

PROSPECTUS

\$50,000,000



Common Stock

We have entered into a certain sales agreement, or the sales agreement, with Cowen and Company, LLC, or Cowen, relating to shares of our common stock offered by this prospectus. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$50.0 million from time to time through Cowen.

Our common stock is traded on the NASDAQ Global Market, or the Exchange, under the symbol "CLSD." On June 29, 2017, the last reported sale price of our common stock was \$9.36 per share.

Sales of our common stock, if any, under this prospectus may be made in sales deemed to be "at the market offerings" as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act. Cowen is not required to sell any specific number or dollar amount of securities, but will act as a sales agent using commercially reasonable efforts consistent with its normal trading and sales practices, on mutually agreed terms between Cowen and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

The compensation to Cowen for sales of common stock sold pursuant to the sales agreement will be an amount equal to up to 3.0% of the gross proceeds of any shares of common stock sold under the sales agreement. In connection with the sale of the common stock on our behalf, Cowen will be deemed to be an "underwriter" within the meaning of the Securities Act and the compensation of Cowen will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Cowen with respect to certain liabilities, including liabilities under the Securities Act or the Exchange Act of 1934, as amended, or the Exchange Act.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "[Risk Factors](#)" on page 7 of this prospectus and under similar headings in the other documents that are incorporated by reference into this prospectus.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS IS TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

Cowen

July 13, 2017.

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ABOUT THIS PROSPECTUS

This prospectus relates to the offering of our common stock. Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus, together with the information incorporated by reference as described under the headings “Where You Can Find More Information” and “Incorporation of Certain Information by Reference” in this prospectus. These documents contain important information that you should consider when making your investment decision.

This prospectus describes the terms of this offering of common stock and also adds to and updates information contained in the documents incorporated by reference into this prospectus. To the extent there is a conflict between the information contained in this prospectus, on the one hand, and the information contained in any document incorporated by reference into this prospectus that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus, on the other hand, you should rely on the information in this prospectus. If any statement in one of these documents is inconsistent with a statement in another document having a later date (for example, a document incorporated by reference into this prospectus) the statement in the document having the later date modifies or supersedes the earlier statement.

You should rely only on the information contained in or incorporated by reference in this prospectus and in any free writing prospectus that we have authorized for use in connection with this offering. We have not, and the sales agent has not, authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and the sales agent is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus, the documents incorporated by reference in this prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus, the documents incorporated by reference in this prospectus, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision.

Unless otherwise mentioned or unless the context requires otherwise, all references in this prospectus to “Clearside,” “company,” “we,” “us” and “our” or similar references refer to Clearside Biomedical, Inc.

PROSPECTUS SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus, including the information incorporated by reference in this prospectus, and the information included in any free writing prospectus that we have authorized for use in connection with this offering, including the information under the heading "Risk Factors" in this prospectus on page 5 and in the documents incorporated by reference into this prospectus.

Company Overview

We are a late-stage clinical biopharmaceutical company developing first-in-class drug therapies to treat blinding diseases of the eye. Our current product candidates focus on treatments for diseases affecting the retina and choroid, especially diseases associated with macular edema, and are injected into the suprachoroidal space, or SCS, using our proprietary SCS Microinjector. With the suprachoroidal injection procedure, our product candidates are more directly administered to the retina and choroid as compared to other ocular drug administration techniques such as intravitreal injections. We believe treatment of eye disease via suprachoroidal injection may provide a number of benefits, including lower frequency of necessary administration and faster onset of therapeutic effect. We hold the exclusive rights to develop and commercialize drugs for treatment via injection into the SCS. Our most advanced product candidates are based on commonly used ophthalmic drugs, which we believe will allow us to more efficiently and predictably pursue the regulatory approval of these product candidates under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

We are developing CLS-TA, our proprietary, preservative-free formulation of the corticosteroid triamcinolone acetonide, or TA, to be administered suprachoroidally for the treatment of patients with non-infectious uveitis. We are currently enrolling patients with macular edema associated with non-infectious uveitis in a pivotal Phase 3 clinical trial. We expect to enroll approximately 150 patients in this trial and to report data in early 2018. We believe, based on our end-of-Phase 2 review with the Food and Drug Administration, or FDA, in May 2015, that only one Clearside-sponsored, pivotal Phase 3 clinical trial will be required to support the filing of a New Drug Application, or NDA, to the FDA.

We are also developing CLS-TA along with an anti-VEGF agent for the treatment of macular edema associated with retinal vein occlusion, or RVO, a sight-threatening disorder resulting from the blockage of a retinal vein. We are exploring whether suprachoroidal injection of CLS-TA together with an intravitreal injection of Eylea, an inhibitor of vascular endothelial growth factor, or VEGF, can provide improved visual acuity, reduced macular edema and reduced injection frequency, as compared to administration of intravitreal Eylea alone.

We have completed a Phase 2 clinical trial in 46 patients with macular edema associated with RVO. In this trial, 23 patients in the active arm initially received a concomitant suprachoroidal injection of CLS-TA and an intravitreal injection of Eylea and 23 patients in the control arm initially received only an intravitreal injection of Eylea. The objective of the trial was to determine whether patients receiving CLS-TA together with Eylea could sustain this improved visual acuity over the three months of the clinical trial while requiring fewer additional Eylea treatments than patients receiving intravitreal Eylea alone. Patients in each arm were evaluated at months one, two and three after the initial treatment using pre-specified criteria to determine if they continued to experience macular edema or reductions in visual acuity and therefore required additional Eylea treatments. The primary objective of the trial was met, with patients in the active arm requiring an aggregate of 60% fewer additional Eylea treatments than patients in the control arm over three months, a result that was statistically significant ($p=0.013$). In addition, 18 of the 23 patients, or 78%, in the active arm of the trial did not require

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additional treatments during the three-month trial compared to 7 of the 23 patients, or 30%, in the control arm, a result that was also statistically significant ($p=0.003$). In the same Phase 2 trial, patients in the active arm experienced greater improvement in visual acuity than those in the control arm, with patients in the active arm experiencing mean BCVA improvements at months one, two and three of 16, 20 and 19 letters, respectively, compared to improvements of 11, 12 and 11 letters, respectively, in the control arm at the same time points. Based on the results of this trial and after incorporating feedback from an end-of-Phase 2 meeting with the FDA held in late 2016, we initiated a Phase 3 clinical program in the first quarter of 2017.

We have recently expanded our CLS-TA development programs to include another retinal vascular condition known as diabetic macular edema, or DME. In November 2016, we began enrolling patients with DME in an open-label, multi-center Phase 1/2 clinical trial to obtain safety data, and to observe efficacy outcomes from administering a combination of intravitreal Eylea and suprachoroidal CLS-TA, as well as suprachoroidal CLS-TA alone, over a six-month evaluation period. We completed enrollment of this trial in April 2017 and expect to release preliminary results in the second half of 2017. We also intend to commence a Phase 2 clinical trial in DME in mid-2017 to evaluate the safety and efficacy of administering a combination of intravitreal Eylea and suprachoroidal CLS-TA, as compared to intravitreal Eylea alone. We expect to report three-month preliminary data from this trial in the first half of 2018. We are also conducting preclinical studies of another product candidate for injection with our SCS Microinjector for the potential treatment of neovascular age-related macular degeneration, also known as wet AMD.

Risks Associated with our Business

Our business is subject to numerous risks and uncertainties, including those highlighted in the section titled “Risk Factors” immediately following this prospectus summary and those described under similar headings in the documents incorporated by reference into this prospectus. These risks include:

- We have incurred significant losses since our inception, expect to incur losses over the next several years and may never achieve or maintain profitability;
- Clinical drug development involves a lengthy and expensive process, with an uncertain outcome, and we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates;
- We rely, and expect to continue to rely, on third parties to conduct our clinical trials for our product candidates, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials;
- If the FDA does not conclude that our product candidates satisfy the requirements for the Section 505(b)(2) NDA regulatory approval pathway, or if the requirements under Section 505(b)(2) are not as we expect, the approval pathway for our product candidates will likely take significantly longer, cost significantly more and entail significantly greater complications and risks than anticipated, and in either case may not be successful;
- Our research and development efforts are focused on the development of product candidates for suprachoroidal injection, which is a novel approach to the treatment of eye diseases, and may fail to achieve and sustain market acceptance;
- If we are unable to establish sales, marketing and distribution capabilities for our product candidates, we may not be successful in commercializing those product candidates, if and when they are approved; and
- If we are unable to obtain and maintain patent protection for our technology and product candidates, or if our licensors are unable to obtain and maintain patent protection for the technology or product candidates that we license from them, or if the scope of the patent protection obtained is not

sufficiently broad, our competitors could develop and commercialize technology and drugs similar or identical to ours, and our ability to successfully commercialize our technology and product candidates may be impaired.

Corporate Information

We were incorporated under the laws of the State of Delaware in May 2011. Our principal executive offices are located at 900 North Point Parkway, Suite 200, Alpharetta, Georgia 30005. Our telephone number is (678) 270-3631. Our common stock is listed on the NASDAQ Global Market under the symbol "CLSD."

Our internet website address is www.clearsidebio.com. The information contained on our website is not incorporated by reference into this prospectus, and you should not consider any information contained on, or that can be accessed through, our website as part of this prospectus or in deciding whether to purchase our securities.

We have proprietary rights to a number of trademarks used in this prospectus which are important to our business, including Clearside®, SCS and the Clearside logo. Solely for convenience, the trademarks and trade names in this prospectus are referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. All other trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners.

Implications of Being an Emerging Growth Company

We qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. An emerging growth company may take advantage of relief from some of the reporting requirements and other burdens that are otherwise applicable generally to public companies. These provisions include:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements; and
- not being required to hold a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the June 1, 2021, (b) in which we have total annual gross revenue of at least \$1.07 billion or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700 million as of the prior June 30th and (2) the date on which we have issued more than \$1 billion in non-convertible debt during the prior three-year period. We may choose to take advantage of some but not all of these reduced burdens. For example, we have taken advantage of the reduced reporting requirements with respect to disclosure regarding our executive compensation arrangements, have presented only two years of

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audited financial statements and only two years of related “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure in our public filings, and have taken advantage of the exemption from auditor attestation on the effectiveness of our internal control over financial reporting. To the extent that we take advantage of these reduced burdens, the information that we provide stockholders may be different than you might obtain from other public companies in which you hold equity interests.

In addition, under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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THE OFFERING

Common Stock Offered By Us	Shares of our common stock having an aggregate offering price of up to \$50.0 million.
Manner of Offering	“At the market offering” that may be made from time to time through our sales agent, Cowen. See “Plan of Distribution” on page 18.
Use of Proceeds	We currently intend to use the net proceeds from this offering primarily to fund the research and development of the drug candidates in our pipeline and for working capital and general corporate purposes. See “Use of Proceeds” on page 9 of this prospectus.
Risk Factors	Investing in our common stock involves significant risks. See “Risk Factors” on page 7 of this prospectus, and under similar headings in other documents incorporated by reference into this prospectus.
NASDAQ Global Market Symbol	“CLSD”

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully review the risks and uncertainties described below and under the section titled “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2016 and in our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, as updated by our annual, quarterly and other reports and documents that are incorporated by reference into this prospectus, before deciding whether to purchase any of the securities being registered pursuant to the registration statement of which this prospectus is a part. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations. Please also read carefully the section below titled “Special Note Regarding Forward-Looking Statements.”

ADDITIONAL RISKS RELATED TO THIS OFFERING

You may experience dilution.

The offering price per share in this offering may exceed the net tangible book value per share of our common stock outstanding prior to this offering. Assuming that an aggregate of 5,341,880 shares of our common stock are sold at a price of \$9.36 per share, the last reported sale price of our common stock on the Exchange on June 29, 2017, for aggregate gross proceeds of \$50.0 million, and after deducting commissions and estimated offering expenses payable by us, you would experience immediate dilution of \$5.59 per share, representing the difference between our as adjusted net tangible book value per share as of March 31, 2017 after giving effect to this offering and the assumed offering price. The exercise of outstanding stock options would result in further dilution of your investment. See the section entitled “Dilution” below for a more detailed illustration of the dilution you would incur if you participate in this offering. Because the sales of the shares offered hereby will be made directly into the market or in negotiated transactions, the prices at which we sell these shares will vary and these variations may be significant. Purchasers of the shares we sell, as well as our existing shareholders, will experience significant dilution if we sell shares at prices significantly below the price at which they invested.

Our management might apply the net proceeds from this offering in ways with which you do not agree and in ways that may impair the value of your investment.

We currently intend to use the net proceeds from this offering primarily to fund the research and development of the drug candidates in our pipeline and for working capital and general corporate purposes. Pending these uses, we expect to invest the net proceeds in short-term, interest bearing obligations, certificates of deposit or direct or guaranteed obligations of the United States. Our management has broad discretion as to the use of these proceeds and you will be relying on the judgment of our management regarding the application of these proceeds. We might apply these proceeds in ways with which you do not agree, or in ways that do not yield a favorable return. If our management applies these proceeds in a manner that does not yield a significant return, if any, on our investment of these net proceeds, it could compromise our ability to pursue our growth strategy and adversely affect the market price of our common stock.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference contain forward-looking statements. These are based on our management's current beliefs, expectations and assumptions about future events, conditions and results and on information currently available to us. Discussions containing these forward-looking statements may be found, among other places, in the Sections entitled "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto, filed with the SEC.

Any statements in this prospectus, or incorporated herein, about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and are forward-looking statements. Within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act, these forward-looking statements include statements regarding:

- our plans to develop and commercialize our product candidates;
- our ongoing and planned clinical trials for our product candidates;
- the timing of the availability of data from our clinical trials;
- the timing of our planned regulatory filings;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- our expectation that CLS-TA, if approved, would be the first drug specifically indicated for macular edema associated with non-infectious uveitis;
- the clinical utility of our product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position;
- our ability to identify additional drug candidates with significant commercial potential that are compatible with suprachoroidal injection and which are consistent with our commercial objectives; and
- our estimates regarding future revenues, expenses and needs for additional financing.

In some cases, you can identify forward-looking statements by the words "may," "might," "can," "will," "to be," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "project," "potential," "likely," "continue" and "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future, although not all forward-looking statements contain these words. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements.

You should refer to the "Risk Factors" section contained in this prospectus and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus, for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Given these risks, uncertainties and other factors, many of which are beyond our control, we cannot assure you that the forward-looking statements in this prospectus will prove to be accurate, and you should not place undue reliance on these forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to revise any forward-looking statements to reflect events or developments occurring after the date of this prospectus, even if new information becomes available in the future.

USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate sales proceeds of up to \$50.0 million from time to time. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. There can be no assurance that we will sell any shares under or fully utilize the sales agreement with Cowen as a source of financing.

We currently intend to use the net proceeds from this offering primarily to fund the research and development of the drug candidates in our pipeline and for working capital and general corporate purposes. We may also use a portion of the net proceeds to invest in or acquire businesses or technologies that we believe are complementary to our own, although we have no current plans, commitments or agreements with respect to any acquisitions as of the date of this prospectus. Pending these uses, we expect to invest the net proceeds in short-term, interest bearing obligations, certificates of deposit or direct or guaranteed obligations of the United States.

DILUTION

Our net tangible book value as of March 31, 2017 was approximately \$67.2 million, or \$2.65 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of March 31, 2017. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the sale of 5,341,880 shares of our common stock in this offering at an assumed offering price of \$9.36 per share, the last reported sale price of our common stock on the Exchange on June 29, 2017, and after deducting estimated offering commissions and offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2017 would have been approximately \$115.4 million, or \$3.77 per share. This represents an immediate increase in net tangible book value of \$1.12 per share to existing stockholders and immediate dilution of \$5.59 per share to investors purchasing our common stock in this offering at the public offering price. The following table illustrates this dilution on a per share basis:

Assumed public offering price per share	\$9.36
Net tangible book value per share of as March 31, 2017	\$2.65
Increase in net tangible book value per share attributable to this offering	<u>\$1.12</u>
As adjusted net tangible book value per share as of March 31, 2017, after giving effect to this offering	<u>\$3.77</u>
Dilution per share to investors purchasing our common stock in this offering	<u>\$5.59</u>

The above discussion and table are based on 25,300,016 shares of our common stock outstanding as of March 31, 2017, and exclude:

- 2,179,092 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2017, at a weighted average exercise price of \$6.14 per share;
- 29,796 shares of our common stock issuable upon the exercise of a warrant outstanding as of March 31, 2017 at an exercise price of \$10.74 per share; and
- 2,120,951 shares of common stock reserved for future issuance under our equity incentive plans, plus any additional shares of our common stock that may become available under our equity incentive plans as a result of annual increases in the share reserves.

The table above assumes for illustrative purposes that an aggregate of 5,341,880 shares of our common stock are sold during the term of the sales agreement with Cowen at a price of \$9.36 per share, the last reported sale price of our common stock on the Exchange on June 29, 2017, for aggregate gross proceeds of \$50.0 million. The shares subject to the sales agreement with Cowen are being sold from time to time at various prices. An increase of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$9.36 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$50.0 million during the term of the sales agreement with Cowen is sold at that price, would increase our adjusted net tangible book value per share after the offering to \$3.83 per share and would increase the dilution in net tangible book value per share to new investors in this offering to \$6.53 per share, after deducting commissions and estimated aggregate offering expenses payable by us. A decrease of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$9.36 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$50.0 million during the term of the sales agreement with Cowen is sold at that price, would decrease our adjusted net tangible book value per share after the offering to \$3.69 per share and would decrease the dilution in net tangible book value per share to new investors in this offering to \$4.67 per share, after deducting commissions and estimated aggregate offering expenses payable by us. This information is supplied for illustrative purposes only.

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To the extent that outstanding options outstanding as of March 31, 2017 have been or may be exercised or other shares issued, investors purchasing our common stock in this offering may experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and provisions of our amended and restated certificate of incorporation and amended and restated bylaws are summaries. You should also refer to the amended and restated certificate of incorporation and the amended and restated bylaws, which are filed as exhibits to the registration statement of which this prospectus is part.

General

Our amended and restated certificate of incorporation authorizes us to issue up to 100,000,000 shares of common stock, \$0.001 par value per share, and 10,000,000 shares of preferred stock, \$0.001 par value per share, all of which shares of preferred stock were undesignated as of July 3, 2017. Our board of directors may establish the rights and preferences of the preferred stock from time to time.

Common Stock

Voting Rights

Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. Under our amended and restated certificate of incorporation and amended and restated bylaws, our stockholders do not have cumulative voting rights. Because of this, the holders of a majority of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they should so choose.

Dividends

Subject to preferences that may be applicable to any then-outstanding preferred stock, holders of common stock are entitled to receive ratably those dividends, if any, as may be declared from time to time by the board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock.

Rights and Preferences

Holders of common stock have no preemptive, conversion or subscription rights and there are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate in the future.

Preferred Stock

Pursuant to our amended and restated certificate of incorporation, our board of directors has the authority, without further action by the stockholders (unless such stockholder action is required by applicable law or stock exchange listing rules), to designate and issue up to 10,000,000 shares of preferred stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the designations, powers, preferences, privileges and relative participating, optional or special rights and the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, voting rights, terms of redemption and liquidation preferences, any or all of which may be greater than the rights of the common stock, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding.

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Our board of directors, without stockholder approval, can issue preferred stock with voting, conversion or other rights that could adversely affect the voting power and other rights of the holders of common stock. Preferred stock could be issued quickly with terms designed to delay or prevent a change in control of our company or make removal of management more difficult. Additionally, the issuance of preferred stock may have the effect of decreasing the market price of the common stock and may adversely affect the voting power of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation.

Our board of directors will fix the designations, voting powers, preferences and rights of the each series, as well as the qualifications, limitations or restrictions thereof, of the preferred stock of each series that we offer under this prospectus and applicable prospectus supplements in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. This description will include:

- the title and stated value;
- the number of shares we are offering;
- the liquidation preference per share;
- the purchase price per share;
- the dividend rate per share, dividend period and payment dates and method of calculation for dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- our right, if any, to defer payment of dividends and the maximum length of any such deferral period;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;
- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock or other securities of ours, including depositary shares and warrants, and, if applicable, the conversion period, the conversion price, or how it will be calculated, and under what circumstances it may be adjusted;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange period, the exchange price, or how it will be calculated, and under what circumstances it may be adjusted;
- voting rights, if any, of the preferred stock;
- preemption rights, if any;
- restrictions on transfer, sale or other assignment, if any;
- whether interests in the preferred stock will be represented by depositary shares;
- a discussion of any material or special U.S. federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;

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- any limitations on issuances of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock being issued as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and
- any other specific terms, rights, preferences, privileges, qualifications or restrictions of the preferred stock.

The Delaware General Corporation Law, the state of our incorporation, provides that the holders of preferred stock will have the right to vote separately as a class (or, in some cases, as a series) on an amendment to our certificate of incorporation if the amendment would change the par value or, unless the certificate of incorporation provided otherwise, the number of authorized shares of the class or change the powers, preferences or special rights of the class or series so as to adversely affect the class or series, as the case may be. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

Registration Rights

We and certain holders of shares of our common stock have entered into an investor rights agreement. The registration rights provisions of this agreement provide those holders with demand, piggyback and Form S-3 registration rights with respect to the shares of common stock currently held by them. Approximately 9.6 million shares of common stock are entitled to these registration rights.

Demand Registration Rights

The holders of at least 40% of the shares held by parties to the investor rights agreement in the aggregate have the right to demand that we file up to two Form S-1 registration statements, as long as the anticipated aggregate offering price, net of underwriting discounts and commissions, would exceed \$10.0 million. These registration rights are subject to specified conditions and limitations, including the right of the underwriters, if any, to limit the number of shares included in any such registration under specified circumstances. Upon such a request, we are required to effect the registration as soon as reasonably possible.

Piggyback Registration Rights

If we propose to register any of our securities under the Securities Act either for our own account or for the account of other stockholders, the parties to the investor rights agreement will each be entitled to notice of the registration and will be entitled to include their shares of common stock in the registration statement. These piggyback registration rights are subject to specified conditions and limitations, including the right of the underwriters to limit the number of shares included in any such registration under specified circumstances. All piggyback registration rights have been waived as they may apply to the filing of the registration statement of which this prospectus is a part.

Registration on Form S-3

The holders of at least 20% of the shares held by parties to the investor rights agreement are entitled to have their shares registered by us on a Form S-3 registration statement at our expense, provided that such requested registration has an anticipated aggregate offering price, net of underwriting discounts and commissions, of at least \$1.0 million and subject to other specified conditions and limitations.

Expenses of Registration

We will pay all expenses relating to any demand, piggyback or Form S-3 registration, other than underwriting discounts and commissions, subject to specified conditions and limitations.

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Termination of Registration Rights

The registration rights granted under the investor rights agreement will terminate upon the earliest to occur of (i) June 1, 2021, which is the fifth anniversary of the completion of our initial public offering or (ii) the closing of a liquidating event.

Anti-Takeover Provisions

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the Delaware General Corporation Law, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding, but not the outstanding voting stock owned by the interested stockholder, those shares owned (i) by persons who are directors and also officers and (ii) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines a “business combination” to include the following:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an “interested stockholder” as an entity or person who, together with the person’s affiliates and associates, beneficially owns, or within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation.

Certificate of Incorporation and Bylaws

Our amended and restated certificate of incorporation provides for our board of directors to be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. Because our stockholders do not have cumulative voting rights, stockholders holding a majority of the shares of common stock outstanding will be able to elect all of our directors. Our amended and restated certificate of incorporation and our amended and restated bylaws also provide that directors may be removed by the

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stockholders only for cause upon the vote of 66 2/3% or more of our outstanding common stock. Furthermore, the authorized number of directors may be changed only by resolution of the board of directors, and vacancies and newly created directorships on the board of directors may, except as otherwise required by law or determined by the board, only be filled by a majority vote of the directors then serving on the board, even though less than a quorum.

Our amended and restated certificate of incorporation and amended and restated bylaws also provide that all stockholder actions must be effected at a duly called meeting of stockholders and will eliminate the right of stockholders to act by written consent without a meeting. Our amended and restated bylaws also provide that only our chairman of the board, chief executive officer or the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors may call a special meeting of stockholders.

Our amended and restated bylaws also provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide timely advance notice in writing, and specify requirements as to the form and content of a stockholder's notice.

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the stockholders cannot amend many of the provisions described above except by a vote of 66 2/3% or more of our outstanding common stock.

The combination of these provisions make it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of us by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change our control.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to reduce our vulnerability to hostile takeovers and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of delaying changes in our control or management. As a consequence, these provisions may also inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts. We believe that the benefits of these provisions, including increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure our company, outweigh the disadvantages of discouraging takeover proposals, because negotiation of takeover proposals could result in an improvement of their terms.

Choice of Forum

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for:

- any derivative action or proceeding brought on our behalf;
- any action asserting a breach of fiduciary duty;
- any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our amended and restated certificate of incorporation, or our amended and restated bylaws; or
- any action asserting a claim against us that is governed by the internal affairs doctrine.

The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with any action, a court could find

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the choice of forum provisions contained in our amended and restated certificate of incorporation to be inapplicable or unenforceable in such action.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company. The transfer agent's address is 6201 15th Avenue, Brooklyn, NY 11219. The transfer agent for any series of preferred stock that we may offer under this prospectus will be named and described in the prospectus supplement for that series.

Listing on the NASDAQ Global Market

Our common stock is listed on the NASDAQ Global Market under the symbol "CLSD."

PLAN OF DISTRIBUTION

We have entered into a sales agreement with Cowen, under which we may issue and sell from time to time up to \$50,000,000 of our common stock through Cowen as our sales agent. Sales of our common stock, if any, will be made at market prices by any method that is deemed to be an “at the market offering” as defined in Rule 415 under the Securities Act. If authorized by us in writing, Cowen may also purchase shares of our common stock as principal.

Cowen will offer our common stock subject to the terms and conditions of the sales agreement on a daily basis or as otherwise agreed upon by us and Cowen. We will designate the maximum amount of common stock to be sold through Cowen on a daily basis or otherwise determine such maximum amount together with Cowen. Subject to the terms and conditions of the sales agreement, Cowen will use its commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us. We may instruct Cowen not to sell common stock if the sales cannot be effected at or above the price designated by us in any such instruction. Cowen or we may suspend the offering of our common stock being made through Cowen under the sales agreement upon proper notice to the other party. Cowen and we each have the right, by giving written notice as specified in the sales agreement, to terminate the sales agreement in each party’s sole discretion at any time.

The aggregate compensation payable to Cowen as sales agent equals up to 3.0% of the gross sales price of the shares sold through it pursuant to the sales agreement. We have also agreed to reimburse Cowen up to \$50,000 of Cowen’s actual outside legal expenses incurred by Cowen in connection with this offering, and for certain other expenses, including Cowen’s FINRA counsel fees in an amount up to \$12,500. We estimate that the total expenses of the offering payable by us, excluding commissions payable to Cowen under the sales agreement, will be approximately \$300,000.

The remaining sales proceeds, after deducting any expenses payable by us and any transaction fees imposed by any governmental, regulatory, or self-regulatory organization in connection with the sales, will equal our net proceeds for the sale of such common stock.

Cowen will provide written confirmation to us following the close of trading on the Nasdaq Global Market on each day in which common stock is sold through it as sales agent under the sales agreement. Each confirmation will include the number of shares of common stock sold through it as sales agent on that day, the volume weighted average price of the shares sold, the percentage of the daily trading volume and the net proceeds to us.

We will report at least quarterly the number of shares of common stock sold through Cowen under the sales agreement, the net proceeds to us and the compensation paid by us to Cowen in connection with the sales of common stock.

Settlement for sales of common stock will occur, unless the parties agree otherwise, on the third business day that is also a trading day following the date on which any sales were made in return for payment of the net proceeds to us. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

In connection with the sales of our common stock on our behalf, Cowen may be deemed to be an “underwriter” within the meaning of the Securities Act, and the compensation paid to Cowen may be deemed to be underwriting commissions or discounts. We have agreed in the sales agreement to provide indemnification and contribution to Cowen against certain liabilities, including liabilities under the Securities Act. As sales agent, Cowen will not engage in any transactions that stabilizes our common stock.

Our common stock is listed on the Nasdaq Global Market and trades under the symbol “CLSD.” The transfer agent of our common stock is American Stock Transfer & Trust Company, LLC.

Cowen and/or its affiliates have provided, and may in the future provide, various investment banking and other financial services for us for which services they have received and, may in the future receive, customary fees.

LEGAL MATTERS

The validity of the common stock offered by this prospectus will be passed upon by Cooley LLP, Reston, Virginia. Duane Morris LLP, Newark, New Jersey is counsel for Cowen in connection with this offering.

EXPERTS

The financial statements of Clearside Biomedical, Inc. appearing in Clearside Biomedical, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2016 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement we filed with the SEC. This prospectus does not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. You should rely only on the information contained in this prospectus or incorporated by reference. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front page of this prospectus, regardless of the time of delivery of this prospectus or any sale of the securities offered by this prospectus.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy the registration statement, as well as any other document filed by us with the SEC, at the SEC's Public Reference Room at 100 F Street NE, Washington, D.C. 20549. You can also request copies of these documents by writing to the SEC and paying a fee for the copying cost. You may obtain information on the operation of the Public Reference Room by calling the SEC at (800) SEC-0330. The SEC maintains a website that contains reports, proxy statements and other information regarding issuers that file electronically with the SEC, including Clearside Biomedical, Inc. The address of the SEC website is www.sec.gov.

We maintain a website at www.clearsidebio.com. Information contained in or accessible through our website does not constitute a part of this prospectus.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The SEC file number for the documents incorporated by reference in this prospectus is 001-37581. The documents incorporated by reference into this prospectus contain important information that you should read about us.

The following documents are incorporated by reference into this document:

- our Annual Report on Form 10-K for the year ended December 31, 2016, filed with the SEC on March 16, 2017;
- our Quarterly Report on Form 10-Q for the three months ended March 31, 2017 filed with the SEC on May 10, 2017;
- our Current Reports on Form 8-K filed with the SEC on February 27, 2017, March 8, 2017, June 22, 2017 and July 3, 2017, to the extent the information in such reports is filed and not furnished; and
- the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on May 20, 2016, including any amendments or reports filed for the purposes of updating this description.

We also incorporate by reference into this prospectus all documents (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items) that are filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (i) after the date of the initial filing of the registration statement of which this prospectus forms a part and prior to effectiveness of the registration statement, or (ii) after the date of this prospectus but prior to the termination of the offering. These documents include periodic reports, such as Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as proxy statements.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus but not delivered with the prospectus, including exhibits that are specifically incorporated by reference into such documents. You should direct any requests for documents to Clearside Biomedical, Inc., Attn: Corporate Secretary, 900 North Point Parkway, Suite 200, Alpharetta GA 30005; telephone: (678) 270-3631.

Any statement contained herein or in a document incorporated or deemed to be incorporated by reference into this document will be deemed to be modified or superseded for purposes of the document to the extent that a statement contained in this document or any other subsequently filed document that is deemed to be incorporated by reference into this document modifies or supersedes the statement.

\$50,000,000



Common Stock

Prospectus

Cowen

July 13, 2017
