Jeffrey Finer, M.D, Ph.D.
President and Chief Executive Officer
Septerna, Inc.
250 East Grand Avenue
South San Francisco, CA 94080

Re: Septerna, Inc.
Draft Registration Statement on Form S-1
Submitted on August 2, 2024
CIK No. 0001984086

Dear Jeffrey Finer M.D, Ph.D.:

We have reviewed your draft registration statement and have the following comments.

Please respond to this letter by providing the requested information and either submitting an amended draft registration statement or publicly filing your registration statement on EDGAR. If you do not believe a comment applies to your facts and circumstances or do not believe an amendment is appropriate, please tell us why in your response.

After reviewing the information you provide in response to this letter and your amended draft registration statement or filed registration statement, we may have additional comments.

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.

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

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.

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.

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

Employees and Human Capital Resources, page 178

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

Management, page 180

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

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.

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.

Please contact Ibolya Ignat at 202-551-3636 or Angela Connell at

202-551-3426 if you
have questions regarding comments on the financial statements and related
matters. Please
contact Tamika Sheppard at 202-551-8346 or Suzanne Hayes at 202-551-3675 with
any other
questions.

Sincerely,

Division of
Corporation Finance

Office of Life
Sciences