

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

&B.□.
(KLACID I.V.)

!;:04:

4VNG0 @5G>28=0: ;0@8B@>;
1 D;0:>= C 500 <3;
4>?>28=8: :8A;>B0 ;0:B>1V>=>20; =0B@VN 3V4@>:A84.

V:0@AL:0 D>@<0. >@>H>; ;V>DV;V7>20=89 4;O ?@83>BC20==O @>7G8=C 4;O V=DC7V9.
A=>2=V DV78:>-EVABV: ?>@>H>; ;V>DV;V7>20=89, CIV;L=5=89, 2V4 1V;>3> 4><0965 1V;>3> :>;L>@C
, 7V A;01:8< 0@><0B8G=8< 70?0E><.

\$0@<0:>B5@0?52B8G=0 3@C?0. @>B81=V 70A>18 4;O A8AB5<=>3> 70AB>AC20==O. 0:@>;V48. >4 "%
J01F A09.

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

\$0@<0:>48=0

;0@8B@>B8: 3@C?8 <0:@>;V4V2. =B810:B5@V0;L=0 4VO ;:0@8B@>3> 72O7C20==O< 7 5OS-@81>A>
<0;L=>N AC1>48=8F5N GCB;828E 10:B5@V9 V ?@83=VG5==O< 1V>A8=B57C 1V;:0. @5?0@0B
28O2;OT 28A>;C 5D5:B82=VABL *in vitro* ?@>B8 H8@>:>3> A?5:B@0 05@>1=8E B0 0=05@>1=8E 3@0
78B82=8E B0 3@0<=530B82=8E >@30=V7A?VB0;L=8E HB0V=V<0;L=V ?@83=VGC20;L=V
>=>F5=B@0FVW () ;:0@8B@>C 420 @078 =86GV 70 5@8B@>
;0@8B@>*in vitro* 28A>;>5D5:B82=89 2V4=>A=> *Legionella pneumophila* V *Mycoplasma pneumoniae*. VT
10:B5@8F84=> 2V4=>A=> *H. Pylori*, 0:B82=VABL ;:0@8B@>N ?@8 =59B@0;L=> *In vitro* B0 *in vivo* 40=V
A2V4G0BL ?@> 28A>;C 5D5:B82=VABL ;:0@8B@>4> ;:V=VG=> 7=0GCI8E HB010:B5@V9. >A;V465==O
in vitro ?>:070;8, I> HB0<8 *Enterobacteriaceae* V *Pseudomonas*, O: V 3@0<=530B82=V 10:B5@VW, I> =5
?@>4C:CNBL ;0:B>7C, =5GCB;82V 4> ;:0@8B@>
V:@>1V>;>3VO
;0@8B@>*in vitro* V 2 ;:V=VG=V9 ?@0:B8FV 2V4=>A=> 1V;LH>ABV HB0>@30=V7:
5@>1=V 3@078B82=V >@30=V7<8: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus*
pyogenes, *Listeria monocytogenes*.
5@>1=V 3@0<=530B82=V >@30=V7<8: *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella*
catarrhalis, *Neisseria gonorrhoeae*, *Legionella pneumophila*
=HV >@30=V7<8: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* (TWAR).
V:>10:B5@VW: *Mycobacterium leprae*, *Mycobacterium kansasii*, *Mycobacterium chelonae*, *Mycobacterium*
fortuitum, *Mycobacterium avium* Aomplex (MAC), O:V 2;:NG0NBL *Mycobacterium avium*, *Mycobacterium*
intracellulare
5B0-;0:B0<078 >@30=V7
V;LHVABL<5B8F8;V=- B0 >:A0F8;V=@578AB5=B=8E HB0>:V2 =5GCB;82V 4> ;:0@8B@>
Helicobacter: *H. Pylori*.
;0@8B@>*in vitro* 2V4=>A=> 1V;LH>ABV HB0>@30=V74=0: ;:V=VG=0 5D5:B82=VABL B0 157?5:0 9>3>
70AB>AC20==O =5 2AB0=>2;5=V:
5@>1=V 3@078B82=V >@30=V7<8: *Streptococcus agalactiae*, *Streptococci* (3@C?8 C,F,G), *Viridans group*
streptococci
5@>1=V 3@0<=530B82=V >@30=V7<8: *Bordetella pertussis*, *Pasteurella multocida*.
=HV >@30=V7<8: *Chlamydia trachomatis*.
=05@>1=V 3@078B82=V >@30=V7<8: *Clostridium perfringens*, *Peptococcus niger*, *Propionibacterium acnes*.
=05@>1=V 3@0<=530B82=V >@30=V7<8: *Bacteriodes melaninogenicus*.
!?V@>E5B8: *Borrelia burgdorferi*, *Treponema pallidum*.
010:B5@VW: *Campylobacter jejuni*.

:0@8B@>B8 :V;L:>E HB0Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae, H. pylori B0 Campylobacter spp.

A=>2=8< <5B01>;VB<< :;0@8B@>@30=V71V>;>3VG=> 0:B82=89 14-3V4@>:A8::0@8B@>. ;O 1V;LH>ABV >@30=V71V>;>3VG=0 0:B82=VABL<5B01>;VBC 4>@V2=NT 01> 2 12 @078 A;01H0 70 <0B5@8=AL:C AC1AB0=FVN, 70 28=OB:<< H. influenzae, ?@>B8 O:>3> 5D5:B82=VABL<5B01>;VBC 2 2 @078 28I0. C<>20E in vitro B0 in vivo <0B5@8=AL:0 AC1AB0=FVO B0 WW >A=>2=89 <5B01>;VB 28O2;ONBL 01> 048B82=89, 01> A8=5@3VG=89 5D5:B ?@>B8 H. Vnfluenzae, 70;56=> 2V4 HB0>@30=V7 \$0@<0:>:V=5B8:0.

:0@8B@>3> >A=>2=89 0:B82=89 14--<5B01>;VB 4>1@5 @>7?>4V;ONBLAO ?> 2AVE B:0=8=0E B0 @V4:8E A5@54>28I0E >@30=V7=F5=B@0FVO C B:0=8=0E, O: ?@028;>, C 45:V;L:0 @07V2 28I0, =V6 C A8@>20BFV :@>2V. 091V;LH0 :>=F5=B@0FVO @5TAB@C20;0AO 2 ?5GV=FV B0 ;535=OE. 86G5 =02545=> ?@8::048 7=0G5=L :>=F5=B@0FVW C B:0=8=0E B0 2 A8@>20BFV :@>2V.

&" &/ (?VA;O 22545==O 250<3 G5@57 :>6=V 12 3>48=)		
84 B:0=8=8	":0=8=0 (!8@>20B:0 :@>2V (
8340;8:8	1,6	0,8
535=V	8,8	1,7

0:A8<0;L=V :>=F5=B@0FVW (!_{max}) :;0@8B@>2;OBL 2V4 5,16 BO3<< 1 3>48=8 2V4?>2V4=>.

!_{max} 14--:;0@8B@>28BL 0,66

5@V>4 =0?V2282545==O :;0@8B@>78 ?@5?0@0BC B0 AB0=>28BL 2V4 3,8 3>4 4> 4,5 3>4. 5@V>4 =0?V2282545==O 14--:;0@8B@> AB0=>28BL 7,3 3>48=8 (?@8 22545==V 500 <3) V 9,3 3>48=8 (?@8 22545==V 1000 <3).

@V2=>206=>IV ?V4 :@82>N «:>=F5=B@0FVO G0A» (AUC) 7V 71V;LH5==O< 4>78 7?>@FV9=>, B>1B> A?>AB5@V30;0AL =5;V=V9=0 70;56=VABL 7=0G5=L AUC 2V422,29 3>4."." AUC 14-- :;0@8B@> 7=0E>48;8AL C <560E 2V4 8,16 3>4." 4> 14,76 3>4."

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

>:070==O.

V:C20==O V=D5:FV9, A?@8G8=5=8E GCB;828<8 4> :;0@8B@>>@30=V7<0<8, ?@8 =5>1EV4=>ABV 70AB>AC20==O ?0@5=B5@0;L=>W B5@0?VW:

- =D5:FVW 25@E=VE 48E0;L=8E H;OEV2.
- =D5:FVW =86=VE 48E0;L=8E H;OEV2.
- =D5:FVW H:V@8 V <O:8E B:0=8=.
- 8A520=V 01> ;>:0;V7>20=V 10:B5@V0;L=V V=D5:FVW, A?@8G8=5=V Mycobacterium avium 01> Mycobacterium intracellulare ;>:0;V7>20=V V=D5:FVW, A?@8G8=5=V Mycobacterium chelonae, Mycobacterium fortuitum 01> Mycobacterium kansasii 7>:@5<0, C -V=DV:>20=8E ?0FVT=BV2.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4><0:@>;V4=8E 0=B81V>B8:V2 01> 4> 1C4L-O:8E 4>?><V6=8E :>=5=BV2 ?@5?0@0BC.

!C?CB=T 70AB>AC20==O :;0@8B@>3> 7 B0:8E ?@5?0@0BV2: 0AB5;, F870?@84, ?V<>784, B5@D5=048= (>A:V;L:8 F5 <>65 ?@8725AB8 4> ?>4>265==O V=B5@20;C QT B0 @>728B:C A5@F528E 0@8BG:>2C B0EV:0@4VN, DV1@8;OFVN H;C=>G:V2 B0 ?V@C5B=C H;C=>G:>2C B0EV:0@4VN (torsade de pointes)), 0;:0;>W48 @V6:V2, =0?@8::04 5@3>B05@3>B0A:V;L:8 F5 <>65 ?@8725AB8 4> 5@3>B>:A8G=>ABV), V=3V1VB>@8 ->@54C:B078 (AB0B8=8), I> 7=0G=>N N <5B01>;V7CNBLAO CYP3A4 (>20AB0B8= 01> A8<20AB0B8=), G5@57 ?V428I5=89 @878: 28=8=:5==O ?0BVW, 2::NG0NG8 @014>;V7 (482. «A>1;82>ABV 70AB>AC20==O», «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

4=>G0A=5 70AB>AC20==O :;0@8B@>@0;L=>3> ;0

>4>265==O V=B5@20;C QT 01> H;C=>G:>2V A5@F52V 0@8Btorsade de pointes) (482. «A>1;82>ABV 70AB>AC20==O», «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

V?>:0;VT4>265==O V=B5@20;C QT).

"O6:0 ?5GV=:>20 =54>AB0B=VABL B0 AC?CB=O =8@:>20 =54>AB0B=VABL.

4=>G0A=5 70AB>AC20==O ;:0@8B@>@V2 CYP3A4) 7 :>;EVF8=>< (482. «A>1;82>ABV 70AB>AC20==O
», «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

4=>G0A=5 70AB>AC20==O ;:0@8B@>@>< 01> @0=>;078=>

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

;:0@8B@>

0AB>AC20==O =86G5707=0G5=8E ?@5?0@0BV2 AC2>@> ?@>B8?>:070=> G5@57 <>6;8289
@>728B>: BO6:8E =0A;V4:V2 270T<>4VW.

&870?@84, ?V<>784, 0AB5;, B5@D5=048=

V428I5==O @V2=V2 F870?@84C, ?V<>784C B0 B5@D5=048=C 2 A8@>20BFV :@>2V

A?>AB5@V30;>AO ?@8 WE AC?CB=L>AC20==V 7 ;:0@8B@><, I> <>65 A?@8G8=8B8 ?>4>265==O
V=B5@20;C QT V ?>O2C 0@8BG:>2>W B0EV:0@4VW, DV1@8;OFVW H;C=>G:V2 Vtorsade de pointes.

>4V1=V 5D5:B8 2V47=0G0;8AO V ?@8 ACAC20==V 0AB5;C B0 V=H8E <0:@>;V4V2.

;:0;>W48 @V6:V2

>AB<0@:5B8=3>2V ?>2V4><;5==O A2V4G0BL, I> >4=>G0A=5 70AB>AC20==O ;:0@8B@>B0 5@3>B0
483V4@>5@3>B0FVN20;>AO 7 ?>O2>N >7=0: 3>AB@>3> 5@3>B87 E0@0:B5@87C20;>AO 207>A?07<>

< B0 VH5: V V=H8E B:0=8=, 2::NG0NG8 F5=B@0;L=C =5@2>2C A8AB54=>G0A=5 ?@87=0G5==O

;:0@8B@>W4V2 @V6:V2 ?@>B8?>:070=5 (482. «@>B8?>:070==O»).

=3V1VB>@8 <3->-@54C:B078 (AB0B8=8)

><1V=>20=5 70AB>AC20==O ;:0@8B@>20AB0B8=>< 01> A8<20AB0B8=>< ?@>B8?>:070=5 (482.

«@>B8?>:070==O»), >A:V;L:8 FV AB0B8=87=0G=>N N <5B01>;V7CNBLAO CYP3A4 V >4=>G0A=5

70AB>AC20==O V7 ;:0@8B@>< ?V428ICT WE :>=F5=B@0FVN C ?;072V, I>, A2>TN G5@3>N, ?V428ICT
@878: 28=8:=5==O ?0BVW, 2::NG0NG8 @014>;V7. >2V4><;O;>AO ?@> @>728B>: @014>;V7C C

?0FVT=BV2 ?@8 ACAC20==V ;:0@8B@> ;V:C20==O ;:0@8B@>< =5<>6;82> C=8:=CB8, B5@0?VN

;>20AB0B8=>< 01> A8<20AB0B8=>< =5>1EV4=> ?@8?8=8B8 ?V4 G0A :C@AC ;V:C20==O.

!;V4 7 >15@56=VABN ?@87=0G0B8 ;:0@8B@>4=>G0A=> 7 V=H8<8 AB0B8=0<8. A8BC0FVOE, :>;8

>4=>G0A=>3> 70AB>AC20==O ;:0@8B@>CYP3A (=0?@8;;04 D;C20AB0B8=C). 5>1EV4=89

<=>VB>@8=3 AB0=C ?0FVT=BV2 I>4> 28O2;5==O >7=0: V A8?0BVW.

?;82 V=H8E ;V:0@AL:8E 70A>1V2 =0 D0@<0:>:V=5B8:C ;:0@8B@>

V:0@AL:V 70A>18, I> T V=4C:B>@0<8 CYP3A (=0?@8;;04 @8D0W=, :0@10<075?V=, D5=>10@1VB0;;

?@5?0@0B8 72V@>1>N), <>6CBL V=4C:C20B8 <5B01>;V7< ;:0@8B@>3> 5D5:B82=>ABV. @V< B>3>

<>65 1CB8 =5>1EV4=8< <=>VB>@8=3 ?;07<>28E @V2=V2 V=4C:B>@0 CYP3A, O:V <>6CBL 1CB8

?V428I5=V G5@57 V=3V1C20==O CYP3A ;:0@8B@>< (482. B0:>6 V=AB@C:FVN 4;O <548G=>3>

70AB>AC20==O 2V4?>2V4=>3> V=4C:B>@0 CYP3A4). 4=>G0A=5 70AB>AC20==O @8D01CB8=C V

;:0@8B@>48;> 4> ?V428I5==O @V2=V2 @8D01CB8=C B0 7=865==O @V2=V2 ;:0@8B@>20BFV :@>2V

7 >4=>G0A=8< ?V428I5==O< @878:C ?>O28 C25WBC.

?;82 =86G5707=0G5=8E ;V:0@AL:8E 70A>1V2 =0 :>=F5=B@0FVN ;:0@8B@>2V 2V4><89 01>

?@8?CA:0TBLAO, B>1CB8 ?>B@V1=0 778 01> 70AB>AC20==O 0;LB5@=0B82=>W B5@0?VW.

D02V@5=F, =52V@0?V=, @8D0

>BC6=V V=4C:B>@8 D5@<5=BV2 F8B>E@> <>6CBL ?@8A:>@N20B8 <5B01>;V7< ;:0@8B@>C ?;072V,

0;5 71V;LHCNG8 :>=F5=B@0FVN 14--;;0@8B@>1V>;>3VG=> 0:B82=>3> <5B01>;VBC. A:V;L:8

1V>;>3VG=0 0:B82=VABL ;:0@8B@>A=> @V7=8E 10:B5@V9, >GV:C20=89 B5@0?52B8G=89 5D5:B

<>65 1CB8 =5 4>AO3=CB89 G5@57 A?V;L=5 70AB>AC20==O ;:0@8B@>@V2 D5@<5=BV2 F8B>E@>

B@02V@8=

VO ;:0@8B@>A;01;N20;0AL 5B@02V@8=><; >4=0: :>=F5=B@0FVW 0:B82=>3> <5B01>;VBC 14-

--;:0@8B@> Mycobacterium avium complex (MAC), 7030;L=0 0:B82=VABL ?@>B8 FL>3> ?0B>35=C <>65

1CB8 773;O=CB8 70AB>AC20==O 0;LB5@=0B82=8E ;:0@8B@>1V2.

\$.N:>=07>;

V2=>206=V :>=F5=B@0FVW 0:B82=>3> <5B01>;VBC 14--;;0@8B@> =5 7AC20==V 7 D;N:>=07>;> 78

;:0@8B@>B@V1=0.

8B>=02V@

0AB>AC20==O @8B>=02V@C B0 ;:0@8B@>48;> 4> 7=0G=>3> ?@83=VG5==O <5B01>;V7_{max}

;:0@8B@>AO =0 31 %, C_{min} =0 182 % V AUC =0 77 %. V47=0G0;>AO ?>2=5 ?@83=VG5==O

CB2>@5==O 14--:;0@8B@>H8@>:89 B5@0?52B8G=89 4V0?07>= 7<5=H5==O 4>78 ;;0@8B@>0< 7 =>@<0;L=>N DC=:FVTN =8@>: =5 ?>B@V1=5. 0FVT=B0< 7 =8@>:2>N =54>AB0B=VABN =5>1EV4=5 :>@83C20==O 4>78: ?@8 CL_{CR} 3060 <;/E2 4>7C ;;0@8B@>1EV4=> 7<5=H8B8 =0 50 %, ?@8 CL_{CR} < 30 <; /E2 =0 75 %. >78 ;;0@8B@> ?5@528ICNBL 1 3/45=L, =5 A;V4 70AB>A>2C20B8 @07< 7 @8B>=02V@> "0:V 6 :>@83C20==O 4>78 A;V4 ?@>2>48B8 ?0FVT=B0< V7 ?>3V@H5=>N DC=:FVTN =8@>: ?@8 70AB>AC20==V @8B>=02V@C O: D0@<0>:V=5B8G=>3> ?V4A8;N20G0 @07< 7 V=H8<8 V=3V1VB>@0<8 -?@>B5078, 2;;NG0NG8 0B070=02V@ V A0:2V=02V@.

?;82 ;:0@8B@>

=B80@8B18

A=CNBL ?>AB<0@:5B8=3>2V ?>2V4><;5==O ?@> @>728B>: ?V@C5B=>W H;C=>G:>2>W B0EV:0@4VW, I> 28=8;;0 ?@8 >4=>G0A=>AC20==V ;;0@8B@>< 01> 487>?V@0<5=4CTBLAO ?@>2>48B8 -<=>VB>@8=3 4;O A2>TG0A=>3> 28O2;5==O ?>4>265==O V=B5@20;C QT. V4 G0A B5@0?VW ;;0@8B@>< A;V4 AB568B8 70 :>=F5=B@0FVO<8 F8E ?@5?0@0BV2 2 A8@>20BFV :@>2V. V4 G0A ?>AB<0@:5B8=3>2>3> 70AB>AC20==O 1C;8 ?>2V4><;5==O ?@> 3V?>3;V:54=>G0A=> AC20==V ;;0@8B@>?V@01EV4=89 <=>VB>@8=3 @V2=O 3;N:>78 :@>2V ?@8 >4=>G0A=>AC20==V F8E 70A>1V2.

5@>@0;L=V 3V?>3;V:518/ V=AC;V=

@8 ACAC20==V 7 ?52=8<8 3V?>3;V:5YP3A, I> <65 A?@8G8=8B8 3V?>3;V:5<5=4>20=89 @5B5;L=89 <=>VB>@8=3 @V2=O 3;N:>78.

CYP3A-?>2O70=V 270T<>4VW

!CAC20==O ;;0@8B@><3> O: V=3V1VB>@ D5@<5=BC CYP3A, V ?@5?0@0BC, I> 3>;>2=8< G8=>< <5B01>;V7CTBLAO CYP3A, <65 ?@8725AB8 4> ?V428I5==O :>=F5=B@0FVW >AB0==L>3> 2 ?;072V, I>, C A2>N G5@3C, <65 ?V4A8;8B8 01> ?>4>268B8 9>3> B5@0?52B8G=89 5D5:B V @878: 28=8:=5==O ?>1VG=8E @50:FV9. !;V4 1CB8 >15@56=8<8 ?@8 70AB>AC20==V ;;0@8B@>CYP3A, >A>1;82> O:I> CYP3A-AC1AB@0B <0T 2C7L:89 B5@0?52B8G=89 4V0?07>= (=0?@8::;04 :0@10<075?V=) V/01> 5:AB5=A82=> <5B01>;V7CTBLAO F8< 5=78<65 1CB8 ?>B@V1=0 778 V ?> <6;82>ABV @5B5;L=89 <=>VB>@8=3 A8@>20B:>28E :>=F5=B@0FV9 ;V:0@AL:>3> 70A>1C, I><5B01>;V7CTBLAO CYP3A, C ?0FVT=V2, O:V >4=>G0A=> 70AB>A>2CNBL ;;0@8B@>

V4>< (01> ?@8?CA:0TBLAO), I> B0:V ;V:0@AL:V ?@5?0@0B8 01> 3@C?8 ?@5?0@0BV2 <5B01>;V7CNBLAO >4=8< V B8< 65 CYP3A-V7>D5@<5=B>;0<, 0AB5;; :0@10<075?V=, F8;>AB07>;, F870?@84, F8;;>A?>@8=, 487>?V@0W48 @V6:V2, ;>20AB0B8=, <5B8;?@54=V7>;=>, ;0<, <5?@07>;, ?5@>@0;L=V 0=B8:>03C;O=B8 (=0?@8::;04 20@D0@8=), ?V<784, EV=V48=, @8D01CB8=, A8;45=0DV;;, A8<20AB0B8=, B0:@>;V;0< V 2V=1;0AB8=, 0;5 F59 A?8A>: =5 T ?>2=8>4V1=89 <5E0=V7< 270T<>4VW 2V47=0G5=89 ?@8 70AB>AC20==V D5=VB>W=C, B5>DV;V=C V 20;L?@>0BC, I><5B01>;V7CNBLAO V=H8< V7>D5@<5=B>< A8AB5<8 F8B>E@>

<5?@07>;

0AB>AC20==O ;;0@8B@>C :><1V=0FVW 7 ><5?@07>;>< C 4>@>A;8E 74>@>28E 4>1@>2>;LFV2 ?@872>48;> 4> ?V428I5==O @V2=>206=8E :>=F5=B@0FV9 ><5?@07>;C. @8 70AB>AC20==V BV;L:8 ><5?@07>;C A5@54=T 7=0G5==O @H;C=:>2>3> A>:C ?@8 28B03< 24 3>48= AB0=>28;> 5,2, ?@8 AC AC20==V ><5?@07>;C 7 ;;0@8B@>< 5,7.

!8;45=0DV;; B040;0DV; V 20@45=0DV;

A=CT 9<>2V@=VABL 71V;LH5==O ?;07<>28E :>=F5=B@0FV9 V=3V1VB>@V2 D>AD>4V5AB5@078 (A8;45=0DV;C, B040;0DV;C V 20@45=0DV;C) ?@8 WE ACAC20==V 7 ;;0@8B@><, I> <65 ?>B@51C20B8 7<5=H5==O 4>78 V=3V1VB>@V2 D>AD>4V5AB5@078.

"5>DV;V=, :0@10<075?V=

57C;LB0B8 ;;V=VG=8E 4>A;V465=L ?>:070;8, I> VA=CT =57=0G=5, 0;5 AB0B8AB8G=> 7=0GCI5 71V;LH5==O :>=F5=B@0FVW B5>DV;V=C 01> :0@10<075?V=C C ?;072V ?@8 WE >4=>G0A=>

AC20==V 7 ;;0@8B@>

">;B5@>48=

">;B5@>48= 3>;>2=8< G8=>< <5B01>;V7CTBLAO 2D6-V7>D>@<>N F8B>E@> (CYP2D6). 4=0: C ?0FVT=V2 157 CYP2D6 <5B01>;V7< 2V41C20TBLAO G5@57 CYP3A. # FV9 ?>?C;OFVW ?@83=VG5==O CYP3A ?@872>48BL 4> 7=0G=>3> ?V428I5==O ?;07<>28E :>=F5=B@0FV9

B>;B5@>48=C. ;O B0:8E ?0FVT=V2 7=865==O 4>78 B>;B5@>48=C <65 1CB8 =5>1EV4=8< C @07V 9>3> 70AB>AC20==O 7 V=3V1VB>@0<8 CYP3A, B0:8<8 O: ;;0@8B@>

"@807>;15=7>4V075?V=8 (=0?@8::;04 0;L?@07>;0<, ;0<, B@807>;0<)

!;V4 C=8:0B8 :><1V=>20=>3> 70AB>AC20==O ?5@>@0;L=>3> ;025==>AC20==V ;0< A;V4 ?@>2>48B8 @5B5;L=89 <=>VB>@8=3 AB0=C ?0FVT=B0 4;O A2>TG0A=>3> :>@83C20==O 4>78.

!;V4 4>B@8807>;0< V 0;L?@07>;04V075?V=V2, 5;V< <0;>9<>2V@=89.

?>AB<0@:5B8=3>2V ?>2V4><;5==O ?@> ;V:0@AL:C 270T<>4VN V @>728B>: ?>1VG=8E O28I 7 1>:C F5=B@0;L=>W =5@2>2>W A8AB5<8 (B0:V O: A>;82VABL V A?;CB0=VABL A2V4>>ABV) ?@8 AC AC20==V ;:0@8B@>807>;0AB5@V30B8 70 ?0FVT=B<<, 2@0E>2CNG8 <>6;82VABL 71V;LH5==O D0@ <0:>;>3VG=8E 5D5:BV2 7 1>:C &!.

=HV 2848 270T<>4V9

3;V:>7848

>15@56=VABN A;V4 70AB>A>2C20B8 ;:0@8B@>4=>G0A=> 7 V=H8<8 >B>B>:A8G=8<8 70A>10<8, >A>1;82> 7 03;V:>7840<8 (482. «A>1;82>ABV 70AB>AC20==O»).

>;EVF8=

>;EVF8= T AC1AB@0B<< CYP3A V P-3;V:>?@>B5W=C (Pgp). V4><>, I> ;:0@8B@>CYP3A V Pgp. @8 >4=>G0A=>AC20==V ;:0@8B@>;EVF8=C ?@83=VG5==O Pgp V CYP3A ;:0@8B@><< <>65 ?@8725AB8 4> ?V428I5==O 5:A?>78FVW :>;EVF8=C. 5>1EV4=> A?>AB5@V30B8 70 AB0=<< ?0FVT=BV2 I>4> 28O2;5==O ;:V=VG=8E A8:A8G=>ABV :>;EVF8=C. >7C :>;EVF8=C A;V4 7=878B8 ?@8 >4=>G0A=> AC20==V 7 ;:0@8B@><< 4;O ?0FVT=BV2 V7 =>@<0;L=>N =8@:>2>N B0 ?5GV=:>2>N DC=:FVTN. !C AC20==O ;:0@8B@>;EVF8=<< ?0FVT=B0< 7 =8@:>2>N 01> ?5GV=:>2>N =54>AB0B=VABN ?@>B8?>:070=5 (482. «@>B8?>:070==O», «A>1;82>ABV 70AB>AC20==O»).

83>:A8=

83>:A8= 22060TBLAO AC1AB@0B<< P-3;V:>?@>B5W=C (Pgp). V4><>, I> ;:0@8B@>AC20==V ?@83=VG5==O Pgp <>65 ?@8725AB8 4> ?V428I5==O 5:A?>78FVW 483>:A8=C. @8 ?>AB<0@:5B8=3>2> A?>AB5@565==V ?>2V4><<O;>AO ?@> ?V428I5==O :>=F5=B@0FVW 483>:A8=C 2 A8@>20BFV :@>2V ?0FVT=BV2, O:V 70AB>A>2C20;8 ;:0@8B@>4=>G0A=> 7 483>:A8=# 45O:8E ?0FVT=BV2 @>728=C;8AO >7=0:8 483VB0;VA=>W B>:A8G=>ABV, C B>B5=V9=> ;5B0;L=V 0@8B :>=B@>;N20B8 :>=F5=B@0FVW 483>:A8=C 2 A8@>20BFV :@>2V C ?0FVT=BV2 ?@8 9>3> 70AB>AC20==V 7 ;:0@8B@>

84>2C48=

4=>G0A=5 70AB>AC20==O B01;5B>: ;:0@8B@>3> 282V;L=5==O V 784>2C48=C C □V -V=DV:>20=8E ?0FVT=BV2 <>65 A?@8G8=OB8 7=865==O @V2=>206=8E :>=F5=B@0FV9 784>2C48=C 2 A8@>20BFV :@>2V. □;0@8B@>L>3> 25;8>N N <>6=0 C=8:=CB8 H;OE>< 4>B@8<0==O 4-3>48==>3> V=B5@20;C <0 <8 ;:0@8B@>2C48=C. @> B0:V 270T<>4W ?@8 70AB>AC20==V ACA?5=7VW ;:0@8B@>2C48=C 01> 48 45>:AVV=>78=C C 4VB59 =5 ?>2V4><<O;>AO. %>G0 ;:0@8B@>AC20==V 2=CB@VH=L> C 4>@>A;8E 2?;8202 =0 01A>@1FVN 784>2C48=C ?VA;O ?5@>@0;L=>3> 70AB>AC20==O, B0:C 270T<>4VN =5 A;V4 >GV:C20B8 ?@8 70AB>AC20==V ;:0@8B@>25==>.

\$5=VB>W= B0 20;L?@>0B

C;8 A?>=B0==V 01> >?C1;V:>20=V ?>2V4><<5==O ?@> 270T<>4VN V=3V1VB>@V2 CYP3A, 2;;NG0NG8 ;:0@8B@>CYP3A (=0?@8;;04 7 D5=VB>W=<< B0 20;L?@>0B<<). 5:<<5=4CTBLAO 287=0G5==O @V2=V2 F8E ;V:0@AL:8E 70A>1V2 C A8@>20BFV :@>2V ?@8 >4=>G0A=>2V4><<O;>AO ?@> ?V428I5==O WE @V2=V2 C A8@>20BFV :@>2V.

2>1VG=> A?@O<>20=V ;V:0@AL:V 270T<>4VW

B070=02V@

0AB>AC20==O ;:0@8B@>CYP3A, ?@872>48;> 4> 71V;LH5==O 5:A?>78FVW ;:0@8B@>AUC 0B070=02V@C =0 28 %. A:V;L:8 ;:0@8B@>1EV4=> 7<5=H8B8 =0 50 % 4;O ?0FVT=BV2 7 ;:V@5=A<< :@50B8=V=C 30-60 <;/E2 V =0 75 % 4;O ?0FVT=BV2 7 ;:V@5=A<< :@50B8=V=C <30 <;/E2. >78 ;:0@8B@>

>:0B>@8 :0;LFVT28E :0=0;V2

'5@57 @878: 0@B5@V0;L=>W 3V?>B5=7VW 7 >15@56=VABN A;V4 70AB>A>2C20B8 ;:0@8B@> 4=>G0A=> 7 1;>:0B>@0<8 :0;LFVT28E :0=0;V2, I> <5B01>;V7CNBLAO CYP3A4 (=0?@8;;04 7 25@0?0<, 0<;>48?V=<<, 48;BV075<<<). @8 270T<>4VW <>6CBL ?V428IC20B8AO ?;07<>2V :>=F5=B@0FVW O: ;:0@8B@>:0B>@V2 :0;LFVT28E :0=0;V2. # ?0FVT=BV2, I> >B@8< 7 25@0?0<, A?>AB5@V30;8AO 0@B5@V0;L=0 3V?>B5=7VO, 1@04V0@8B0F84>7.

B@0:>=07>;

;0@8B@>=07>; T AC1AB@0B0<8 B0 V=3V1VB>@0<8 CYP3A, 2 7207:C 7 G8< ;0@8B@>< ?0FVT=B8 ?>28==V ?5@51C20B8 ?V4 ?8;L=8< =03;04>< 4;O 2802;5==O ?@>O2V2 G8 A83> 01> ?@>;>=3>20=>3> D0@<0;>;>3VG=>3> 5D5:BC.

!0:2V=02V@

0AB>AC20==O ;0@8B@>CYP3A, C 12 74>@>28E 4>1@>2>;Lfv2 ?@872>48;> 4> 71V;LH5==O AUC @V2=>206=>3> AB0=C =0 177 % B0 !_{max} =0 187 % ?>@V2=O=> V7 70AB>AC20==O< BV;L:8 A0:2V=02V@C. @8 FL>AUC B0 !_{max} ;0@8B@> =0 40 % ?>@V2=O=> V7 70AB>AC20==O< BV;L:8 ;0@8B@>70E/ ;V:0@AL:8E D>@<0E. 57C;LB0B8 4>A;V465==O ;V:0@AL:>W 270T<>4VW V7 70AB>AC20==O< <O:8E 65;0B8=>28E :0?AC; <>6CBL =5 2V4?>2V40B8 5D5:B0<, O:V A?>AB5@V30NBLAO ?@8 70AB>AC20==V A0:2V=02V@C C D>@28E :0?AC; . 57C;LB0B8 4>A;V465==O ;V:0@AL:>W 270T<>4VW V7 70AB>AC20==O< ;8H5 A0:2V=02V@C <>6CBL =5 2V4?>2V40B8 5D5:B0<, O:V A?>AB5@V30NBLAO ?@8 B5@0?VW A0:2V=02V@>=02V@>;8 A0:2V=02V@ 70AB>A>2CNBL @07>< V7 @8B@>=02V@><, =5>1EV4=> 2@0E>2C20B8 <>6;82V 5D5:B8 @8B@>=02V@C =0 ;0@8B@>

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

5@54 70AB>AC20==O< @5:><5=4CTBLAO ?@>2>48B8 H:V@=C ?@>1C =0 ?5@5=>A8 ;0@8B@>

"@820;5 01> ?>2B>@=5 70AB>AC20==O 0=B81V>B8:0 <>65 A?@8G8=OB8 =04AC20==O ;0@8B@> 7?>G0B8 2V4?>2V4=C B5@0?VN.

>15@56=VABN A;V4 70AB>A>2C20B8 ?@5?0@0B ?0FVT=B0< V7 BO6:>N =8@>2>N =54>AB0B=VABN.

V4 G0A 70AB>AC20==O ;0@8B@>2V4><;O;>AO ?@> ?>@CH5==O DC=:FVW ?5GV=:8, 2;;NG0NG8 ?V428I5=89 @V25=L ?5GV=:>28E D5@<5=BV2, V ?@> 35?0B>F5;N;O@=89 B0/01> E>;5AB0B8G=89 35?0B8B 7 6>2BO=8F5N 01> 157 =5W. &5 ?>@CH5==O DC=:FVW ?5GV=:8 <>65 1CB8 BO6:>3> ABC?5=O B0 T 70728G09 >1>@>B=82V4><;O;>AO ?@> ?5GV=:>2C =54>AB0B=VABL 7 ;5B0;L=8< =0A;V4:><, O:0 2>A=>2=>FV9>20=0 7 A5@9>7=8<8 >A=>2=8<8 70E2>@N20==O<8 B0/01> AC?CB=V< <548:0<5=B>7=8< ;V:C20==O1EV4=> =5309=> ?@8?8=8B8 70AB>AC20==O ;0@8B@>O2V2 B0 A8 @5:AVO, 6>2BO=8FO, ?>B5<=V==O A5GV, A25@1V6 01> 1V;L C 4V;O=FV 682>B0.

@> @>728B>: 4V0@5W 2V4 ;53:>3> ABC?5=O 4> ?A524><5<1@0=>7=>3> :>;VBC 7 ;5B0;L=8< =0A;V4:> <, A?@8G8=5=>3> *Clostridium difficile*(CDAD), ?>2V4><;O;>AO ?@8 70AB>AC20==V ?@0:B8G=> 2AVE 0=B810:B5@V0;L=8E ?@5?0@0BV2, C B>*Clostridium difficile* C 2AVE ?0FVT=BV2 7 4V0@5TN ?VA;O 70AB>AC20==O 0=B81V>B8:V2. @V< B>3>, =5>1EV4=> @5B5;L=> 7V1@0B8 0=0<=57, >A:V;L:8 ?@> @>728B>: 4V0@5W, A?@8G8=5=>W *Clostridium difficile*, ?>2V4><;O;>AO =02VBL G5@57 2 AC20==O 0=B810:B5@V0;L=8E ?@5?0@0BV2.

;0@8B@> 282>48BLAO 3>;>2=8< G8=>< G5@57 ?5GV=:C. ">;V4 1CB8 >15@56=8< ?@8 70AB>AC20==V ?@5?0@0BC ?0FVT=B0< V7 ?>@CH5==O< DC=:FVW ?5GV=:8, 0 B0:>6 V7 A5@54=V< 01> BO6:8< ABC?5=5< ?>@CH5==O DC=:FVW =8@>:.

>2V4><;O;>AO ?@> @>728B>: :>;EVF8=>2>W B>:A8G=>ABV (C B>AC20==V ;0@8B@>;EVF8=C, >A>1;82> C ?0FVT=BV2 ;VB=L>3> 2V:C, C B>2>W =54>AB0B=>ABV (482. «□70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»). !CAC20==O ;0@8B@>;EVF8=>< ?@>B8?>:070=5 (482. «@>B8?>:070==O»).

>15@56=VABN A;V4 70AB>A>2C20B8 >4=>G0A=> ;0@8B@>;15=7>4V075?V=8, =0?@8;;04 B@807>;0<, 2=CB@VH=L>25==89 ;0< (482. «□70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T <>4V9»).

>15@56=VABN A;V4 70AB>A>2C20B8 ;0@8B@>4=>G0A=> 7 V=H8<8 >B>B>:A8G=8<8 70A>10<8, >A>1;82> 7 03;V:>7840<8. !;V4 ?@>2>48B8 <=>VB>@8=3 25AB81C;O@=>W B0 A;CE>2>W DC=:FVW ?V4 G0A B0 ?VA;O ;V:C20==O.

'5@57 @878: ?>4>265==O V=B5@20;C QT A;V4 7 >15@56=VABN 70AB>A>2C20B8 ;0@8B@>N E2>@>1>N A5@FO, BO6:>N A5@F52>N =54>AB0B=VABN, 3V?>03=VT @07>< 7 V=H8<8 ?@5?0@0B0 <8, I> 0A>FVNNBLAO 7 ?>4>265==O< V=B5@20;C QT (482. «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»). ;0@8B@>QT 01> 7V H;C=>G:>2>N A5@F52>N 0@8B =52<>=VO

A;V;L:8 <>6;825 VA=C20==O @578AB5=B=>ABV Streptococcus pneumoniae 4> <0:@>;V4V2, 206;82> ?@>2>48B8 B5AB =0 GCB;82VABL ?@8 ?@87=0G5==V ;:0@8B@>A?VB0;L=>W ?=52<=>VW. # @07V 3>A?VB0;L=>W ?=52<=>VW ;:0@8B@>B@V1=> 70AB>A>2C20B8 C :><1V=0FVW 7 V=H8<8 2V4?>2V4=8<8 0=B81V>B8:0<8.

=D5:FVW H:V@8 B0 < O:8E B:0=8= 2V4 ;53:>3> 4> ?>3> ABC?5=O

0=V V=D5:FVW =09G0ABVH5 A?@8G8=5=V>@30=V7<0<8 Staphylococcus aureus B0 Streptococcus pyogenes, :>65= 7 O:8E <>65 1CB8 @578AB5=B=8< 4> <0:@>;V4V2. "> ?@>2>48B8 B5AB =0 GCB;82VABL. /:I> =5<>6;82> 70AB>AC20B8 15B0-;0:B0<=V 0=B81V>B8:8 (=0?@8::04 ?@8 0;5@3VW), O: ?@5?0@0B8 ?5@H>3> 281>@C <>6=0 70AB>A>2C20B8 V=HV 0=B81V>B8:8, =0?@8::04 ;:V=40 Corynebacterium minutissimum, acne vulgaris, 15H8E>2>3> 70?0;5==O, B0 C A8BC0FVOE, :>;8 =5 <>6=0 70AB>A>2C20B8 ?5=VF8;V=8.

28?04:C @>728B:C B06:8E 3>AB@8E @50:FV9 3V?5@GCB;82>ABV, B0:8E O: 0=0DV;0:AVO, A8=4@> < !BV25=A0 6>=A>=0, B>:A8G=89 5?V45@<0;L=89 =5:@>;V7, DRESS, E2>@>10 (5=;59=05=>E0, B5@0?VN ;:0@8B@>< A;V4 =5309=> ?@8?8=8B8 B0 >4@07C 6 @>7?>G0B8 2V4?>2V4=5 ;V:C20==O. ;:0@8B@>B@V1=> 70AB>A>2C20B8 7 >15@56=VABN ?@8 >4=>G0A=>@<8 D5@<5=BC F8B>E@>!Y 3A4 (482. «□70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

!;V4 725@=CB8 C203C =0 <>6;82C ?5@5E@5A=C @578AB5=B=VABL< B0 V=H8<8 <0:@>;V40<8, 0 B0:>6 ;V=:> V ;:V=40

=3V1VB>@8 <3->-@54C:B078 (AB0B8=8)

><1V=>20=5 70AB>AC20==O ;:0@8B@>20AB0B8=>< 01> A8<20AB0B8=>< ?@>B8?>:070=5 (482. «@>B8?>:070==O»). !;V4 7 >15@56=VABN ?@87=0G0B8 ;:0@8B@>4=>G0A=> 7 V=H8<8 AB0B8=0<8. >2V4><;O>;AO ?@> @>728B>: @014>;V7C C ?0FVT=BV2 ?@8 ACAC20==V ;:0@8B@>1EV4=89 <=>VB>@8=3 ?0FVT=BV2 I>4> 28O2;5==O >7=0: V A8?0BVW. A8BC0FVOE, :>;8 >4=>G0A=>3> 70AB>AC20==O ;:0@8B@>CYP3A (=0?@8::04 D;C20AB0B8=C) (482. «□70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

5@>@0;L=V 3V?>3;V:518/V=AC;V=

><1V=>20=5 70AB>AC20==O ;:0@8B@>@0;L=8E 3V?>3;V:51V2 (=0?@8::04 ?>EV4=8E AC;LD>=V;A5G>28=8) B0/01> V=AC;V=C <>65 A?@8G8=OB8 28@065=C 3V?>3;V:5<5=4>20=89 @5B5;L=89 <=>VB>@8=3 @V2=O 3;N:>78.

5@>@0;L=V 0=B8:>03C;O=B8

@8 ACAC20==V ;:0@8B@>< VA=CT @878: 28=8:=5==O A5@9>7=>W :@>2>B5GV, 7=0G=>3> ?V428I5==O ?>:07=8:0 ! (4=5 =>@<0;V7>20=5 A?V22V4=>H5==O) B0 ?@>B@><1V=>2>3> G0AC. >:8 ?0FVT=B8 >B?@84=>G0A=> ;:0@8B@>@0;L=V 0=B8:>03C;O=B8, ?>B@V1=> G0AB> :>=B@>;N20B8 ?>:07=8: ! B0 ?@>B@><1V=>289 G0A.

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

57?5:0 70AB>AC20==O ;0F84C .. 4;O 2=CB@VH=L>25==>3> 22545==O C ?5@V>4 203VB=>ABV B0 3>4C20==O 3@C44N =5 1C;0 2AB0=>2;5=0. ">AC20==O ?@5?0@0BC FV9 :0B53>@VW 6V=>: =5 @5:> <5=4CTBLAO 157 @5B5;L=>W >FV=:8 A?V22V4=>H5==O :>@8ABL/@878.;:0F84 .. ?@>=8:0T C 3@C4=5 <>;>:.

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

0=V ?@> ??;82 2V4ACB=V. 4=0: A;V4 1@0B8 4> C2038<>6;825 28=8:=5==O ?>1VG=8E @50:FV9 7 1>:C =5@2>2>W A8AB5<8, B0:8E O: AC4<8, 70?0<>@>G5==O, 25@B83>, 30;NF8=0FVW, A?;CB0=VABL A2V4><>ABV, 457>@VT=B0FVO B>I>, I><>65 ??;8=CB8 =0 H284:VABL ?A8E<>B>@=8E @50:FV9.

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

;O ?0FVT=BV2 2V:>< 2V4 18-B8 @>:V2 A5@54=O 4>70 AB0=>28BL 500<3 2 @078 =0 45=L 7 V=B5@20;>< 12 3>48= C 283;04V 2=CB@VH=L>25==>W B@820;>W (?@>BO3< 60 E28;8=) V=DC7VW ?VA;O @>72545==O ?@5?0@0BC 2 =5>1EV4=>7G8=V.

;0F84 .. =5 70AB>A>2CNBL 4;O 1>;NA=>3> 01> 2=CB@VH=L><O7>2>3> 22545==O.

0AB>AC20==O ?0FVT=B0< 7 10:B5@V0;L=>N V=D5:FVTN.

%2>@8< 7 ;>:0;V7>20=8<8 V 48A520=8<8 10:B5@V0;L=8<8 V=D5:FVO<8, I> A?@8G8=5=V M.Ovium, M.i ntracellulare M.chelonae, M.fortuitum, M.kansasii@5:><5=4>20=0 4>70 ;0@8B@>@>A;8E AB0=>28BL 1 3 =0 4>1C C 283;O4V 2 V=DC7V9.

V:C20==O ?@>4>26CNBL ?@>BO3< 25 4=V2 70;56=> 2V4 BO6:>ABV AB0=C E2>@>3>, 0 ?>BV< ?@8 <>6;82>ABV ?5@5E>4OBL =0 ?@89< ?@5?0@0BC 4;O ?5@>@0;L=>3> 70AB>AC20==O.

0AB>AC20==O ?0FVT=B0< 7 =8@:>2>N =54>AB0B=VABN: ?0FVT=B0< 7 =8@:>2>N =54>AB0B=VABN (:;V@5=A :@50B8=V=C <5=H5 30 <;E2) 4>7C ;:0@8B@>A;V4 7<5=H8B8 4> ?>;>28=8 728G09=>W @5:> <5=4>20=>W 4>78.

@83>BC20==O V=DC7V9=>3> @>7G8=C.

1. V43>BC20B8 ?>G0B:>289 @>7G8= ;0F84C .. 4;O 2=CB@VH=L>25==>3> 22545==O, 4>40NG8 10 <; AB5@8;L=>W 2>48 4;O V=T:FV9 C D;0:>= 7 500 <3 ;:0@8B@>A>2C20B8 BV;L:8 AB5@8;L=C 2>4C 4;O V=T:FV9, >A;V;L:8 V=HV @>7G8==8:8<>6CBL A?@8G8=8B8 CB2>@5==O >A04C. 5 70AB>A>2C20B8 @>7G8==8:8, I> =A5@20=B8 G8 =5>@30=VG=V A>;V.

%VBO3< 48 3>48= ?@8 715@V30==V ?@8 B5°! B0 24 3>48=8 ?@8 B5°!. 1V>;>3VG=>W B>G:8 7>@C @>72545=89 ?@5?0@0B A;V4 =5309=> 70AB>A>2C20B8. /:I> 9>3> =5 1C45 =5309=> 70AB>A>20=>, A;V4 70157?5G8B8 9>3> 715@V30==O 2 0A5?B8G=8E C<>20E, 70728G09 =5 4>2H5 24 3>48= ?@8 B5 8 □

!.

2. 5@54 22545==O< ?>G0B:>289 @>7G8= ;0F84C .. (500 <3 C 10 <; 2>48 4;O V=T:FV9) A;V4 @>725AB8 >7G8= 3;N:>78 2 ;0:B0B=>7G8=V V=35@0, 5 % @>7G8= 3;N:>78, ;0:B0B=89 @>7G8= V=35@0, 5 % @ >7G8= 3;N:>78 2 0,3 % @>7G8=V =0B@VN E;>@84C, >@<>A>;-C 5 % @>7G8=V 3;N:>78, >@<>A>;-R C 5 % @>7G8=V 3;N:>78, 5 % @>7G8= 3;N:>78 2 0,45 % @>7G8=V =0B@VN E;>@84C B0 0,9 % @>7G8= =0B@VN E;>@84C.

%VBO3< 48 3>48= ?@8 715@V30==V ?@8 B5°! B0 6 3>48= ?@8 B5°!. 1V>;>3VG=>W B>G:8 7>@C, ?@83>B>20=89 @>7G8= A;V4 =5309=> 28:>@8AB0B8. /:I> @>7G8= =5 1C45 28:>@8AB0=89 =5309=>, A;V4 70157?5G8B8 9>3> 715@V30==O 2 0A5?B8G=8E C<>20E, 70728G09 =5 4>2H5 24 3>48= ?@8 B5 8 □

!.

>4=V ;V:8 G8 @5035=B8 =5 <>6=0 4>4020B8 4> V=DC7V9=>3> @>7G8=C ;0F84C ..., ?>:8 =5 1C45 287=0G5=> WE=V9 2?;82 =0 EV7G8=C 0=B81V>B8:0.

VB8.

0=8E I>4> @5:><5=40FV9 AB>A>2=> @5687C20==O 4;O 2=CB@VH=L>25==>3> 70AB>AC20==O ;:0@8B@>O< 2V:< 4> 12-B8 @>:V2 =54>AB0B=L>. 82. V=AB@C:FVN 4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC ;0F84® C D>@BC20==O ACA?5=7VW.

>7C20==O 4;O 4VB59 2V:< 1218 @>:V2 B0:5 6, O: V 4;O 4>@>A;8E.

5@54>7C20==O.

@07V ?5@54>7C20==O A;V4 ?@8?8=8B8 70AB>AC20==O ;:0@8B@>?>G0B8 2V4?>2V4=5 A8 <0B8G=5 ;V:C20==O.

A=CNGV ?>2V4<;5==O 2:07CNBL =0 B5, I> ?5@54>7C20==O ;:0@8B@< ?@8 70AB>AC20==V 2=CB@VH=L> <>65 A?@8G8=8B8 ?>O2C A8:C H;C=>2>-:8H:>2>3> B@0:BC. # >4=>3> ?0FVT=B0 7 1V?>;O@=8< ?A8E>7>< 2 0=0<=57V, O:89 ?@89=O2 8 3 ;:0@8B@>728=C;8AO 77C<>2>3> AB0=C, ?0@0=>W40;L=0 ?>254V=:0, 3V?>:0;VT:A51VG=V @50:FVW, I> AC?@>2>46CNBL ?5@54>7C20==O, A;V4 ;V:C20B8 70 4>?>>3>N 5;V4V2 B0 A8<0B8G=>W B5@0?VW. /: VI>4> V=H8E <0:@>;V4V2, <0;>9 <>2V@=>, I> 35<>4V0;V7 01> ?5@8B>=50;L=89 4V0;V7 ACBBT2> 2?;820NBL =0 220BFV :@>2V.

>1VG=V @50:FVW.

09G0ABVH8<8 B0 =09?>H8@5=VH8<8 ?>1VG=8<8 @50:FVO<8 ?@8 ;V:C20==V ;:0@8B@< 4>@>A;8E B0 4VB59 T 1V;L C 682>BV, 4V0@5O, =C4>B0, 1;N20==O B0 A?>B2>@5==O A0:C. &V ?>1VG=V @50:FVW 70728G09 =57=0G=> 28@065=V B0 C73>46CNBLAO V7 2V4<>8< ?@>DV;5< 157?5:8 <0:@>;V4=8E 0=B81V>B8:V2. V4 G0A ;V=VG=8E 4>A;V465=L =5 1C;> 28O2;5=> ACBBT2>W @V7=8FV C G0AB>BV F8E ?>1VG=8E @50:FV9 10:B5@V0;L=V V=D5:FVW. 86G5 =02545=V ?>1VG=V @50:FVW, I> 28=8;;8 ?V4 G0A ;V=VG=8E 4>A;V465=L B0 ?@8 ?>AB <0@:5B8=3>2>AC20==V @V7=8E ;V:0@AL:8E D>@< V 4>7C20=L ;:0@8B@>@>H:C ;V>DV;V7>20=>3>.

>1VG=V @50:FVW, I=>09<5=H V<>2V@=> ?>2O70=V 7 ;:0@8B@<, @>7?>4V;5=V 70 A8AB5<0<8
>@30=V2 V 70 G0AB>B>N 28=8:=5==O: ?>=04 10 % 4C65 G0ABV, 1-10 % G0ABV, 0,1-1 % =5G0ABV, 7
=52V4><>N G0AB>B>N* (?>1VG=V @50:FVW 7 ?>AB<0@:5B8=3>2>3> A?>AB5@565==O; G0AB>BC
287=0G8B8 =5<>6;82> 7 =0O2=8E 40=8E). <560E :>6=>W 3@C?8 ?>1VG=V @50:FVW ?@54AB02;5=V 2
?>@O4:C 7<5=H5==O BO6:>ABV ?@>O2V2, O:I> BO6:VABL 240;>AO >FV=8B8.
=D5:FVW B0 V=207VW: =5G0ABV F5;N;VB1, :0=484>7 @>B>2>W ?>@>6=8=8, 30AB@>5=B5@8B2,
V=D5:FVO3, 203V=0;L=0 V=D5:FVO; 7 =52V4><>N G0AB>B>N ?A524><5<1@0=>7=89 :>;VB,
15H8E>25 70?0;5==O.
>@CH5==O 7 I>:C :@>2V V ;VW A8AB5<8: =5G0ABV ;59:>?5=VO, =59B@>?5=VO4, B@<1>F8B53,
5>78=>DV;VO4; 7 =52V4><>N G0AB>B>N 03@0=C;>F8B>7, B@<1>F8B>?5=VO.
>@CH5==O 7 I>:C VW A8AB5<8: =5G0ABV 0=0DV;0:B>W4=V @50:FVW1, 3V?5@GCB;82VABL; 7
=52V4><>N G0AB>B>N 0=0DV;0:B8G=V @50:FVW, 0=3V>=52@>B8G=89 =01@O:.
>@CH5==O 7 I>:C <5B01>;V7=5G0ABV 0=>@5:AVO, 7=865==O 0?5B8BC;7 =52V4><>N G0AB>B>N
3V?>3;V:5
>@CH5==O 7 I>:C ?A8EV:8: G0ABV 157A>==O; =5G0ABV B@82>6=VABL, =5@2>7=VABI3; 7 =52V4>
<>N G0AB>B>N ?A8E>78, A?>CB0=VABL A2V4><>ABV, 45?5@A>=0;V70FVO, 45?@5AVO,
457>@VT=B0FVO, 30;NF8=0FVW, :>H<0@=V A=>284V==O, <0=VO.
>@CH5==O 7 I>:C F5=B@0;L=>W =5@2>2>W A8AB5<8: G0ABV 4873527VO (?>@CH5==O A
<0:>2>W GCB;82>ABV), 3>;>2=89 1V;L, A?>B2>@5==O A<0:C; =5G0ABV 2B@0B0 A2V4><>ABV1,
48A:V=57VO1, 70?0<>@>G5==O, A>;82VABL, B@5><@; 7 =52V4><>N G0AB>B>N AC4><8, 03527VO
(2B@0B0 A<0:>2>W GCB;82>ABV), ?0@>AA
>@CH5==O 7 I>:C >@30=V2 A;CEC V ;01V@8=B=V ?>@CH5==O: =5G0ABV 70?0<>@>G5==O,
?>3V@H5==O A;CEC, 472V= C 2CE0E; 7 =52V4><>N G0AB>B>N 2B@0B0 A;CEC.
0@4V0;L=V ?>@CH5==O: =5G0ABV 7C?8=:0 A5@FO1, DV1@8;OFVO ?5@54A5@4L1, ?>4>265==O
V=B5@20;C QT, 5:AB@0A8AB>;81, 2V4GCBBO A5@F518BBO; 7 =52V4><>N G0AB>B>N ?V@C5B=0
H;C=>G:>20 B0EV:0@4VO (torsades de pointes), H;C=>G:>20 B0EV:0@4VO.
!C48==V ?>@CH5==O: G0ABV 207>48;0B0FVO1; 7 =52V4><>N G0AB>B>N :@>2>28;82.
>@CH5==O 7 I>:C 48E0;L=>W A8AB5<8, >@30=V2 3@C4=>W :;VB:8 B0 A5@54>ABV==O:
=5G0ABV 0AB<01, =>A>20 :@>2>B5G02, 5<1>;VO AC48= ;535=V21.
>@CH5==O 7 I>:C B@02=>W A8AB5<8: G0ABV 4V0@5O, 1;N20==O, 48A?5?AVO, =C4>B0, 1V;L C
682>BV; =5G0ABV 57>D03VB1, 30AB@>57>D0350;L=0 @5D;N:A=0 E2>@>102, 30AB@8B, ?@>:B0;3VO
2, AB>0B8B, 3;>A8B, 74CBBO 682>B04, 70?>@, ACEVABL C @>BV, 2V4@86:0,<5B5>@87<; 7 =52V4>
<>N G0AB>B>N 3>AB@89 ?0=:@50B8B, 7;L>@C O78:0, 7;L>@C 7C1V2.
>@CH5==O 35?0B>1V;V0@=>W A8AB5<8: G0ABV 2V4E8;5==O 2V4 =>@<8 DC=:FV>=0;L=V2
B5ABV2 ?5GV=:8; =5G0ABV E>;5AB074, 35?0B8B4, ?V428I5==O @V2=O ", !", "4; 7 =52V4><>N
G0AB>B>N ?5GV=:>20 =54>AB0B=VABL, E>;5AB0B8G=0 6>2BO=8FO, 35?0B>F5;N;O@=0
6>2BO=8FO.
>@CH5==O 7 I>:C H:V@8 V ?V4H:V@=>W :;VB:>28=8: G0ABV 28A8?0==O, 3V?5@3V4@>7;
=5G0ABV 1C;L>7=89 45@<0B8B1, A25@1V6, :@>?82O=:0, <0:C;>?0?C;L>7=89 28A8?3; 7 =52V4><>N
G0AB>B>N A8=4@< !BV25=A06>=A>=0, B>:A8G=89 5?V45@<0;L=89 =5:@>;V7, <548:0<5=B>7=0
H:V@=0 @50:FVO, I> AC?@>2>46CTBLAO 5>78=>DV;VTN B0 A8AB5<8<8 ?@>O20<8 (DRESS), 0:=5,
E2>@>10 (5=;59=05=>E0.
>@CH5==O 7 I>:C >?>@=>-@CE>2>W A8AB5<8 B0 A?>;CG=>W B:0=8=8: =5G0ABV <O7>2V A?07
<83, A:5;5B=><O7>20 @83V4=VABL, 2; 7 =52V4><>N G0AB>B>N @014>;V72 (70 45O:8<8 ?>2V4>
<;5==O<8, @014>;V7 28=8:02, :>;8 :;0@8B@>A>2C20;8 AC 7 V=H8<8 ;V:0@AL:8<8 70A>10<8, ?@> O:V
2V4><>, I> 2>=8 0A>FVNNBLAO V7 @014>;V7>< (B0:V O: AB0B8=8, DV1@0B8, :>;EVF8= 01>
0;>?C@8=>;), ?0BVO.
>@CH5==O 7 I>:C =8@>: V A5G>284V;L=>W A8AB5<8: =5G0ABV ?V428I5==O :@50B8=V=C :@>2V1
, ?V428I5==O A5G>28=8 :@>2V1; 7 =52V4><>N G0AB>B>N =8@>:20 =54>AB0B=VABL,
V=B5@AB8FV0;L=89 =5D@8B.
030;L=V ?>@CH5==O B0 4C65 G0ABV D;51VB C 1; G0ABV 1V;L C 1, 70?0;5==O C 1, 1V;L ?@8
?0;L?0FVW; =5G0ABV =574C60==O4, ;8E><0=:03, 0AB5=VO, 1V;L C 3@C4OE4, >7=>14, ?V428I5=0 2B>
<;N20=VABL4.

01>@0B>@=V 4>A;V465==O: =5G0ABV 7H5==O 0;L1C1C;V=1, ?V428I5==O @V2=O ;C6=>W
D>AD0B078 2 :@>2V4, ?V428I5==O @V2=O ;0:B0B453V4@>35=078 2 :@>2V4; 7 =52V4><N
G0AB>B>N ?V428I5==O 4=>3> =>@<0;V7>20=>3> A?V22V4=>H5==O, 71V;LH5==O ?@>B@>
<1V=>2>3> G0AC, 7;L>@C A5GV.

* '0AB>B0 =52V4><0, >A:V;L:8 ?@> FV @50:FVW ?>2V4><;O;>AO 4>1@>2V;L=> 7 ?>?C;OFVW
?0FVT=BV2 =52AB0=>2;5=>W :V;L:>ABV. 5 702648<>6=0 B>G=> 2AB0=>28B8 WE G0AB>BC
01> ?@8G8==89 72 O7>: 7 ?@89><>< ?@5?0@0BC. 030;L=89 4>A2V4 70AB>AC20==O
;0@8B@>-4=V2.

1,2,3,4@> FV ?>1VG=V @50:FVW ?>2V4><;O;>AO BV;L:8 ?@8 70AB>AC20==V ?@5?0@0BC C
D>@ 1 ?>@>H:0 ;V>DV;V7>20=>3> 4;O ?@83>BC20==O @>7G8=C 4;O V=DC7V9, 2 B01;5B>:
?@>;>=3>20=>W 4VW, 3 ACA?5=7VW, 4 B01;5B>: =5309=>3> 282V;L=5==O.

@>B03>< ;V=VG=8E 28?@>1C20=L ?5@>@0;L=8E D>@< ;0@8B@>6 ?>2V4><;O;>AO ?@>
0@B@0;3VN.

C;8 4C65 @V4:VA=V ?>2V4><;5==O ?@> C25WB, ?5@5206=> C ?0FVT=BV2, I> >4=>G0A=> ?@89<0;8
@8D01CB8=. V;LHVABL 28?04:V2 1C;8 >1>@>B=8<8.

0FVT=B8 7 ?>@CH5==O< VW A8AB5<8.

E2>@8E =0 !B0 V=H8E ?0FVT=BV2 7 ?>@CH5==O< VW A8AB5<8, O:V 70AB>A>2C20;8 28A>:V 4>78
;0@8B@>2H5, =V6 @5:><5=4>20=> 4;O ;V:C20==O 10:B5@V0;L=8E V=D5:FV9, =5 702648 <>6=0
2V4@V7=8B8 ?>1VG=V @50:FVW, ?>2O70=V V7 70AB>AC20==O< ?@5?0@0BC, B0 A8<8 >A=>2=>3>
01> AC?CB=VE 70E2>@N20=L.

4>@>A;8E E2>@8E, O:V >B@81>2V9 4>7V 1000 <3, =09G0ABVH8<8 ?>1VG=8<8 5D5:B0<8 1C;8
=C4>B0, 1;N20==O, A?>B2>@5==O A<0:C, 1V;L C 682>BV, 4V0@50, 28A8?0==O, 74CBBO 682>B0,
3>;>2=89 1V;L, 70?>@, ?>@CH5==O A;CEC, ?V428I5==O 228=8:0;8 48A?=>5, 157A>==O B0 ACEVABL C
@>BV. # 2 3 % ?0FVT=BV2 A?>AB5@V30;>AO 7=0G=5 ?V428I5==O @V2=V2 " B0 !" B0 7=0G=5
7=865==O :V;L:>ABV ;59:>F8BV2 B0 B@><1>F8BV2 C :@>2V. # 45;V;L:>E ?0FVT=BV2
A?>AB5@V30;>AO ?V428I5==O 228=8 C :@>2V.

"5@ABV. 4 @>:8.

#<>28 715@V30==O. 15@V30B8 C =54>ABC?=>, 70E8I5=>?@8 B5

5AC. ;O @>7G8=5==O ?>@>H:C =5>1EV4=> 70AB>A>2C20B8 BV;L:8 @5:><5=4>20=V @>7G8==8:8.

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

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

8@>1=8:. \$0<0@ T3;L, \$@0=FVO/ Famar L` □ iple, France.

VAF57=0E>465==O 28@>1=8:0 B0 04@5A0 20465==O 9>3> 4VO;L=>ABV..7V= 45 !5= 5 Usine de Saint
Remy, rue de l Isle, 28380 Saint Remy Sur Avre, France.