**No. 24-1576(L), 24-1600, 24-1617**

# In the United States Court of Appeals for the Fourth Circuit

AMY BRYANT, M.D.,
*Plaintiff-Appellee,*

v.

TIMOTHY K. MOORE, ET AL.,
*Intervenors/Defendants-Appellants*

and

JOSHUA H. STEIN, IN HIS OFFICIAL CAPACITY AS ATTORNEY GENERAL FOR THE STATE OF NORTH CAROLINA, ET AL.,
*Defendants-Appellees.*

On Appeal from the United States District Court
for the Middle District of North Carolina
Case No. 1:23-cv-00077-CCE-LPA

## BRIEF OF PHARMACEUTICAL COMPANIES, EXECUTIVES, AND INVESTORS AS *AMICI CURIAE* IN SUPPORT OF APPELLEE AND AFFIRMANCE-IN-PART AND REVERSAL-IN-PART

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October 17, 2024

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

**DISCLOSURE STATEMENT**

- In civil, agency, bankruptcy, and mandamus cases, a disclosure statement must be filed by **all** parties, with the following exceptions: (1) the United States is not required to file a disclosure statement; (2) an indigent party is not required to file a disclosure statement; and (3) a state or local government is not required to file a disclosure statement in pro se cases. (All parties to the action in the district court are considered parties to a mandamus case.)
- In criminal and post-conviction cases, a corporate defendant must file a disclosure statement.
- In criminal cases, the United States must file a disclosure statement if there was an organizational victim of the alleged criminal activity. (See question 7.)
- Any corporate amicus curiae must file a disclosure statement.
- Counsel has a continuing duty to update the disclosure statement.

No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Allay Therapeutics
(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☐ YES ☑ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Allay Therapeutics



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

**DISCLOSURE STATEMENT**

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No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Arcutis Biotherapeutics, Inc.

(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☑ YES ☐ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
   If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
   If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Arcutis Biotherapeutics, Inc.



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

**DISCLOSURE STATEMENT**

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- In criminal and post-conviction cases, a corporate defendant must file a disclosure statement.
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- Counsel has a continuing duty to update the disclosure statement.

No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Ashvattha Therapeutics

(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☐ YES ☑ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
   If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
   If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Ashvattha Therapeutics



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

**DISCLOSURE STATEMENT**

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No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

C4 Therapeutics, Inc.

(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☑ YES ☐ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
   If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
   If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: C4 Therapeutics, Inc.



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

**DISCLOSURE STATEMENT**

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No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Capstan Therapeutics
(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☐ YES ☑ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Capstan Therapeutics



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

**DISCLOSURE STATEMENT**

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No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Dare Bioscience, Inc.

(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☑ YES ☐ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
   If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
   If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Dare Bioscience, Inc.



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

**DISCLOSURE STATEMENT**

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No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Foghorn Therapeutics Inc.
(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☑ YES ☐ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Foghorn Therapeutics Inc.



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Iolyx Therapeutics

(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☐ YES ☑ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Iolyx Therapeutics



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Nkarta, Inc.

(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☑ YES ☐ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
If yes, the debtor, the trustee, or the appellant (if neither the debtor nor the trustee is a party) must list (1) the members of any creditors' committee, (2) each debtor (if not in the caption), and (3) if a debtor is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of the debtor.

7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Nkarta, Inc.



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Praxis Precision Medicines, Inc.
(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☑ YES ☐ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
   If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
   If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

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7. Is this a criminal case in which there was an organizational victim? ☐YES ☑NO
If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Praxis Precision Medicines, Inc.



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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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- Counsel has a continuing duty to update the disclosure statement.

No. 24-1576 Caption: Bryant v. Moore et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

RA Capital Management LP

(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☐ YES ☑ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
   If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
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4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation? ☐YES ☑NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐YES ☑NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐YES ☑NO
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If yes, the United States, absent good cause shown, must list (1) each organizational victim of the criminal activity and (2) if an organizational victim is a corporation, the parent corporation and any publicly held corporation that owns 10% or more of the stock of victim, to the extent that information can be obtained through due diligence.

Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: RA Capital Management LP



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Recludix Pharma
(name of party/amicus)

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Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Recludix Pharma



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Renasent Bio

(name of party/amicus)

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Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Renasent Bio



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Pursuant to FRAP 26.1 and Local Rule 26.1,

Siolta Therapeutics
(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

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Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Siolta Therapeutics



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Pursuant to FRAP 26.1 and Local Rule 26.1,

Tivic Health Systems, Inc.

(name of party/amicus)

who is amicus curiae, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

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Signature: /s/ Samantha Hong Date: 10/17/2024

Counsel for: Tivic Health Systems, Inc.



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## INTEREST OF AMICI CURIAE[1]

*Amici curiae* are pharmaceutical companies, pharmaceutical company executives, and pharmaceutical industry investors. A reversal of the district court's decision would set a precarious precedent permitting and encouraging individual states to enact a patchwork of restrictions on pharmaceutical products for which the U.S. Food and Drug Administration (FDA) has determined additional controls are necessary to protect patient safety. Such individual state restrictions would upend the FDA approval process for this category of drugs, under which such additional controls are implemented uniformly, nationwide, as Risk Evaluation and Mitigation Strategies (REMS). This federal regulatory framework provides certainty and clarity to *amici* who are dedicated to researching and developing innovative drugs to benefit the public health. Many *amici* are, or work with, pre-clinical or clinical stage companies focused on developing therapies to address unmet needs and rare conditions – the very types of drugs for which REMS are often necessary. Thus, *amici* are intimately familiar with the drug development and approval process, including with respect to REMS drugs, and are well-positioned to explain to the Court how state restrictions that effectively modify FDA-approved REMS requirements can stifle innovation and negatively impact the public health.

[1] No party or counsel for a party—nor any person other than *amici* and their counsel—authored this brief in whole or in part or contributed any money intended to fund its preparation or submission.

A full list of *amici* is included as an Appendix to this brief.

## INTRODUCTION AND SUMMARY OF ARGUMENT

Congress, through the Federal Food, Drug, and Cosmetic Act and its amendments (FD&C Act), entrusts FDA as the sole entity responsible for implementing a carefully constructed framework to oversee the development and approval of novel drugs to benefit public health. Drug sponsors, patients, and the health care system at large all rely upon FDA as the gatekeeper of drug approvals, including approval of the conditions for use that dictate how and under what circumstances a drug may be distributed. Congress expanded FDA's authority in 2007 to encompass drugs with important benefits that, due to their safety risks, would otherwise be unavailable but for an FDA-approved REMS, which can include specific controls called Elements to Assure Safe Use (ETASU). In so doing, Congress made clear that when determining appropriate REMS with ETASU FDA must evaluate whether a drug's risks outweigh its benefits while also ensuring that there is no undue burden to patient access or on the health care delivery system – a responsibility for the public health that only FDA is legally authorized to carry out.

The district court recognized FDA's responsibility over this "comprehensive federal strategy" to decide "what safety restrictions on higher-risk drugs are necessary to make use of those drugs less risky." JA 632. Under this comprehensive strategy, FDA must conduct ongoing evaluations of REMS requirements and

approve any modifications to REMS to ensure that the careful balance between drug safety and patient access remains appropriate over time. However, state laws that impose requirements that differ from existing REMS requirements—such as North Carolina's medication abortion restrictions—have the practical effect of modifying the REMS, which, under the FD&C Act, may only be modified with FDA approval. Such state laws upset the statutory scheme, frustrate FDA's ability to strike the balance of considerations required by law, and prevent FDA from serving as a reliable gatekeeper to ensure that patients have safe access to important drugs.

Moreover, laws such as North Carolina's medication abortion restrictions result in state-to-state disparities and create significant uncertainty for drug sponsors tasked with complying with FDA-approved REMS requirements. This reality significantly *increases* the burden on the health care system and, in turn, on patient access, which directly contradicts the underpinnings of the balance FDA strikes with REMS and ETASU. A proliferation of state law restrictions that have the effect of modifying REMS requirements for any number of drugs would be completely untenable.

Accordingly, *amici* urge this Court to affirm the district court's decision preempting certain North Carolina restrictions and reverse the decision with respect to the restrictions the district court held were not preempted.

## ARGUMENT

### I. Congress Established a Comprehensive Statutory Framework for the Regulation of REMS Drugs by FDA

In the United States, drugs intended for distribution in interstate commerce are regulated exclusively by FDA under the FD&C Act. 21 U.S.C. § 355(a). The FD&C Act, as originally enacted in 1938, established the foundational framework for drug regulation and prohibited the distribution of any new drug in interstate commerce absent a drug application demonstrating the drug's safety. *See* Pub. L. No. 75-717, 52 Stat. 1040, 1052 (1938). Congress amended the FD&C Act in 1962 to require that FDA only approve a new drug upon a determination that it is both safe *and* effective under the conditions of use prescribed in the drug's labeling as established through adequate and well-controlled clinical studies. *See* Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781-82; 21 U.S.C. §§ 355(a), (d). This hallmark principle of safety and efficacy demonstrated by substantial evidence governs FDA's drug approval process to this day and is recognized as the "gold standard" worldwide. *See FDA v. Alliance for Hippocratic Med.*, 602 U.S. 367, 374-375 (2024).

In 2007, Congress expanded FDA's authority to enable access to higher risk drugs for which additional controls are necessary to ensure that a drug's benefits outweigh its risks. *See* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901, 121 Stat. 823, 926. In order to approve these higher-risk drugs

that still provide important therapeutic benefits, FDA requires that applicants submit a proposed strategy for additional controls, collectively referred to as REMS, as part of the drug application. 21 U.S.C. § 355-1(a).

FDA can further require that the REMS include additional necessary ETASU for drugs "with known serious risks that would *otherwise be unavailable*." *Id.* § 355-1(f) (heading) (emphasis added). Such drugs are ones that have been shown to be effective but are associated with serious risks that cannot be sufficiently mitigated absent ETASU; they would otherwise not be approved or would be withdrawn. *Id.* § 355-1(f)(1). Many approved REMS drugs are orphan drugs, or those intended to treat patients with rare diseases and unmet needs. *See* 21 U.S.C. § 360bb.[2]

Significantly, the FD&C Act requires ETASU be "commensurate" with the drug's risk and must "not be unduly burdensome on patient access," taking into account vulnerable patient populations and, to the extent practicable, minimizing the burden on the health care delivery system. 21 U.S.C. §§ 355-1(f)(2)(A), (B). With respect to patient access, the Act requires FDA to particularly consider patients with serious or life-threatening diseases or conditions, patients who have difficulty

[2] *See Approved Risk Evaluation and Mitigation Strategies*, FDA.gov, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (last accessed Oct. 14, 2024); *Orphan Drug Designations and Approvals*, FDA.gov, https://www.accessdata.fda.gov/scripts/opdlisting/oopd/ (last accessed Oct. 14, 2024).

accessing health care (such as patients in rural or medically underserved areas), and patients with functional limitations. *Id.* § 355-1(f)(2)(B).

Even after FDA approves a REMS program, the FD&C Act requires that FDA review periodic assessments, conduct periodic evaluations of REMS and ETASU, and approve modifications as appropriate to ensure that, over time, the REMS elements continue to represent this careful balance of considerations. *Id.* §§ 355-1(f)(5), (g). The REMS history for mifepristone, as set forth in detail in Plaintiff's opening brief (at 13–17), is just one example of how FDA's continued monitoring of existing REMS requirements results in modifications over time and it is not usual. According to FDA's REMS database, FDA has approved updates, often multiple times, to the vast majority of REMS requirements for the 73 currently approved REMS drugs (69 of which are REMS with ETASU) since their initial approvals,[3] reflecting the agency's ongoing process of diligent monitoring and reevaluation.

As the district court described, "Congress has delegated to the FDA the authority to regulate higher-risk drugs through a REMS program" with the "clear and manifest purpose [] to create a comprehensive federal strategy under which the FDA is responsible for deciding what safety restrictions on higher-risk drugs are

[3] *See Approved Risk Evaluation and Mitigation Strategies*, FDA.gov, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (last accessed Oct. 7, 2024).

necessary to make use of those drugs less risky." JA 626; JA 632. That the authority to implement this comprehensive regulatory framework lies solely with FDA properly signifies the agency's unique position and expertise to ensure safe access to drugs that would otherwise be unavailable "without unnecessarily reducing patient access or burdening the health care system," JA 631.

## II. State Laws that Have the Practical Effect of Modifying FDA-Approved REMS Contravene, and are Detrimental to, the Federal Regulatory Scheme

FDA is the only entity authorized by law to approve drugs for distribution in interstate commerce and, if appropriate, to require a REMS with ETASU as part of the drug approval with which drug sponsors must comply. State laws that impose requirements on drugs that differ from or are otherwise inconsistent with FDA-approved REMS have the practical effect of modifying the REMS and thereby completely upend the regulatory scheme mandated by Congress.

Defendant-intervenors nevertheless rely on *Wyeth v. Levine*, 555 U.S. 555 (2009) to assert that in enacting the REMS statute, Congress established "a federal floor, not a ceiling" with respect to FDA-approved REMS requirements. Defendant's Br. 17. The district court correctly rejected this argument. *Wyeth* did not involve a REMS drug and did not in any way assess the REMS statute. Rather, the Court in *Wyeth* concluded that FDA regulations permitted the manufacturer of a non-REMS drug to "unilaterally strengthen its warning" on the product labeling without FDA's

prior approval. *Wyeth*, 555 U.S. at 573. This holding is simply not applicable to drugs subject to REMS requirements under 21 U.S.C. § 355-1, which FDA determined require special controls to balance safety restrictions with patient access and thus that the agency must approve both the initial strategy and any subsequent modifications. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 624-626 (2011) (distinguishing *Wyeth* in the context of a different regulatory scheme applicable to generic drugs).

Indeed, the FD&C Act is unyielding on the requirement for compliance with FDA approval of all facets of a REMS. It prohibits drug sponsors from taking any action that deviates from an approved REMS. A drug sponsor may not distribute a REMS drug in interstate commerce if it fails to maintain compliance with approved REMS requirements. 21 U.S.C. §§ 355(p)(1), 331(d). A drug for which a sponsor fails to comply with approved REMS requirements is also deemed misbranded and cannot be introduced into interstate commerce on that basis as well. 21 U.S.C. §§ 352(y); 331(a). And only FDA can approve a modification to an existing REMS either at the request of a drug sponsor or on its own initiative in consultation with the drug sponsor – a drug sponsor cannot unilaterally modify a REMS without FDA approval (either to add or to remove restrictions) as doing so would be noncompliant with approved REMS requirements. 21 U.S.C. §§ 355-1(g)(4), (h). In the case of mifepristone, FDA has already considered and rejected REMS modifications such as those imposed by the North Carolina medication abortion laws. *See* Plaintiff's Br.

35–43. FDA would certainly deny a proposal from mifepristone sponsors to modify the REMS requirements to be consistent with North Carolina laws. *Cf. Merck, Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 302-03 (2019).

As set forth above, the REMS statute in its effort to balance drug safety with patient access is so comprehensive and unyielding—requiring FDA approval of each element to ensure that, on the one hand, restrictions provide for the drug's safe use and, on the other hand, such restrictions are not unduly burdensome on patient access or the healthcare delivery system—that it necessarily establishes *both a floor and a ceiling* for REMS requirements. *Cf. PLIVA*, 564 U.S. at 614-617. To be clear, however, the Court here need not reach this conclusion to find for the Plaintiff. North Carolina's medication abortion laws reflect the state's determination that the FDA-approved REMS for mifepristone was inadequate "[b]ased on a disagreement with FDA over what safety restrictions on the use of mifepristone are necessary," JA 652, and impose additional restrictions that FDA has *already considered and rejected*. For the reasons described in Plaintiff's brief, North Carolina's laws are preempted on this basis alone. Plaintiff's Br. at 35–43.

Importantly, the fact that a state's requirements, like North Carolina's medication abortion laws, attach to the health care provider and not the drug manufacturer does not change the fact that such laws have the practical effect of modifying FDA-approved REMS. These laws merely function as an end-run around

the clear statutory scheme charging FDA with the weighty task of balancing a drug's risks and benefits while simultaneously ensuring that patient access is not unduly burdened. By creating new restrictions that affect access to REMS drugs that are already subject to carefully considered and FDA-approved requirements, states like North Carolina actively interfere with the consistent application of the FD&C Act and create significant uncertainty for drug manufacturers as well as patients, providers, pharmacies, and the health care system as a whole. This reality is unsustainable and in contravention to Congress's intent.

## III. Individual State Restrictions Frustrate FDA's Ability to Achieve the Balance Between Patient Safety and Access to Otherwise Unavailable Drugs that Congress Contemplated

Congress made clear that the driving principle behind FDA's determination as to whether and how to implement a REMS with ETASU for a drug must be to "provid[e] safe access for patients to drugs with known serious risks that would *otherwise be unavailable*" while also "assuring access and minimizing burden." 21 U.S.C. §§ 355-1(f), 355-1(f)(2) (headings) (emphasis added); *see Ellis v. Werfel*, 86 F.4th 1032, 1036-37 (4th Cir. 2023) (heading of a statutory section can be useful to support statutory interpretation); *United States v. Clawson*, 650 F.3d 530, 536 (4th Cir. 2011) (same). FDA takes this mandate seriously and has emphasized the importance of "[a]ssessing the impact of REMS on patient access to the drug and its burden on the healthcare delivery system," where "burden reflects the additional effort that

healthcare professionals and other stakeholders expend in complying with the REMS requirements beyond what is required for good clinical care."[4]

Consistent with this holistic approach, while the initial task of developing and proposing a REMS with ETASU for any specific drug lies with the drug applicant seeking approval, the applicant often submits such a proposal at FDA's behest upon the agency's determination that ETASU are necessary to ensure safety. 21 U.S.C. § 355-1(f)(1)(A); *see also id.* 21 U.S.C. § 355-1(f)(1)(B) (FDA may require that an already approved REMS be modified to add ETASU). Further, Congress requires FDA to evaluate ETASU by "seek[ing] input from patients, physicians, pharmacists, and other health care providers" about how ETASU may be "standardized" so as not to be unduly burdensome on patient access or the health care delivery system. 21 U.S.C. § 355-1(f). In addition, to minimize burdens on the health care delivery system, Congress requires that ETASU "conform with [ETASU] for other drugs with similar, serious risks" and "be designed to be compatible with established distribution, procurement, and dispensing systems for drugs," to the extent practicable. *Id.* § 355-1(f)(2)(D). FDA, as the sole agency responsible for assessing and approving REMS for all drugs, is uniquely positioned to carry out these tasks. Indeed, FDA recognizes that "[r]obust collaborations between FDA and other

[4] FDA Draft Guidance, *REMS Assessment: Planning and Reporting, Guidance for Industry* (Jan. 2019) ("REMS Draft Guidance"), 1, 14, *available at* https://www.fda.gov/media/119790/download.

regulatory agencies, applicants, and the research community can help advance the science of post-market assessment of effectiveness of risk mitigation strategies."[5]

Individual state restrictions, like the North Carolina medication abortion laws, that have the practical effect of modifying an approved REMS with ETASU do not, and cannot, take into account the multitude of factors that Congress requires FDA to consider when developing a REMS. States do not have the requisite information or expertise, let alone the approval authority, to assess both the adequacy of the balance struck by a REMS between burdens on patient access and drug safety *and* the overarching standardization and consistency across all REMS programs that Congress directed. If states were to effectively enact their own state-by-state versions of REMS for specific drugs, they would supplant their own differently informed judgments with those of FDA and impede the agency's ability to implement Congress's directives.

The North Carolina laws precisely demonstrate this point. Despite FDA's over 20 years of thorough review and ongoing evaluation of mifepristone, North Carolina enacted additional restrictions on mifepristone access that do not reflect a balance between patient safety and ensuring that patient access and the health care delivery system are not unduly burdened. Instead, these additional restrictions actively fail to achieve this balance as demonstrated by the fact that all of them were considered by

[5] REMS Draft Guidance, 5.

FDA and rejected as part of the current REMS requirements. For example, FDA reviewed data from nearly a dozen scientific studies to conclude that non-physician healthcare providers, such as physician assistants and nurse practitioners, could be certified prescribers of mifepristone under the REMS. JA238-240. We are not aware that North Carolina conducted such a careful, science-based review in requiring that only physicians may prescribe the drug. *See* N.C. Gen. Stat. §§ 90-21.83A(b)(2)a, 90-21.83B(a). Nor are we aware that North Carolina considered how its restrictions compared to those for analogous drugs with serious risks similar to mifepristone.

## IV. State Law Restrictions Contrary to Approved REMS Requirements are Detrimental to Patients and Healthcare Providers and Will Discourage the Development of Innovative Therapies

If North Carolina's medication abortion laws are upheld, other states will be encouraged to enact similar provisions that have the practical effect of modifying FDA-approved REMS programs, not only for mifepristone but also for *any* REMS drug. *Amici* are deeply concerned that the North Carolina medication abortion laws represent just the tip of an iceberg of potential state modifications of REMS programs for various drugs that will grow if this Court determines that North Carolina provisions are not preempted by federal law. This outcome would result in uncertainty and inconsistency in requirements applicable to REMS drugs that is detrimental to patients, their healthcare providers, and the healthcare system as a

whole, and that will discourage the development of new therapies that could not be available but for REMS programs.

The consequences for patients and healthcare providers may include:

- *State-to-state disparities in patient access to FDA-approved drugs*. For example, if a state were to impose restrictions (such as the North Carolina medication abortion laws) requiring *multiple* in-person medical visits when such visits are not required by an FDA-approved REMS, patients in rural or medically underserved areas in that state would have significantly impeded access to FDA-approved REMS drugs, or no access at all, as compared to similar patients in states without such restrictions.
- *Increased burdens (including increased costs) on the healthcare system*. For example, if a state were to impose restrictions (such as those in the North Carolina medication abortion laws) requiring dispensing procedures and patient information different than those required by an FDA-approved REMS, pharmacies and healthcare providers operating in that state would be burdened with increased labor and costs (and increased risk of liability for errors) when implementing both the FDA-approved REMS and the state requirements, and when reconciling inconsistencies between them. Keeping track of patients who move

between states with different restrictions would further increase these burdens.

- *State-to-state differences in risk information provided to patients*. For example, if a state were to impose restrictions requiring patients to receive warnings different than those provided under an FDA-approved REMS, patients and healthcare providers could question why they are exposed to inconsistent information from state-to-state, which would reduce confidence in (and raise liability risks for) the adequacy of warnings provided for REMS drugs.

Such consequences are inconsistent with the goals of the REMS program as mandated by Congress in 21 U.S.C. § 355-1.

The pharmaceutical industry would also experience adverse consequences. Currently, FDA is the gatekeeper to the marketplace for REMS drugs. If states are permitted to build additional gates (in the form of restrictions on the prescribing, dispensing, and access to such drugs) at any time, and without the collaboration and input of drug manufacturers, the pharmaceutical industry would be unable to rely on FDA approval as its gateway to market and would be discouraged from developing innovative REMS drugs. This would not only deter the development of novel products, especially those for vulnerable patient populations with unmet needs (because of the added time and expense that a company would need to build into its

development program to compensate for uncertainty regarding the scope of present and future state regulatory requirements), but also would also be unfair to the extent that, as in the case of the North Carolina medication abortion laws, FDA has already considered and rejected the restrictions imposed.

Moreover, federal drug regulation is critical to maintaining pharmaceutical industry investment in innovation, through programs that affect the supply and demand for drugs.[6] The REMS program importantly provides a degree of stability and certainty that enables pharmaceutical manufacturers to plan for the supply and demand for REMS drugs. For example, uniform distribution requirements in a nationwide REMS program support planning for a predictable supply of drugs, because the labor and costs associated with REMS compliance can be reasonably predicted during the development and approval process. Similarly, uniform patient access requirements in a nationwide REMS program support planning for a predictable demand for drugs, because the dispensing, warning and other requirements in the REMS define the drug's patient population and the requirements for obtaining the drug.

If states were to impose restrictions (such as those in the North Carolina medication abortion laws) affecting both the distribution of REMS drugs and patient

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[6] *See e.g.*, Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* (April 2021) at 2, *available at* https://www.cbo.gov/publication/57126.

access different than those in the FDA-approved REMS, planning the supply and predicting the demand for REMS drugs would be more difficult and expensive, thereby reducing pharmaceutical companies' ability to develop such drugs. This in turn would call into question the drug industry's ability to recoup investments in the research and development of these drugs and destabilize the investment environment. Further, a significant proportion of drug innovation is conducted by smaller biotechnology and pharmaceutical companies, such as *amici*, which lack the funding and resources to devote to the burdensome task of tracking and ensuring compliance with state-by-state restrictions. These companies would effectively be forced to steer clear of contributing to the development of important drugs to serve patients in need for which REMS are necessary.

Individual states do not have the authority to alter FDA's REMS requirements. Congress has carefully crafted the rules in 21 U.S.C. § 355-1 to be a *national* framework for REMS drugs. Pharmaceutical companies and other parties (including *amici*) rely on that national framework when developing such drugs, and patients and healthcare providers rely on that national framework when dispensing and using them. We respectfully request that this Court protect that national framework and not permit it to be undermined, weakened or compromised. Doing so will promote the strength and stability of the REMS program and the best interests of the healthcare system and patients nationwide.

## CONCLUSION

*Amici* respectfully request that this Court affirm with respect to North Carolina restrictions the district court held were preempted and reverse with respect to the restrictions the district court held were not preempted.

Respectfully submitted,

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## CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 27(d)(2)(A) because it contains 4,034 words, excluding the parts exempted by Rule 32(f). This brief complies with the typeface requirements of Rule 32(a)(5) and the type-style requirements of Rule 32(a)(6) because it has been prepared in proportionally spaced typeface using Microsoft Word in 14-point Baskerville font.

October 17, 2024

*/s/ Samantha N. Hong*
SAMANTHA N. HONG

## CERTIFICATE OF SERVICE

I hereby certify that on October 17, 2024, I electronically filed the foregoing brief with the Clerk of the Court for the U.S. Court of Appeals for the Fourth Circuit by using the CM/ECF system. I certify that all participants in the case are registered CM/ECF users, and that service will be accomplished by the CM/ECF system.

October 17, 2024

*/s/ Samantha N. Hong*
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