

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

!#&«»
(DOXORUBICIN «EBEWE»)

!,:04:
4VNG0 @5G>28=0: doxorubicin;
1 <; @>7G8=C
4>?>28=8: =0B@VN E;>@84, :8A;>B0 E;>@8AB>2>4=520 @>72545=0, 2>40 4;O V=T: FV9.

V:0@AL:0 D>@<0. >=F5=B@0B 4;O @>7G8=C 4;O V=DC7V9.
A=>2=V DV78:>-EVABV: ?@>7>@89 @>7G8= :@8202>-G5@2>=>3> :>;L>@C.

\$0@<0:>B5@0?52B8G=0 3@C?0.
=B8=5>?;0AB8G=V 70A>18. =B@0F8;;V=8 B0 A?>@V4=5=V A?>;C:8.
>4 "% L01D B01.

\$0@<0:>;>3VG=V 2;0AB82>ABV.
\$0@<0:>48=0
:A?5@8<5=B8 =0 B20@8=0E V ;;V=VG=V 4>A;V465==O 4>25;8 0=B8=5>?;0AB8G=C 0:B82=VABL
4>:A>@C1VF8=C, ?@>B5 <5E0=V7< 9>3> 4VW (O: V V=H8E 0=B@0F8;;V=V2) I5 B>G=> =5
70A>20=89. C;8 28AC=CBV ?@8?CI5==O I>4> B@L>E 3>;>2=8E 1V>EV:A>@C1VF8=C. &5
V=B5@:0;OFVO C ?>42V9=C A?V@0;L , 7207C20==O 7 ;;VB8==8<8 <5<1@0=0<8 B0 <5B01>;VG=0
0:B820FVO G5@57 2V4=>2;5==O.
4=VTN 7 3>;>2=8E ?@8G8= =55D5:B82=>ABV ;V:C20==O 4>:A>@C1VF8=× B0 V=H8<8 0=B@0F8;;V=0
<8 T @>728B>: @578AB5=B=>ABV. ;O ?>4>;0==O ;;VB8==>W @578AB5=B=>ABV 4> 4>:A>@C1VF8=C
A;V4 70AB>A>2C20B8 0=B03>=VAB8 :0;LFVN (=0?@8;;04, 25@0?0:CT ?>2V;L=V :0;LFVT2V :0=0;8 V
<>65 ?>A8;N20B8 ;;VB8==5 70E>;5==O 4>:A>@C1VF8=C. :A?5@8<5=B8 =0 B@L>E ;;VB8==8E
;V=VOE @0:C ?V4H;C=:>2>W 70;>78 ?>:070;8, I> 25@0?0B5= FVNT F8B>B>:A8G=C 4VN
4>:A>@C1VF8=C in vitro !;V4 707=0G8B8, I> ?@8 :<1V=>20=>AC20==V 4>:A>@C1VF8=C V 25@0?0
AB5@V30NBLAO BO6:V B>:A8G=V 5D5:B8. >:A>@C1VF8=>; (3>;>2=89 <5B01>;VB 4>:A>@C1VF8=C,
O:89 28O2;OTBLAO C ?;072V ;N48=8) =5 2?;820T =0 2=CB@VH=L>;VB8==C :C:A>@C1VF8=C.
\$0@<0:>:V=5B8:0.
VA;O 2=CB@VH=L>25==>3> 22545==O ?@5?0@0BC A?>AB5@V30TBLAO H284:89 ;;V@5=A
4>:A>@C1VF8=C 7 ?;07<8 :@>2V (?5@V>4 =0?V2282545==O 10 E28;8=) V 7=0G=5 7207C20==O 7
B:0=8=0<8. 5@V>4 =0?V2282545==O C B5@28BL ?@81;87=> 30 3>48=. >:A>@C1VF8= G0AB:>2>
<5B01>;V7CTBLAO 7 CB2>@5==O< ?5@5206=> 4>:A>@C1VF8=>;C V <5=H>N N 03;V:>=C
4>:A>@C1VF8=C, 7 =0ABC?=>N :>=N30FVTN 7 CB2>@5==O< 3;N:C@>=V4C V AC;LD0BC.
:A:@5BCTBLAO 4>:A>@C1VF8= ?5@5206=> 7 6>2GN V :0;> 10 % 4>78 282>48BLAO =8@:0<8.
207C20==O 4>:A>@C1VF8=C 7 1V;;0<8 ?;07<8 :@>2V AB0=>28BL 50-85 %, 0 >1T< @>7?>4V;C 800-
3500 ;<2.
>:A>@C1VF8= =5 01A>@1CTBLAO ?@8 ?5@>@0;L=>AC20==V. V= =5 ?@>=8:0T :@V7L 35
<0B>5=F5D0;VG=89 10@T@.
@8 =002=>ABV ?>@CH5=L DC=:FVW ?5GV=:8 ;;V@5=A 4>:A>@C1VF8=C B0 9>3><5B01>;VBV2
<>65 7=86C20B8AO.

;V=VG=V E0@0:B5@8AB8:8.
>:070==O.
V:C20==O H8@>;>3> A?5:B@0 =5>?;0AB8G=8E 70E2>@N20=L, C B>AB@>W ;59:5<8, 7;>O:VA=8E
=>2>CB2>@5=L C 4VB59 B0 A>;V4=8E ?CE;8= C 4>@>A;8E, 7>:@5<0 :0@F8=><8 <>;>G=>W 70;>78 B0
;535=L.

@>B8?>:070==O.

V?5@GCB;82VABL 4> 4>:A8@C1VF8=C 01> 4> V=H8E :>5=BV2 ?@5?0@0BC, V=H8E 0=B@0F8;V=V2 01> 0=B@0F5=4V>=V2. 03VB=VABL, ?5@V>4 3>4C20==O 3@C44N.

@8 2=CB@VH=L>25==>

?5@A8ABCNG0 AC?@5AVO (C B>8< @878:>< :@>2>B5G); BO6:V ?>@CH5==O DC=:FVW ?5GV=:8; BO6:V ?>@CH5==O DC=:FVW :0@40; =5AB01V;L=0 AB5=>:0@4VO; =5I>402=> ?5@5=5A5=89 V=D0@:B :0@40; BO6:0 0@8BAB0B=VABL 4 AB.; 3>AB@0 70?0;L=0 :0@4V>?0BVO; 3>AB@89 V=D0@:B :0@40; 3>AB@0 V=D5:FVO; AB<0B8B; =002=VABL 28@07>: @>B>2>W ?>@>6=8=8; ?@>4@><0;L=8<8 A8<0<8 <>65 1CB8 2V4GCBBO ?5GV==O; ?>4>265==O ;V:C20==O ?@8 =002=>ABV FL>3> A8<5=4>20=5; 3>AB@89 @>728B>: A5@F52>W =54>AB0B=>ABV; ?>?5@54=T ;V:C20==O<0:A8 <0;L=8<8 :C

@8 2=CB@VH=L>2>

V=D5:FVW A5G>284V;L=>3> B@0:BC; 70?0;5==O A5G>2>3>

5 28:>@8AB>2C20B8 V=B@0257V:0;L=> 4;O ;V:C20==O @0:C A5G>2>3>@8E 7V AB5=>7< C@5B@8, C O:8E =5 <>6;820 :0B5B5@870FVO; C E2>@8E 7 V=20782=8<8 ?CE;8=0<8, O:V ?@>=8;:8 :@V7L ABV=:8 A5G>2>3>

A>1;82V 70E>48 157?5:8.

>?CA:0TBLAO ;8H5 >4=>@07>289 2V41V@ ?@5?0@0BC 7 D;0:>=0.

@8 <0=V?C;OFVOE 7 ?@5?0@0B>< =5>1EV4=> 4>B@81>B8 7 F8B>B>:A8G=8<8 @5G>28=0<8.

@0E>2CNG8 B>:A8G=VABL ?@5?0@0BC, @5:>5=4CNBLAO B0:V 70?>1V6=V 70E>48:

" 5@A>=0; =5>1EV4=> >7=09><8B8 7 ?@028;0<8 @>1>B8 7 ?@5?0@0B>

03VB=8< <548G=8< ?@0FV2=8:0< 701>@>=OTBLAO ?@0FN20B8 7 ?@5?0@0B>

" @8 <0=V?C;OFVOE 7 ?@5?0@0B>< =5>1EV4=> :>@8ABC20B8AO 70E8A=8< >4O3>< (>4=>@07>28 <8 @C:028G:0<8, <0A:0<8, >:C:O@0<8, E0;0B0<8, H0?>G:0<8).

" 528:>@8AB0=V 70;8H:8 ;V:0@AL:>3> 70A>1C V 2AV V=AB@C<5=B8 B0 <0B5@V0;8, O:V

28:>@8AB>2C20;8 ?@8 ?@83>BC20==V @>7G8=V2 4;O V=DC7V9 V 22545==V ?@5?0@0BC,

2;:NG0NG8 @C:028G:8, =5>1EV4=> 7=8IC20B8 73V4=> V7 70B25@465=>N ?@>F54C@>N

CB8;V70FVW 2V4E>4V2 F8B>B>:A8G=8E @5G>28= (CA5 >1;04=0==O, 70AB>A>20=5 4;O 22545==O

?@5?0@0BC 01> >G8I5==O, C B>4V2 28A>:>3> @V2=O @878:C, B0 7=8IC20B8 H;OE>< A?0;5==O ?@8 28A>:V9 B5.

@07V 28?04:>2>3> ?>B@0?;O==O @>7G8=C 4>:A>@C1VF8=C =0 H:V@C 01> 2 >GV C@065=5 ?@> <8B8 25;8:>N :V;L:VABN 2>48, 2>4>N 7<8;>< 01> @>7G8=>< =0B@VN 1V:0@1>=0BC V 725@=CB8AO 70 <548G=>N 4>?><>3>N.

@8 @>71@87:C20==V 01> @>7;820==V @>7G8=C 4>:A>@C1VF8=C 701@C4=5=5 1EV4=> >1@>18B8 (70;8B8) @>72545=8< @>7G8=>< =0B@VN 3V?>E;>@8BC (7 :>=F5=B@0FVTN 0:B82=>3> E;>@C 1 %), 1060=> =0 B@820;89 G0A (=0 =VG), 0 ?>BV< ?@><8B8 2>4>N. #AV<0B5@V0;8, O:V 28:>@8AB>2C20;8 ?V4 G0A ?@818@0==O, =5>1EV4=> 7=8IC20B8, O: F5 707=0G5=> 28I5. 5:>5=4>20=8<8 4>

70AB>AC20==O @>7G8=0<8 4;O ?@83>BC20==O @>7G8=C 4;O V=DC7V9 T @>7G8= E;>@84C =0B@VN 4;O 2=CB@VH=L>25==8E V=DC7V9, 0,9 %, A?V22V4=>H5==O <0A0/>1 T<, 5 % @>7G8=

3;N:>78 4;O 2=CB@VH=L>25==8E V=DC7V9, A?V22V4=>H5==O <0A0/>1 T<, 01> C AC7G8=V2

E;>@84C =0B@VN B0 3;N:>78 4;O 2=CB@VH=L>25==8E V=DC7V9 (482. «A>1;82>ABV

70AB>AC20==O»).

7 C@0EC20==O< @V7=8E @5:><5=4>20=8E @5687C20==O 22545==O ?@5?0@0BC A;V4 74V9A=N20B8

28=OB:>2> ?V4 =03;04>< A?5FV0;VAB0, I><0T =0;56=89 4>A2V4 C 30;C7V B5@0?VW V7

70AB>AC20==O< @5G>28= F8B>B>:A8G=>W 4VW.

018@0B8 @>7G8= 7 D;0:>=0 =5>1EV4=> 157?>A5@54=L> ?5@54 28:>@8AB0==O

1V>;>3VG=>W B>G:8 7>@C ?@5?0@0B A;V4 22>48B8 >4@07C 6 ?VA;O 2V41>@C 7 D;0:>=0, 0

@>7G8= 4;O V=DC7V9 >4@07C 6 ?VA;O ?@83>BC20==O. /:I> ?@5?0@0B 01> @>7G8= 4;O V=DC7V9

=5 28:>@8AB0;8 =5309=>, 70 B@820;VABN V C<>20<8 WE 715@V30==O <0T AB568B8 <548G=89

?5@A>=0; . 0728G09 G0A 715@V30==O =5 ?>28=5= ?5@528IC20B8 24 3>48=8 ?@8 B5 BV;L:8 2AV

<0=V?C;OFVW =5 28:>=C20;8 C :>=B@>;L>20=8E V 0B5AB>20=8E 0A5?B8G=8E C<>20E. >A;V465==O

=5 28O28;8 VAB>B=8E DV78G=8E V EV3> 2V4:@8BBO C?0:>2:8, 0 B0:>6 @>7G8=V2 4;O V=DC7V9

?VA;O 715@V30==O ?@>B03> 24 3>48= ?@8 B5 8 ! C 70E8I5=> =5 70E8I5=> @8 715@V30==V

;V:0@AL:>3> 70A>1C 2 E>;>48;L=8:C 2V=<>65 =01CB8 65;5?>4V1=>3> 283;04C. V4=>2;5==O

:>=A8AB5=FVW 2V41C20TBLAO G5@57 2-4 3>48=8 ?@8 :V<=0B=V9 B52 ?>E8BC20==O D;0:>=0 7

@>7G8=>

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

>:A>@C1VF8= ?5@5206=> A;V4 70AB>A>2C20B8 C :<1V=0FVW V7 V=H8<8 F8B>B>:A8G=8<8
?@5?0@0B0<8. >65 2V41C20B8AO 048B82=89 5D5:B B>:A8G=>ABV, >A>1;82> AB>A>2=> 2?;82C =0
:VAB:>289 <7>:/35<0B>;>3VN B0 H;C=:>2>-.8H:>289 B@0:B. @8 70AB>AC20==V 4>:A>@C1VF8=C C
:<1V=>20=V9 EVB5@0?VW V7 V=H8<8 ?>B5=FBV9=> :0@V4>B>:A8G=8<8 A?>;C:0<8 01> C :>
<1V=0FVW 7 V=H8<8 ?@5?0@0B0<8, I> 2?;820NBL =0 A5@F5 (=0?@8::04 I;:>:0B>@0<8 :0;LFVT28E
:0=0;V2 V 25@0?0<), C ?5@V>4 ;V:C20==O =5>1EV4=> :>=B@>;N20B8 DC=:FVN A5@FO. 0:A8<0;L=0
:>=F5=B@0FVO 4>:A>@C1VF8=C C ?;072V, B5@4 =0?V2282545==O V >1T< @>7?>4V;C<>6CBL
71V;LHC20B8AO ?@8 >4=>G0A=>AC20==V 25@0?0. : AC?CB=L>3> ;V:C20==O <>6CBL 7V=H8<8
:0@4V>B>:A8G=8<8 01> ?@>B8?CE;8==8<8 (>A>1;82> B>:A8G=8<8) ?@5?0@0B0<8 =5>1EV4=0
>15@56=VABL. 4=>G0A=5 70AB>AC20==O V=H8E ?@>B8?CE;8==8E ?@5?0@0BV2, B0:8E O:
0=B@0F8;:V=8 (40C=>@C1VF8=, 5?V@C1VF8=, V40@C1VF8=), F8A?;0B8=, F8;:>D>AD0A?>@8=,
F8B0@01V=, 40:0@107V=, 40:BV=>@C@0F8;:, <>65 ?>A8;N20B8 @878: A?@8G8=5=>W
4>:A>@C1VF8=>< 70ABV9=>W A5@F52>W =54>AB0B=>ABV.
;>70?V= <>65 71V;LH8B8 @878: V A5@9>7=VABL 35<0B>;>3VG=>W B>:A8G=>ABV 4>:A>@C1VF8=C.
>:A>@C1VF8= <>65 A?@8G8=OB8 703>AB@5==O 35<>@03VG=>3> F8AB8BC, O:89 @>728=C2AO
2=0A;V4>: ?>?5@54=L>W B5@0?VW F8;:>D>AD0<.
A:V;L:8 4>:A>@C1VF8= H284:> <5B01>;V7CTBLAO V 282>48BLAO ?5@5206=> 7 6>2GN, ?@8
>4=>G0A=>AC20==V 35?0B>B>:A8G=8E EVB5@0?52B8G=8E 70A>1V2 (=0?@8::04 6-
<5@:0?B>?C@8=C, <5B>B@5:A0BC, AB@5?B>7>F8=C) B>:A8G=VABL 4>:A>@C1VF8=C ?>B5=FBV9=>
<>65 71V;LHC20B8AO 2=0A;V4>: 7=865==O ?5GV=:>2>3> ;V@5=AC ?@5?0@0BC. >7C20==O
4>:A>@C1VF8=C A;V4 :>@83C20B8, O:I> AC?CB=O B5@0?VO 35?0B>B>:A8G=8<8 ;V:0@AL:8<8
70A>10<8 T>1>2O7:>2>N.
@8 :<1V=>20=V9 B5@0?VW F8;:>A?>@8=>< C 28A>:8E 4>70E V 4>:A>@C1VF8=<
:>=F5=B@0FVW >1>E A?>;C: C A8@>20BFV :@>2V ?V428ICNBLAO. <1V=>20=0 B5@0?VO
F8;:>A?>@8=>< V 4>:A>@C1VF8=< <>65 ?@8725AB8 4> 270T<=>3> 7=865==O <5B01>;V71>E
@5G>28= 7 ?>A;V4>2=8< 71V;LH5==O< WE 22V. &5<>65 A?@8G8=8B8 1V;LH 28@065=5
?@83=VG5==O DC=:FVW :VAB:>2>3><>7:C B0 =04AC?@5AVN.
0AB>AC20==O @07>< 7 ?@5?0@0B0<8, O:V 2?;820NBL =0 W4=C DC=:FVN (C B.G.
0=B8@5B@>2V@CA=V ?@5?0@0B8, 040@>=, D5=VB>W=, F8B>AB0B8:8, AC;LD>=V;0@0;), <>65
A?@8G8=8B8 ?>@CH5==O DC=:FVW :@>2>B2>@5==O.
@8 :<1V=>20=V9 B5@0?VW 4>:A>@C1VF8=< V F8B>AB0B8:0<8 (C B.G. F8B0@01V=><,
F8A?;0B8=><) ?>A8;NNBLAO B>:A8G=V 5D5:B8 =0 >@30=V7< ?0FVT=B0.
!;V4 C=8:0B8 :<1V=0FVW 4>:A>@C1VF8=C 7 0B5@5F8=>< G5@57 28=8:=5==O OA:@02>
28@065=>W =5D@>B>:A8G=>ABV.
@8 70AB>AC20==V 4>:A>@C1VF8=C @07>< 7 @8B>=02V@>< ?>2V4><;O;>AO ?@> ?V428I5==O
@V2=O 4>:A>@C1VF8=C C A8@>20BFV :@>2V.
0AB>AC20==O 10@1VBC@0BV2 <>65 ?@825AB8 4> ?@8A:>@5=>3> 282545==O 4>:A>@C1VF8=C 7
?;07<8 :@>2V.
1A>@1FVO ?@>B85?V;5?B8G=8E 70A>1V2 (=0?@8::04 :0@10<075?V=C, D5=VB>W=C, 20;L?@>0BC)
7=86CTBLAO ?VA;O >4=>G0A=>3> 70AB>AC20==O 4>:A>@C1VF8=C.
0AB>AC20==O ;V:0@AL:8E 70A>1V2, O:V 70B@82>W :8A;>B8 (=0?@8::04 ,AC;LD0=V;0B0 45O:8E
4VC@5B8:V2) <>65 ?@8725AB8 4> 3V?5@C@8:5
>:A>@C1VF8= <>65 7=878B8 1V>4>ABC?=VABL ?@8 ?5@>@0;L=>483>:A8=C. "> :>=B@>;N20B8
@V25=L 483>:A8=C C ?;072V ?V4 G0A B5@0?VW 4>:A>@C1VF8=< .
V4 G0A ;V:C20==O V7 70AB>AC20==O< 4>:A>@C1VF8=C 3V4@>E;>@84C ?0FVT=B0< =5 A;V4
?@>2>48B8 20:F8=0FVN. 878: 71V;LHCTBLAO C ?0FVT=BV2 7 V<, >A;01;5=8< G5@57 >A=>2=5
70E2>@N20==O. V4 G0A ;V:C20==O 4>:A>@C1VF8=< ?0FVT=B8 <0NBL B0:>6 C=8:0B8 :>=B0:BC
>A>10<8, O:8< =5402=> 1C;> ?@>2545=5 I5?;5==O ?@>B8 ?>;V>
>:A>@C1VF8= 7207CTBLAO 7 35?0@8=>< B0 5-DB>@C@0F8;><, I> ?@872>48BL 4> 28?040==O
>A04C B0 2B@0B8 5D5:B82=>ABV >1>E ?@5?0@0BV2.
=3V1VB>@8 D5@<5=BV2 A8AB5<8 F8B>E@>F8<5B848= V @0=8B848=) <>6CBL C?>2V;L=N20B8
<5B01>;V7< 4>:A>@C1VF8=C, I> ?@872>48BL 4> ?>A8;5==O B>:A8G=8E 5D5:BV2. =4C:B>@8 D5@
<5=BV2 A8AB5<8 F8B>E@> D5=>10@1VB0; B0 @8D0 <>6CBL AB8

>:A>@C1VF8= ?>B5= FVNT 4VN >?@<5=520 B5@0?VO ?>A8;NT :0@4V>B>:A8G=VABL B0
35?0B>B>:A8G=VABL.
@8 :<1V=>20=V9 B5@0?VW 4>F5B0:A5;>< V 4>:A>@C1VF8=< 28I0 V<2V@=VABL @>728B:C
=59B@>?5=VW.
@8 :<1V=>20=V9 B5@0?VW 4>:A>@C1VF8=< V F8;:>D>AD0<, ?0.;VB0:A5;><, 4>F5B0:A5;><,
@8BC:A8<01><, B@0ABC7C<01>< 01> 7>AC:2840@>< B>:A8G=V 5D5:B8 <6CBL ?>A8;N20B8AO.
0FVT=B8, O:V 70AB>A>2CNBL 0=B@0F8;;V=8 (=0?@8;;04 4>:A>@C1VF8=) ?VA;O ?@8?8=5==O
;V:C20==O V=H8<8 :0@4V>B>:A8G=8<8 ?@5?0@0B0<8, >A>1;82> 7 4>238< ?5@V>4<<
=0?V2282545==O, B0:8<8 O: B@0ABC7C<01><, B0:>6 <6CBL <0B8 ?V428I5=89 @878: @>728B:C
:0@4V>B>:A8G=>ABV. 5@V>4 =0?V2282545==O B@0ABC7C<01C AB0=>28BL ?@81;87=> 28 - 38
4=V2, V ?@5?0@0B <65 ?@>4>26C20B8 F8@:C;N20B8 2 :@>2V 4> 27 B86=V2. "> 0=B@0F8;;V=8
?@87=0G0B8 @0=VH5 FL>3> B5@ :>=B@>;N20B8 DC=:FVN A5@FO.
/I> 4> ?>G0B:C 22545==O 4>:A>@C1VF8=C 70AB>A>2C20;8 ?0.;VB0:A5; , F5 <65 ?@8725AB8 4>
71V;LH5==O :>=F5=B@0FVW 4>:A>@C1VF8=C B0/01> 9>3> <5B01>;V BV2. 52=V 40=V 2:07CNBL =0
<5=H5 7@>AB0==O :>=F5=B@0FV9, O:I> 4>:A>@C1VF8= 70AB>A>2C20B8 ?5@54 ?0.;VB0:A5;>
:A>@C1VF8=C V ?V428I5==O G0AB>B8 28?04:V2 =59B@>?5=VW V AB<0B8BC.
>A8;5==O =59B@>?5=VW V B@<1>F8B>?5=VW 1C;8 70@5TAB@>20=V ?VA;O >4=>G0A=>3>
70AB>AC20==O ?@>35AB5@>=C.
V428I5==O (21 %-47 %) 01> 2V4ACB=VABL 7:07=8:0 AUC 4>:A>@C1VF8=C A?>AB5@V30;>AO ?@8
ACAC20=V V7 A>@0D5=V1>< C 4>7V 400 <3 2 @078 =0 4>1C. ;V=VG=0 7=0GCIVABL F8E 40=8E
=52V4><0.

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

V:C20==O 4>:A>@C1VF8=< <0T 74V9A=N20B8AO ?V4 :>=B@>;5< 4>A2V4G5=>3> ;V:0@O->=:>;>30.
5:<5=4CTBLAO, I>1 ?@8=09<=V ?5@H0 D070 B5@0?VW 4>:A>@C1VF8=< ?@>E>48;0 2 C<20E
AB0FV>=0@C, >A:V;L:8 2 F59 G0A ?0FVT=B8 ?>B@51CNBL @5B5;L=>3> =03;04C V @53C;O@=>3>
:>=B@>;N 3>;>2=8E ;01>@0B>@=8E ?>:07=8:V2. >78 4>:A>@C1VF8=C 287=0G0B8 7 C@0EC20==O<
284C ?CE;8=8, DC=:FVW A5@FO V ?5GV=:8, 0 B0:>6 AC?CB=L>W EVB5@0?VW. > ?>G0B:C ;V:C20==O
4>:A>@C1VF8=< =5>1EV4=> ?@>25AB8 4>A;V465==O DC=:FVW A5@FO V ?5GV=:8, 0 B0:>6 0=0;V7
:@>2V 7 287=0G5==O< 3>;>2=8E 35<0B>;>3VG=8E ?>:07=8:V2.
A>1;82C >15@56=VABL A;V4 ?@>O2;OB8 4> E2>@8E, O:8< ?@87=0G5=0 2 <8=C;> <091CB=L><5=520
B5@0?VO. @8 70AB>AC20=V 4>:A>@C1VF8=C <6;820 B06:0 ?@>2V4><;O;>AO ?@> ?>2O70=C 7 F8
< B06:C, G0AB:>2> ;5B0;L=C 35?0B>B>:A8G=VABL.
>?5@54=T ?>@>ABV==O ?V428ICT :0@4V>B>:A8G=VABL 4>:A>@C1VF8=C. # FL>7C 400 <3/<2 ?>;IV
?>25@E=V BV;0.
> 01> ?V4 G0A B5@0?VW 4>:A>@C1VF8=< A;V4 ?@>25AB8 =0ABC?=V 4>A;V465==O (G0AB>B0 WE
?@>2545==O 70;568BL 2V4 7030;L=>3> AB0=C ?0FVT=B0, ?@87=0G5=>W 4>78 B0 AC?CB=L>W
B5@0?VW): D;N>@>3@0DVO 3@C4=>W ;VB8=8; ?@>2545==O ; @53C;O@=89 <=>VB>@8=3
D@0:FVW 28:84C ;V2>3> H;C=>G:0 (\$), =0?@8;;04, 70 4>?<>3>N 5E>:0@4V>3@0DVW 01>
@04V>=C.;V4=>W 0=3V>3@0DVW; I>45==89 >3;O4 ?>@>6=8=8 @>B0 V 3>;B:8 4;O 28O2;5==O
28@07>: A;87>28E >1>;>=>; 0=0;V78 :@>2V (4;O 287=0G5==O 35<0B>:@8BC, B@<1>F8BV2, 35
<0B>;>3VG=8E ?>:07=8:V2, " , !" , , 1V;V@C1V=C, A5G>2>W :8A;>B8. /I> =0O2=89 35?0B8B B 01>
35?0B8B C 2 0=0<=57V (70 =5>1EV4=>ABV, ?@>25AB8 B5AB =0 0=B8BV;0), =5>1EV4=> @>18B8
?5GV=:>2V ?@>18 ?V4 G0A V ?VA;O ;V:C20==O, >A:V;L:8<6;820 @50:B820FVO E2>@>18.
"O6:V V=D5:FVW B0/01> :@>2>B5GV =5>1EV4=> H284:> V 5D5:B82=> ;V:C20B8. A=CNGV V=D5:FVW
A;V4 ;V:C20B8 4> ?>G0B:C B5@0?VW.
!B0= ?0FVT=B0 ?>28=5= 2V4=>28B8AO ?VA;O 3>AB@>3> B>:A8G=>3> 2?;82C ?>?5@54=L>3>
;V:C20==O F8B>B>:A8G=8<8 70A>10<8 (=0?@8;;04, ?@8 AB<0B8BV, =59B@>?5=VW, B@>
<1>F8B>?5=VW B0 35=5@0;V7>20=V9 V=D5:FVW) ?5@54 ?>G0B:< ;V:C20==O 4>:A>@C1VF8=>
?0FVT=V2 V7 >68@V==O< (B>1B> >130 % V450;L=>W <0A8 BV;0) A8AB5<=89 ;V@5=A
4>:A>@C1VF8=C 7=865=89.
@8 B5@0?VW 4>:A>@C1VF8=< =C4>B0, 1;N20==O V 70?0;5==O A;87>28E >1>;>=>: G0AB> 1C20NBL
B06:8<8 V 28<030NBL 2V4?>2V4=>3> ;V:C20==O.
>:A>@C1VF8=5 A;V4 22>48B8 V=B@0B5:0;L=> 01> 2=CB@VH=L<O7>2>, ?V4H:V@=>, 01> C D>@
23>B@820;>W V=DC7VW (>A:V;L:8 T ?>2V4<;5==O ?@> B5, I> 4>:A>@C1VF8= C :<1V=0FVW V7
35?0@8=< B0 5-DB>@C@0F8;< CB2>@NT >A04; B0:>6 9>3> =5 <6=0 7

@8=002=>ABV C ?0FVT=B0 ?>@CH5=L DC=:FVW =8@>: :>@5:FVO 4>7 70728G09 =5 ?>B@V1=0.
0FVT=B8 @5?@>4C:B82=>3> 2V:C (V 6V=:8, V G>:2V:8)<0NBL :>@8ABC20B8AO 5D5:B82=8<8
:=>B@0F5?B82=8<8 70A>10<8 ?V4 G0A V I>=09<5=H5 ?@>BO3>< 3 :A>@C1VF8=>
:AB@02070FVO
:AB@02070FVO 4>:A>@C1VF8=C A?@8G8=OT BO6:89 V ?@>3@5ACNG89 =5:@>7 B:0=8=. !8<0<8
5:AB@02070FVW T 1V;L B0/01> ?5GV==O C25==>3> 22545==O ?@5?0@0BC. # @07V ?V4>7@N20=>W
5:AB@02070FVW A;V4 =5309=> ?@8?8=8B8 22545==O 4>:A>@C1VF8=C V ?@>4>268B8 9>3> 2 V=HC
25=C. > C@065=>3> 1EV4=> ?@8::0AB8 ?0:5B 7 ;L>4>2V4><;O;>AO ?@> 26820==O 2 B0:8E 28?04:0E 7
@V7=8< CA?VE>< B0:8E 70E>4V2, O:: ?@><820==O A>;L>28< @>7G8=><;, ;>:0;L=5 22545==O
:>@B8:>AB5@>W4=8E 70A>1V2 01> @>7G8=C 1V:0@1>=0BC =0B@VN (8,4 %), 0 B0:>6
70AB>AC20==O 4V<5B8;AC;LD>:A84C. !?@8OB;8289 2?;82 70157?5GCTBLAO # @07V
5:AB@02070FVW A;V4 ?@>:=AC;LBC20B8AO 7 D0EV2F5< 7 ?;0AB8G=>W EV@C@3VW AB>A>2=>
=5>1EV4=>ABV H8@>:>3> @>7B8=C C@065=>W 4V;O=:8.
0@4V>B>:A8G=VABL
V:C20==O 0=B@0F8;;V=0<8 0A>FV9>20=5 V7 @878:>< :0@4V>B>:A8G=>ABV, I><>65
<0=VD5ABC20B8 C 283;04V @0==VE (3>AB@8E) B0 ?V7=VE (2V4AB@>G5=8E) ?@>O2V2.
@>O28 @0==L>W (3>AB@>W) :0@4V>B>:A8G=>ABV. 0==V ?@>O28 :0@4V>B>:A8G=>3> 2?;82C
4>:A>@C1VF8=C ?5@5206=> O2;ONBL A>1>N A8=CA>2C B0EV:0@4VN B0/01> =5A?5F8DVG=V 7
?>2V4><;O;>AO ?@> B0EV0@8BG:>2V 5:AB@0AB8AB>;8, H;C=>G:>2C B0EV:0@4VN B0
1@048:0@4VN, 0 B0:>6 ?5@54A5@4>-H;C=>G:>2C 1;>:04C B0 1;>:04C =V6>: ?CG:0 VA0. /: ?@028;>, FV
?@>O28 =5 AC?@>2>46CNBLAO 28=8=:5==O< 2V4AB@>G5=>W :0@4V>B>:A8G=>ABV, V 7030;>=5
28<030NBL ?@8?8=5==O ;V:C20==O 4>:A>@C1VF8=>
V7=V (2V4AB@>G5=V) ?@>O28 :0@4V>B>:A8G=>ABV. V4AB@>G5=0 :0@4V>B>:A8G=VABL, O:
?@028;>, 28=8:0T C ?V7=V9 ?5@V>4 70AB>AC20==O ?@5?0@0BC 01> G5@57 2-3 2V4><;O;>AO ?@>
@>728B>: 1V;LH ?V7=VE ?@>O2V2 G5@57 :V;L:0 @>:V2 ?VA;O 7025@H5==O ;V:C20==O. V440;5=0
:0@4V>?0BVO ?@>O2;OTBLAO 7<5=H5==O< D@0:FVW 28:84C ;V2>3> H;C=>G:0 (\$) B0/01> >7=0:0<8
B0 A8<0<8 70ABV9=>W A5@F52>W =54>AB0B=>ABV, B0:8-8 O: 48A?=>5, =01@O: ;535=V2,
?5@8D5@8G=89 =01@O:, :0@4V><530;VO V 35?0B<530;VO, >;V3C@VO, 0AF8B, ?;52@0;L=89 28?VB
V @8B< 30;>?C. V47=0G5=V B0:>6 ?V43>AB@V ?@>O28, B0:V O: ?5@8:0@48B:0@48B. 09206G>N V
=5157?5G=>N 4;O 68BBO D>@<>N 0=B@0F8;;V=-V=4C:>20=>W :0@4V>?0BVW T 70ABV9=0 A5@F520
=54>AB0B=VABL, O:0 T :C
878: @>728B:C A5@F52>W =54>AB0B=>ABV 2 >=:>;>3VG=8E ?0FVT=BV2, O:V ;V:C20;8AO
4>:A>@C1VF8=><, 715@V30TBLAO 2?@>4>26 2AL>3> 68BBO. !5@F520 =54>AB0B=VABL,
A?@8G8=5=0 4>:A>@C1VF8=><, <>65 1CB8 @578AB5=B=>N 4> B@048FV9=>3> ;V:C20==O.
A:V;L:8 2AB0=>2;5=>, I> 7V 71V;LH5==O< :CW 4>78 0=B@0F8;;V=V2 7@>AB0T @878: @>728B:C
:0@4V>?0BVW, :C70 4>:A>@C1VF8=C =5 ?>28==0 ?5@528IC20B8 450-550 <3/<2 ?>25@E=V BV;0. @8
28I8E 4>70E @878: @>728B:C A5@F52>W =54>AB0B=>ABV 7=0G=> 7@>AB0T. @V< B>3>, ?5@54
?>G0B>< :>6=>3> :C@AC B5@0?VW C B0:8E ?0FVT=BV2 =5>1EV4=> 283> H;C=>G:0.
@8=002=>ABV C ?0FVT=B0 :0@4V>;>3VG=8E 70E2>@N20=L, ?VA;O ?@><5=52>W B5@0?VW
4V;O=:8 A5@FO 01> A5@54>ABV==O, 0 B0:>6 ;V:C20==O V=H8<8 :0@4V>B>:A8G=8<8
=50=B@0F8;;V=>28<8 ?@>B8?CE;8==8<8 ?@5?0@0B0<8 :C70 =5 ?>28==0 ?5@528IC20B8 400 <3/<2
?>25@E=V BV;0 V =5>1EV4=89 @5B5;L=89<=>VB>@8=3 DC=:FVW A5@FO.
0FVT=B0< 3@C?8 ?V428I5=>3> @878:C @>728B:C :0@4V>;>3VG=>W ?0B>;>3VW 4>:A>@C1VF8=
@5:><5=4CTBLAO 22>48B8 H;OE>< 24-3>48==8E 157?5@5@2=8E 2=CB@VH=L>25==8E V=DC7V9, 0
=5 V=T:FV9. @8 B0:>A>1V 22545==O :0@4V>B>:A8G=V 5D5:B8 A?>AB5@V30NBLAO @V4H5, 0
5D5:B82=VABL ;V:C20==O =5 7<5=HCTBLAO.
878: @>728B:C :0@4V>B>:A8G=8E C@065=L 28I89 C ?0FVT=BV2, O:V >B@8<5=52C B5@0?VN =0
4V;O=:C A5@54>ABV==O 01> ?5@8:0@40, ;V:C20;8AO @0=VH5 0=B@0F8;;V=0<8 B0/01>
0=B@0F5=4V>=0<8, E2>@8E 7 :0@4V>;>3VG=8<8 70E2>@N20==O<8 2 0=0<=57V, ?0FVT=BV2
;VB=L>3> 2V:C (2V4 70 @>:V2) V 4VB59 (4> 15 @>:V2).
0@4V>B>:A8G=V 5D5:B8 <>6CBL ?@>O2;OB8AO ?@8 4>70E =86G5 @5:><5=4>20=>W <0:A8<0;L=>W
:CW 4>78. 5>1>@>B=0 70ABV9=0 A5@F520 =54>AB0B=VABL<>65 @>728=CB8AO =02VBL ?@8
7030;L=V9 4>7V 240 <3/<2 ?>25@E=V BV;0. ">?CAB8<>W :CW 4>78 4;O :>6=>3> ?0FVT=B0 A;V4
2@0E>2C20B8 ?>?5@54=N 01> AC?CB=N B5@0?VN V=H8<8 ?>B5=V9=> :0@4V>B>:A8G=8<8
?@5?0@0B0<8, 7>:@5<0 F8;;>D>AD0< (2=CB@VH=L>25==>), < ! 01> 40:0@1078=><, V=H8<8
0=B@0F8;;V=0<8 (=0?@8::04, 40C=>@C1VF8=><), 0 B0:>6 ?@><5=52C B5@0?VN =0 4V;O=:C

A5@54>ABV==O 01> ?5@8:0@4C.
>2V4><;O>AO ?@> @>728B>: 3>AB@8E BO6:8E 0@8B G5@57 :V;L:0 3>48= ?VA;O 22545==O
4>:A>@C1VF8=C.
@8 ;V:C20==V 4>:A>@C1VF8=< <>6CBL A?>AB5@V30B8AO B0:V 7=30FVO A8AB>;VG=>3>
V=B5@20;C, 0 B0:>6 7=865==O D@0:FVW 28:84C ;V2>3> H;C=>G:0.
0FVT=B8, O:V >B@8 0=B@0F8;;V=8 ?@87=0G0NBL @0=VH5 FL>3> B5@ :>=B@>;N20B8 DC=:FVN
A5@FO.
A>1;820 >15@56=VABL =5>1EV4=0 ?@8 ;V:C20==V 4>:A>@C1VF8=< E2>@8E 7 :0@4V>;>3VG=8<8
70E2>@N20==O<8 2 0=0<=57V (B0:8<8 O: =5I>402=V9 V=D0@:B :0@40, A5@F520 =54>AB0B=VABL,
:0@4V>?0BVO, ?5@8:0@48B, 0@8B6 ?0FVT=BV2, O:V >B@8B>:A8G=V ?@5?0@0B8, =0?@8;;04,
F8;;>D>AD0
4VB59 B0 ?V4;VB:V2 28I89 @878: 28=8:=5==O ?@>O2V2 2V440;5=>W :0@4V>B>:A8G=>ABV
2=0A;V4>: 70AB>AC20==O 4>:A>@C1VF8=C. V@>3V4=VABL :0@4V>B>:A8G=>ABV C 6V=>: 1V;LH0,
=V6 C G>;>2V:V2. ;O :>=B@>;N B0:>3> 2?;82C ?@5?0@0BC @5:<5=4>20=V ?>40;LHV
:0@4V>;>3VG=V >1AB565==O.
A=CT V<>2V@=VABL B>3>, I> B>:A8G=89 2?;82 4>:A>@C1VF8=C B0 V=H8E 0=B@0F8;;V=V2 01>
0=B@0F5=54V>=V2 <>65 1CB8 048B82=8
>=B@>;L DC=:FVW A5@FO
\$C=:FVN A5@FO =5>1EV4=> >FV=N20B8 4> ?>G0B:C ;V:C20==O 4>:A>@C1VF8=<, @53C;O@=>
:>=B@>;N20B8 C ?@>F5AV ;V:C20==O, 0 B0:>6 ?5@52V@OB8 ?VA;O 70:V=G5==O B5@0?VW
4>:A>@C1VF8=<<5=4CTBLAO ?@>2>48B8 -4>A;V465==O 4> V ?VA;O :>6=>3> 22545==O ?@5?0@0BC.
"0:V 7 V=25@AVO 7C1FO ", 45?@5AVO A53=5=BC S" 01> 0@8BB5 ABV9:5 7=865==O 0 QRS V
?>4>265==O A8AB>;VG=>3> V=B5@20;C 22060NBLAO >7=0:0<8 @>728B:C :0@4V>B>:A8G=8E
C@065=L, A?@8G8=5=8E 0=B@0F8;;V=0<8. @8 7=865==V =0 30 % 0QRS 01> 7<5=H5==V =0 5 %
D@0:FVW 2:>@>G5==O ;V:C20==O 4>:A>@C1VF8=< @5:<5=4CTBLAO ?@8?8=8B8.
?B8<0;L=8< <5B>4>< ?@>3=>7C20==O @>728B:C :0@4V>?0BVW T >FV=:0 7=865==O D@0:FVW
28:84C ;V2>3> H;C=>G:0 (\$), O:0 287=0G0TBLAO 70 4>?><>3>N C;LB@072C:>2>3> 01>
AF8=B83@0DVG=>3> 4>A;V465==O A5@FO. \$(=5>1EV4=> 287=0G0B8 4> ?>G0B:C ;V:C20==O
4>:A>@C1VF8=<< V ?5@52V@OB8 :>6=>3> @07C ?VA;O 71V;LH5==O :CW 4>78 =0 100 <3/<2
?>25@E=V BV;0. >A;V465==O B0:>6 A;V4 ?@>2>48B8 ?@8 ?>O2V 1C4L-O:8E ;;V=VG=8E >7=0:
@>728B:C A5@F52>W =54>AB0B=>ABV. /: ?@028;>, 7=865==O 01A>;NB=>3> ?>:07=8:0 \$(4> @V2=O
=86G5 50 % 01> 1V;LH5 =V6 =0 10 % C ?0FVT=BV2 7 =>@<0;L=8<8 ?>G0B:>28<8 ?>:07=8:0<8 \$(>50 %)
22060TBLAO >7=0:0<8 @>728B:C ?>@CH5=L DC=:FVW A5@FO. # B0:8E 28?04:0E =5>1EV4=>
@5B5;L=> >FV=N20B8 ?>B5=FV9=89 @878: V :>@8ABL 2V4 ?@>4>265==O B5@0?VW
4>:A>@C1VF8=>
VT;>AC?@5AVO
A:V;L:8 ?@8 B5@0?VW 4>:A>@C1VF8=< G0AB> A?>AB5@V30TBLAO ?@83=VG5==O DC=:FVW
:VAB:>2>3> <>7:C, =5>1EV4=89 @53C;O@=89 <=>VB>@8=3 35<0B>;>3VG=8E ?>:07=8:V2. @8 :>
<1V=>20=V9 EVB5@0?VW AC?@5AVO <>65 1CB8 1V;LH 28@065=>N 2=0A;V4>: 048B82=>W 4VW
?@5?0@0BV2. '0ABVH5 70 2A5 @>72820TBLAO =59B@>?5=VO, @V4H5 B@><1>F8B>?5=VO B0 0=5
AC?@5AVW T 30@OG:0, V=D5:FVW, A5?A8A/A5?B8F5, :@>2>B5G0, B:0=8==0 3V?>:AVO 01>
;5B0;L=89 =0A;V4>:.
"5@0?VN 4>:A>@C1VF8=<=5 <>6=0 @>7?>G8=0B8 01> ?@>4>26C20B8, O:I> :V;L:VABL
?>;V=C::50@=8E 3@0=C;>F8BV2 <5=H0 70 2000/<<3. @8 ;V:C20==V 3>AB@>3> ;59:>7C FO<560,
70;56=> 2V4 >1AB028=, <>65 1CB8 =86G>N.
#=0A;V4>: BO6:>W AC?@5AVW <>6CBL @>72820B8AO :@>2>B5GV 01> AC?5@V=D5:FVO, I>
A2V4G8BL ?@> =5>1EV4=VABL 7=865==O 4>7 01> ?@87C?8=5==O B5@0?VW 4>:A>@C1VF8=>
A:V;L:8 4>:A>@C1VF8= 4VT O: VAC?@5A>@, A;V4 26820B8 70E>48 4;O 70?>1V30==O @>728B:C
2B>@8==>W V=D5:FVW.
B>@8==89 ;59:>7. B>@8==89 ;59:>7 V7 ?@5;59:5N D07>N 01> 157 =5W, 2V47=0G02AO C ?0FVT=BV2,
O:V ;V:C20;8AO 0=B@0F8;;V=0<8. B>@8==89 ;59:>7 G0ABVH5 @>72820TBLAO C 28?04:C
70AB>AC20==O B0:8E ?@5?0@0BV2 C :><1V=0FVW V7 -?>H:>46CNG8<8 0=B8=5>;0AB8G=8<8
70A>10<8, :>;8 ?0FVT=B8 BO6:> ?5@5=5A;8 ?>?5@54=T ;V:C20==O F8B>B>:A8G=8<8 ?@5?0@0B0<8
01> ?@8 ?V428I5==V 4>7 0=B@0F8;;V=V2. @8 B0:8E ;59:>70E ;0B5=B=89 ?5@V>4 <>65 B@820B8 2V4
1 4> 3 @>:V2.

>@CH5==O 7 I>:C H;C=:>2>-.8H:>2>3> B@0:BC
>:A>@C1VF8=<0T 5<5B>35==V 2;0AB82>ABV. 0?0;5==O A;87>2>W >1>;>=:8 01> AB<0B8B 70728G09
28=8:0NBL =524>27V ?VA;O ?>G0B:C ;V:C20==O V C 206:8E 28?04:0E<>6CBL ?@>3@5AC20B8 4>
28@07:8 A;87>28E >1>;>=: ?@>BO3< 45;V;L:>E 4=V2. V;LHVABL ?0FVT=BV2 >4C6CT 2V4 F8E
?>1VG=8E 5D5:BV2 2?@>4>26 B@5BL>3> B86=O B5@0?VW.
B>@8==V =>2>CB2>@5==O C @>B>2V9 ?>@>6=8=V
C;8 ?>2V4><;5==O ?@> 4C65 @V4:V 28?04:8 @0:C @>B>2>W ?>@>6=8=8 C ?0FVT=BV2, O:V
?@>E>48;8 B@820;C (1V;LH5 1 @>:C) B5@0?VN 4>:A>@C1VF8=< 01> >B@87C ?@5?0@0BC, I>
?5@528IC20;0 720 <3/<2. 8?04:8 2B>@8==>3> @0:C @>B>2>W ?>@>6=8=8 4V03=>ABC20;8 O: ?V4 G0A
;V:C20==O 4>:A>@C1VF8=<, B0: V 4> 6 @>:V2 ?VA;O >AB0==L>W 4>78. 0FVT=BV2 A;V4
@53C;O@=> >1AB56C20B8 =0=0O2=VABL 28@07:8 @>B>2>W ?>@>6=8=8 01> 1C4L-O:>3> 48A:>
@BC, O:89 <>65 A2V4G8B8 ?@> 2B>@8==89 @0: @>B>2>W ?>@>6=8=8.
(:V@=V @50:FVW C
\$;51>A;;5@>7 <>65 28=8:0B8 ?@8 22545==V 2 <0;V 25=8 01> ?@8 ?>2B>@=>4=C V BC 6 25=C. !C2>@5
4>B@8<0==O 2AB0=>2;5=>3> A?>A>1C 22545==O 7=86CT @878: D;51VBC/ B@<1>D;51VBC C
535=520 B>:A8G=VABL
@07V :<1V=>20=>W EVB5@0?VW 7 V=H8<8 F8B>AB0B8:0<8 (=0?@8;:04, 35<, 1;5< , B0:A0=0<8 01>
@8BC:A8<01<) C ?>T4=0==V 7 ?@><5=52>N B5@0?VTN =0 4V;O=:C A5@54>ABV==O 01> 157 =5W, 0
B0:>6 ?@8 ;V:C20==V ?0FVT=BV2 7V AE8;L=VABN 4> ;535=528E 70E2>@N20=L =5>1EV4=>
2@0E>2C20B8 <>6;82VABL B>:A8G=>W 4VW 4>:A>@C1VF8=C =0 ;535=V.
V?5@C@8:5
/: V ?@8 ;V:C20==V V=H8<8 0=B8=5>?;0AB8G=8<8 ?@5?0@0B0<8, ?@8 B5@0?VW 4>:A>@C1VF8=<
H284:89 ;V78A ?CE;8=8 <>65 A?@8G8=8B8 3V?5@C@8:5728B:< 3>AB@>W ?>403@8 01> C@0B=>W
=5D@>?0BVW.
5>1EV4=> @53C;O@=> :>=B@>;N20B8 @V25=L A5G>2>W :8A;>B8 C :@>2V. 0FVT=B8 ?>28==V
26820B8 4>AB0B=N :V;L:VABL @V48=8 ?>25@E=V BV;0 =0 4>1C). @8 =5>1EV4=>ABV <>6=0
70AB>A>2C20B8 V=3V1VB>@8 :A0=B8=>:A84078 (0;>?C@8=>;).
>@CH5==O DC=:FVW ?5GV=:8
A;V;L:8 4>:A>@C1VF8= 5:A:@5BCTBLAO ?5@5206=> 7 6>2GN, ?@8 =0O2=>ABV ?>@CH5=L
DC=:FVW ?5GV=:8 01> ?5GV=:>2>W =54>AB0B=>ABV 282545==O 4>:A>@C1VF8=C <>65
C?>2V;L=N20B8AO, 0 B>:A8G=V 5D5:B8 ?>A8;N20B8AO. ">G0B:< V 2 ?@>F5AV B5@0?VW @5:>
<5=4CTBLAO ?@>2>48B8 DC=:FV>=0;L=V ?5GV=:>2V B5AB8 (287=0G0B8 @V2=V 0;0=V=0
B@0=AD5@078, 0A?0@B0B0B@0=AD5@078, ;C6=>W D>AD0B078 V 1V;V@C1V=C). 0FVT=B0< V7
BO6:>N D>@<>N ?>@CH5==O DC=:FVW ?5GV=:8 =5 A;V4 ?@87=0G0B8 4>:A>@C1VF8=.
0FVT=BV2 A;V4 ?>?5@5460B8, I> 4>:A>@C1VF8= <>65 7010@2;N20B8 A5GC C G5@2>=89 :>;V@,
>A>1;82> =57010@< ?VA;O 22545==O. &5 =5 ?>28==> 28;:8:0B8 C =8E B@82>3C.
=H5. >:A>@C1VF8= <>65 ?>B5=FVN20B8 B>:A8G=VABL V=H8E ?@>B8?CE;8==8E ?@5?0@0BV2.
>2V4><;O>AO ?@> 28?04:8 703>AB@5==O 35<>@03VG=>3> F8AB8BC, A?@8G8=5=>3> F8;:>D>AD0
:0@4, A;87>2V >1>;>=:8, H:V@C B0 ?5GV=:C).
/: V C 28?04:C 70AB>AC20==O V=H8E F8B>B>:A8G=8E 70A>1V2, ?@8 70AB>AC20==V
4>:A>@C1VF8=C V=:>;8 2V47=0G0;8AO 28?04:8 B@<1>D;51VBC B0 B@<1>5<1>;VG=8E O28I, C B>
!8=4@< ;V78AC ?CE;8=. >:A>@C1VF8= <>65 28;:8:0B8 3V?5@C@8:5: 5:AB5=A82=>3> :0B01>;V7
AC?@>2>46CT H284:89 ;V78A =5>?;0AB8G=8E ;VB8= (A8=4@< ;V78AC ?CE;8=8), V=4C:>20=89
?@5?0@0B>G0B:C ;V:C20==O 2 :@>2V A;V4 287=0G8B8 @V25=L A5G>2>W :8A;>B8, :0;VN, D>AD0BC
:0;LFDV V :@50B8=V=C. V4@0B0FVO, 0;:0;V70FVO A5GV V ?@>DV;0:B8:0 3V?5@C@8:5?C@8=>;<
<>6CBL 725AB8 4>
0:F8=0FVO. 0AB>AC20==O 6828E 01> 6828E >A;01;5=8E 20:F8= C ?0FVT=BV2 V7 ?>A;01;5=8< V<
2=0A;V4>: EVB5@0?VW, C B>:A>@C1VF8=C, <>65 ?@8725AB8 4> A5@9>7=8E 01> ;5B0;L=8E
V=D5:FV9. !;V4 C=8:0B8 I5?;5==O 682>N 20:F8=>N C ?0FVT=BV2, O:V 70AB>A>2CNBL
4>:A>@C1VF8=. 59B@0;V7>20=0 01> V=0:B82>20=0 20:F8=0 <>65 1CB8 ?@87=0G5=0, 0;5 2V4?>2V4L
=0 B0:C 20:F8=0FVN <>65 1CB8 A;01:0.

=CB@VH=L>25 22545==O 4>:A>@C1VF8=C <>65 ?@8725AB8 4> 28=8:=5==O A83> F8AB8BC (B0:8E
O: 487C@VO, ?>;VC@VO, =>:BC@VO, CB@C4=5=5 A5G>28?CA:0==O, 35<0BC@VO, 2V4GCBBO 48A:>
@BC C 4V;O=FV A5G>2>3>7 ABV=:8 2>3> A>1;82C C203C A;V4 ?@84V;8B8 ?@>1;5<0<
:0B5B5@870FVW (=0?@8:;04, ?@8 >1AB@C:FVW C@5B@8 7 ?@8G8=8 >1T<=8E 2=CB@VH=L>28E
?CE;8=).

=CB@VH=L>20 B5@0?VO ?>25@E=52>3> @0:C A5G>2>3> <8 in situ
?B8<0;L=0 B@820;VABL ;V:C20==O 4>B5?5@ =5 287=0G5=0, 2>=0<>65 1CB8 C <560E 2V4 6 4> 12 2>
AC20==V (=0 2V425==>3>) =5<0T >1<565==O <0:A8<0;L=>W :CW 4>78, >A:V;L:8 C FL>
2545==O C A5G>289 :070=5 ?0FVT=B0< V7 V=20782=8<8 ?CE;8=0<8 V7 ?@>=8:=5==O< C ABV=:C
A5G>2>3>

>:A>@C1VF8= =5 <>6=0 70AB>A>2C20B8 V=B@0B5:0;L=>, 2=CB@VH=L< O7>2> 01> ?V4H:V@=>.
>:A>@C1VF8= =5 A;V4 7

=CB@VH=L>0@B5@V0;L=5 70AB>AC20==O 4>:A>@C1VF8=C (B@0=A:0B5B5@=0 0@B5@V0;L=0 5
<1>;V70FVO) <>6=0 70AB>A>2C20B8 4;O ;>:0;V7>20=>W 01> @53V>=0;L=>W B5@0?VW ?5@28==>W
35?0B>F5;N;O@=>W :0@F8=><8 01> <5B0AB07V2 C ?5GV=FV. =CB@VH=L>0@B5@V0;L=5 22545==O
<>65 A?@8G8=8B8 (>:@V< ?@>O2V2 A8AB5<=>W B>:A8G=>ABV, O:VA=> ?>4V1=8E 4> B8E, I>
A?>AB5@V30NBLAO ?@8 2=CB@VH=L>25==>:A>@C1VF8=C) 28@07:8 H;C=:0 B0 420=04FOB8?0;>W
:8H:8 (2V@>3V4=>, C @57C;LB0BV @5D;N:AC ?@5?0@0BC 2 0@B5@VW H;C=:0) B0 72C65==O
6>2G=8E ?@>B>:V2 2=0A;V4>: <548:0<5=B>7=> V=4C:>20=>3> A:;5@>7CNG>3> E>;0=3VBC. &59
H;OE 22545==O <>65 ?@8725AB8 4> ?>H8@5=>3> =5:@>7C B:0=8= C 7>=V ?5@DC7VW.

0=F5@>35=57, @CH5==O D5@B8;L=>ABV.>:A>@C1VF8= ?@>O2;O2 35=>B>:A8G=V B0 ABV C
B5AB0E in vitroB0 in vivo.

6V=>: 4>:A>@C1VF8= <>65 A?@8G8=OB8 157?;V44O ?@>BO3< G0AC 70AB>AC20==O
?@5?0@0BC. >:A>@C1VF8= <>65 A?@8G8=OB8 0<5=>@5N. 2C;OFVO B0 <5=AB@C0;L=89 F8;;
?>25@B0NBLAO 4> =>@<8 ?VA;O 7025@H5==O B5@0?VW, E>G0<>6;825 ?5@54G0A=5 =0AB0==O
<5=>?0C78.

>:A>@C1VF8= ?@>O2;OT ABV V <>65 A?@8G8=OB8 ?>H:>465==O E@><>A>< C A?5@<0B>7>W40E
;N48=8. ;V3>A?5@ 07>>A?5@

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

@>B8?>:070=5. ?V4AB028 22060B8, I> 4>:A>@C1VF8= <>65 A?@8G8=OB8 A5@9>7=V 2048 @>728B:C
?;>40, B>3> =5 A;V4 70AB>A>2C20B8 C ?5@V>4 203VB=>ABV. >A;V465==O @5?@>4C:B82=>W
B>:A8G=>ABV =0 B20@8=0E ?>:070;8, I> 4>:A>@C1VF8= T B5@0B>35==8< B0 5<1@V>B>:A8G=8
0FVT=B:8 @5?@>4C:B82=>3> 2V:C <0NBL :>@8ABC20B8AO 5D5:B82=8<8 :>=B@0F5?B82=8<8 70A>10
<8 C ?5@V>4 ;V:C20==O V I>=09<5=H5 ?@>BO3<< 6

>:A>@C1VF8= ?@>=8:0T C <0B5@8=AL:5 <>;>:, B>

>:A>@C1VF8= <>65 A?@8G8=OB8 0<5=>@5N V 157?;V44O. 2C;OFVO B0 <5=AB@C0;L=89 F8;;
?>25@B0NBLAO 4> =>@<8 ?VA;O 7025@H5==O B5@0?VW, E>G0<>6;825 ?5@54G0A=5 =0AB0==O
<5=>?0C78.

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.

?;82 4>:A>@C1VF8=C =5 2AB0=>2;5=89 =0 740B=VABL :5@C20B8 02B>B@0=A?>@B< 01> V=H8<8
<5E0=V7<0<8. /:I> C ?0FVT=B0 A?>AB5@V30NBLAO B0:V ?>1VG=V 5D5:B8 O: 70?0<>@>G5==O,
=C4>B0 01> 1;N20==O, 9>B@0=A?>@B< 01> V=H8<8 <5E0=V7<0<8.

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

@5?0@0B 22>48B8 2=CB@VH=L>25==> B0 2=CB@VH=L>0@B5@V0;L=> 01> C 283;04V
2=CB@VH=L>2>3> 22545==O. 5 <>6=0 70AB>A>2C20B8 4>:A>@C1VF8= O: 0=B810:B5@V0;L=89
70AV1.

=CB@VH=L>25 22545==O 4>:A>@C1VF8=C T 0;LB5@=0B82=8< A?>A>1< 22545==O ?@8 ;V:C20==V
?>25@E=52>3> @0:C A5G>2>3> -.;VB8==>W :0@F8=><8, ?0?V;O@=8E ?CE;8= <8 in situ, 01> O:

04N20=B=>W B5@0?VW =87L:>48D5@5=FV9>20=>3> "0-@0:C A5G>2>3> W @575:FVW.

=CB@VH=L>25==5 22545==O:

@83>B>2;5=89 @>7G8= 22>4OBL C 283;O4V 2=CB@VH=L>25==>W V=DC7VW V7 2V;L=8< ?>B>:<@>V48=8, ?@>BO3<=5 <5=H5 3 0;5 =5 1V;LH5 10 E28;8=. 0728G09. ;O @>72545==O 28:>@8AB>2CNBL @>7G8=8 =0B@VN E;>@84C 4;O V=T:FV9, 5 % 3;N:>78 01> @>7G8= =0B@VN E;>@84C B0 3;N:>78. 2545==O H;OE>< AB@C<5=52>W V=T:FVW =5 @5:<5=4>20=> G5@57 @878: 5:AB@02070FVW, I> <>65 2V41C20B8AO =02VBL ?@8 =0O2=>ABV 045:20B=>3> 72>@>B=>3> B>:C :@>2V ?@8 0A?V@0FVW G5@57 3>;:C. 030;L=0 4>70 4>:A>@C1VF8=C =0 F8;; <>65 1CB8 @V7=>N, 70;56=> 2V4 ?52=>W AE5<8 ;V:C20==O (=0?@8;;04, ?@8 <=>B5@0?VW 01> C :<1V=0FVW 7 V=H8<8 F8B>B>:A8G=8<8 ?@5?0@0B0<8) B0 ?>:070=L. >70 70728G09 @>7@0E>2CTBLAO =0 >A=>2V ?;>IV ?>25@E=V BV;0. @8 <=>B5@0?VW @5:> <5=4>20=0 AB0=40@B=0 ?>G0B:>20 4>70 4>:A>@C1VF8=C =0 F8;; 4;O 4>@>A;8E AB0=>28BL 60-90<3/ <2 ?;>IV ?>25@E=V BV;0. 030;L=0 ?>G0B:>20 4>70 =0 F8;;<>65 1CB8 22545=0 70 >48= @07, 1CB8 ?>4V;5=0 =0 B@8 22545==O ?@>BO3< B@L>E ?>A;V4>2=8E 4=V2 01> 22>48B8AO 70 420 @078 2 45=L 1-9 B0 8-9. 0 C<>28 =>@<0;L=>3> >4C60==O ?VA;O B>:A8G=>3> 2?;82C ?@5?0@0BC (7>:@5<0 ?@83=VG5==O :VAB:>2>3><>7:C B0 AB<0B8BC), :>65= :C@A ;V:C20==O <>6=0 ?>2B>@N20B8 :>6=V 3-4 B86=V. /I> ?@5?0@0B 70AB>A>2C20B8 C :<1V=0FVW V7 V=H8<8 ?@>B8?CE;8==8<8 70A>10<8, I> <>6CBL ?>B5=FDN20B8 B>:A8G=89 2?;82, <>65 1CB8 =5>1EV4=8< 7<5=H5==O 4>78 4>:A>@C1VF8=C 4> 30-40 <3/<2 :>6=V B@8 B86=V. /I> 4>7C @>7@0E>2C20B8 28E>4OG8 V7 <0A8 BV;0, A;V4 22>48B8 1,2-2,4 <3/3 ?@5?0@0BC C 283;O4V @07>2>W 4>78 :>6=V B@8 B86=V. !?>AB5@V30;>AO, I> ?@8 22545==V 4>:A>@C1VF8=C C 283;O4V @07>2>W 4>78 :>6=V B@8 B86=V 7=0G=8< G8=>< 7<5=HCNBLAO ?@>O28 =5A?@8OB;82>3> B>:A8G=>3> 2?;82C, 78BC. 4=0: 45O:V A?5FV0;VAB8 22060NBL, I> @>7?>4V; 4>78 4;O 22545==O ?@>BO3< B@L>E ?>A;V4>2=8E 4=V2 (0,4- 0,8 <3/3 01> 20-25 <3/<2 I>4=O) 70157?5GCT 1V;LHC 5D5:B82=VABL, E>G0 70 @0EC=>: 1V;LH>W B>:A8G=>ABV. C;> ?>:070=>, I> I>B86=525 70AB>AC20==O 4>:A>@C1VF8=C 5D5:B82=5 B0: A0<>, O: V 22545==O 1 @07 =0 B@8 B86=V. 5:<5=4>20=0 4>70 AB0=>28BL 20<3/<2 1 @07 =0 B8645=L, E>G0 >1'T:B82=0 @50:FVO A?>AB5@V30;0AO ?@8 6-12 <3/<2. @8 I>B86=52>AC20==V 7<5=HCTBLAO :0@4V>B>:A8G=VABL. >65 1CB8 =5>1EV4=8< 7<5=H5==O 4>78 C ?0FVT=V2, O:V @0=VH5 >B@8 <5=H5==O ?>G0B:>28E 4>7 01> 71V;LH5==O V=B5@20;V2 B0 ?@8 70AB>AC20==V C :C@AV :> <1V=>20=>W B5@0?VW @07> 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 7 ?>4V1=8< ?@>DV;5< B>:A8G=>ABV (482. @>74V; «A>I;82>ABV 70AB>AC20==O»). >@5:FVO 4>7 4;O >A>I;828E 3@C? ?0FVT=V2 >@CH5==O DC=:FVW ?5GV=:8. @8 ?>@CH5==V DC=:FVW ?5GV=:8 4>7C 4>:A>@C1VF8=C A;V4 7<5=H8B8 O: ?>:070=> C B01;8FV:

V2=V 1V;V@C1V=C C A8@>20BFV :@>2V	5:<5=4>20=0 4>70
1,2-3 <3/100 <; > 3 <3/100 <;	50 % 728G09=>W 4>78 25 % 728G09=>W 4>78

>:A>@C1VF8= =5 A;V4 70AB>A>2C20B8 ?0FVT=B0< V7 B06:8<8 ?>@CH5==O<8 DC=:FVW ?5GV=:8. =CB@VH=L>0@B5@V0;L=5 22545==O. =CB@VH=L>0@B5@V0;L=5 22545==O 70AB>A>2C20;8 ?@8 A?@>10E ?>A8;8B8 ;>:0;L=C 0:B82=VABL ?@8 =87L:V9 7030;L=V9 4>7V V, B0:8< G8=><, 7<5=H8B8 7030;L=C B>:A8G=VABL. !;V4 =03>;>A8B8, I> B0:0 B5E=V:0 ?>B5=FDV9=> 4C65 @878:>20=0 V<>65 ?@8725AB8 4> ?>H8@5=>3> =5:@>7C ?5@DC7>20=>W B:0=8=8, O:I> =5 268B8 2V4?>2V4=8E 70AB5@56=8E 70E>4V2. >78 ?@5?0@0BC B0 V=B5@20;8 22545==O ?@8 2=CB@VH=L>0@B5@V0;L=> AC20==V <>6CBL 1CB8 @V7=8<8. =CB@VH=L>0@B5@V0;L=> ?@5?0@0B ?>28==V 22>48B8 ;8H5 A?5FV0;VAB8 7 4>AB0B=V< 4>A2V4< 28:>=0==O B0:8E V=T:FV9. =CB@VH=L>25 22545==O. >:A>@C1VF8= 2A5 G0ABVH5 70AB>A>2CNBL 4;O 2=CB@VH=L>2>3> 22545==O 7 <5B>N ;V:C20==O ?5@5EV4=>:;VB8==>3> @0:C, ?0?V;O@=8E ?CE;8=<8 in situ. 5 A;V4 2=CB@VH=L>2> 22>48B8 ?@5?0@0B 4;O ;V:C20==O V=20782=8E ?CE;8=, O:V ?@>@>A;8 G5@57 ABV=:C A5G>2>3> FV;L=8< B0:>6 T 22545==O 4>:A>@C1VF8=C C A5G>289 A;V;L:8 =0 40=89 G0A 70AB>A>2CNBL 1030B> AE5< ;V:C20==O, I> CA::04=NT V=B5@?@5B0FVN, 40;V =02545=0 4>?>@<0FVO: · @5:<5=4>20=0 4>70 ?@8 2=CB@VH=L>2>

. 4;O C=8:=5==O =51060=>3> @>7102;5==O A5G5N A;V4 ?>?5@548B8 ?0FVT=BV2, I>1 2>=8 CB@8
<0;8AL 2V4 A?>6820==O =0?>W2 ?@>BO3< 12 3>48= 4> V=AB8;OFVW. &5<0T 7<5=H8B8
284V;5==O A5GV 4> ?@81;87=> 50<; =0 3>48=C;
. ?VA;O 22545==O ?@5?0@0BC ?0FVT=BC A;V4 7;>65==O BV;0 =0 90 3@04CAV2 :>6=V 15E28;8=
VW @>7G8=C ?@5?0@0BC ?@>BO3< 1 3>48=8 70728G09 4>AB0B=L>; ?VA;O 7025@H5==O
?@>F54C@8 ?0FVT=BC A;V4 28?>@>6=8B8 A5G>289

VB8.

@5?0@0B 70AB>A>2C20B8 7 =0@>465==O.
VBO< 4>:A>@C1VF8= ?@87=0G0B8 C =86G8E 4>70E G5@57 ?V428I5=89 @878: :0@4V>B>:A8G=8E
5D5:BV2 (>A>1;82> 2V4AB@>G5=8E). FVTW 6 ?@8G8=8 @5:><5=4CTBLAO ?@>2>48B8 @53C;O@=V
:0@4V>;>3VG=V >1AB565==O ?0FVT=BV2 ?VA;O 70:V=G5==O B5@0?VW 4>:A>@C1VF8=>
#=0A;V4>: ?@83=VG5==O DC=:FVW :VAB:>2>3><7:C :V;L:VABL D>@>5=8E 5;5<5=BV2 :@>2V C
4VB59 7=86CTBLAO 4> G0B:C ;V:C20==O, ?@>B5 ?>BV< 35<0B>;>3VG=V ?>:07=8:8 70728G09 H284:>
=>@<0;V7CNBLAO 7024O:8 25;8:8< @575@20< :VAB:>2>3><7:C C 4VB59 ?>@V2=O=> 7 4>@>A;8<8.

5@54>7C20==O.

07>2V 4>78 C 250 <3 B0 500 <3 4>:A>@C1VF8=C T ;5B0;L=8<8. "0:V 4>78 <>6CBL A?@8G8=8B8
3>AB@C 4535=5@0FVN A5@F52>3> <'O70 ?@>BO3<< 24 3>48= B0 BO6:C AC?@5AVN (?5@5206=>
;59:>?5=VN B0 B@><1>F8B>?5=VN), 2?;828 O:8E 4>AO30NBL <0:A8AC20==O. 5B>N ;V:C20==O
?>28==> 1CB8 ?V4B@8<0==O AB0=C ?0FVT=B0 ?@>BO3<< FL>3> ?5@V>4C; A;V4 ?@>2>48B8
?5@5;820==O :@>2V B0 AB2>@8B8 C<>28 70E8A=>W V7>;OFVW ?0FVT=B0.
>AB@5 ?5@54>7C20==O 4>:A>@C1VF8=>< ?@872>48BL 4> B>:A8G=>3> 2?;82C =0 H;C=:>2>:8H:>289
B@0:B (?5@5206=> 78BC). 0728G09 F5 ?@>O2;OTBLAO =0 ?>G0B:C 70AB>AC20==O ?@5?0@0BC, 0;5
1V;LHVABL ?0FVT=BV2 >4C6CNBL ?@>BO3< 3 B86=V2.
V440;5=0 A5@F520 =54>AB0B=VABL<>65 ?@>O28B8AO G5@57 6 7C20==O. !;V4 @5B5;L=>
:=B@>;N20B8 AB0= ?0FVT=BV2, B0 C 28?04:C >7=0: A5@F52>W =54>AB0B=>ABV ?@>25AB8
7030;L=>?@89=OB5 ;V:C20==O.
A:V;L:8 2=0A;V4>: BO6:>W - B0 VAC?@5AVW <>6CBL @>72820B8AO :@>2>B5GV B0 V=D5:FVW,
A;V4 26820B8 2V4?>2V4=V 70E>48. # B0:8E 28?04:0E <>6CBL 1CB8 =5>1EV4=8<8 ?5@5;820==O :@>2V
B0 V7>;OFVO E2>@8E C AB5@8;L=8E ;V:0@=O=8E 1>:A0E.
5<>4V0;V7 C @07V ?5@54>7C20==O =55D5:B82=89, >A:V;L:8 4>:A>@C1VF8= 5:A:@5BCTBLAO
?5@5206=> 7 6>2GN V G5@57 :8H5G=8:.

>1VG=V@50:FVW.

>7>;VB5@0?52B8G=8E ?@5?0@0BV2 (AB@5?B>7>F8=C, <5B>B@5:A0BC, F8;;>D>AD0
I>:C A5@F52>W A8AB5<8
0@4V>?0BVO, A5@F520 =54>AB0B=VABL; A8<8 :0@4V>B>:A8G=>ABV, 7>:@5<0 0@8B:@5<0 >7=0:8
1;>:048 A5@FO, A?;>I5==O 7C1FO " V 45?@5AVO A53<5=BC ST) <>6CBL A?>AB5@V30B8AO 4> 42>E
B86=V2 ?VA;O 22545==O 4>:A>@C1VF8=C, A8=CA=0 B0EV:0@4VO;<>6;82V ?5@8:0@48B V:0@48B,
0@B5@V0;L=0 3V?5@B5=7VO, 7048H:0, 207>48;0B0FVO, B0EV0@8B25=B@8:C;O@=0 1;>:040, 1;>:040
=V6>: ?CG:0 VA0, 0A8<0B8G=5 7<5=H5==O D@0:FVW 28:84C ;V2>3> H;C=>G:0 B0 70ABV9=0 A5@F520
=54>AB0B=VABL. 0@4V>B>:A8G=VABL<>65 ?@>O2;OB8AO C 283;O4V B0EV:0@4VW, C B>G:>2>W
B0EV:0@4VW B0 7@CH5==O<8 DC=:FVW A5@FO @5:><5=4>20=> @53C;O@=89 :=B@>;L B0
>15@56=5 70AB>AC20==O ?@5?0@0BC. "O6:0 A5@F520 =54>AB0B=VABL<>65 28=8:0B8 @0?B>2>,
157 ?>?5@54=VE 72V4><;O;>AO ?@> =04H;C=>G:>2V B0 H;C=>G:>2V 5:AB@0A8AB>;8,
B@0=78B>@=0 0@8BA>1;82> A8=CA>20 0@8B
878: @>728B:C :0@4V>?0BVW 7@>AB0T V7 7@>AB0==O< AC:C?=>W 4>78 ?@5?0@0BC. 5 A;V4
?5@528IC20B8 AC:C?>C 4>7C 2 450 550 <3/<2 ?>25@E=V BV;0, E>G0 =572>@>B=0 70ABV9=0 A5@F520
=54>AB0B=VABL<>6;820 V ?@8 >B@8<0=V ?@5?0@0BC 4>7>N 240 <3/<2 ?>25@E=V BV;0.
\$0:B>@0<8 @878:C A;V4 22060B8 2V: 2V4 70 @>:V2 01> 4> 15 @>:V2. "0:>6 T ?>2V4<;5==O ?@> B5, I>
?>?5@54=T 01> >4=>G0A=5 >B@8<0=O D>AD0 40:0@1078=C A?@8OT @>728B:C :0@4V>?0BVW,
V=4C:>20=>W 22545==O< 4>:A>@C1VF8=C.

/28I0 :0@4V>B>:A8G=>3> 2?;82C <>6CBL A?>AB5@V30B8AL G5@57 45:V;L:0 B86=V2, =02VBL @>:V2 ?VA;O
7025@H5==O B5@0?VW V7 70AB>AC20==O< 4>:A>@C1VF8=C. 878: @>728B:C A5@F52>W
=54>AB0B=>ABV C ?0FVT=BV2 V7 >=:;>3VG=8<8 70E2>@N20==O<8 ?@8 >B@8<0==V 4>:A>@C1VF8=C
715@V30TBLAO ?@>BO3>< CAL>3> 68BBO.
=D5:FVW B0 V=207VW
=D5:FVW, A5?A8A, A5?B8F5.
I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8
VT;>AC?@5AVO, ;59:>?5=VO, =59B@>?5=VO, 0=5<1>F8B>?5=VO. '5@57 <>6;82C 45?@5AVN
:VAB:>2>3><>7:C, I> <>65 ?@>O28B8AO ?@81;87=> G5@57 10 4=V2 ?VA;O 22545==O ?@5?0@0BC,
A;V4 @53C;O@=> :>=B@>;N20B8 35<0B>;>3VG=V ?>:07=8:8, C ?0FVT=BV2 V7 35<0B>;>3VG=8<8 B0
=5 35<>B>;>3VG=8<8 70E2>@N20==O<8. ;V=VG=8<8 ?@>O20<8 B>:A8G=>3> 2?;82C 4>:A>@C1VF8=C
=0 :VAB:>289<>7>:/35<0B>;>3VG=V ?0@0<5B@8 <>6CBL 1CB8 30@OG:0, V=D5:FVW, A5?A8A
/A5?B8F5:, :@>2>B5G0, B:0=8==0 3V?>:AVO 01> ;5B0;L=89 =0A;V4>:.
I>:C VW A8AB5<8. =0DV;0:AVO.
I>:C >@30=V2 7>@C. >=N=:B82VB, ?>A8;5=5 A;L>7>284V;5==O, =5GVB:VABL 7>@C, :5@0B8B.
I>:C A8AB5<8 48E0==O, >@30=V2 3@C4=>W ;:VB:8 B0 A5@54>ABV==O. # ?>>48=>:8E 28?04:0E
<>6;82V B>:A8G=5 C@065==O ;535=V2 (7 B0:8<8 ?@>O20<8 O: G0AB5 48E0==O, O4CE0/?;52@0;L=89
28?VB, >1;VB5@CNG89 1@>=EV>;VB 7 ?=52<>=VTN, I> >@30=V7CTBLAO; 1@>=E>F5=B@8G=89
3@0=C;5<0B>7/?@83=VG5==O 48E0==O, I> 703@>6CT 68BBN; A8=4@<, I> =0304CT ?>AB?C;L
<>=5:B>
I>:C B@02=>3> B@0:BC
'5@57 5-10 4V1 ?VA;O 22545==O 4>:A>@C1VF8=C <>6CBL A?>AB5@V30B8AO =C4>B0, 1;N20==O,
70?0;5==O A;87>28E>1>;>=: (AB<0B8B, 57>D03VB, ?@>:B8B), 3V?5@?V3<5=B0FVO A;87>2>W
>1>;>=:8 @>B0, 4V0@5O, 1V;L C 682>BV, :>;VB, 0=>@5:AVO, 70?>@, 48A?5?AVO, 1V;L C @>BV,
:0=484>7 A;87>2>W >1>;>=:8 @>B0, 30AB@8B, 48AD03VO, ACEVABL C @>BV, <5B5>@87<,
3V=3V2VB. #@065==O H;C=:>2>-.8H:>2>3> B@0:BC <>65 A?@8G8=8B8 CB2>@5==O 28@07>:,
5@>7VN A;87>2>W >1>;>=:8 H;C=:0, :@>2>B5GV, =5:@>7 V ?5@D>@0FVN :8H5G=8:C.
0?0;5==O A;87>28E>1>;>=: (78B) =09G0ABVH5 ?>G8=0TBLAO V7 2V4GCBBO ?5GV==O 2 @>B>2V9
?>@>6=8=V B0 3>@>V G5@57 5 10 4=V2 ?VA;O 22545==O ?@5?0@0BC, B0<>65 ?@>3@5AC20B8 4>
CB2>@5==O 28@07>:, 0A>FV9>20=8E V7 @878:< 2B>@8==>W V=D5:FVW. C:>78B <>65 B0:>6 C@060B8
?VE2C, ?@OE4.
I>:C =8@>: B0 A5G>284V;L=>W A8AB5<8
@8 2=CB@VH=L>2>AC20==V 4>:A>@C1VF8=C <>6;82V B0:V ?>1VG=V 5D5:B8 O: 35<0BC@VO,
487C@VO, ?>4@07=5==O A5G>2>3> 7 ABV=:8 A5G>2>3> 28?CA:0==V, ?>;VC@VO, ?>;0:VC@VO,
AB@0=3C@VO, =>:BC@VO. 0728G09 FV @50:FVW ?>W B06:>ABV B0 =5B@820;V. @8 2=CB@VH=L>
2>AC20==V B0:>6 V=:>;8 @>72820TBLAO 35<>@03VG=89 F8AB8B, I> <>65 A?@8G8=8B8 7<5=H5==O
ABV A5G>2>3> :A>@C1VF8= <>65 7010@2;N20B8 A5GC C G5@2>=89 :>;V@. >6;82V V=D5:FVW
A5G>284V;L=8E H;OE2, 3>AB@0=8@>:20 =54>AB0B=VABL, 487C@VO B0 203V=VB.
I>:C H:V@8 B0 ?V4H:V@=8E B:0=8=
1>@>B=0 0;>?5FVO @>72820TBLAO C 1V;LH>ABV ?0FVT=BV2. >6;82V 3V?5@?V3<5=B0FVO
=V3BL>2>3> ;>60 V H:V@=8E A;:04>:, 0=<0;L=0 ?V3<5=B0FVO, 7=510@2;5==O H:V@8, ?>O20 7
<>@H>:, >=VE>;V7, ACEVABL H:V@8; 4>;>==>?V4>H>2=0 5@8B@>4875AB57VO (), 2V4:@8BV
?>H:>465==O H:V@8 (=535@?5B8G=V), 3@81:>20 V=D5:FVO, 1C;L>7=89 28A8?, 45@<0B8B, 5@8B5
<0B>7=89 28A8?, 45D5:B8 =V3BV2, ;C15==O H:V@8, 2578:C;>1C;L>7=89 28A8?, 5:AD>;V0B82=89 45@
<0B8B, <0:C;>?0?C;L>7=89 28A8?, ?VB;82VABL, 0:=5, >?5@V7C20;L=89 35@?5A, ?5B5EVW.
>:A>@C1VF8= A?@8G8=OT A8;L=5 ?>4@07=5==O B:0=8=, ?@8 5:AB@02070FVW C
?>2V4><;5==O ?@> @50:FVW 3V?5@GCB;82>ABV, 7>:@5<0 H:V@=V @50:FVW (28A8?0==O, 5@8B5
<0, A25@1V6, :@>?82O=:0, 0=3V>=52@>B8G=89 =01@O:, ?@>?0A=8FO, 0=0DV;0:AVO),
D>B>A5=A81V;V70FVO. >:A>@C1VF8= ?>B5=VNT @50:FVN =>@<0;L=8E B:0=8= =0 ?>@>?@>W
H:V@8, 0:@0;L=0 5@8B5<0. # @07V 70AB>AC20==O 4>:A>@C1VF8=C G5@57 45O:89 G0A ?VA;O
70:V=G5==O :C@AC ?@><5=52>W B5@0?VW B0:>6 <>6;820 ?V7=O @50:FVO (?>25@=5==O A83>
C@065==O).
I>:C >?>@=>:@CE>2>3> 0?0@0BC B0 A?>;CG=>W B:0=8=8
5=5@0;V7>20=0
I>:C 5=4>:@8==>W A8AB5<8

=>;8 A?>AB5@V30;8AO ?>@CH5==O @>ABC B0 5=4>:@8==V ?>@CH5==O C 4VB59
?@5?C15@B0B=>3> 2V:C ?@8 V=B5=A82=V9 EVB5@0?VW.
I>:C <5B0I>;V7=>@5:AVO, 453V4@0B0FVO, 3V?5@C@8:5:0;LFVT:0;VT<03=VT=0B@VT
>I@>O:VA=V V 7;>O:VA=V =>2>CB2>@5==O (2.;NG0NG8 :VAB8 B0 ?>;V?8)
4VB59 <>6;8289 ?V428I5=89 @878: @>728B:C C <091CB=L>@8==8E =5>;0AB8G=8E 70E2>@N20=L,
>A>1;82> 3>AB@>3> W4=>3> B0 ;VW4=>3> ;59:>7V2.
V4:> ?>2V4><;O;>AO ?@> 2B>@8==89 3>AB@89 W4=89 ;59:>7 (7 ?5@54;59:>7=>N D07>N 01> 157
=5W) C ?0FVT=BV2, O:V ;V:C20;8AO 4>:A>@C1VF8=× C ?>T4=0==V 7 V=H8<8 0=B8=5>;0AB8G=8<8
?@5?0@0B0<8, I> ?>H:>46CNBL . 0B5=B=89 ?5@V>4 C B0:8E 28?04:0E <>65 1CB8 :>@>B:8< (1-3 @>:8).
I>:C AC48==>W A8AB5<8. \$;51VB, B@><1>D;51VB, B@><1>5<1>;VO, ?@8?;828 :@>2V, H>;,
:@>2>B5G0.
I>:C 35?0B>1V;V0@=>W A8AB5<8. 57=0G=5 B@0=78B>@=5 ?V428I5==O @V2=V2 ?5GV=:>28E D5@
<5=BV2, ?V428I5==O @V2=O 7030;L=>3> 1V;V@C1V=C. # @07V AC?CB=L>W ?@>×5=52>W
B5@0?VW =0 4V;O=:C ?5GV=:8 <>6;82V BO6:V 35?0B>B>:A8G=V 5D5:B8, I> <>6CBL ?@8725AB8 4>
F8@>7C ?5GV=:8.
I>:C @5?@>4C:B82=>W A8AB5<8. <5=@5O, >;V3>A?5@A?5@
I>:C =5@2>2>W A8AB5<8. 0@5AB57VO, A>;82VABL, ?5@8D5@8G=0 =59@>?0BVO, 3>;>2=89 1V;L,
70?0<>@>G5==O, 157A>==O, B@82>6=VABL, 45?@5AVO, =52@0;3VO, ;5B0@3VO, ?5@8D5@8G=0
A5=A>@=0 =59@>?0BVO. ?>@CH5==O A<0:C.
D5:B8 7030;L=>3> E0@0:B5@C B0 @50:FVW 2 # ?>>48=>:8E 28?04:0E 2V47=0G0NBLAO 0AB5=VO,
30@OG:0, 2V4GCBBO 2B><8, =574C60==O, A;01:VABL, C @07V 70=04B> H284:>3> 22545==O
?@5?0@0BC <>6;825 ?>G5@2>=V==O >1;8GGO. 878: B@><1>D;51VBC C =HV 5D5:B8
\$>;V:C;VB, 1V;L C 3@C4OE, AC4×8 =V3, =01@O:8, =01@O: =V3, =>A>20 :@>2>B5G0, 1V;L C A?8=V,
=574C60==O, 7=865==O <0A8 BV;0, :0E5:AVO, ?V428I5==O @V2=O :@50B8=V=C 2 A8@>20BFV :@>2V,
453V4@0B0FVO.
IAB565==O. V4E8;5==O ?>:07=8:V2 2V4 =>@<8.
>1VG=V ?@>O28 C E2>@8E, O:V >B@8:A8@C1VF8= C O:>ABV 04N20=B=>W B5@0?VW @0:C
<>;>G=>W 70;>78. 0 @57C;LB0B0<8 @0=4>20=>3> 2V4:@8B>3> 4>A;V465==O 70AB>AC20==O
4>:A>@C1VF8=C V F8:;>D>AD02C7;8 =09G0ABVH8< ?>1VG=8< ?@>O2>× 1C;0 (>:@V< E0@0:B5@=8E
4;O 4>:A8@C1VF8=C) 2B@0B0 2038.

"5@ABV.

2 @>:8.

#<>28 715@V30==O.

15@V30B8 2 >@83V=0;L=V9 C?0:>2FV ?@8 B5

15@V30B8 C =54>ABC?=>

5AC

5 <>6=0 4>?CA:0B8 :>=B0:BC ?@5?0@0BC 7 1C4L-O:8<8 ;C6=8<8 @>7G8=0<8, >A:V;L:8 F5 A?@8G8=OT
3V4@>;V7 4>:A>@C1VF8=C.

57 ?@>2545==O 4>A;V465=L ACABV >:A>@C1VF8= «1525» =5 A;V4 7< V 5-DB>@C@0F8;<;>A:V;L:8
?@8 FL>

#?0:>2:0.

> 5 <; (10 <3), 25 <; (50 <3), 50 <; (100 <3) 01> 100 <; (200 <3) C D;0:>=V 7 :>@8G=52>3> A:;0 7 ?@>1:>N 7
:0CGC:C B0 0;N

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

0 @5F5?B>

8@>1=8:.

\$0@<0 5A.
EBEWE Pharma Ges.m.b.H. Nfg. KG.

VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.
>=475THB@0AA5 11, 4866 #=B5@0E 0< BB5@75T, 2AB@VO/
Mondseestrasse 11, 4866 Unterach am Attersee, Austria.