





AMICUS THERAPEUTICS, INC.

Common Stock

The selling stockholders of Amicus Therapeutics, Inc. listed beginning on page 9, together with any additional selling stockholders listed in any applicable prospectus supplement, may offer and resell up to 5,921,771 shares of our common stock, par value \$0.01 per share. The selling stockholders acquired these shares from us in connection with our acquisition of Scioderm, Inc., or Scioderm, pursuant to the terms of (i) the Agreement and Plan of Merger, dated as of August 30, 2015, as amended on September 30, 2015, by and among Amicus Therapeutics, Inc., Titan Merger Sub Corp., Scioderm, Inc. and Fortis Advisors LLC, as Shareholders' Agent or (ii) the Additional Purchase Price Agreement, dated as of August 30, 2015, by and among Amicus Therapeutics, Inc. and all of the holders of Scioderm's Series B preferred stock.

We are not selling any shares of our common stock under this prospectus and we will not receive any of the proceeds from the sale of shares by the selling stockholders. The selling stockholders may sell the shares of common stock described in this prospectus through public or private transactions at market prices prevailing at the time of sale or at negotiated prices. We provide more information about how the selling stockholders may sell their shares of common stock in the section of this prospectus entitled "Plan of Distribution."

Our common stock is listed on the NASDAQ Global Market under the symbol "FOLD." On September 29, 2015, the last reported sale price for our common stock on the NASDAQ Global Market was \$12.96 per share.

Investing in our common stock involves a high degree of risk. Before investing, you should carefully consider the matters described under the caption "Risk Factors" beginning on page 4.

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.

The date of this prospectus is September 30, 2015.

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ABOUT THIS PROSPECTUS

This prospectus is part of an automatic shelf registration statement that we filed with the Securities and Exchange Commission (referred to as the SEC or the Commission) as a "well-known seasoned issuer" as defined in Rule 405 under the Securities Act of 1933, as amended (referred to as the Securities Act), utilizing a "shelf" registration process. Under this process, selling stockholders named in this prospectus or in one or more supplements to this prospectus may sell shares of common stock from time to time. Each time any selling stockholder not named herein sells shares of common stock under the registration statement of which this prospectus is a part, such selling stockholder will provide a copy of this prospectus and any applicable prospectus supplement, as required by law. Any applicable prospectus supplement may add, update, or change information contained in this prospectus.

The selling stockholders may offer and sell shares of common stock directly to purchasers, through agents selected by the selling stockholders, or to or through underwriters or dealers. A prospectus supplement, if required, may describe the terms of the plan of distribution and set forth the names of any agents, underwriters, or dealers involved in the sale of shares of common stock. See "Plan of Distribution."

You should read this prospectus together with any applicable prospectus supplement, as well as additional information described under the heading "Where You Can Find More Information." You should rely only on the information contained or incorporated by reference in this prospectus, any accompanying prospectus supplement and any applicable "free writing prospectus." We have not authorized, and no selling stockholder has authorized, anyone else to provide you with different or additional information. No offer of shares of common stock is being made in any jurisdiction where the offer or sale is not permitted.

You should not assume that the information in this prospectus, any accompanying prospectus supplement, or any document incorporated by reference herein or therein is accurate as of any date other than their respective dates. Our business, financial condition, results of operations, and prospects may have changed since those dates. You should carefully read the entire prospectus, as well as the documents incorporated by reference in the prospectus, any applicable prospectus supplement and any applicable "free writing prospectus" before making an investment decision.

References in this prospectus to the terms "the Company," "Amicus," "we," "our" and "us" or other similar terms mean Amicus Therapeutics, Inc. and our wholly owned subsidiaries, unless we state otherwise or the context indicates otherwise.

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus. This summary does not contain all information that you should consider before investing in our common stock. You should read the following summary together with the more detailed information regarding Amicus, the common stock being registered hereby, our financial statements and notes thereto and our risk factors, before deciding whether to purchase shares of our common stock from the selling stockholders.

Our Company

We are a biopharmaceutical company focused on the discovery, development and commercialization of next-generation medicines for a range of rare and orphan diseases, with a focus on improved therapies for lysosomal storage disorders ("LSDs"). Our lead product candidate is a small molecule that has completed late stage clinical trials to support the candidate being used as a monotherapy and in combination with enzyme replacement therapy ("ERT") for Fabry disease. Our development programs also include next-generation ERTs for LSDs, including Fabry disease, Pompe disease and Mucopolysaccharoidosis Type I ("MPS I"). We believe that our platform technologies and our advanced product pipeline uniquely position us at the forefront of developing therapies for rare and orphan diseases.

We were incorporated under the laws of the State of Delaware on February 4, 2002. Our principal executive offices are located at 1 Cedar Brook Drive, Cranbury NJ 08512 and our telephone number is (609) 662-2000. Our website address is www.amicusrx.com. We make available free of charge on our website our annual, quarterly and current reports, including amendments to such reports, as soon as reasonably practicable after we electronically file such material with, or furnish such material to, the SEC. Information contained on our website is not incorporated by reference into this prospectus, and you should not consider information contained on our website as part of this prospectus.

The Offering

Common stock offered by the selling stockholders	5,921,771 shares
Our common stock is listed on the NASDAQ Global Market under the symbol	FOLD
Use of proceeds	All of the shares of common stock being offered under this prospectus are being sold by the selling stockholders. Accordingly, we will not receive any proceeds from the sale of these shares.

Recent Developments

Scioderm Merger. On August 30, 2015, we entered into an Agreement and Plan of Merger (the "Merger Agreement"), by and among Amicus Therapeutics, Inc Titan Merger Sub Corp., Scioderm Inc. ("Scioderm") and Fortis Advisors LLC, as Shareholders' Agent. The Merger Agreement was amended on September 30, 2015 Pursuant to the terms of the Merger Agreement, on September 30, 2015, Titan Merger Sub Corp. merged with and into Scioderm, with Scioderm as the surviving corporation and our wholly-owned subsidiary.

Pursuant to the terms and subject to the conditions of Merger Agreement, at the closing Amicus paid holders of Scioderm's capital stock, options to purchase Scioderm's common stock, restricted stock units of Scioderm and warrants to purchase Scioderm's common stock (collectively, the "Effective Time Holders"), an amount equal to (i) \$220 million, plus (ii) the exercise price of all outstanding options and warrants to purchase Scioderm's common stock (which amounts are deducted from the merger

consideration payable to the applicable holders of Scioderm options and warrants), plus (iii) Scioderm's cash and cash equivalents (with an adjustment to account for closing working capital and Scioderm's fees and expenses (which Amicus will pay on Scioderm's behalf), which include employee bonuses and certain severance payments) (collectively, the "Initial Amount"). \$135,547,983.08 million of the Initial Amount was paid in cash and the remaining amount was paid in 5,689,623 shares of our common stock, the deemed value of such shares for the purpose of the transaction being based on a share price of \$14.93.

Amicus has also agreed to pay up to an additional \$350 million to Scioderm shareholders in cash or stock upon achievement of certain clinical and regulatory milestones and \$250 million to Scioderm shareholders in cash or stock upon achievement of certain sales milestones (collectively, the "Milestone Payments"). The Milestone Payments will be in cash, shares of Amicus's common stock, or a combination of both, at the election of Amicus. In addition to the Milestone Payments, if Amicus obtains a Rare Pediatric Disease Priority Review Voucher ("PRV") and sells or otherwise transfers such PRV to a third party, Amicus will pay to the Effective Time Holders an amount equal to the lesser of (i) \$100 million and (ii) 50% of the total proceeds from the PRV sale. If Amicus elects to retain the PRV for its own use, it will pay the Effective Time Holders \$100 million. Payment of the PRV proceeds will be in cash, to the extent it is sold for cash, and otherwise in cash, shares of Amicus's common stock, or a combination of both, at the election of Amicus. For purposes of paying the Milestone Payments and the PRV payment, the shares of Amicus's common stock will be valued based on the average closing prices for the five trading days prior to achievement of the milestone or consummation of the PRV sale, as applicable, and the five trading days including and following the achievement of the milestone or consummation of the PRV sale, as applicable.

Simultaneously with the execution and delivery of the Merger Agreement, on August 30, 2015, Amicus entered into an agreement with all of the holders of Scioderm's Series B preferred stock (the "Additional Purchase Price Agreement"), pursuant to which Amicus will make payments in the aggregate amount of up to \$27 million (pro rata based on the number of shares of Scioderm Series B preferred stock held, which is in addition to the payment of the Initial Amount and the Milestone Payments) directly to the holders of Scioderm's Series B preferred stock. Pursuant to the terms and subject to the conditions of the Additional Purchase Price Agreement, at the closing of the merger on September 30, 2015, Amicus paid \$5,512,180.23 in cash and delivered 232,148 shares of common stock to the holders of Scioderm's Series B preferred stock, and the remainder of such payments shall be made as and to the extent Milestone Payments are made.

In connection with the merger, each Effective Time Holder receiving stock consideration is required to enter into a lock-up agreement in order to receive shares of our common stock that among other things provides for a lock-up period of 30 days for one-third of the shares of our common stock issued in connection with the Initial Amount and 60 days for one-third of the shares of our common stock issued in connection with the Initial Amount. Under the terms of the Merger Agreement, we agreed to file with the SEC a registration statement on Form S-3 covering the resale of the shares of common stock received by the Effective Time Holders as part of the Initial Amount.

The foregoing is a summary of the material provisions of the Merger Agreement. This summary is not intended to be complete and is qualified in its entirety by reference to the Merger Agreement, which we filed with the SEC as an exhibit to our current report on Form 8-K dated as of August 30, 2015 and the amendment thereto, which we filed with the SEC as an exhibit to our current report on Form 8-K dated as of September 30, 2015. Our stockholders are not third-party beneficiaries under the Merger Agreement and should not rely on the representations, warranties and covenants or any descriptions thereof as characterizations of the actual state of facts or condition of Amicus, Scioderm or any of their respective subsidiaries.

Throughout this prospectus, when we refer to the shares of our common stock, the offer and sale of which are being registered on behalf of the selling stockholders, we are referring to the shares of common stock held by former holders of capital stock of Scioderm that we agreed to register pursuant to the Merger Agreement. When we refer to the "selling stockholders" in this prospectus, we are referring to former holders of capital stock of Scioderm.

RISK FACTORS

Investing in our securities involves risk. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed below and under the heading "Risk Factors" in any prospectus supplement, together with all of the other information contained or incorporated by reference in this prospectus or any prospectus supplement. You should also consider the risks, uncertainties and assumptions discussed under the heading "Risk Factors" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2014 filed on March 3, 2015, and on Form 10-Q for the period ended June 30, 2015, filed on August 5, 2015, with the Commission, which is incorporated herein by reference, and may be amended, supplemented or superseded from time to time by other reports we file with the Commission in the future. The risks and uncertainties we have described therein and below are not the only risks that we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations.

We may not realize all of the anticipated benefits of the acquisition of Scioderm.

The success of our acquisition of Scioderm will depend, in part, on our ability to realize the anticipated growth opportunities and synergies from combining the businesses of our company and Scioderm. Our ability to realize these benefits, and the timing of this realization, depend upon a number of factors and future events, many of which we and Scioderm, individually or collectively, cannot control. These factors and events include:

- integrating Scioderm's technology platform into our company;
- obtaining and maintaining patent rights relating to the Scioderm technology;
- effectively consolidating research and development operations;
- retaining and attracting key employees;
- consolidating corporate and administrative functions;
- the success of on-going or later clinical trials for Zorblisa;
- maintaining orphan drug market exclusivity; and
- minimizing the diversion of management's attention from ongoing business concerns.

We cannot assure you that any of the foregoing factors will not have an adverse effect on our business, financial condition and prospects.

Acquisitions involve risks, including inaccurate assessment of undisclosed, contingent or other liabilities or problems. Following the completion of the merger, the surviving corporation, which is now a wholly-owned subsidiary of our company, possesses not only all of the assets, but also all of the liabilities of Scioderm. It is possible that undisclosed, contingent or other liabilities or problems may arise in the future of which we were previously unaware. These undisclosed liabilities could have an adverse effect on our business, financial condition and prospects.

If the selling stockholders immediately sell our common stock received in the merger, they could cause our common stock price to decline.

The issuance of our common stock in connection with the Scioderm merger could have the effect of depressing the market price for our common stock, through dilution of earnings per share or otherwise. Once the registration statement, of which this prospectus is a part, is declared effective, all of the shares of common stock issued to the former security holders of Scioderm in connection with the closing of the merger will be available for resale in the public market, subject to certain lockup restrictions applicable to certain of such former security holders of Scioderm which will expire 30 days

after the closing date of the merger for one-third of the shares of our common stock issued at the closing and 60 days for one-third of the shares of our common stock issued in at the closing. One-third of the shares of our common stock issued at the closing are not subject to lockup and may be sold immediately.

In addition, many of the former security holders of Scioderm may decide not to hold the shares of our common stock they will receive in the merger. Other former security holders of Scioderm, such as funds with limitations on their permitted holdings of stock in individual issuers, may be required to sell the shares of our common stock that they receive in the merger. Such sales of our common stock could have the effect of depressing the market price for our common stock and may take place promptly following the merger and the expiration of the applicable lock-up periods. In addition, future events and conditions could increase the dilution that is currently projected, including adverse changes in market conditions, additional transaction and integration related costs and other factors such as the failure to realize some or all of the benefits anticipated in the merger. Any dilution of, or delay of any accretion to, our earnings per share could cause the price of shares of our common stock to decline or grow at a reduced rate. These sales may also make it more difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate to raise funds through future offerings of our common stock.

FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference herein contain, and any prospectus supplement and the documents incorporated therein may contain, forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, included in this prospectus, any prospectus supplement or the documents incorporated herein and therein by reference regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "will," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus and the documents incorporated herein by reference include, among other things, statements about:

- the progress and results of our clinical trials of our drug candidates, including migalastat HCl ("migalastat");
- the cost of manufacturing drug supply for our clinical and preclinical studies, including the significant cost of new enzyme replacement therapy ("ERT") cell line development and manufacturing as well as the cost of manufacturing Pompe ERT;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our product candidates including those testing the use of pharmacological chaperones co-formulated and co-administered with ERT and for the treatment of lysosomal storage diseases ("LSDs");
- the future results of on-going or later clinical trials for Zorblisa, including our ability to obtain regulatory approvals and commercialize Zorblisa and market acceptance of Zorblisa;
- the costs, timing and outcome of regulatory review of our product candidates;
- the number and development requirements of other product candidates that we pursue;
- the costs of commercialization activities, including product marketing, sales and distribution;
- the emergence of competing technologies and other adverse market developments;
- the costs of preparing, filing and prosecuting patent applications and maintaining, enforcing and defending intellectual property related claims;
- the extent to which we acquire or invest in businesses, products and technologies;
- our ability to successfully incorporate Scioderm and its products and technology into our business, including the possibility that the expected benefits of the transaction will not be fully realized by us or may take longer to realize than expected; and
- our ability to establish collaborations and obtain milestone, royalty or other payments from any such collaborators.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus, particularly under "Risk Factors," that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures, collaborations or investments we may make.

You should read this prospectus, any prospectus supplement and the documents that we incorporate by reference herein and therein completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements.

USE OF PROCEEDS

The selling stockholders will make offers and sales pursuant to this prospectus and any applicable prospectus supplement. We will not receive any proceeds from the sale or other disposition by the selling stockholders of the shares of our common stock covered hereby, or interests therein. The selling stockholders will pay any expenses incurred by the selling stockholders for brokerage, accounting, tax or legal services or any other expenses incurred by the selling stockholders in disposing of these shares. We will bear all other costs, fees and expenses incurred in effecting the registration of the shares covered by this prospectus, including, without limitation, all registration fees, listing fees of the NASDAQ Global Market and fees and expenses of our counsel and our accountants.

SELLING STOCKHOLDERS

We are registering for resale an aggregate of 5,921,771 shares of our common stock that may be sold by the selling stockholders set forth herein. Such shares include: (i) 5,689,623 shares of our outstanding common stock issued to the former stockholders of Scioderm in connection with the closing of the merger pursuant to the terms of the Merger Agreement and (ii) 232,148 shares of our outstanding common stock issued to the former Series B preferred stockholders of Scioderm in connection with the Additional Purchase Price Agreement.

Pursuant to Section 6.10 of the Merger Agreement, we agreed to file a registration statement with the Commission to register for resale the shares of our common stock that we issued at the closing as part of the consideration for the merger. We agreed to keep such registration statement effective until the earlier of (i) the date on which all such shares of common stock having been sold pursuant to an effective registration statement or (ii) at such time as none of shares of common stock held by the selling stockholders are restricted from transferring such common stock under Rule 144 under the Securities Act or any other rule of similar effect.

Beneficial ownership is determined in accordance with the rules of the Commission, and includes voting or investment power with respect to our common stock. To our knowledge, the selling stockholders have sole voting and investment power with respect to their respective shares of common stock, unless otherwise noted below.

The selling stockholders may sell some, all or none of their respective shares of common stock offered by this prospectus from time to time. We do not know how long the selling stockholders will hold their respective shares of common stock covered hereby before selling them. The selling stockholders have agreed, subject to certain exceptions, to limitations on their ability to sell shares through November 29, 2015. Other than the Merger Agreement and the agreements contemplated thereby, we currently have no agreements, arrangements or understandings with the selling stockholders regarding the sale of any of the shares of common stock being offered hereunder.

<u>Name of Selling Stockholder</u>	<u>Prior to the Offering</u>		<u>Number of Shares of Common Stock Being Registered for Resale(4)</u>	<u>After the Offering</u>	
	<u>Number of Shares of Common Stock Beneficially Owned</u>	<u>Percent of Shares of Common Stock Outstanding(3)</u>		<u>Number of Shares of Common Stock Beneficially Owned(5)</u>	<u>Percent of Shares of Common Stock Outstanding</u>
Morgenthaler Venture Partners IX, L.P.	1,783,948	1.43%	1,783,948	0	0
Technology Partners Fund VIII, LP(1)	1,776,334	1.43%	1,776,334	0	0
Redmile Entities(2)	8,180,733	6.55%	1,631,410	6,549,323	5.25%
John F. Crowley	273,005	*	25,087	247,918	*
All Other Selling Stockholders	706,292	*	704,992	1,300	*

* Less than 1%.

(1) Includes shares beneficially owned.

(2) Includes P Redmile Ltd., Redmile Capital Fund, LP, Redmile Capital Fund, Ltd., Redmile Capital Offshore Fund II, Ltd. and Redmile Special Opportunities Fund, Ltd.

(3) Based on 118,927,867 shares outstanding as of September 28, 2015 plus 5,921,771 shares issued pursuant to the acquisition of Scioderm.

(4) Represents the number of shares being registered on behalf of the selling stockholder pursuant to this registration statement, which may be less than the total number of shares beneficially owned by such selling stockholder.

- (5) Assumes that the selling stockholders dispose of all of the shares of common stock covered by this prospectus and do not acquire beneficial ownership of any additional shares. The registration of these shares does not necessarily mean that the selling stockholders will sell all or any portion of the shares covered by this prospectus.

Certain Relationships and Related Party Transactions

John F. Crowley, the Chairman and Chief Executive Officer of the Company, is also a director of Scioderm. Amicus' board of directors was afforded the opportunity to discuss the transaction with only the outside and independent directors of the board. Additionally, Mr. Crowley removed himself from all of Scioderm's board of director's discussions related to the transaction. Any profits made by Mr. Crowley in connection with the merger will be donated in full to Epidermolysis Bullosa foundations. Mr. Crowley did not personally benefit from the merger as a result of his position as a director of Scioderm.

Redmile Group, LLC beneficially owns approximately 6,549,323 shares of our common stock. P Redmile Ltd., Redmile Capital Fund, LP, Redmile Capital Fund, Ltd., Redmile Capital Offshore Fund II, Ltd. and Redmile Special Opportunities Fund, Ltd, affiliates of Redmile Group, LLC, together beneficially own approximately 5,499,877 shares of Scioderm common stock. These affiliates of Redmile Group, LLC will receive \$32,782,036.30 and 1,631,410 shares of our common stock as consideration pursuant to the Merger Agreement. The foregoing summary of the Merger Agreement is subject to, and qualified in its entirety by, the full text of the Merger Agreement, a copy of which we filed with the SEC as an exhibit to our current report on Form 8-K dated as of September 3, 2015, and the amendment thereto which we filed with the SEC as Exhibit 2.2 to our current report on Form 8-K dated as of September 30, 2015.

PLAN OF DISTRIBUTION

The selling stockholders and any of their pledgees, assignees and successors-in-interest may, from time to time in one or more transactions on NASDAQ or any other organized market where our shares of common stock may be traded, sell any or all of their shares of our common stock offered hereby through underwriters, dealers or agents, directly to one or more purchasers or through a combination of any such methods of sale. The selling stockholders may distribute the shares of our common stock offered hereby from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

The selling stockholders may use any one or more of the following methods when selling the shares offered hereby:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- one or more block trades in which the broker-dealer will attempt to sell such shares as agent or principal of all of such shares held by the selling stockholder;
- purchases by a broker-dealer as principal and resale by such broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- short sales;
- agreements between broker-dealers and the selling stockholder to sell a specified number of such shares at a stipulated price per share; and
- any other method permitted pursuant to applicable law.

If the selling stockholders effect such transactions by selling shares of common stock offered hereby to or through underwriters, broker-dealers or agents, such underwriters, broker-dealers or agents may receive commissions in the form of discounts, concessions or commissions from the selling stockholders or commissions from purchasers of the shares of common stock offered hereby for whom they may act as agent or to whom they may sell as principal (which discounts, concessions or commissions as to particular underwriters, broker-dealers or agents may be in excess of those customary in the types of transactions involved). In connection with sales of the shares of common stock offered hereby or otherwise, the selling stockholders may enter into hedging transactions with broker-dealers, which may in turn engage in short sales of the shares of common stock offered hereby in the course of hedging in positions they assume. The selling stockholders may also sell shares of common stock offered hereby short and deliver shares of common stock covered by this prospectus to close out short positions and to return borrowed shares in connection with such short sales. The selling stockholders may also loan or pledge shares of common stock offered hereby to broker-dealers that in turn may sell such shares.

The selling stockholders may pledge or grant a security interest in some or all of the shares of common stock offered hereby and owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell such shares of common stock from time to time pursuant to this prospectus or any amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act, amending, if necessary, the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling

stockholders under this prospectus. The selling stockholders also may transfer and donate the shares of common stock offered hereby in other circumstances, in which case the transferees, donees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

The selling stockholders and any broker-dealer participating in the distribution of the shares of common stock offered hereby may be deemed to be "underwriters" within the meaning of the Securities Act, and any commission paid, or any discounts or concessions allowed to, any such broker-dealer may be deemed to be underwriting commissions or discounts under the Securities Act. At the time a particular offering of the shares of common stock offered hereby is made, a prospectus supplement, if required, will be distributed which will set forth the aggregate amount of shares of common stock being offered and the terms of the offering, including the name or names of any broker-dealers or agents, any discounts, commissions and other terms constituting compensation from the selling stockholders and any discounts, commissions or concessions allowed or reallocated or paid to broker-dealers.

Under the securities laws of some states, the shares of common stock offered hereby may be sold in such states only through registered or licensed brokers or dealers. In addition, in some states the shares of common stock offered hereby may not be sold unless such shares have been registered or qualified for sale in such state or an exemption from registration or qualification is available and is complied with.

There can be no assurance that the selling stockholders will sell any or all of the shares of common stock registered pursuant to the registration statement of which this prospectus forms a part.

The selling stockholders and any other person participating in such distribution will be subject to applicable provisions of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and the rules and regulations thereunder, including, without limitation, Regulation M of the Exchange Act, which may limit the timing of purchases and sales of any of the shares of common stock offered hereby by the selling stockholders and any other participating person. Regulation M may also restrict the ability of any person engaged in the distribution of the shares of common stock offered hereby to engage in market-making activities with respect to the shares of common stock offered hereby. All of the foregoing may affect the marketability of the shares of common stock offered hereby and the ability of any person or entity to engage in market-making activities with respect to the shares of common stock offered hereby.

Once sold under the registration statement, of which this prospectus forms a part, the shares of common stock offered hereby will be freely tradable in the hands of persons other than our affiliates.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the Commission. You may read and copy information filed by us with the Commission at the Commission's public reference section, 100 F Street, N.E., Washington, D.C. 20549. Information regarding the operation of the public reference section can be obtained by calling 1-800-SEC-0330. The Commission also maintains an Internet site at <http://www.sec.gov> that contains reports, statements and other information about issuers, such as us, who file electronically with the Commission. We maintain an Internet site at <http://www.amicusrx.com>. However, the information on our Internet site is not incorporated by reference in this prospectus and any prospectus supplement and you should not consider it a part of this prospectus or any accompanying prospectus supplement.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The Commission allows us to "incorporate by reference" into this prospectus the information in other documents that we file with it. This means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be a part of this prospectus, and information in documents that we file later with the Commission will automatically update and supersede information contained in documents filed earlier with the Commission or contained in this prospectus. We incorporate by reference in this prospectus (i) the documents listed below, (ii) all documents that we file with the Commission under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of the initial filing of the registration statement of which this prospectus is included and prior to the effectiveness of such registration statement, and (iii) any future filings that we may make with the Commission under Sections 13(a), 13(c), 14, or 15(d) of the Exchange Act prior to the termination of the offering under this prospectus; provided, however, that we are not incorporating, in each case, any documents or information deemed to have been furnished and not filed in accordance with Commission rules (including Items 2.02 and 7.01 of Form 8-K):

- Our Annual Report on Form 10-K for the year ended December 31, 2014 filed with the SEC on March 3, 2015;
- Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 filed with the SEC on May 5, 2015;
- Our Quarterly Report on Form 10-Q for the quarter ended June 30, 2015 filed with the SEC on August 5, 2015;
- Our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 29, 2015, to the extent incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2014;
- Our Current Reports on Form 8-K filed with the SEC on January 12, 2015, January 15, 2015, February 27, 2015, April 13, 2015, April 28, 2015, May 19, 2015, June 4, 2015, June 10, 2015, August 31, 2015 and September 3, 2015; September 14, 2015; and September 30, 2015;
- The description of our common stock contained in our registration statement on Form 8-A (File No. 001-33497) filed on May 23, 2007, under the Exchange Act, including any amendment or report filed for the purpose of updating such description.

You may obtain a copy of any or all of the documents referred to above which may have been or may be incorporated by reference into this prospectus, except for exhibits to those documents (unless the exhibits are specifically incorporated by reference into those documents) at no cost to you by writing or telephoning us at the following address: Office of the Corporate Secretary, Amicus Therapeutics, Inc., 1 Cedar Brook Drive, Cranbury, NJ 08512, telephone (609) 662-2000.

LEGAL MATTERS

The validity of the shares of common stock offered by this prospectus has been passed upon for us by Skadden, Arps, Slate, Meagher & Flom LLP, Chicago, Illinois.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2014 and the effectiveness of our internal control over financial reporting as of December 31, 2014, as set forth in their reports, which are incorporated by reference in the prospectus and elsewhere in this registration statement. Our consolidated financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

The consolidated financial statements of Scioderm, Inc. appearing in Amicus Therapeutics, Inc.'s Current Report on Form 8-K dated September 30, 2015 have been audited by Ernst & Young LLP, independent auditors, as set forth in their report thereon included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

PART II
INFORMATION NOT REQUIRED IN THE PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution.

Set forth below is an estimate (except in the case of the registration fee) of the amount of fees and expenses to be incurred in connection with the issuance and distribution of the offered securities registered hereby, other than underwriting discounts and commissions, if any, incurred in connection with the sale of the offered securities. All such amounts will be borne by Amicus.

SEC Registration Fee	\$ 9,096.81
Legal Fees and Expenses	\$ 25,000
Accounting Fees and Expenses	\$ 30,000
Miscellaneous Fees and Expenses	\$ 10,000
Total:	<u>\$ 74,096.81</u>

Item 15. Indemnification of Directors and Officers.

Section 102 of the Delaware General Corporation Law permits a corporation to eliminate the personal liability of directors of a corporation to the corporation or its stockholders for monetary damages for a breach of fiduciary duty as a director, except where the director breached his or her duty of loyalty, failed to act in good faith, engaged in intentional misconduct or knowingly violated a law, authorized the payment of a dividend or approved a stock repurchase in violation of Delaware corporate law or obtained an improper personal benefit. The registrant's restated certificate of incorporation provides that no director of the registrant shall be personally liable to it or its stockholders for monetary damages for any breach of fiduciary duty as director, notwithstanding any provision of law imposing such liability, except to the extent that the Delaware General Corporation Law prohibits the elimination or limitation of liability of directors for breaches of fiduciary duty.

Section 145 of the Delaware General Corporation Law provides that a corporation has the power to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that the person is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees), judgments, fines and amounts paid in settlements actually and reasonably incurred by the person in connection with an action, suit or proceeding to which he or she is or is threatened to be made a party by reason of such position, if such person acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the best interests of the corporation, and, in any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful, except that, in the case of actions brought by or in the right of the corporation, no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Delaware Court of Chancery or other adjudicating court determines that, despite the adjudication of liability but in view of all of the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Delaware Court of Chancery or such other court shall deem proper.

The registrant's restated certificate of incorporation provides that the registrant will, to the fullest extent permitted by Section 145 of the Delaware General Corporation Law and the registrant's by-laws (each as amended from time to time), indemnify each person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that he or she is or was, or has agreed to become, a director or officer of the registrant, or is or was serving, or has agreed to serve, at the request of the registrant, as a director, officer, partner, or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise, including any employee benefit plan (all such persons being referred to hereafter as an "Indemnitee"), or by reason of any

action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by, or on behalf of, the Indemnitee in connection with such action, suit or proceeding and any appeal therefrom. Such indemnification may include payment by the registrant of expenses in defending an action or proceeding in advance of the final disposition of such action or proceeding upon receipt of an undertaking by the Indemnitee (such undertaking acceptable by the registrant without reference to the financial ability of the Indemnitee) to repay such payment if it is ultimately determined that the Indemnitee is not entitled to indemnification under the registrant's restated certificate of incorporation; however, the registrant will not indemnify any person seeking indemnification in connection with a proceeding (or part thereof) initiated by such person, unless such initiation was approved by the registrant's board of directors. Also, the indemnification rights provided in the registrant's restated certificate of incorporation (i) are not exclusive of any other rights to which those indemnified may be entitled under any law, agreement or vote of stockholders or disinterested directors or otherwise, and (ii) will inure to the benefit of the heirs, executors and administrators of such persons. The registrant may, to the extent authorized from time to time by its board of directors, grant indemnification rights to other employees of the registrant or other persons serving the registrant and such rights may be equivalent to, or greater or less than, those set forth in the registrant's restated certificate of incorporation.

The registrant has entered into indemnification agreements with each of its directors. These agreements require the registrant to, among other things, indemnify each director to the fullest extent permitted by Delaware law, including indemnification of expenses such as attorneys' fees, judgments, fines and settlement amounts incurred by the director in any action or proceeding, including any action or proceeding by or in right of the registrant, arising out of the person's services as a director.

The registrant maintains a general liability insurance policy that covers certain liabilities of the registrant's directors and officers arising out of claims based on acts or omissions in their capacities as directors or officers. In any underwriting agreement that the registrant enters into in connection with the sale of common stock being registered hereby, the underwriters will agree to indemnify, under certain conditions, the registrant, its directors, its officers and persons who control the registrant within the meaning of the Securities Act, against certain liabilities.

Item 16. Exhibits

A list of exhibits filed herewith is contained in the exhibit index that immediately precedes such exhibits and is incorporated herein by reference.

Item 17. Undertakings.

The undersigned registrant hereby undertakes:

(1) to file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement: (i) to include any prospectus required by Section 10(a)(3) of the Securities Act; (ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and (iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement; *provided, however*, that paragraphs (i), (ii) and (iii) do not apply if the registration statement is on Form S-3 and the

information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to Section 13 or Section 15(d) of the Exchange Act that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement;

(2) that, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof;

(3) to remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering; and

(4) that, for the purpose of determining liability under the Securities Act to any purchaser: (A) each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and (B) each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5) or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii) or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which the prospectus relates, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof; *provided, however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Exchange Act that is incorporated by reference in this registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the provisions described under Item 15 above, or otherwise, the registrant has been advised that in the opinion of the Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<hr/> <i>/s/ ROBERT ESSNER</i>		
Robert Essner	Director	September 30, 2015
<hr/> <i>/s/ DONALD J. HAYDEN, JR.</i>		
Donald J. Hayden, Jr.	Director	September 30, 2015
<hr/> <i>/s/ TED W. LOVE, M.D.</i>		
Ted W. Love, M.D.	Director	September 30, 2015
<hr/> <i>/s/ MARGARET G. MCGLYNN, R.PH.</i>		
Margaret G. McGlynn, R.Ph.	Director	September 30, 2015
<hr/> <i>/s/ MICHAEL G. RAAB</i>		
Michael G. Raab	Director	September 30, 2015
<hr/> <i>/s/ GLENN SBLENDORIO</i>		
Glenn Sblendorio	Director	September 30, 2015

EXHIBIT INDEX

<u>Exhibit</u>	<u>Description</u>
2.1	Agreement and Plan of Merger, dated August 30, 2015, by and among Amicus Therapeutics, Inc., Titan Merger Sub Corp., Scioderm, Inc. and Fortis Advisors LLC, as Shareholders' Agent (incorporated by reference to Exhibit 2.1 of the registrant's Current Report on Form 8-K filed with the Commission on September 3, 2015)
2.2	Amendment to Agreement and Plan of Merger, dated September 30, 2015, by and among Amicus Therapeutics, Inc., Titan Merger Sub Corp., Scioderm, Inc., Fortis Advisors LLC, as Shareholders' Agent and certain shareholders of Scioderm, Inc. (incorporated by reference to Exhibit 2.2 of the registrant's Current Report on Form 8-K filed with the Commission on September 30, 2015)
3.1	Restated Certificate of Incorporation of the registrant (incorporated by reference to Exhibit 3.1 of the registrant's Annual Report on Form 10-K filed with the Commission on February 28, 2012)
3.2	Certificate of Amendment to the Restated Certificate of Incorporation of the registrant (incorporated by reference to Exhibit 3.1 of the registrant's Current Report on Form 8-K filed with the Commission on June 10, 2015)
3.3	Restated By-laws of the of the registrant (incorporated by reference to Exhibit 3.4 of the registrant's Registration Statement on Form S-1/A (Registration No. 333-141700), as amended, originally filed with the Commission on April 27, 2007)
4.1	See Exhibits 3.1, 3.2 and 3.3 for instruments defining rights of holders of common stock
4.2	Specimen Stock Certificate evidencing shares of common stock (incorporated by reference to Exhibit 4.1 of the registrant's Registration Statement on Form S-1/A (Registration No. 333-141700), as amended, originally filed with the Commission on May 17, 2007)
5.1	Opinion of Skadden, Arps, Slate, Meagher & Flom LLP (filed herewith)
23.1	Consent of Skadden, Arps, Slate, Meagher & Flom LLP (included in Exhibit 5.1)
23.2	Consent of Ernst & Young LLP (filed herewith)
23.3	Consent of Ernst & Young LLP (filed herewith)
24.1	Power of attorney (included on the signature page hereto)

[Letterhead of Skadden, Arps, Slate, Meagher & Flom LLP]

September 30, 2015

Amicus Therapeutics, Inc.
1 Cedar Brook Drive
Cranbury, NJ 08512

RE: Amicus Therapeutics, Inc.
Registration Statement on Form S-3

Ladies and Gentlemen:

We have acted as special counsel to Amicus Therapeutics, Inc., a Delaware corporation (the "*Company*"), in connection with the automatic shelf registration statement on Form S-3 (the "*Registration Statement*") to be filed on the date hereof by the Company with the U.S. Securities and Exchange Commission (the "*Commission*") under the Securities Act of 1933, as amended (the "*Act*"). The Registration Statement relates to the offer and sale from time to time by certain stockholders of the Company (the "*Selling Stockholders*"), pursuant to Rule 415 of the General Rules and Regulations promulgated under the Act, of up to 5,921,771 shares (the "*Shares*") of Common Stock, par value \$0.01 per share (the "*Common Stock*"), of the Company.

This opinion is being furnished in accordance with the requirements of Item 601(b)(5) of Regulation S-K under the Act.

In rendering the opinions stated herein, we have examined and relied upon the following:

- (1) the Registration Statement;
- (2) a copy of the Restated Certificate of Incorporation of the Company, as amended to the date hereof and currently in effect, certified by the Secretary of State of the State of Delaware and the Assistant Corporate Secretary of the Company (the "*Certificate of Incorporation*");
- (3) a copy of the Restated By-laws of the Company, as amended to the date hereof and currently in effect, certified by the Assistant Corporate Secretary of the Company (the "*By-laws*");
- (4) a copy of certain resolutions adopted by the board of directors of the Company (the "*Board of Directors*") thereof relating to the registration of the Shares and related matters, adopted on August 27, 2015;
- (5) the Agreement and Plan of Merger, dated August 30, 2015 (as amended on September 30, 2015), by and among the Company, Scioderm, Inc. and the other parties named therein (the "*Merger Agreement*"); and
- (6) a specimen certificate evidencing the Common Stock.

We have also examined originals or copies, certified or otherwise identified to our satisfaction, of such records of the Company and such agreements, certificates and receipts of public officials, certificates of officers or other representatives of the Company and others, and such other documents as we have deemed necessary or appropriate as a basis for the opinions stated below.

In our examination, we have assumed the genuineness of all signatures, including endorsements, the legal capacity and competency of all natural persons, the authenticity of all documents submitted to us as originals, the conformity to original documents of all documents submitted to us as facsimile, electronic, certified or photostatic copies, and the authenticity of the originals of such copies. In making our examination of executed documents or documents to be executed, we have assumed that the parties thereto, other than the Company, had or will have the power, corporate or other, to enter into and perform all obligations thereunder and have also assumed the due authorization by all requisite action, corporate or other, and the execution and delivery by such parties of such documents and, as to parties other than the Company, the validity and binding effect thereof on such parties.

As to any facts relevant to the opinions stated herein that we did not independently establish or verify, we have relied upon statements and representations of officers and other representatives of the Company and others and of public officials. We have also assumed that the Company received consideration for the Shares pursuant to the Merger Agreement.

We do not express any opinion with respect to the laws of any jurisdiction other than the General Corporation Law of the State of Delaware (the "*DGCL*") and, to the extent that judicial or regulatory orders or decrees or consents, approvals, licenses, authorizations, validations, filings, recordings or registrations with governmental authorities are relevant, to those required under such laws (all of the foregoing being referred to as "*Opined on Law*"). We do not express any opinion with respect to the law of any jurisdiction other than *Opined on Law* or as to the effect of any such non-*Opined on Law* on the opinions herein stated.

Based upon the foregoing and subject to the qualifications and assumptions stated herein, we are of the opinion that with respect to any Shares to be offered by the Selling Stockholders pursuant to the Registration Statement, the Shares have been duly authorized by all corporate action on the part of the Company and were validly issued and are fully paid and nonassessable.

We hereby consent to the filing of this opinion with the Commission as an exhibit to the Registration Statement. We also hereby consent to the reference to our firm under the heading "Legal Matters" in the prospectus which forms a part of the Registration Statement. In giving this consent, we do not thereby admit that we are within the category of persons whose consent is required under Section 7 of the Act or the rules and regulations of the Commission promulgated thereunder. This opinion is expressed as of the date hereof unless otherwise expressly stated, and we disclaim any undertaking to advise you of any subsequent changes in the facts stated or assumed herein or of any subsequent changes in applicable laws.

Very truly yours,

/s/ Skadden, Arps, Slate, Meagher & Flom LLP

QuickLinks

[Exhibit 5.1](#)

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3 No. 333-00000) and related Prospectus of Amicus Therapeutics, Inc. for the registration of 5,921,771 shares of its common stock and to the incorporation by reference therein of our reports dated March 3, 2015, with respect to the consolidated financial statements of Amicus Therapeutics, Inc. and the effectiveness of internal controls over financial reporting of Amicus Therapeutics, Inc., included in its Annual Report (Form 10-K) for the year ended December 31, 2014, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

MetroPark, New Jersey
September 30, 2015

QuickLinks

[Exhibit 23.2](#)

[CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM](#)

CONSENT OF INDEPENDENT AUDITORS

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3) and related Prospectus of Amicus Therapeutics, Inc. for the registration of 5,921,771 shares of its common stock and to the incorporation by reference therein of our report dated August 21, 2015, with respect to the consolidated financial statements of Scioderm, Inc., included in Amicus Therapeutics, Inc.'s Current Report on Form 8-K dated September 30, 2015, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

Raleigh, North Carolina
September 30, 2015

QuickLinks

[Exhibit 23.3](#)

[CONSENT OF INDEPENDENT AUDITORS](#)