Please show all your calculations and make sure your numerical answers have units.

1. Benjamin is given an i.v. bolus injection of Drug A. Below are the properties of the drug:

<table>
<thead>
<tr>
<th>Volume of distribution</th>
<th>400 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>130 mL/min</td>
</tr>
<tr>
<td>Therapeutic range</td>
<td>1 – 2 mg/L</td>
</tr>
</tbody>
</table>

Calculate a dosing regimen (multiple IV doses) that will maintain the serum drug concentrations within the therapeutic range. (2pts; Two answer choices possible)

\[ CL = k_e \cdot V_d \]
\[ k_e = \frac{CL}{V_d} = \frac{130 \text{ mL/min}}{400L} \cdot \frac{60 \text{ min}}{1h} \cdot \frac{1L}{1000mL} = 0.0195h^{-1} \]
\[ F = \frac{C_{p_{ss,max}}}{C_{p_{ss,min}}} = \frac{2 \text{ mg/L}}{1 \text{ mg/L}} = 2 \]
\[ \tau = \frac{\ln(F)}{k_e} = \frac{\ln(2)}{0.0195h^{-1}} = 35.5h \sim 36h \]
\[ \bar{C}_{p_{ss}} = \frac{D}{CL \cdot \tau} \]
\[ D = \bar{C}_{p_{ss}} \cdot CL \cdot \tau = 1.5 \frac{mg}{L} \cdot \frac{130 \text{ mL/min}}{1h} \cdot \frac{60 \text{ min}}{1000mL} \cdot 36h = 420mg \]
Or for a more patient compliant dosing regimen, once a day dosing would be better.
\[ \tau = 24h \]
\[ D = \bar{C}_{p_{ss}} \cdot CL \cdot \tau = 1.5 \frac{mg}{L} \cdot \frac{130 \text{ mL/min}}{1h} \cdot \frac{60 \text{ min}}{1000mL} \cdot 24h = 280mg \]
So Benjamin would be given a 420mg (1pt) i.v. bolus injection every 36hrs (1pt). OR
For a more patient compliant dosing regimen: 280mg (1pt) every 24hrs (1pt).

2. For the following scenarios for a multiple dose i.v. bolus therapy, determine what will happen to the average steady-state concentration, the peak concentration, and the fluctuation. Use arrows to indicate if it increases, decreases, or stays the same. Use ‘Multiple IV bolus injection’ simulation. (4pts)
   a) The clearance is doubled. (0.33pt for each answer; 1pt total)
b) The volume of distribution is halved. (0.33pt for each answer; 1pt total)
c) The dose is doubled. (0.33pt for each answer; 1pt total)
d) The number of doses given per a day is halved. So \( \tau \) doubles. (0.33pt for each answer; 1pt total)

<table>
<thead>
<tr>
<th></th>
<th>( C_{avg,ss} )</th>
<th>( C_{max} )</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) CL</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>b) ( V_d )</td>
<td>⇔</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>c) D</td>
<td>↑</td>
<td>↑</td>
<td>⇔</td>
</tr>
<tr>
<td>d) # of D</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

3. True/False: Please state if each of the following is true or is false. (4pts; 1 each)
a) The shorter dosing interval, the higher steady state average concentration.
   True. \[
   C_{avg,ss} = \frac{D}{CL \cdot \tau}
   \]
b) The higher half-life, the larger fluctuation. False.
   \[\downarrow t_{1/2} = \downarrow k_e \quad F = \frac{C_{max}}{C_{min}} = e^{k_e \cdot \tau}\]
c) The shorter the half-life, the smaller degree of accumulation. True.
   \[\downarrow t_{1/2} = \uparrow k_e \quad R_{ss} = \frac{1}{(1 - e^{-k_e \cdot \tau})}\]
d) The longer dosing interval, the longer to achieve steady state. False. Time to achieve steady state is about 5 half-lives.