

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

\$!®
(FRAXIPARINE")

!,:04:
4VNG0 @5G>28=0: =04@>?0@8= :0;LFVN;
1 <; @>7G8=C ?0@8=C :0;LFVN;
1 ?>?5@54=L> 70?>2=5=89 H?@8F (0,6 <;) ?0@8=C :0;LFVN;
1 ?>?5@54=L> 70?>2=5=89 H?@8F (0,8 <;) ?0@8=C :0;LFVN;
4>?>28=8: @>7G8= :0;LFVN 3V4@>:A84C (01> :8A;>B0 E;>@8AB>2>4=520 @>72545=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. □=B8B@><1>B8G=V 70A>18. @C?0 35?0@8=C.
>4 "!" 0106.

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

>:070==O.

@>DV;0:B8:0 B@<1>5<1>;VG=8E CA::04=5=L
C @57C;LB0BV 7030;L=8E 01> >@B>?548G=8E EV@C@3VG=8E 2B@CG0=L;
C E2>@8E V7 28A>:8< @878:>< B@<1>5<1>;VG=8E CA::04=5=L (48E0;L=0 =54>AB0B=VABL V/01>
V=D5:FV9=V 70E2>@N20==O 48E0;L=8E H;OE2, V/01> A5@F520 =54>AB0B=VABL),
3>A?VB0;V7>20=8E C 2V44V;5==O V=B5=A82=>W B5@0?VW.
V:C20==O B@<1>5<1>;VG=8E CA::04=5=L.
@>DV;0:B8:0 73>@B0==O :@>2V ?@8 35<>4V0;V7V.
V:C20==O =5AB01V;L=>W AB5=>:0@4VW B0 V=D0@:BC:0@40 157 ?0B>;>3VG=>3> 7C1FO Q =0 .

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> =04@>?0@8=C :0;LFVN 01> 4> 1C4L-O:>3> V=H>3> :>5=B0 ?@5?0@0BC,
01> 35?0@8=C, 01> V=H8E =87L:><;5:C;O@=8E 35?0@8=V2.

"@><1>F8B>?5=VO, ?>2O70=0 V7 70AB>AC20==O< =04@>?0@8=C 2 0=0<=57V.

7=0:8 :@>2>B5GV 01> ?V428I5=89 @878: :@>2>B5G, ?>2O70=8E V7 ?>@CH5==O< 35<>AB07C, 70
28=OB:>< !-A8=4@>3> 35?0@8=>

@30=VG=V C@065==O 7V AE8;L=VABN 4> :@>2>B>G82>ABV (=0?@8::04, 3>AB@0 28@07:>20
E2>@>10 H;C=:0 01> 420=04FOB8?0;>W :8H:8).

5<>@03VG=V F5@51@>20A:C;O@=V B@02<8.

>AB@89 V=D5:FV9=89 5=4>:0@48B.

V015B8G=0 01> 35<>@03VG=0 @5B8=>?0BVO.

"O6:0 =8@:>20 =54>AB0B=VABL (;V@5=A :@50B8=V=C<5=H5 30 <;/E2) C E2>@8E ?@8 ;V:C20==V
B@<1>5<1>;VG=8E CA::04=5=L.

"O6:0 =8@:>20 =54>AB0B=VABL (;V@5=A :@50B8=V=C<5=H5 30 <;/E2) C E2>@8E ?@8 ;V:C20==V
=5AB01V;L=>W AB5=>:0@4VW B0 V=D0@:BC:0@40 157 ?0B>;>3VG=>3> 7C1FO Q =0 .

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

!;V4 725@=CB8 >A>1;82C C203C=0 A?5F8DVG=V 4>7>2V @5:>5=40FVW I>4> 70AB>AC20==O
:>6=>3> >:@5<>3> ?@5?0@0BC 3@C?8 =87L:><;5:C;O@=8E 35?0@8=V2, >A:V;L:8 @V7=V >48=8FV 28
48=8FV 01> ?0@8= =5 <>6=0 70AB>A>2C20B8 O: 703> =87L:><;5:C;O@=>3> 35?0@8=C ?V4 G0A
:C@AC ;V:C20==O.

5>1EV4=V >A>1;820 >15@56=VABL V 4>B@8<0==O :>=:@5B=8E V=AB@C:FV9 4;O 70AB>AC20==O
4;O :>6=>W D>@<8 28?CA:C =04@>?0@8=C.

\$@0:A8?0@8= =5 ?@87=0G5=89 4;O 2=CB@VH=L><O7>2>3> 22545==O.

5>1EV4=89 :>=B@>;L :V;L:>ABV B@<1>F8BV2 ?V4 G0A ;V:C20==O =04@>?0@8=>

!;V4 4>B@8<5=40FV9 AB>A>2=> G0AC 4>7C20==O =04@>?0@8=C ?V4 G0A A?V=0;L=>W /5?V4C@0;L=>W 0=5AB57VW 01> ;N<10;L=>W ?C=:FVW (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

"5E=V:0 ?V4H:V@=>3> 22545==O. 5:><5=4CTBLAO 22>48B8 ?V4H:V@=C V='T:FVN \$@0:A8?0@8=C C ?5@54=L>;0B5@0;L=C ABV=:C 682>B0, ?>?5@5 C ?@02C B0 ;V2C.)>1 C=8:0B8 2B@0B8 ?@5?0@0BC, =5 A;V4 2840;OB8 ?CE8@5FL ?>2VB@O 7 ?>?5@54=L> =0?>2=5=>3> H?@8F0 ?5@54 V='T:FVTN. >;C =5>1EV4=> 22>48B8 ?5@?5=48:C;O@=>, 0 =5 ?V4 :CB<, C 70B8A=5=C A;;04:C H:V@8, O:C B@8<0B8 >@>A;V

@>DV;0:B8:0 B@><1>5<1>;VG=8E CA;:04=5=L

030;L=0 EV@C@3VO

5:><5=4>20=>N 4>7>N \$@0:A8?0@8=C T 0,3 <; (2 850 0=B8-%0-D0:B>@=>W 0:B82=>ABV), O:C 22>48B8 ?V4H:V@=> 70 2-4 3>48=8 4> EV@C@3VG=>3> 2B@CG0==O. >40;LHV 4>78 22>48B8 1 @07 =0 4>1C ?@>BO3>< =0ABC?=8E 4=V2. V:C20==O<0T B@820B8 =5 <5=H5 7 4V1 V ?@>BO3< CAL>3> ?5@V>4C @878:C 4> ?5@52545==O E2>@>3> =0 0<1C;0B>@=5 ;V:C20==O.

@B>?548G=V EV@C@3VG=V 2B@CG0==O

@5?0@0B 22>48B8 ?V4H:V@=> C 4>70E, I> 70;560BL 2V4 <0A8 BV;0 ?0FVT=B0 (482. "01;8FN 1). >78 287=0G0B8 7 @>7@0EC=:C 38 0=B8-%0-D0:B>@=>W 0:B82=>ABV =0 1 :3 <0A8 BV;0 E2>@>3> B0 71V;LHC20B8 =0 50 % =0 G5B25@B89 ?VA;O>?5@0FV9=89 45=L. >G0B:>2C 4>7C 22>48B8 70 12 3>48= 4> >?5@0FVW, 4@C3C 4>7C G5@57 12 3>48= ?VA;O >?5@0FVW. 0ABC?=V 4>78 22>48B8 1 @07 =0 4>1C ?@>BO3>< CAL>3> ?5@V>4C @878:C B0 4> ?5@52545==O E2>@>3> =0 0 <1C;0B>@=5 ;V:C20==O. V=V<0;L=0 B@820;VABL ;V:C20==O AB0=>28BL 10 4V1.

"01;8FO 1

0A0 BV;0 E2>@>3>, :3	>70 \$@0:A8?0@8=C, I> 22>48BLAO 70 12 3>48= ?5@54 V ?VA;O >?5@0FVW B0 ?>BV< 1 @07 =0 4>1C 4> 3-3> 4=O ?VA;O >?5@0FVW		>70 \$@0:A8?0@8=C, I> 22>48BLAO 1 @07 =0 4>1C, ?>G8=0NG8 7 4-3> 4=O ?VA;O >?5@0FVW	
	1 □T< 22545==O, <;	V;L:VABL 0=B8- %- 0:B82=>ABV	1 □T< 22545==O, <;	V;L:VABL 0=B8- %- 0:B82=>ABV
□50	0,2	1900	0,3	2850
50-69	0,3	2850	0,4	3800
□70	0,4	3800	0,6	5700

%2>@V 7 28A>:8< @878:>< B@><1>5<1>;VG=8E CA;:04=5=L (48E0;L=0 =54>AB0B=VABL V/01> V=D5:FV9=V 70E2>@N20==O 48E0;L=8E H;OEV2, V/01> A5@F520 =54>AB0B=VABL)

\$@0:A8?0@8= 70AB>A>2C20B8 ?V4H:V@=> 1 @07 =0 45=L. >70 @>7@0E>2CTBLAO 2V4?>2V4=> 4> <0A8 BV;0 ?0FVT=B0, O: =02545=> C "01;8FV 2. V:C20==O<0T B@820B8 25AL ?5@V>4 @878:C 28=8:=5==O B@><1>5<1>;VW.

"01;8FO 2

0A0 BV;0 E2>@>3> , :3	1 @07 =0 4>1C	
	1 □T< 22545==O, <;	V;L:VABL 0=B8-%- 0:B82=>ABV
≤ 70	0,4	3800
>70	0,6	5700

V:C20==O B@><1>5<1>;VG=8E CA;:04=5=L

@8 ;V:C20==V B@><1>5<1>;VG=8E CA;:04=5=L A;V4 70AB>A>2C20B8 ?5@>@0;L=V 0=B8:>03C;O=B8 O:><>30 A:>@VH5 ?@8 2V4ACB=>ABV ?@>B8?>:070=L 4;O WE ?@87=0G5==O. V:C20==O \$@0:A8?0@8=><=5 <>6=0 ?@8?8=OB8 @0=VH5 4>AO3=5==O 2V4?>2V4=>3> @V2=O 4=>3> =>@ <0;V7>20=>3> 2V4=>H5==O ().

5:><5=4CTBLAO 70AB>A>2C20B8 \$@0:A8?0@8= ?V4H:V@=> 2 @078 =0 4>1C (:>6=V 12 3>48=),
70728G09 ?@>BO3>< 10 4=V2. >70 @>7@0E>2CTBLAO 73V4=> 7 <0A>N BV;0 E2>@>3>, O: =02545=>
C "01;8FV 3, 7 @>7@0EC=:C 86 0=B8-%0-D0:B>@=>W 0:B82=>ABV =0 1 :3 <0A8 BV;0 E2>@>3>.

"01;8FO 3

0A0 BV;0 E2>@>3>, :3	2 @078 =0 4>1C ?@8 728G09=V9 B@820;>ABV ;V:C20==O C 10 4V1	
	1 □T< 22545==O, <;	V;L:VABL 0=B8-%-0:B82=>ABV
<50	0,4	3800
50-59	0,5	4750
60-69	0,6	5700
70-79	0,7	6650
80-89	0,8	7600
≥90	0,9	8550

@>DV;0:B8:0 73>@B0==O :@>2V ?@8 35<>4V0;V7V
>70 \$@0:A8?0@8=C 4>18@0TBLAO V=482V4C0;L=>, 2@0E>2CNG8 B0:>6 B5E=VG=V C<>28
?@>2545==O 35<>4V0;V7C.
\$@0:A8?0@8= 70AB>A>2C20B8 70728G09 C 283;O4V >4=>@07>2>3> V=B@020A:C;O@=>3> 22545==O
2 0@B5@V0;L=89 :@>2>?@>2V4=8: 5:AB@0:>@?>@0;L=>3> :>=B@C@C =0 ?>G0B:C :>6=>3> A50=AC
35<>4V0;V7C. ;O E2>@8E 157 ?V428I5=>3> @878:C 28=8:=5==O :@>2>B5G ?>G0B:>20 4>70
@>7@0E>2CTBLAO 73V4=> 7 <0A>N BV;0 V T 4>AB0B=L>N 4;O A50=AC 35<>4V0;V7C B@820;VABN
4> 4 3>48= (482. "01;8FN 4).

"01;8FO 4

0A0 BV;0 E2>@>3>, :3	2545==O 2 0@B5@V0;L=89 HC=B =0 ?>G0B:C 4V0;V7C	
	1 □T< 22545==O, <;	V;L:VABL 0=B8-%-0:B82=>ABV
<50	0,3	2850
50-69	0,4	3800
≥70	0,6	5700

@8 ?V428I5=>2>B5G 4>7C A;V4 7<5=H8B8 =0?>;>28=C.
@8 B@820;>ABV A50=AC 35<>4V0;V7C ?>=04 4 3>48=8 4>40B:>2> <>65 1CB8 22545=0 <5=H0 4>70
?@5?0@0BC. &O 4>70 2AB0=>2;NTBLAO 70;56=> 2V4 V=482V4C0;L=>W @50:FVW E2>@>3>, O:89
25AL G0A <0T 7=0E>48B8AL ?V4 @5B5;L=8< :>=B@>;5< 4;O 28O2;5==O >7=0: :@>2>B5GV 01>
73>@B0==O :@>2V C 4V0;V7=V9 A8AB5
V:C20==O =5AB0IV;L=>W AB5=>:0@4VW B0 V=D0@:BC:0@40 157 ?0B>;>3VG=>3> 7CIFO Q =0
5:><5=4CTBLAO 70AB>AC20==O =04@>?0@8=C ?V4H:V@=> 2 @078 =0 4>1C (:>6=V 12 3>48=).
0728G09 B@820;VABL ;V:C20==O 6 4V1. # ::V=VG=8E 4>A;V465==OE 4;O ;V:C20==O ?0FVT=V2 7
=5AB0IV;L=>N AB5=>:0@4VTN B0 V=D0@:B< :0@40 157 7CIFO Q =0 \$@0:A8?0@8= 70AB>A>2C20;8
C :><1V=0FVW 7 325 <3 0F5B8;A0;VF8;>2>W :8A;>B8 =0 4>1C.
>G0B:>2C 4>7C 22>48B8 C 283;O4V 2=CB@VH=L>25==>W 1>;NA=>W V=T:FVW, =0ABC?=V 4>78
22>48B8 ?V4H:V@=>. >7@0EC=>: 4>78 107CTBLAO =0 <0AV BV;0 E2>@>3> 7 @>7@0EC=:C 86 0=B8-%0-D0:B>@=>W 0:B82=>ABV =0 1 :3 <0A8 BV;0 E2>@>3> (482. "01;8FN 5).

"01;8FO 5

0A0 BV;0 E2>@>3>, :3	>G0B:>20 2=CB@VH=L>25==0 4>70	0ABC?=0 ?V4H:V@=0 4>70 (:>6=V 12 3>48=)	V;L:VABL 0=B8-%-0:B82=>ABV
<50	0,4 <;	0,4 <;	3800
50-59	0,5 <;	0,5 <;	4750
60-69	0,6 <;	0,6 <;	5700
70-79	0,7 <;	0,7 <;	6650

80-89	0,8 <;	0,8 <;	7600
90-99	0,9 <;	0,9 <;	8550
≥100	1,0 <;	1,0 <;	9500

0FVT=B8 ;VB=L>3> 2V:C

7C =5 ?>B@V1=>, O:I> BV;L:8 =5<0T ?>@CH5==O DC=:FVW =8@>:. 5@54 ?>G0B:<;V:C20==O @5:>
<5=4CTBLAO ?5@52V@8B8 DC=:FVN =8@>:.

8@>:20 =54>AB0B=VABL

@>DV:0:B8:0 B@><I>5<I>;VG=8E CA:;04=5=L

5 ?>B@V1=> 77C E2>@8< 7 =8@>:2>N =54>AB0B=VABN ;53:>3> ABC?5=O (:;V@5=A :@50B8=V=C
1V;LH89 01> AB0=>28BL 50<;E2).

> BO6:0 =8@>:20 =54>AB0B=VABL 0A>FVNTBLAO 7V 71V;LH5=8< 2?;82< =04@>?0@8=C. "0:V
?0FVT=B8 <0NBL ?V428I5=89 @878: 28=8:=5==O B@><I>5<I>;VW B0 :@>2>B5G.

/:I> 7<5=H5==O 4>78 T 4>FV;L=8< C E2>@8E 7 ?>N =8@>:2>N =54>AB0B=VABN (:;V@5=A
:@50B8=V=C 1V;LH89 01> AB0=>28BL 30<;E2 V <5=H5 50 <;E2), <0NG8 =0 C207V V=482V4C0;L=V
D0:B>@8 @878:C I>4> 28=8:=5==O :@>2>B5G V B@><I>5<I>;VW, 4>7C A;V4 7<5=H8B8 =0 25-33 %.
E2>@8E V7 BO6:>N =8@>:2>N =54>AB0B=VABN (:;V@5=A :@50B8=V=C<5=H5 30 <;E2) 4>7C A;V4
7<5=H8B8 =0 25-33 %.

V:C20==O B@><I>5<I>;VG=8E CA:;04=5=L, =5AB01V;L=>W AB5=>:0@4VW B0 V=D0@:BC :0@40
157 ?0B>;>3VG=>3> 7CIFO Q =0

5 ?>B@V1=> 77C E2>@8< 7 =8@>:2>N =54>AB0B=VABN ;53:>3> ABC?5=O (:;V@5=A :@50B8=V=C
1V;LH89 01> AB0=>28BL 50<;E2).

> BO6:0 =8@>:20 =54>AB0B=VABL 0A>FVNTBLAO 7V 71V;LH5=8< 2?;82< =04@>?0@8=C. "0:V
?0FVT=B8 <0NBL ?V428I5=89 @878: 28=8:=5==O B@><I>5<I>;VW B0 :@>2>B5G.

/:I> 7<5=H5==O 4>78 T 4>FV;L=8< C E2>@8E V7 ?>N =8@>:2>N =54>AB0B=VABN (:;V@5=A
:@50B8=V=C 1V;LH89 01> AB0=>28BL 30<;E2 V <5=H5 50 <;E2), <0NG8 =0 C207V V=482V4C0;L=V
D0:B>@8 @878:C I>4> 28=8:=5==O :@>2>B5G V B@><I>5<I>;VW, 4>7C A;V4 7<5=H8B8 =0 25-33 %.
;O ;V:C20==O F8E AB0=V2 4;O E2>@8E V7 BO6:>N =8@>:2>N =54>AB0B=VABN \$@0:A8?0@8=
?@>B8?>:070=89.

5GV=:>20 =54>AB0B=VABL

;V=VG=8E 4>A;V465=L C FV9 3@C?V E2>@8E =5 ?@>2>48;>AL.

>1VG=V @50:FVW.

>1VG=V @50:FVW, =02545=V =86G5, :;0A8DV:>20=V 70 >@30=0<8 V A8AB5<0<8 B0 70 G0AB>B>N
28=8:=5==O: 4C65 G0AB> (≥ 1/10), G0AB> (≥ 1/100 B0 < 1/10), =5G0AB> (≥ 1/1000 B0 < 1/100), @V4:>
(≥ 1/10000 B0 < 1/1000), 4C65 @V4:> (< 1/10000).

@>2 V ;V

C65 G0AB>: :@>2>B5GV @V7=8E ;>:0;V70FV9, I> 28=8:0NBL G0ABVH5 C ?0FVT=V7 D0:B>@0<8
@878:C.

V4>: B@><I>F8B>?5=VO (2:;NG0NG8 35?0@8=V=4C:>20=C B@><I>F8B>?5=VN), B@><I>F8B>7.

C65 @V4>: 5>78=>DV;VO, >1>@>B=0 ?@8 ?@8?8=5==V ;V:C20==O.

C65 @V4>: @50:FVW 3V?5@GCB;82>ABV (2:;NG0NG8 0=3V>=52@>B8G=89 =01@O: V H:V@=V
@50:FVW), 0=0DV;0:B>W4=0 @50:FVO.

5B0I>;V7< V @>7;048 B@02;5==O

C65 @V4>: >1>@>B=0 3V?5@:0;VT2O70=0 7 35?0@8=V=4C:>20=8< ?@83=VG5==O< 0;L4>AB5@>=C,
3>;>2=8< G8=>< C E2>@8E V7 D0:B>@0<8 @878:C.

5?0B>1V;V0@=0 A8AB5<0

'0AB>: ?V428I5==O @V2=O B@0=A01>@>B=5.

5?@>4C:B82=0 A8AB5<0

C65 @V4>: ?@V0?V7

(:V@0 B0 ?V4H:V@=0 B:0=8=0

V4>: 28A8?0==O, :@>?82O=:0, 5@8B5<0, A25@1V6.

C65 @V4>: =5:@>7 H:V@8, 3>;>2=8< G8=>< C 74V; «A>1;82>ABV 70AB>AC20==O»).

030;L=V?>@CH5==O B0 7
C65 G0AB>: =525;8:V 35<0B><8 C
45O:8E 28?04:0E <>6;820 ?>O20 B25@48E 2C7;8:V2, I> =5 >7=0G0NBL >AC2C20==O 35?0@8=C B0
7=8:0NBL G5@57 :V;L:0 4=V2.
'0AB>: @50:FVW C
V4>: :0;LF8=>7 C
0;LF8=>7 G0ABVH5 28=8:0T C ?0FVT=BV2 7V 7

5@54>7C20==O.

>;2=>N ;V=VG=>N >7=0:>N ?5@54>7C20==O ?@8 ?V4H:V@=> 2=CB@VH=L>25==>2>B5G0.
V;L:VABL B@<1>F8BV2 B0 V=HV ?0@0<5B@8 73>@B0==O :@>2V <0NBL 1CB8 ?5@52V@5=V.
57=0G=V :@>2>B5GV 4C65 @V4:> ?>B@51CNBL A?5F8DVG=8E 70E>4V2 ;V:C20==O. /: ?@028;>,
4>AB0B=V< 1C45 7<5=H5==O 4>78 01> 2V4B5@2>W 4>78 =04@>?0@8=C.
BO6:8E 28?04:0E ?>:070=> 70AB>AC20==O ?@>B0N N =59B@0;V7CT 0=B8:>03C;O=B=89 5D5:B
=04@>?0@8=C, 0;5 45O:0 0=B8-%0-0:B82=VABL 70;8H0TBLAO. 0,6<; ?@>B0 950 0=B8-%0-
D0:B>@=>W 0:B82=>ABV =04@>?0@8=C. @8 28@VH5==V ?8B0==O ?@> :V;L:VABL ?@>B0EV4=>
225AB8, A;V4 1@0B8 4> C2038 G0A, I> ?@>9H>2 ?VA;O 22545==O 35?0@8=C, >A:V;L:8<>65
7=04>18B8AO 7<5=H5==O 4>78.

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

;V=VG=8E 4>A;V465=L I>4> 282G5==O 2?;82C \$@0:A8?0@8=C =0 D5@B8;L=VABL =5<0T. >A;V465==O
=0 B20@8=0E =5 ?>:070;8 B5@0B>35==>3> 01> D5B>B>:A8G=>3> 5D5:BC \$@0:A8?0@8=C. 4=0:
;V=VG=V 40=V, I> AB>ACNBLAO B@0=A?;0F5=B0@=>3> ?0A06C =04@>?0@8=C C 203VB=8E, >1
<565=V. ">AC20==O \$@0:A8?0@8=C C ?5@V>4 203VB=>ABV =5 @5:<5=4CTBLAO, :@V< 28?04:C,
:>;8 B5@0?52B8G=0 :>@8ABL ?5@52060T <>6;8289 @878:.
0=V 2V4=>A=> 5:A:@5FVW =04@>?0@8=C C 3@C4=5 <>;> >1<565=V, B>AC20==O =04@>?0@8=C
?V4 G0A 3>4C20==O 3@C44N =5 @5:<5=4CTBLAO.

VB8.

\$@0:A8?0@8= =5 @5:<5=4CTBLAO 4;O ;V:C20==O 4VB59, >A:V;L:8 =54>AB0B=L> 40=8E I>4>
157?5:8 B0 5D5:B82=>ABV 70AB>AC20==O ?@5?0@0BC 4;O 287=0G5==O 4>7C20==O C FVTW 3@C?8
?0FVT=BV2.

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

5?0@8=V=4C:>20=0 B@><1>F8B>?5=VO

A:V;L:8 VA=CT @878: ?>O28 35?0@8=V=4C:>20=>W B@<1>F8B>?5=VW, ?V4 G0A CAL>3> :C@AC
;V:C20==O \$@0:A8?0@8=< A;V4 :>=B@>;N20B8 :V;L:VABL B@<1>F8BV2.

>2V4><;O;>AO ?@> ?>>48=>:V 28?04:8 B@<1>F8B>?5=VW, V=:>;8 BO6:>W, I><>65

AC?@>2>46C20B8AO 0@B5@V0;L=8< 01> 25=>7=8< B@<1>7><, I> 4C65 206;82> 2@0E>2C20B8 C

B0:8E A8BC0FVOE: ?@8 B@<1>F8B>?5=VW, ?@8 1C4L-O:<1>7C, 7 ?@82>4C O:>3> ?@87=0G5=5

;V:C20==O, ?@8 ?>O2V B@<1>7C ?V4 G0A ;V:C20==O, ?@8 A8=4@>20=>3>

2=CB@VH=L>AC48==>3> 73>@B0==O. # @07V ?>O28 F8E O28I ;V:C20==O \$@0:A8?0@8=< A;V4

?@8?8=8B8.

8I5707=0G5=V 5D5:B8 <0NBL V0;5@3VG=C ?@8@>4C, V O:I> ;V:C20==O 70AB>A>2CTBLAO 2?5@H5,

28=8:0NBL

%2>@8< =0 B@<1>F8B>?5=VN, I> 28=8;;0 ?@8 ;V:C20==V 35?0@8=< (O: AB0=40@B=8<, B0: V

=87L:><>;5:C;O@=8<) 2 0=0<=57V, ;V:C20==O \$@0:A8?0@8=< ?@8 =5>1EV4=>ABV ?@87=0G0B8

<>6=0. # B0:>1EV4=5 @5B5;L=5 ;V=VG=5 A?>AB5@565==O B0 287=0G5==O :V;L:>ABV B@>

<1>F8BV2 :>6=>3> 4=O. # @07V ?>O28 B@<1>F8B>?5=VW ;V:C20==O \$@0:A8?0@8=< A;V4

?@8?8=8B8=5309=>.

@07V ?>O28 B@<1>F8B>?5=VW ?@8 ;V:C20==V 35?0@8=< (O: AB0=40@B=8<, B0: V =87L:>

<>;5:C;O@=8<) A;V4 @>73;O=CB8 <>6;82VABL ?@87=0G5==O 0=B8B@<1>B8G=8E ?@5?0@0BV2

V=H>3> ;0AC. /:I> B0:>3> ?@5?0@0BC =5<0T 2 =002=>ABV, <>6=0 70<>;5:C;O@=8E 35?0@8=V2, O:I>

70AB>AC20==O 35?0@8=C T =5>1EV4=8<1>F8BV2 A;V4 ?5@52V@OB8 =5 <5=H5 1 @07C =0 45=L V

;V:C20==O ?@8?8=OB8 O:><>30 @0=VH5, O:I> ?>G0B:>20 B@<1>F8B>?5=VO 715@V30TBLAO

?VA;O 70

In vitro B5AB =0 03@530FVN B@><1>F8BV2 <0T >1<565=5 7=0G5==O 4;O CAB0=>2;5==O 4V03=>7C
35?0@8=V=4C:>20=>W B@><1>F8B?5=VW.
!8BC0FVW, ?@8 O:8E 71V;LHCTBLAO @878: :@>2>B5G
04@>?0@8= A;V4 7 >15@56=VABN 70AB>A>2C20B8 C A8BC0FVOE, I> 0A>FVNNBLAO 7V 71V;LH5=8
< @878:>< 28=8:=5==O :@>2>B5G, B0:8E O:
?5GV=:>20 =54>AB0B=VABL;
B06:0 0@B5@V0;L=0 3V?5@B5=7VO;
28@07:0 H;C=:0 01> 420=04FOB8?0;>W :8H:8 G8 V=HV >@30=VG=V C@065==O 7V AE8;L=VABN 4>
:@>2>B5G;
AC48==V 70E2>@N20==O E>@V>@5B8=8;
?5@V>4 ?VA;O >?5@0FV9 =0 3>;>2=>
8@: >20 =54>AB0B=VABL
V4><>, I> =04@>?0@8= 282>48BLAO 3>;>2=8< G8=>< =8@:0<8, I> ?@872>48BL 4> 1V;LH>3> 2?;82C
=04@>?0@8=C C E2>@8E V7 =8@:>2>N =54>AB0B=VABN. # E2>@8E V7 =8@:>2>N =54>AB0B=VABN
71V;LH5=89 @878: 28=8:=5==O :@>2>B5G, V ;V:C20B8 WE B@510 7 >15@56=VABN.
VH5==O ?@> <>6;82VABL 7<5=H5==O 4>78 4;O ;V:C20==O E2>@8E V7 ;V@5=A< :@50B8=V=C 2V4
30 4> 50 <;E2 <0T 107C20B8AO =0 ;V=VG=V9 >FV=FV ;V:0@5< V=482V4C0;L=8E D0:B>@V2 @878:C
:>6=>3> ?0FVT=B0 I>4> @878:C 28=8:=5==O :@>2>B5G ?>@V2=O=> 7 @878:>< 28=8:=5==O B@><1>5
<1>;VW.
0FVT=B8 ;VB=L>3> 2V:C
5:><5=4CTBLAO ?5@54 ?>G0B:>< ;V:C20==O ?5@52V@8B8 DC=:FVN =8@>:.
V?5@:0;VT
5?0@8= <>65 ?@83=VGC20B8 04@5=0;>2C A5:@5FVN 0;L4>AB5@>=C V A?@8G8=OB8 3V?5@:0;VT
A>1;82> C ?0FVT=BV2 7 ?V428I5=8< @V2=5< :0;VN C ?;072V 01> 7 @878:< B0:>3> ?V428I5==O C ?;07
2V C E2>@8E =0 FC:@>289 4V015B, ?0FVT=BV2 7 E@>=VG=>N =8@:>2>N =54>AB0B=VABN, 7
<5B01>;VG=8< 0F84>7>< 01> C E2>@8E, O:V ?@89<0NBL ?@5?0@0B8, I> <>6CBL A?@8G8=OB8
3V?5@:0;VT@8 0=3V>B5=78=?5@5B2>@N20;L=>3> D5@<5=BC, =5AB5@>W4=V ?@>B870?0;L=V
70A>18).
878: 3V?5@3;V:5 7V 71V;LH5==O< B@820;>ABV ;V:C20==O, 0;5 70728G09 3V?5@3;V:52V.
!?V=0;L=0/5?V4C@0;L=0 0=5AB57VO, A?8==><>7:>20 ;N<10;L=0 ?C=:FVO V AC?CB=V ;V:0@AL:V
70A>18
878: 28=8:=5==O A?V=0;L=8E/5?V4C@0;L=8E 35<0B>< 71V;LHCTBLAO ?@8 70AB>AC20==V
5?V4C@0;L=>3> :0B5B5@0 01> ?@8 AC?CB=L>AC20==V V=H8E ?@5?0@0BV2, I> <>6CBL 2?;820B8 =0
35<>AB07, B0:8E O: =5AB5@>W4=V ?@>B870?0;L=V 70A>18, V=3V1VB>@8 03@530FVW B@>
<1>F8BV2 01> V=HV 0=B8:>03C;O=B8. 878: B0:>6 71V;LHCTBLAO ?@8 B@02<0B8G=V9 01>
?>2B>@=V9 5?V4C@0;L=V9, 01> A?8==><>7:>2V9 ?C=:FVW, B> @VH5==O ?@> :><1V=>20=5
70AB>AC20==O =59@>0:A80;L=>W 1;>:048 B0 0=B8:>03C;O=BV2 ?@89<0TBLAO ?VA;O >FV=:8
A?V22V4=>H5==O :>@8ABL/@878: C :>6=>
C E2>@8E, O:V 265 ;V:CNBLAO 0=B8:>03C;O=B=8<8 70A>10<8, :>@8ABL 2V4 70AB>AC20==O
=59@>0:A80;L=>W 1;>:048 <0T 1CB8 @5B5;L=> 710;0=A>20=0 7 <>6;828< @878:<;
C E2>@8E, O:V 3>BCNBLAO 4> ?;0=>2>3> EV@C@3VG=>3> 2B@CG0==O 7 =59@>0:A80;L=>N
1;>:04>N, :>@8ABL 2V4 70AB>AC20==O 0=B8:>03C;O=BV2 <0T 1CB8 @5B5;L=> 710;0=A>20=0 7
<>6;828< @878:>
@8 ?@>2545==V A?8==><>7:>2>W ;N<10;L=>W ?C=:FVW, A?V=0;L=>W 01> 5?V4C@0;L=>W
0=5AB57VW A;V4 28B@8<0B8 V=B5@20; C 12 3>48= ?@8 70AB>AC20==V =04@>?0@8=C C
?@>DV;0:B8G=8E 4>70E B0 24 3>48=8 ?@8 70AB>AC20==V =04@>?0@8=C C ;V:C20;L=8E 4>70E
2840;5==O< A?V=0;L=>3>/5?V4C@0;L=>3> :0B5B5@0 01> 3>;:8. %2>@8< 7 =8@:>2>N
=54>AB0B=VABN F59 V=B5@20; <>65 1CB8 ?>4>265=89.
%2>@V <0NBL 7=0E>48B8AL ?V4 @5B5;L=8< =03;O4>< 4;O 28O2;5==O >7=0: V A8;>3VG=8E
?>@CH5=L. # @07V WE ?>O28 =5>1EV4=5 =5309=5 2V4?>2V4=5 ;V:C20==O.
!0;VF8;0B8, =5AB5@>W4=V ?@>B870?0;L=V 70A>18 B0 V=3V1VB>@8 03@530FVW B@><1>F8BV2
;O ?@>DV;0:B8:8 01> ;V:C20==O 25=>7=8E B@><1>5<1>;VG=8E CA;04=5=L V 4;O ?@>DV;0:B8:8
73>@B0==O :@>2V ?V4 G0A 35<>4V0;V7C AC?CB=T 70AB>AC20==O 0F5B8;A0;VF8;>2>W :8A;>B8,
V=H8E A0;VF8;0BV2, =5AB5@>W4=8E ?@>B870?0;L=8E 70A>1V2 B0 V=3V1VB>@V2 03@530FVW
B@><1>F8BV2 =5 @5:><5=4CTBLAO, >A;V;L:8 2>=8 <>6CBL 71V;LHC20B8 @878: :@>2>B5GV. /:I>

70AB>AC20==O B0:>W :><1V=0FVW C=8:=CB8 =5 <>6=0, A;V4 74V9A=N20B8 @5B5;L=89 ;V=VG=89 =03;O4.

:;V=VG=8E 4>A;V465==OE 7 ;V:C20==O E2>@8E =0 =5AB01V;L=C AB5=>:0@4VN B0 V=D0@:B :0@40 157 ?0B>;>3VG=>3> 7C1FO Q =0 =04@>?0@8= 70AB>A>2C2020;8 C :><1V=0FVW 7 0F5B8;A0;VF8;>2>N :8A;>B>N C 4>7V 325 <3/4>1C.

5:@>7 H:V@8

>2V4><;O>;AO ?@> 4C65 @V4:VA=V 28?04:8 28=8:=5==O =5:@>7C H:V@8. &L>O20 ?C@?C@8 01> V=DV;LB@>20=8E 1>;VA=8E 5@8B5<0B>7=8E 5;5<5=BV2 7 01> 157 7030;L=8E A8 ?@8?8=8B8.

:5@3VO =0 ;0B5:A

0E8A=89 :>2?0G>: =0 3>;FV ?>?5@54=L> =0?>2=5=>3> H?@8F0 3> ;0B5:AC, I> <>65 A?@8G8=OB8 0;5@3VG=V @50:FVW 2 >AV1, GCB;828E 4> ;0B5:AC.

40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> @>1>BV 7 V=H8<8 <5E0=V7<0<8.

5 2?;820T.

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

04@>?0@8= A;V4 7 >15@56=VABN 70AB>A>2C20B8 4;O ;V:C20==O E2>@8E, O:V ?@89<0NBL ?5@>@0;L=V 0=B8:>03C;O=B8, A8AB5<=V 3;N:>:>@B8:>AB5@>W48 V 45:AB@0=8. /:I> 4;O ;V:C20==O E2>@8E, O:V 70AB>A>2CNBL =04@>?0@8=, A;V4 ?@87=0G8B8 ?5@>@0;L=V 0=B8:>03C;O=B8, ;V:C20==O =04@>?0@8=< B@510 ?@>4>268B8 4> AB01V;V70FVW =0 FV;L>2> 4=>3> =>@<0;V70FV9=>3> 2V4=>H5==O (INR).

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

\$0@<0:>48=0

04@>?0@8= =87L:><>;5:C;O@=89 35?0@8=, @>7@>1;5=89 H;OE<< 45?>;V<5@870FVW AB0=40@B=>3> 35?0@8=C. /2;OT A>1>N 3;V:>703;V:0= V7 A5@54=L>N<>;5:C;O@=>N <0A>N 4300 40;LB>=. 04@>?0@8= 28O2;OT 28A>:89 @V25=L 72O7C20==O 7 1V;;< ?;07<8 0=B8B@><1V=<< . "0:0 A?>@V4=5=VABL 7C<>2;NT ?@8A:>@5=C V=3V1VFN %0-D0:B>@0, I> T 3>;>2=8< 2=5A:<< C 28A>:C 0=B8B@><1>B8G=C 0:B82=VABL =04@>?0@8=C. =H8<8 <5E0=V7<0<8 0=B8B@><1>B8G=>W 0:B82=>ABV =04@>?0@8=C T AB8@C H;OEC B:0=8==>3> D0:B>@0, 0:B820FVO DV1@8=>;V7C H;OE> < ?@O<>3> 282V;L=5==O 0:B820B>@0 B:0=8==>3> ?;0735=0 7 ;VB8= 5=4>B5;VN, <>48DV:0FVO 35 <>@5>;>3VG=8E ?0@0<5B@V2 (7<5=H5==O 2O7:>ABV :@>2V B0 71V;LH5==O B5:CG>ABV <5<1@0= B@><1>F8BV2 V 3@0=C;>F8BV2). 04@>?0@8= <0T 28A>:89 @V25=L A?V22V4=>H5==O;>=3>20=C 0=B8B@><1>B8G=C 4VN. >@V2=O=> 7 =5D@0:FV>=>20=8< 35?0@8=<< =04@>?0@8= <5=H>N N 2?;820T =0 DC=:FVN B0 03@530FVN B@><1>F8BV2 V 4C65 <0;> 2?;820T =0 ?5@28==89 35<>AB07.

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

\$0@<0:>:V=5B8G=V 2;0AB82>ABV 287=0G0NBLAO 28< 0=B8-%0-D0:B>@=>W 0:B82=>ABV ?;07<8 :@>2V.

V>4>ABC?=VABL

VA;O ?V4H:V@=>3> 22545==O ?V: 0=B8-%0-0:B82=>ABV (Cmax) 4>AO30TBLAO G5@57 3-5 3>48= (Tmax). V>4>ABC?=VABL<0965 ?>2=0 (1;87L:> 88 %).

VA;O 2=CB@VH=L>25==>3> 22545==O ?V: 0=B8-%0-0:B82=>ABV (Cmax) 4>AO30TBLAO <5=H =V6 70 10 E28;8= 7 ?5@V>4<< =0?V2282545==O 2 3>48=8.

82545==O

VA;O ?V4H:V@=>3> 22545==O ?5@V>4 =0?V2282545==O AB0=>28BL ?@81;87=> 3,5 3>48=8. 4=0: 0=B8-%0-0:B82=VABL 715@V30TBLAO ?@>BO3< I=>09<5=H5 18 3>48= ?VA;O V=T:FVW =04@>?0@8=C C 4>7V 1900 0=B8-%0 .

A>1;82V 3@C?8 ?0FVT=BV2

0FVT=B8 ;VB=L>3> 2V:C

A:V;L:8 DV7V>;>3VG=0 DC=:FVO =8@>: 7 2V:< 7=86CTBLAO, 282545==O ?@5?0@0BC A?>2V;L=NTBLAO. !;V4 7206C20B8 =0 <>6;82VABL @>728B:C =8@:>2>W =54>AB0B=>ABV C FVTW 3@C?8 ?0FVT=BV2 V 2V4?>2V4=> :>@53C20B8 4>7C ?@5?0@0BC.

8@:>20 =54>AB0B=VABL

0 40=8<8 ;:V=VG=8E 4>A;V465=L V7 282G5==O D0@<0>:V=5B8G=8E ?0@0<5B@V2 =04@>?0@8=C,
?@8 9>3> 2=CB@VH=L>25==>@8< V7 @V7=8< ABC?5=5< =8@>:2>W =54>AB0B=>ABV 1C;0 ?>:070=0
:>@5;OFVO < =04@>?0@8=C V ;:V@5=A< :@50B8=V=C. # E2>@8E V7 ?>N =8@>:2>N
=54>AB0B=VABN (:;V@5=A :@50B8=V=C 36-43<:/E2) A5@54=O ?>I0 ?V4 :@82>N «>=F5=B@0FVO
/G0A» (AUC) V ?5@V>4 =0?V2282545==O 71V;LHC20;8AL =0 52 % V 39 % 2V4?>2V4=> ?>@V2=O=> 7
B0:8< C 74>@>28E 4>1@>2>;LFFV2. # F8E ?0FVT=BV2 A5@54=V9 ?>07<>289 ;:V@5=A =04@>?0@8=C 7
<5=HC202AO 4> 63 % 2V4 =>@<8. !?>AB5@V30;0AO H8@>:0 V=482V4C0;L=0 20@V015;L=VABL. #
E2>@8E V7 BO6:>N =8@>:2>N =54>AB0B=VABN (:;V@5=A :@50B8=V=C 10-20<:/E2) AUC V ?5@V>4
=0?V2282545==O 71V;LHC20;8AL =0 95 % V 112 % 2V4?>2V4=> ?>@V2=O=> 7 B0:8< C 74>@>28E
4>1@>2>;LFFV2. ;07<>289 ;:V@5=A C E2>@8E V7 BO6:>N =8@>:2>N =54>AB0B=VABN 7<5=HC202AO
4> 50 % ?>@V2=O=> 7 ?0FVT=B0<8 7 =>@<0;L=>N DC=:FVTN =8@>:.. # ?0FVT=BV2 V7 BO6:>N
=8@>:2>N =54>AB0B=VABN (:;V@5=A :@50B8=V=C 3-6<:/E2), O:V ?5@51C20;8 =0 35<>4V0;V7V,
A5@54=V AUC B0 ?5@V>4 =0?V2282545==O 71V;LHC20;8AL =0 62 % B0 65 % 2V4?>2V4=>
?>@V2=O=> 7V 74>@>28<8 4>1@>2>;LFO<8. ;07<>289 ;:V@5=A C ?0FVT=BV2 V7 BO6:>N =8@>:2>N
=54>AB0B=VABN, O:V ?5@51C20;8 =0 35<>4V0;V7V, 7<5=HC202AO 4> 67 % 2V4 B0:>3> C ?0FVT=BV2
7 =>@<0;L=>N DC=:FVTN =8@>:.

\$0@<0F52B8G=V E0@0:B5@8AB8:8.
A=>2=V DV78:-EVABV: ?@>7>@89 01> 7;53:0 >?0;5AFNNG89, 15710@2=89 01> A2VB;>-6>2B>3>
:>;L>@C @>7G8=.

5AC 5 7
"5@ABV.3 @>:8.

#<>28 715@V30==O. 15@V30B8 ?@8 B5□. 15@V30B8 C =54>ABC?=>
#?0:>2:0.> 2 ?>?5@54=L> =0?>2=5=8E A;:O=8E H?@8F8 7 02B<<0B8G=>N A8AB5<>N 157?5:8 C
1;VAB5@V; ?> 5 1;VAB5@V2 C :0@B>==V9 :>@>1FV.
>7G8=8 4;O V=T:FV9 C ?>?5@54=L> 70?>2=5=8E H?@8F0E

1□T<, <;	(?@8F	04@>?0@8= :0;LFFVN, 0=B8-%0
0,6	@04C9>20=89	5 700
0,8	@04C9>20=89	7 600

0B53>@VO 2V4?CA:C. 0 @5F5?B>
8@>1=8:.
A?5= >B5@ 0< 45 >=452V;L, \$@0=FVO
Aspen Notre Dame de Bondeville, France.

iAF57=0E>465==O.
1, @N 45 ; 1105, 76960 >B5@ 0< 45 >=452V;L, \$@0=FVO
1, rue de l'Abbaye, 76960 Notre Dame de Bondeville, France.