 :@>2V B0

:>=B@>;L 70 ;V:C20==O< 203VB=8E 6V=>;, E2>@8E =0 4V015B, ?@>B03>< CAL>3> ?5@V>4C

203VB=>ABV, 0 B0:>6 ?@8 ?V4>7@V =0 203VB=VABL, >A;V;L:8 ?@8 =5045:20B=>B@>;V 4V015BC O: 3V?>3;V:5728B:C B0 703815;V ?;>40.

>B@510 2 V=AC;V=V 70728G09 7=86CTBLAO C B@8<5AB@V 203VB=>ABV B0 VAB>B=> 7@>AB0T C B0

B@8<5AB@0E.

VA;O ?>;>3V2 ?>B@510 2 V=AC;V=V H284:> ?>25@B0TBLAO 4> ?>G0B:>2>3> @V2=O.

1<565=L I>4> ;V:C20==O 4V015BC V=AC;V=< C ?5@V>4 3>4C20==O 3@C44N B0:>6 =5<0T, >A;V;L:8

;V:C20==O <0B5@V =5 AB2>@NT 1C4L-O:>3> @878:C 4;O 48B8=8. 4=0: <>65 28=8:=CB8

=5>1EV4=VABL :>@5:FVW 4>78 B0/01>4VTB8 4;O <0B5@V.

\$5@B8;L=VABL

>A;V465==O @5?@>4C:B82=>W B>:A8G=>ABV =0 B20@8=0E V7 70AB>AC20==O< ;N4AL:>3>

V=AC;V=C

=5 28O28;8 1C4L-O:>3> =530B82=>3> 2?;82C =0 D5@B8;L=VABL.

40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> V=H8<8 <5E0=V7<0<8.

50:FVO E2>@>3> B0 9>3> 740B=VABL :>=F5=B@C20B8 C203C<>6CBL 1CB8 ?>@CH5=V ?@8

3V?>3;V:5

&5 <>65 AB0B8 D0:B>@< @878:C C A8BC0FVOE, :>;8 FO 740B=VABL =01C20T >A>1;82>3>

7=0G5==O (=0?@8::04, ?@8 :5@C20==V 02B><>1V;5< 01> <5E0=V7<0<8).

%2>@8< A;V4 @5:<5=4C20B8 268B8 70E>4V2 7 ?@>DV;0:B8:8 3V?>3;V:55?V7>48 3V?>3;V:5. 0 B0:8E

>1AB028= A;V4 72068B8 4>FV;L=VABL :5@C20==O 02B<>1V;5

! ?>AV1 70AB>AC20==O B0 4>78.

V:AB0@4® 30 T 42>D07=8< V=AC;V=> 9>3> A::04C 2E>4OBL V=AC;V= :>@>B:>W 4VW B0 V=AC;V=

B@820;>W 4VW. 2>D07=89 V=AC;V= (ACB>2;5=0 2 C<>20E ?@><8A;>2>3> 28@>1=8FB20) 70728G09

22>48B8 1 01> 2 @078 =0 45=L, :>;8 =5>1EV4=> >45@60B8 H284:89 ?>G0B:>289 5D5:B ?>@O4 7

?>40;LH8< 1V;LH B@820;8< 5D5:B>

>7C20==O.

>7C20==O V=AC;V=C V=482V4C0;L=5 V 287=0G0TBLAO ;V:0@5< 2V4?>2V4=> 4> ?>B@51 E2>@>3>.

=482V4C0;L=0 4>1>20 ?>B@510 2 V=AC;V=V 70728G09 AB0=>28BL 2V4 0,3 4> 1,0 /:3/4>1C. >1>20

?>B@510 2 V=AC;V=V <>65 7@>AB0B8 C E2>@8E 7 @578AB5=B=VABN 4> V=AC;V=C (=0?@8::04, C

?C15@B0B=>4V 01> ?@8 >68@V==V) V 7=86C20B8AO C E2>@8E V7 70;8H:>28< 5=4>35==8<

?@>4C:C20==O< V=AC;V=C.

=T:FVN A;V4 @>18B8 70 30 E28;8= 4> >A=>2=>3> 01> 4>40B:>2>3> ?@89> 48.

>@5:FVO 4>78.

!C?CB=V 70E2>@N20==O, >A>1;82> V=D5:FVW B0 30@OG:>2V AB0=8, 70728G09 ?V428ICNBL

?>B@51C E2>@>3> 2 V=AC;V=V. !C?CB=V 70E2>@N20==O =8@>;, ?5GV=:8 01> C@065==O

=04=8@:>28E 70;>7, 3V?>DV70 01> I8B>284=>W 70;>78 28<030NBL 77V V=AC;V=C.

>@5:FVO 4>78 <>65 B0:>6 1CB8 ?>B@V1=0 ?@8 7

2545==O.

V:AB0@4® 30 ?@87=0G5=89 BV;L:8 4;O ?V4H:V@=8E V=T:FV9. !CA?5=7VN V=AC;V=C =V:>;8 =5 <>6=0 22>48B8 2=CB@VH=L>25==>.

V:AB0@4® 30 70728G09 A;V4 22>48B8 ?V4 H:V@C AB53=0 01> 4V;O=:8 ?5@54=L>W G5@52=>W ABV=:8. >6=0 B0:>6 22>48B8 C 4V;O=:C AV4=8FL 01> 45;LB>284=>3><O70 ?;5G0.

@8 ?V4H:V@=8E V=T:FVOE C 4V;O=:C ?5@54=L>W G5@52=>W ABV=:8 2A<:BC20==O V=AC;V=C 2V41C20TBLAO H284H5, =V6 ?@8 22545==V 2 V=HV 4V;O=:8 BV;0.

2545==O C 2V4BO3=CB C A;:04:C H:V@8 7=0G=> 7=86CT @878: ?>?040==O C <□O7.

VA;O V=T:FVW 3>;:0 ?>28==0 70;8H0B8AO ?V4 H:V@>N =5<5=H5 6 A5:C=4. &5 70157?5G8BL 22545==O ?>2=>W 4>78.

;O 7=865==O @878:C ;V?>48AB@>DVW

V:AB0@4® 30 C D;0:>=0E A;V4 70AB>A>2C20B8 7V A?5FV0;L=8<8 V=AC;V=>28<8 H?@8F0<8, O:V <0NBL 2V4?>2V4=5 3@04CN20==O. V:AB0@4® 30 ?>AB0G0TBLAO 7 V=AB@C:FVTN 2 C?0:>2FV V7 4>;:04=>N V=D>@<0FVTN 4;O 70AB>AC20==O.

=AB@C:FVW I>4> 70AB>AC20=O ?@5?0@0BC V:AB0@4® 30 4;O ?0FVT=B0.

5 70AB>A>2C20B8 ?@5?0@0B V:AB0@4® 30 :

2 V=DC7V9=8E =0A>A0E;

O:I> C ?0FVT=B0 0;5@3VO (3V?5@GCB;82VABL) 4> ;N4AL:>3> V=AC;V=C 01> 1C4L-O:>3> V=H>3> V=3@54VT=B0 ?@5?0@0BC;

O:I> ?0FVT=B ?V4>7@NT, I> C =L>3> @>72820TBLAO 3V?>3;V:52V);

O:I> 70?>1V6=0 ?;0AB<0A>20 :@8H5G:0 =5IV;L=> ?@8;O30T 4> D;0:>=0 01> 2V4ACB=O.

>65= D;0:>= <0T 70E8A=C ?;0AB<0A>2C :@8H5G:C 4;O V=48:0FVW 2V4:@8BBO.

./I> ?@8 >B@8<0==V D;0:>=C :@8H5G:0 =5IV;L=> ?@8;O30T 4> D;0:>=0 01> 2V4ACB=O, D;0:>= A;V4 ?>25@=CB8 4> 0?B5:8;

O:I> ?@5?0@0B 715@V302AO =5=0;56=8< G8=>< 01> 1C2 70<>@>65=89;

O:I> ACA?5=7VO V=AC;V=C =5 AB0T @V2=> 1V;>N B0 :0;0N ?VA;O ?5@5

5@54 70AB>AC20==O< ?@5?0@0BC V:AB0@4® 30 :

?5@52V@8B8 5B8:5B:C, I>1 ?5@5:>=0B8AO 2 B> B8? V=AC;V=C 2V4?>2V40T ?@87=0G5=>

► 2840;8B8 70?>1V6=C ?;0AB<0A>2C :@8H5G:C.

0AB>AC20==O FL>3> ?@5?0@0BC V=AC;V=C.

V:AB0@4® 30 22>48B8 H;OE>< V=T:FVW ?V4 H:V@C (?V4H:V@=>). V:>;8 =5 22>48B8 V=AC;V= 157?>A5@54=L> C 25=C 01> <□O7. 02648 7 4;O 7=865==O @878:C @>728B:C CIV;L=5=L 01> 2VA?8= =0 H:V@V. 09:@0I8<8

2545==O FL>3> ?@5?0@0BC V=AC;V=C.

!;V4 ?5@5:>=0B8AO C 28:>@8AB0==V V=AC;V=>2>3> H?@8F0, O:89 <0T 2V4?>2V4=5 3@04CN20==O.

01@0B8 2 H?@8F >1T< ?>2VB@O, O:89 4>@V2=NT =5>1EV4=V9 4>7V V=AC;V=C.

□>B@8 V=AB@C:FV9, I> 1C;8 =040=V ;V:0@5< 01> <54A5AB@>N.

57?>A5@54=L> ?5@54 28:>@8AB0==O< ?>:0B0B8 ;>=O<8 D;0:>= 7 V:AB0@4® 30 , ?>:8 @V48=0 =5 AB0=5 1V;>3> :>;L>@C B0 @V2=>:0;0N. 5@5;8 V=AC;V= =03@V20TBLAO 4> :V<=0B=>W B5

@>18B8 ?V4H:V@=C V=T:FVN V=AC;V=C. 8:>@8AB>2C20B8 B5E=V:C V=T:FVW, O:C ?>@5:> <5=4C202 ;V:0@ 01> <54A5AB@0.

#B@8;:C ?V4 H:V@>N =5 <5=H5 6 A5:C=4, I>1 C?52=8B8AO, I> 22545=> ?>2=C 4>7C.

VB8.

@5?0@0B8 1V>A8=B5B8G=>3> ;N4AL:>3> V=AC;V=C T 5D5:B82=8<8 V 157?5G=8<8 ;V:0@AL:8<8 70A>10<8 ?@8 ;V:C20==V FC:@>2>3> 4V015BC @V7=8E 2V:>28E 3@C? 4VB59 B0 ?V4;VB:V2.

>1>20 ?>B@510 2 V=AC;V=V C 4VB59 B0 ?V4;VB:V2 70;568BL 2V4 AB04VW E2>@>18,<0A8 BV;0, 2V:C, 4VTB8, DV78G=8E =020=B065=L, ABC?5=O V=AC;V=>@578AB5=B=>ABV B0 48=0

5@54>7C20==O.

%>G0 4;O V=AC;V=C A?5F8DVG=5 ?>=OBBO ?5@54>7C20==O =5 AD>@20=5, >4=0: ?VA;O 9>3> 22545==O <>65 @>728=CB8AO 3V?>3;V:5A;V4>2=8E AB04V9, O:I> 70AB>A>2C20;8 70=04B> 28A>:V ?>@V2=O=> 7 ?>B@510<8 ?0FVT=B0 4>78.

53:C 3V?>3;V:5@8<=0 4V015B @5:><5=4CTBLAO ?>ABV9=> <0B8 ?@8 A>1V 45:V;L:0 ?@>4C:BV2, I> 48.

28?04:C BO6:>W 3V?>3;V:5;8 E2>@89 7=0E>48BLAO C =5?@8B><=>A>18, O:V ?@>9H;8 2V4?>2V4=89 V=AB@C:B06, ?>28==V 225AB8 9>= ?V4H:V@=> 01> 2=CB@VH=L><O7>2> (2V4 0,5 4> 1,0 <3). 548G=89 ?@0FV2=8: <>65 225AB8 E2>@>7C 2=CB@VH=L>25==>. ;N:>7C B0:>6 ?>B@V1=> 22>48B8 2=CB@VH=L>25==> C 28?04:C, O:I> E2>@89 =5 @503CT =0 22545==O 3;N:03>=C ?@>B03< 10-15 E28;8=.

VA;O B>3> O: E2>@89 >?@8B<=VT, 9>4C:B8, I> 48, 4;O 70?>1V30==O @5F8482C.

>1VG=V @50:FVW.

09G0ABVH8< ?>1VG=8< 5D5:B>< B5@0?VW T 3V?>3;V:5@8E, ?@8 @V7=8E @568<0E 4>7C20==O B0 @V2=OE :>=B@>;N 3;V:5@<0FVN =86G5).

0 ?>G0B:C V=AC;V=>B5@0?VW <>6CBL A?>AB5@V30B8AO ?>@CH5==O @5D@0:FVW, =01@O: B0 @50:FVW C

V7:5 ?>;V?H5==O :>=B@>;N 3;V:5: V=B5=A8DV:0FVW V=AC;V=>B5@0?VW <>65

AC?@>2>46C20B8AO B828< 703>AB@5==O< 4V015B8G=>W @5B8=>?0BVW, 2 B>9 G0A O: B@820;89 4>1@5 =0;03>465=89 :>=B@>;L 3;V:5

0 40=8<8 ;;V=VG=8E 4>A;V465=L =86G5 =02545=> ?>1VG=V @50:FVW, ;;0A8DV:>20=V 70 G0AB>B>N B0 ;;0A0<8 A8AB5< >@30=V2 73V4=> 7 MedDRA.

0 G0AB>B>N 28=8:=5==O FV @50:FVW 1C;> @>7?>4V;5=> =0 B0:V, I> 28=8:0NBL 4C65 G0AB> (>=1/10), G0AB> (>=1/100 4> <1/10), V=>4V (>=1/1000 4> <1/100), @V4:> (>=1/10000 4> <1/1000), 4C65 @V4:> (<1/10000), 7 =52V4><>N G0AB>B>N (=5 <>6=0 287=0G8B8 =0 >A=>2V =0O2=8E 40=8E).

I>:C VW A8AB5<8.

@>?82O=:0, A25@1V6 V=>4V.

=0DV;0:B8G=V @50:FVW* 4C65 @V4:>.

I>:C <5B0I>;V7

V?>3;V:5* 4C65 G0AB>.

I>:C =5@2>2>W A8AB5<8.

5@8D5@8G=V =59@>?0BVW (1>;VA=V =59@>?0BVW) V=>4V.

I>:C >@30=V2 7>@C.

>@CH5==O @5D@0:FVW V=>4V.

V015B8G=0 @5B8=>?0BVO 4C65 @V4:>.

I>:C H:V@8 B0 ?V4H:V@=>W ;;VB:>28=8.

V?>48AB@>DVO* V=>4V.

5=5@0;V7>20=V ?>@CH5==O B0 @50:FVW C

50:FVW C

01@O: V=>4V.

*- 82. V=D>@<0FVN =86G5.

?8A >:@5<8E ?>1VG=8E @50:FV9.

=0DV;0:B8G=V @50:FVW.

!8<8 35=5@0;V7>20=>W 3V?5@GCB;82>ABV (2;;NG0NG8 35=5@0;V7>20=V H:V@=V 28A8?0==O,

A25@1V6, ?VB;82VABL, ?>@CH5==O B@02;5==O, 0=3V>=52@>B8G=89 =01@O:, CB@C4=5=5

48E0==O, ?@8A:>@5=5 A5@F518BBO, 7=865==O 0@B5@V0;L=>3> B8A:C B0 70?0<>@>G5==O/

2B@0BC A2V4>>ABV) 7CAB@VG0NBLAO 4C65 @V4:>, 0;5 <>6CBL 1CB8 ?>B5=V9=> =5157?5G=8 <8 4;O 68BBO.

V?>3;V:5

09G0ABVH8< ?>1VG=8< 5D5:B>< T 3V?>3;V:5=0 <>65 28=8:=CB8, :>;8 4>70 7=0G=> ?5@528ICT

?>B@518 E2>@>3> 2 V=AC;V=V. "O6:0 3V?>3;V:52<8 01> ?>ABV9=8<8 ?>@CH5==O<8 DC=:FVW

3>;>2>3> <>7:C V =02VBL 4> ;5B0;L=>3> =0A;V4:C. !8<8 3V?>3;V:52>. >=8 <>6CBL 2;;NG0B8

E>;>4=89 ?VB, 1;V4VABL V ?>E>;>40==O H:V@8, AB<;N20=VABL, 7=5@2>20=VABL 01> B@5<>@,

B@82>6=VABL, =5728G09=5 AB<;N20==O 01> A;01:VABL, A?;CB0=VABL A2V4>>ABV,

CB@C4=5==O :>=F5=B@0FVW C2038, A>=;82VABL, =04>4, 7@C, 3>;>2=89 1V;L, =C4>BC B0

?@8A:>@5=5 A5@F518BBO.

V?>48AB@>DVO.

@> ;V?>48AB@>DVN ?>2V4<;O;>AO V=>4V.V?>48AB@>DVO (2 B>3V?5@B@>DVO,
;V?>0B@>DVO) <>65 @>72820B8AO C
"5@ABV.30

#<>28 715@V30==O.

528:>@8AB0=V D;0:>=8 V:AB0@4C® 30 A;V4 715@V30B8 2 E>;>48;L=8:C ?@8 B5 1;87L:> 4>
<>@>78;L=>W :0<5@8). 5 70<>@>6C20B8.

15@V30B8 2 >@83V=0;L=V9 C?0:>2FV B0 =54>ABC?=>

5 ?V44020B8 4VW B5?;0 01> ?@O<8E A>=OG=8E ?@<5=V2.

>65= D;0:>= <0T 70E8A=C, :>4>20=C 70 :>;L>@< ?;0AB<0A>2C :@8H5G:C. /:I> 70E8A=0 ?;0AB<0A>20
:@8H5G:0 =5IV;L=> ?@8;O30T 4> D;0:>=0 01> 2V4ACB=O, D;0:>= A;V4 ?>25@=CB8 4> 0?B5:8.

\$;0:>=8 V:AB0@4C® 30 , O:8<8 :>@8ABCNBLAO, =5 A;V4 715@V30B8 2 E>;>48;L=8:C. E <>6=0

715@V30B8 ?@8 :V<=0B=V9 B5BO3<< 6 B86=V2 ?VA;O ?5@H>3> 2V4:@8BBO 01> ?@>BO3< 5
B86=V2 ?@8 B5 30 □.

@5?0@0B8 V=AC;V=C, O:V 1C;> 70<>@>65=>, 70AB>A>2C20B8 =5 <>6=0.

5 A;V4 70AB>A>2C20B8 V=AC;V= ?VA;O 70:V=G5==O B5@ABV, 707=0G5=>3> =0 C?0:>2FV.

5 A;V4 70AB>A>2C20B8 V:AB0@4® 30 , O:I> ?VA;O ?5@5=0 @V48=0 =5 AB0T 1V;>N B0 @V2=> :0;0N.

5AC

!CA?5=7VW V=AC;V=C =5 <>6=0 7

#?0:>2:0. > 10 <; C D;0:>=V; ?> 1 D;0:>=C 2 :0@B>==V9 :>@>1FV.

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

8@>1=8:. A/T >2> >@4VA: (0=VO).

VAF57=0E>465==O28@>1=8:0 B0 9>3> 04@5A0 20465==O 4VO;L=>ABV.

>2> ;;T, -2880, 03A205@4, 0=VO.