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September 11, 2024

VIA EDGAR

United States Securities and Exchange Commission
Division of Corporation Finance
Office of Life Sciences
100 F. Street, N.E.
Washington, D.C. 20549
Attention: Ibolya Ignat, Angela Connell, Tamika Sheppard and Suzanne Hayes

Re: Septerna, Inc.
Draft Registration Statement on Form S-1
Submitted August 2, 2024
CIK 0001984086

Dear Ladies and Gentlemen:

This letter is confidentially submitted on behalf of Septerna, Inc. (the "**Company**"), in response to the comments of the staff of the Division of Corporation Finance (the "**Staff**") of the U.S. Securities and Exchange Commission (the "**Commission**") with respect to the Company's Draft Registration Statement on Form S-1, originally confidentially submitted on August 2, 2024 (the "**Draft Registration Statement**"), as set forth in the Staff's letter, dated September 5, 2024, addressed to Jeffrey Finer, M.D., Ph.D. (the "**Comment Letter**"). The Company is concurrently confidentially submitting Amendment No. 1 to the Draft Registration Statement ("**Amendment No. 1**"), which includes changes to reflect responses to the Staff's comments and other updates.

For reference purposes, the text of the Comment Letter has been reproduced herein with responses below each numbered comment. For your convenience, we have italicized the reproduced Staff comments from the Comment Letter. Unless otherwise indicated, page references in the descriptions of the Staff's comments refer to the Draft Registration Statement, and page references in the responses refer to Amendment No. 1. All capitalized terms used and not otherwise defined herein shall have the meanings set forth in Amendment No. 1.

The responses provided herein are based upon information provided to Goodwin Procter LLP by the Company.

Draft Registration Statement on Form S-1

Prospectus Summary
Overview, page 1

1. *Please delete the overly speculative statements included in the Summary and throughout your filing. Given the early stage of your candidates' development, your unproven, novel technologies, the limited evidence supporting the feasibility of developing therapeutic treatments based on your platform, and the number of other companies focused on GPCRs and platform technologies, these statements are do not appear supportable. Illustrative examples include:*

    - *we have transformed GPCR oral small molecule drug discovery to an industrialized and iterative structure-based drug design approach to expand the landscape of druggable GPCR targets with novel oral small molecule medicines for patients.*
    - *we believe our team, scientific and technical advisors, and our proprietary Native Complex PlatformTM uniquely positions us to become the leading GPCR-focused biotechnology company.*
    - *we believe we are at the forefront of industrial-scale GPCR drug discovery and development.*
    - *we are advancing cutting-edge science and rigorously developing a broad and deep portfolio of GPCR-targeted programs for patients.*

    We note there are other companies with platforms focused on GPCR drug discovery, which are led by teams with extensive experience in the pharmaceutica/biotechnology industry.

    RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 1, 2, 3, 5, 105, 106, 124, 125, 126, 127, 130, 132, 134 and 135 of Amendment No. 1 in response to the Staff's comment.

2. *Your summary presents an unbalanced discussion of your business and potential opportunity by providing limited information that can put your statements in the proper context and isolating such information towards the end of the Summary. Please revise your summary to include balance by including equally prominent disclosure of information about your status as a company with no commercial products, information about the competitive conditions in the industry, and the status of your product candidates. For example:*

    - *Balance the statement that SEP-786 is the only clinical stage, oral small molecule agonist targeting Parathyroid Hormone 1 Receptor for the treatment of hypoparathyroidism with statements that there are other product candidates in development that target PTH1R for hypoparathyroidism, including a candidate that is in Phase 3 and has recently been granted fast track status by the FDA.*

- *Balance your belief that your team, scientific and technical advisors, and our proprietary Native Complex PlatformTM uniquely positions you to become the leading GPCR-focused biotechnology company to clarify that there are other companies that have developed platforms in use to develop GPCR-focused product candidates, some of which are led by leadership teams with extensive experience in the pharmaceutical/biotechnology field. Many of these companies are private companies, therefore there may not be a lot of information publicly available about their platforms, product candidates and current stage of development.*
- *Balance your belief that you are at the forefront of industrial-scale GPCR drug discovery and development with information that there are other companies with platforms that are focused on GPCR drug discovery.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 1 to 5 of Amendment No. 1 in response to the Staff's comment.

3. *Please refer to Item 503 of Regulation S-K and note that the Summary should be brief, should not contain all the detailed information in the prospectus and should focus on providing a brief overview of the key aspects of the offering without merely repeating the text of the prospects. As currently drafted the first eight pages of your Summary are repeated almost word for word on the first eight pages of your Business section, and much of the information was also repeated in Management's Discussion and Analysis of Financial Condition and Results of Operations and Management. The only subsections that were summarized were the discussions of your strategy and risk factors. Please revise your summary to eliminate the repetitive information from within the Summary and avoid merely repeating detailed discussions from the prospectus. To the extent you decide to keep both graphics summarizing your pipeline on pages 2 and 5. Please why both are necessary as most of the information in the graphic on page 2 is also in the graphic on page 5.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 2 and 5 of Amendment No. 1 in response to the Staff's comment.

4. *We note your explanation of your Native Complex Platform. We understand that there are other companies focused on developing GPCR-targeting drugs using alternate technologies, given the difficulty in isolating GCPRs. Please explain why the "unique position" of your technology will be sufficient to make up for the competitive advantage other companies, who may be further along developing similar drugs.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 2, 106 and 125 of Amendment No. 1 in response to the Staff's comment.

5. Please define agonists, antagonists and allosteric modulators the first time the terms are used.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 1, 105 and 124 of Amendment No. 1 in response to the Staff's comment.

Our Pipeline and Programs, page 4

6. Please remove the "Other Therapeutic Areas of Interest/Focus" from your pipeline table. The pipeline table should only include references to your currently material product candidates and programs.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the pipeline table appearing on pages 2, 105 and 128 of Amendment No. 1 in response to the Staff's comment.

SEP-786 - Oral Small Molecule PTH1R Agonist for Hypoparathyroidism, page 5

7. Please remove statements about your conclusions from your preclincial studies from the summary. Such statements should be accompanied by a description of the studies, which is more appropriate for the Business section. Similarly revise the descriptions of your other product candidates and programs.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 4 and 5 of Amendment No. 1 in response to the Staff's comment.

Our future ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited., page 47

8. Please quantify your current net operating loss carryforward.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 44 of Amendment No. 1 in response to the Staff's comment.

We are conducting, and will conduct, clincial trials for our current product candidates outside of the United States..., page 48

9. We note your disclosure on page 143 that you have submitted a CTN in Australia. Please revise to clarify your plans to conduct trials in Australia and indicate whther you currently have plans to conduct trials in other jurisdictions.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 142 of Amendment No. 1 in response to the Staff's comment.

We may not be able to obtain orphan drug designation for our product candidates..., page 52

10. Please clarify which candidates, if any, may qualify for orphan drug status. Similarly revise the risk factor titled "While we may in the future seek designations for our product candidates with the FDA, EMA and other comparable foreign regulatory authorities that are intended to confer benefits..." to identify other candidates that may qualify for programs providing for an accelerated regulatory pathway or regulatory excusivity.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 49 and 50 of Amendment No. 1 in response to the Staff's comment.

We currently depend and in the future may continue to depend on single or limited-source suppliers..., page 68

11. We note you currently depend on single and limited source suppliers. Please clarify whether you have supply agreements in place. If you do, please file such agreements as exhibits pursuant to Item 601(b)(10)(ii)(B) of Regulation S-K.

RESPONSE: The Company respectfully acknowledges the Staff's comment regarding single and limited source suppliers and advises the Staff that while it currently has agreements in place with third-party manufacturers, vendors and/or suppliers for certain components and raw materials used in the development of its product candidates, it does not believe that any of such agreements are required to be filed as exhibits pursuant to Item 601(b)(10) of Regulation S-K. Item 601(b)(10) states in relevant part that "if the contract is such as ordinarily accompanies the kind of business conducted by the registrant…it will be deemed to have been made in the ordinary course of business and need not be filed unless it [is] a contract upon which the registrant's business is substantially dependent, as in the case of continuing contracts to sell the major part of registrant's products or services or to purchase the major part of registrant's requirements of goods, services or raw materials or any franchise or license or other agreement to use a patent, formula, trade secret, process or trade name upon which registrant's business depends to a material extent."

The Company's existing supply agreements are contracts that ordinarily accompany the kind of business conducted by the Company and other similarly situated clinical-stage biotechnology companies. Additionally, the Company's business is not substantially dependent on agreements with any of its existing suppliers, individually or in the aggregate, as such suppliers do not provide a volume of materials or unique services that the Company could not replace in the event the relationship was terminated or such supplier was otherwise unable to perform its obligations. The Company also believes that the components obtained under these agreements are generally available upon comparable commercial terms from other suppliers with whom the Company can partner in lieu of its current arrangements with the existing suppliers. In most cases, the Company has not entered into long-term supply or ongoing agreements that dictate or bind the terms of its relationships with and reliance on these parties. Instead, the Company purchases various supplies under separate, standalone purchase orders, meaning that the Company is not committed to any supply agreements for a material amount of time. Additionally, the existing supply agreements only cover components and materials for the Company's Phase 1 clinical trial and do not extend into Phase 2 or beyond, and accordingly, the Company will not be relying on its current agreements beyond the Phase 1 clinical trial. The current supply agreements are also for low-volume production, intended for small clinical trials in which the Company will test different doses, formulations and formats (e.g., tablet or capsule). The commercial-ready format is yet to be determined, and once established, the Company plans to negotiate commercial supply agreements and consider secondary suppliers. Given these factors, the Company does not consider its existing supply agreements to be material in scope or amount, further supporting the conclusion that these agreements do not warrant filing under Item 601(b)(10)(ii)(B) of Regulation S-K.

For the reasons stated above, the Company respectfully advises the Staff that it does not plan to file the existing supply agreements as exhibits. However, should the Company enter into any future supply agreements, or if any of its existing supply agreements become material in a future period, the Company will file such agreements as exhibits to a subsequent amendment to the Draft Registration Statement, a registration statement, or a periodic report for the relevant reporting period.

We intend to rely on third parties to conduct, supervise and monitor our preclinical studies..., page 68

12. *We note your disclosure that if your relationships with your CROs terminates, you may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Please identify any CROs you are substantially dependent on and file agreements with these parties as exhibits to the registration statement. In an appropriate location in your registration statement, include descriptions of the material terms of these agreements.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it does not believe it is substantially dependent on any of the existing agreements with its current contract research organizations ("CROs"), either individually or in the aggregate.

In response to the Staff's comment regarding the filing of the Company's CRO agreements, the Company respectfully acknowledges the Staff's comment and advises the Staff that it does not believe that it has any CRO agreements that constitute material agreements under Item 601(b)(10) of Regulation S-K. Item 601(b)(10)(i) defines a "material contract" as follows: "Every contract not made in the ordinary course of business that is material to the registrant and is to be performed in whole or in part at or after the filing of the registration statement or report" and that was entered into not more than two years before such filing. In addition, Item 601(b)(10)(ii) provides that if a contract is one that ordinarily accompanies the kind of business conducted by the registrant and its subsidiaries, it will be deemed to have been made in the ordinary course of business and need not be filed unless, among other things, it is a contract "upon which the registrant's business is substantially dependent, as in the case of continuing contracts...to purchase the major part of [the] registrant's requirements of goods, services or raw materials...."

The Company's primary business consists of the discovery and development of novel small molecule medicines for the treatment of endocrinology, immunology and inflammation, and metabolic diseases. As is typical among similarly situated, small clinical-stage companies in the pharmaceutical and biotechnology industries, the Company is focused on the development of novel product development candidates and does not own or operate facilities for drug manufacturing, storage, distribution or quality testing or have the capability to produce such drugs in quantities necessary to submit applications to regulatory agencies and conduct clinical studies. Thus, to conduct certain research, pre-clinical and clinical testing activities, the Company, and similarly situated clinical-stage biotechnology companies, must contract with CROs, contract manufacturing organizations, third-party vendors, and suppliers to screen and test certain candidate molecules, bulk drug substances, drug products, raw materials, samples, components, or other materials and reports. Similar to arrangements used widely throughout the pharmaceutical and biotechnology industries, the existing CRO agreements reflect ordinary course service arrangements between the Company and CROs in support of its research and pre-clinical studies and clinical trials, pursuant to which specific projects are agreed to on a purchase order basis through statements of work. Moreover, such agreements with existing CROs are non-exclusive, may be cancelled or terminated by either party, with or without cause, and do not provide for any long-term contractual commitments or other terms which are individually or in the aggregate material to the business of the Company,

and the Company believes that there is no CRO with whom it works that could not be replaced. The Company also selects CROs for specific projects and activities, especially when specialized insights are required. The existing set of CROs may vary substantially from project to project. Furthermore, the Company has only recently initiated early clinical studies, and as a result it will be years before it commercializes a product candidate, and accordingly, any anticipated revenues associated with the activities to be performed under such CRO agreements are even further distant. As part of its overall risk management strategy, the Company continues to identify alternative CROs among the many in the marketplace and believes that it could enter into agreements and procure alternative service providers on a timely basis and on similar terms as its current CROs, if necessary and replacing a CRO would not substantively disrupt the process of ongoing clinical trials.

For the reasons stated above, the Company respectfully advises the Staff that it does not believe that it is "substantially dependent" on the existing CRO agreements to a material extent, and therefore, such agreements need not be filed as exhibits or disclosed in the registration statement pursuant to Item 601(b)(10)(ii)(B) of Regulation S-K.

Risks Related to Intellectual Property, page 69

13. *Please revise your discussion of risk relating to intellectual property to include a disclosure, as mentioned on page 157, that your proprietary Native Complex Platform is not patented. Specifically, discuss the additional risk associated with protecting this intellectual property with things such as confidentiality agreements in lieu of patent protection.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 78 of Amendment No. 1 in response to the Staff's comment.

Our insurance policies are expensive and only protect us from some business risks ..., page 95

14. *Please expand the discussion to identify commonly insured risks for which you are currently not carrying insurance coverage. To the extent that you are aware that you are maintaining a policy with a coverage amount that is less than adequate, please provide information about the risk and quantify the shortfall.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 92 of Amendment No. 1 in response to the Staff's comment. The Company is not aware of any instances where its current insurance policies provide inadequate coverage or have any shortfall.

Use of Proceeds, page 100

15. We note your intention to advance the development of your two lead product candidates with the proceeds of this offering. Please expand on this discussion to disclose how far along in the development process you expect to get with the proceeds of this offering.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 9 and 97 of Amendment No. 1 in response to the Staff's comment.

Management's Discussion and Analysis of Financial Condition and Results of Operations Critical Accounting Estimates, Significant Judgments and Use of Estimates Stock-based compensation, page 120

16. Once you have an estimated offering price or range, please explain to us how you determined the fair value of the common stock underlying your equity issuances and the reasons for any differences between the recent valuations of your common stock leading up to the initial public offering and the estimated offering price. This information will help facilitate our review of your accounting for equity issuances. Please discuss with the staff how to submit your response.

RESPONSE: The Company respectfully acknowledges the Staff's comment and undertakes that, once an estimated offering price is available, it will provide the Staff with a supplemental letter containing the fair value underlying its equity issuances and an analysis explaining the reasons for any differences between the Company's recent fair value determinations and the estimated offering price, if any.

Our Solution: Oral Small Molecule MRGPRX2 NAM, page 144

17. Please remove statements here and elsewhere that SEP-631 has the potential to be an "insurmountable" NAM. Given the development stage of this treatment, such statements appear to be premature and inappropriately assume regulatory approval at this stage.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 144 of Amendment No. 1 in response to the Staff's comment.

Our solution: Oral Small Molecule Single- and Multi-Incretin Receptor Agonists, page 153

18. Please include a textual description explaining what the table in Figure 14 is intended to convey.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 152 to 153 of Amendment No. 1 in response to the Staff's comment.

Government Regulation, page 159

19. We note that you have submitted a CTN in Australia to conduct your SEP-786 Phase 1 clincial trial. To the extent you are planning to seek approval of this candidate in Australia, please discuss the applicable review and approval process or clarify that it is not your intention to seek approval in Australia.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 142 of Amendment No. 1 in response to the Staff's comment.

Employees and Human Capital Resources, page 178

20. Please revise to quantify the number of full-time employees.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 40 and 177 of Amendment No. 1 in response to the Staff's comment.

Management, page 180

21. Please disclose where Ms. Sharp has been employed since October 2020.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that Ms. Sharp has not been employed since October 2020, and therefore has no employment history to disclose as would be required under Item 401 of the Securities Act.

Principal Stockholders, page 211

22. Please identify in a footnote to the table all natural persons who have voting and/or investment power over the shares held by Samsara BioCapital, L.P., Invus Public Equities, L.P., and Deep Track Biotechnology Master Fund, Ltd.

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 209 to 210 of Amendment No. 1 to include footnote numbering and will supplementally provide the requested information.

General

23. Please supplementally provide us with copies of all written communications, as defined in Rule 405 under the Securities Act, that you, or anyone authorized to do so on your behalf, present to potential investors in reliance on Section 5(d) of the Securities Act, whether or not they retain copies of the communications.

RESPONSE: The Company respectfully advises the Staff that it will provide the Staff, on a confidential basis under separate cover, copies of all written communications presented to potential investors in reliance on Section 5(d) of the Securities Act, whether or not they retain copies of such communications, and will provide any additional copies going forward.

If you should have any questions concerning the enclosed matters, please contact the undersigned at (212) 459-7072.

Enclosures

Sincerely,

/s/ Adam V. Johnson
Adam V. Johnson

cc: Jeffrey Finer, M.D., Ph.D., *Septerna, Inc.*
Liz Bhatt, M.S., M.B.A., *Septerna, Inc.*
Mitchell S. Bloom, *Goodwin Procter LLP*
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