Filed Pursuant to Rule 424(b)(5)
Registration No. 333-238948

Prospectus Supplement
(To Prospectus dated June 15, 2020)

3,000,000 Shares

Common Stock

We are offering 3,000,000 shares of our common stock, par value $0.0001 per share. Our common stock is listed on The Nasdaq Global Market under the trading symbol "APLT." On February 9, 2021, the last reported price of our common stock was $28.65 per share.

We are an "emerging growth company" as that term is used in the Jumpstart Our Business Startups Act of 2012 and, as such, have elected to comply with certain reduced public company reporting requirements for the prospectus supplement and future filings.

Investing in our common stock involves a number of risks. See "Risk Factors" on page S-11 of this prospectus supplement and the risk factors described in the documents that we file with the Securities and Exchange Commission that are incorporated herein by reference for a discussion of certain risks you should consider before deciding to invest in our common stock.

	Per Share	Total
Public offering price	$23.00	$69,000,000
Underwriting discounts and commissions[(1)]	$ 1.38	$ 4,140,000
Proceeds, before expenses, to us	$21.62	$64,860,000

(1) We have agreed to reimburse the underwriters for certain FINRA-related expenses. See "Underwriting" for a description of the compensation payable to the underwriters.

We have granted the underwriters an option to purchase up to an additional 450,000 shares of our common stock at the public offering price, less the underwriting discounts and commissions, for a period of 30 days following the date of this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved these securities or determined if this prospectus supplement or the accompanying prospectus is accurate or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares to purchasers on or about February 17, 2021.

Joint Book Running Managers

Goldman Sachs & Co. LLC **Cowen** **UBS Investment Bank**

Lead Manager

Baird

Prospectus supplement dated February 11, 2021

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document contains two parts. The first part is this prospectus supplement, which describes the specific terms of this offering and the securities offered hereby, and also adds to and updates information contained in the accompanying prospectus and the documents incorporated into each by reference. The second part, the accompanying prospectus, gives more general information about us, some of which may not apply to this offering. This prospectus supplement is deemed to be incorporated by reference into the accompanying prospectus solely for the purpose of this offering. When we refer only to the "prospectus," we are referring to both parts combined.

If there is any inconsistency between information in or incorporated by reference into the accompanying prospectus and information in or incorporated by reference into this prospectus supplement, the information contained in the most recently dated document shall control. This prospectus supplement, the accompanying prospectus and the documents incorporated into each by reference include important information about us, the common stock being offered and other information you should know before investing. You should read this prospectus supplement and the accompanying prospectus together with the additional information described under the heading "Where You Can Find More Information" before investing in our common stock.

Neither we nor the underwriters have authorized anyone to provide any information or to make any representations other than those contained in this prospectus supplement, the accompanying prospectus or in any free writing prospectuses prepared by or on behalf of us or to which we have referred you. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement is not an offer to sell or solicitation of an offer to buy these securities in any circumstances under which the offer or solicitation is unlawful. We are offering to sell, and seeking offers to buy, our securities offered hereby only in jurisdictions where offers and sales are permitted. You should not assume that the information we have included in this prospectus supplement or the accompanying prospectus is accurate as of any date other than the date of this prospectus supplement or the accompanying prospectus, respectively, or that any information we have incorporated by reference is accurate as of any date other than the date of the document incorporated by reference, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any of our securities. Our business, financial condition, results of operations and prospects may have changed since those dates.

"Applied Therapeutics," the Applied Therapeutics logo and other trademarks, trade names or service marks of Applied Therapeutics, Inc. appearing in this prospectus supplement and the accompanying prospectus are the property of Applied Therapeutics, Inc. All other trademarks, trade names and service marks appearing in this prospectus supplement and the accompanying prospectus are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus supplement and the accompanying prospectus may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert their rights thereto.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC under the Securities Exchange Act of 1934, or the Exchange Act. Our SEC filings are available to the public at the SEC's website at www.sec.gov.

The SEC allows us to "incorporate by reference" information into this prospectus supplement and the accompanying prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus supplement and the accompanying prospectus, except for any information superseded by information contained directly in this prospectus supplement and the accompanying prospectus, any subsequently filed document deemed incorporated by reference or any free writing prospectus prepared by or on behalf of us. This prospectus supplement incorporates by reference the documents set forth below that we have previously filed with the SEC (other than information deemed furnished and not filed in accordance with SEC rules, including Items 2.02 and 7.01 of Form 8-K):

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, filed with the SEC on March 13, 2020;
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2019 from our definitive proxy statement on Schedule 14A, filed with the SEC on April 23, 2020;
- our Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2020, June 30, 2020 and September 30, 2020, filed with the SEC on May 11, 2020, August 11, 2020 and November 12, 2020, respectively;
- our Current Reports on Form 8-K, filed with the SEC on February 14, 2020, April 1, 2020, April 21, 2020 (only with respect to Item 8.01), May 26, 2020, June 5, 2020, and August 17, 2020; and
- the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on May 6, 2019, and any amendment or report filed for the purpose of updating such description.

All documents filed by us pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement and the accompanying prospectus and before the termination of the offering also shall be deemed to be incorporated herein by reference. We are not, however, incorporating by reference any documents or portions thereof that are not deemed "filed" with the SEC, including any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K.

Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, including any amendments to those reports, and other information that we file with or furnish to the SEC pursuant to Section 13(a) or 15(d) of the Exchange Act, can also be accessed free of charge from our website at http://www.appliedtherapeutics.com. These filings will be available as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information contained on our website is not part of this prospectus.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement and any documents incorporated by reference contain “forward-looking statements” within the meaning of Section 27A of the Securities Act, and Section 21E of the Exchange Act about us and our industry that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this prospectus supplement and the accompanying prospectus and any documents incorporated by reference, including statements regarding our strategy, future financial condition, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “aim,” “anticipate,” “assume,” “believe,” “contemplate,” “continue,” “could,” “design,” “due,” “estimate,” “expect,” “forecast,” “goal,” “intend,” “may,” “objective,” “plan,” “predict,” “positioned,” “potential,” “seek,” “should,” “target,” “will,” “would” and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of known and unknown risks, uncertainties and assumptions, including risks described in the section titled “Risk Factors” and elsewhere in this prospectus supplement and the accompanying prospectus and any documents incorporated by reference, regarding, among other things:

- the potential impact of the Covid-19 pandemic on the timing and progress of our ongoing clinical trials, our business, results of operations, liquidity, and operations and our ability to mitigate those potential impacts;
- our plans to develop and commercialize our product candidates;
- the initiation, timing, progress and results of our current and future preclinical studies and clinical trials and our research and development programs;
- our ability to take advantage of expedited regulatory pathways for any of our product candidates;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to successfully acquire or in-license additional product candidates on reasonable terms;
- our ability to maintain and establish collaborations or obtain additional funding;
- our ability to obtain regulatory approval of our current and future product candidates;
- our expectations regarding the potential market size and the rate and degree of market acceptance of such product candidates;
- our ability to fund our working capital requirements and expectations regarding the sufficiency of our capital resources;
- the implementation of our business model and strategic plans for our business and product candidates;
- our intellectual property position and the duration of our patent rights;
- developments or disputes concerning our intellectual property or other proprietary rights;
- our expectations regarding government and third-party payor coverage and reimbursement;
- our ability to compete in the markets we serve;
- the impact of government laws and regulations and liabilities thereunder;
- developments relating to our competitors and our industry;
- our expected use of proceeds from this offering; and
- other factors that may impact our financial results.

The foregoing list of risks is not exhaustive. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

In light of the significant uncertainties in these forward-looking statements, you should not rely upon forward-looking statements as predictions of future events. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus supplement and the accompanying prospectus and any documents incorporated by reference, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur at all. You should refer to the sections titled “Risk Factors” in this prospectus supplement and the accompanying prospectus, or documents incorporated by reference for discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. Except as required by law, we undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise.

SUMMARY

This summary highlights key aspects of this offering and certain information contained elsewhere in this prospectus supplement and the accompanying prospectus and the documents incorporated by reference. This summary is not complete and does not contain all of the information that may be important to you or that you should consider before investing in our common stock. You should read carefully the other information included and incorporated by reference in this prospectus supplement and the accompanying prospectus before investing in our common stock. You should pay special attention to the risks and uncertainties identified under the captions "Risk Factors," "Cautionary Note Regarding Forward-Looking Statements" and elsewhere in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein or therein, including our Quarterly Report on Form 10-Q for the three and nine months ended September 30, 2020, when determining whether an investment in our common stock is appropriate for you. Unless the context otherwise requires, the terms "Applied Therapeutics," "the company," "we," "us," "our" and similar references in this prospectus refer to Applied Therapeutics, Inc.

Overview

We are a clinical-stage biopharmaceutical company developing a pipeline of novel product candidates against validated molecular targets in indications of high unmet medical need. We focus on molecules and pathways whose role in the disease process is well known based on prior research, but have previously failed to yield successful products due to poor efficacy and tolerability. Our unique approach to drug development leverages recent technological advances to design improved drugs, employs early use of biomarkers to confirm biological activity and focuses on abbreviated regulatory pathways. We develop product candidates with increased potency and selectivity by leveraging recent technological advances in high throughput crystallography and in situ structural design. Our strategy is also informed by early use of biomarkers to confirm biological activity and target engagement. The result of this unique multifaceted approach to drug development is a portfolio of highly specific and selective product candidates that we believe are significantly de-risked and can move quickly through the development process.

Our first molecular target is aldose reductase, or AR, the first enzyme and rate-limiting step in the polyol pathway, an alternative glucose metabolism pathway. AR is a redox-regulated enzyme that is activated by an altered redox state within the cell, such as oxidative stress, which occurs during hyperglycemia and ischemia. AR activity produces excess sorbitol, which causes osmotic dysregulation within cells and tissues, and is implicated in multiple diseases. The detrimental consequences of aberrant AR activation include broad effects, such as mitochondrial dysfunction and cell death, as well as tissue-specific changes, such as neuronal degeneration in peripheral nerves, collagen crosslinking and fibrosis in cardiac tissue, and damage to blood vessels in the lens of the eye. Prior attempts to inhibit this enzyme were hindered by nonselective, nonspecific inhibition, which resulted in limited efficacy and significant off-target safety effects. Our AR inhibitor, or ARI, program currently includes three small molecules, which are all designed to be potent and selective ARIs, and are engineered to have unique tissue permeability profiles to target different disease states, including diabetic complications, heart disease and a rare pediatric metabolic disease.

Our first product candidate, AT-001, is a novel ARI with broad systemic exposure and peripheral nerve permeability, that we are developing for the treatment of diabetic cardiomyopathy, or DbCM, a fatal fibrosis of the heart, for which no treatments are available. DbCM is estimated to afflict 17% of diabetic patients, equating to an estimated 77 million patients globally. We initially plan to target the 50% of these patients who are within the symptomatic stages of disease we believe most likely to be responsive to treatment — patients at a high risk of progression to overt heart failure. We are also developing AT-001 for diabetic peripheral neuropathy, or DPN, a debilitating neurodegenerative disease that significantly reduces quality of life, and for which there are currently no approved treatments in the United States. Approximately 50% of the global diabetic population, or 226 million diabetic patients, suffer from DPN. We recently completed a Phase 1/2 clinical trial evaluating AT-001 in approximately 120 patients with type 2 diabetes, in which no drug-related adverse effects or tolerability issues were observed. This trial also demonstrated target engagement and proof of biological activity, as measured

by reduction in sorbitol, a biomarker of AR activity, and NTproBNP, a marker of cardiac stress. In September 2019 we initiated a pivotal Phase 2/3 clinical trial of AT-001 for the treatment of DbCM in patients at high risk of progression. This global registrational trial, called ARISE-HF, is designed to characterize the impact of AT-001 on cardiac functional capacity as measured by Peak VO2 vs. placebo in 675 patients over 15 months of treatment. Secondary endpoints include progression to overt heart failure, morbidity and mortality over 27 months of treatment. In this study, we are also collecting data on motor nerve conduction velocity, or MNCV, in DbCM patients that also have DPN, which we expect will provide a basis for dose selection in Phase 3 clinical trials of DPN.

Our second product candidate, AT-007, is a central nervous system, or CNS, penetrant ARI that we are developing for the treatment of CNS rare diseases, including galactosemia, a devastating rare pediatric metabolic disease that affects how the body processes a simple sugar called galactose, and for which there is no known cure or approved treatment available. We estimate that the U.S. galactosemia population is approximately 3,000 patients, based on newborn screening data identifying 2,500 infants through 2014, and the estimated birth rate of 80 patients per year. High levels of galactose circulating in the blood and tissues of galactosemia patients enable AR to convert galactose to a toxic metabolite, galactitol, which results in long-term complications ranging from CNS dysfunction to cataracts. We have demonstrated in an animal model of galactosemia that treatment with AT-007 reduces toxic galactitol levels and prevents disease complications. We believe that galactosemia may qualify for accelerated approval, as well as for the rare pediatric disease priority review voucher, or RPD-PRV, program. Additionally, the U.S. Food and Drug Administration, or FDA, recently released draft guidance for industry on drug development for low prevalence, slowly progressing rare metabolic diseases, for which we believe galactosemia qualifies. The guidance allows for a biomarker-based development program if clinical efficacy and a link to a relevant biomarker can be demonstrated in an animal model of disease. In June 2019 we initiated a pivotal Phase 1/2 study in healthy volunteers and adults with galactosemia to evaluate safety, pharmacokinetics, and biomarker endpoints in adults with galactosemia.

The study is a double-blind placebo-controlled trial evaluating safety and pharmacokinetics of AT-007 in healthy volunteers, as well as safety, pharmacokinetics, and biomarker effects in adult galactosemia patients over 28 days of once daily oral dosing. The key biomarker outcome of the study was reduction in plasma galactitol, an aberrant toxic metabolite of galactose, formed by Aldose Reductase in galactosemia patients.

In January 2020, we announced positive topline results. AT-007 treatment resulted in a statistically significant and robust reduction in plasma galactitol versus placebo in adult galactosemia patients. Reductions in galactitol were dose dependent, with higher concentrations of AT-007 resulting in a greater magnitude of reduction in galactitol. At the two highest doses tested (20mg/kg and 40mg/kg), AT-007 significantly reduced plasma galactitol approximately 50% from baseline versus placebo (with a p value of less than 0.01). Galactitol reduction was rapid and sustained over time. No substantial change from baseline was observed in placebo treated patients. AT-007 was well tolerated, with no drug-related adverse events noted to date in galactosemia patients or in the 72 healthy volunteers treated in Part 1 of the trial. In December 2020, we announced magnetic resonance spectroscopy (MRS) data on reduction of galactitol levels in the brain of galactosemia patients treated with AT-007 in the ACTION-Galactosemia adult study. Overall, plasma reduction in galactitol correlated with brain reduction in galactitol. At the two doses which demonstrated statistically significant reduction in plasma galactitol, 20 and 40mg/kg, 3 out of 4 patients displayed substantial galactitol reduction ranging from 61.94% to 69.80% reduction from baseline. We continue to characterize AT-007 safety in adult galactosemia patients in a long-term safety extension study. We plan to submit an NDA in late 2021.

In June 2020 we initiated a galactosemia pediatric study, ACTION-Galactosemia Kids. Initially, the ACTION-Galactosemia Kids program was split into two separate clinical studies — a dose escalation and biomarker study followed by a separate long-term clinical outcomes study. The pediatric program was placed on partial clinical hold by the FDA in August 2020 in order to address design and operational aspects of the study to ensure continuity of treatment and the opportunity for all children to receive the potential for clinical benefit. We worked closely with the FDA to modify the trial, with the shared goal of ensuring that all patients have the opportunity to receive clinical benefit. On Feb 1, 2021 we announced that the FDA hold had been lifted, and the pediatric study resumed immediately. The two studies have

now been combined into a single two-part study to ensure that all patients who complete the dose escalation and biomarker portion of the study will seamlessly continue into the long-term outcomes study without treatment interruption. Additionally, the dose-escalation portion of the study has been operationally modified to ensure continuous drug treatment and participation throughout the study.

Aldose Reductase has also recently been implicated in two additional CNS rare diseases — SORD Deficiency and PMM2-CDG. SORD Deficiency is a newly characterized genetic cause of Charcot-Marie-Tooth Type 2 Disease (CMT2) and distal hereditary neuropathy, in which patients are deficient in the enzyme Sorbitol Dehydrogenase (SORD). SORD is the enzyme which follows AR in the polyol pathway and converts sorbitol to fructose. Patients who are deficient in SORD cannot metabolize sorbitol normally, and sorbitol levels accumulate to unnaturally high levels (10-20-fold higher vs healthy control levels). Sorbitol, like galactitol, has been shown to be toxic to cells, especially neurons, resulting in progressive neuronal degeneration. Patients with SORD Deficiency develop progressive neuropathy, which greatly impacts mobility and motility, and significantly affects quality of life. Genetic studies indicate that approximately 7 – 9% of CMT2 cases are caused by SORD Deficiency, estimating the U.S. population around 3,000 patients. There are no FDA approved disease modifying treatments for CMT2 or SORD Deficiency. Substrate reduction through AR inhibition in patient fibroblasts and a drosophila model of disease have demonstrated preclinical proof of concept in SORD Deficiency, significantly reducing sorbitol levels and normalizing the drosophila disease phenotype. We plan to initiate a Phase 2 study in SORD Deficient patients in the first half of 2021.

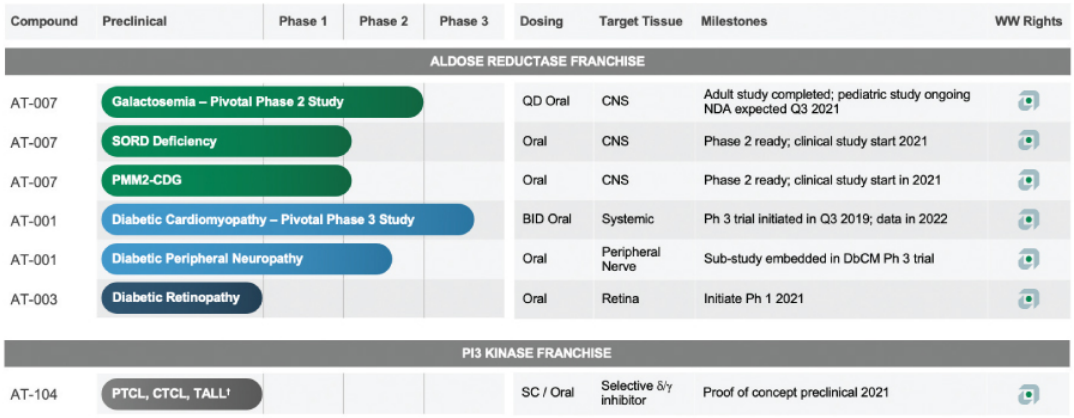
PMM2-CDG is a glycosylation disorder in which patients have only partial function of the phosphomannomutase 2 enzyme (PMM2). As a result, patients do not process sugars properly to support protein glycosylation, which results in systemic problems and multi-organ failure. PMM2-CDG is a severe disease, resulting in and high mortality in children, with no FDA approved treatments. Recently, AR inhibition was demonstrated to positively impact protein glycosylation in PMM2-CDG patient fibroblasts and a C. elegans model of disease. It is believed that AR inhibition results in increased protein glycosylation by shifting the balance of sugar production to support PMM2 activity. In preclinical studies in PMM2-CDG patient fibroblasts, AT-007 significantly improved PMM2 activity. Based on this data, we have received both Orphan Designation and Pediatric Rare Disease designation from the FDA. We plan to initiate a clinical study in children with PMM2-CDG in 2021.

We are also developing AT-003, an ARI designed to cross through the back of the eye when dosed orally, which has demonstrated strong retinal penetrance, for the treatment of diabetic retinopathy, or DR. DR is an ophthalmic disease that occurs in diabetic patients and for which treatments are currently limited to high-cost biologics requiring intravitreal administration. DR afflicts approximately 35% of diabetic patients, equating to an estimated 158 million patients globally. DR has been linked to AR activity, including elevations in sorbitol and subsequent changes in retinal blood vessels, which distorts vision and leads to permanent blindness. We are currently in late stages of preclinical development of AT-003. AT-003 displayed significant retinal penetration when dosed orally in diabetic rats. The drug was observed to be well tolerated with no adverse effects. Efficacy of AT-003 is currently being explored in two animal models of DR — an ischemic injury model (acute damage) and chronic diabetic treatment model. We intend to advance AT-003 into a Phase 1 clinical trial in late 2021.

Applying our strategy from our ARI program, we have also developed a program targeting selective inhibition of phosphatidylinositol 3-kinase, or PI3K, subunits that has resulted in an early-stage oncology pipeline. We expect to initially target orphan hematological oncology indications, including peripheral T-cell lymphoma, cutaneous T-cell lymphoma and T-cell acute lymphoblastic leukemia. We are additionally developing selective alpha/gamma inhibitors to target solid tumors that constitutively express PI3K alpha.

Our Pipeline

The following table shows the status of our current ARI and PI3K inhibitor programs:



†Peripheral T-cell lymphoma, cutaneous T-cell lymphoma and T-cell acute lymphoblastic leukemia

Our Strategy

Our goal is to bring potentially transformative therapies to market across a range of fatal or debilitating diseases for which no treatments are available. The critical components of our strategy include:

- ***Leveraging our unique approach to develop our pipeline of novel ARIs***. We target molecules and pathways that have a proven role in disease, but have previously failed to yield successful products due to poor efficacy and tolerability. Our unique approach to drug development utilizes recent technological advances to design improved drugs, employs early use of biomarkers to confirm biological activity and focuses on abbreviated regulatory pathways. We develop product candidates with increased potency and selectivity by leveraging recent technological advances in high throughput crystallography and in silico structural design. Our strategy is also informed by early use of biomarkers to confirm biological activity and target engagement. Early proof of biological activity through biomarkers in clinical trials combined with data from prior clinical development programs on first generation drugs significantly de-risks clinical development in our target indications. AR is our first molecular target that has been implicated in multiple diseases and for which sorbitol levels can be assessed as a biomarker of enzyme activity. Prior AR-targeting compounds produced nonselective inhibitors and failed to demonstrate adequate safety and efficacy. We intend to apply our strategy to a wide range of validated targets across multiple disease indications, which we believe will result in additional pipeline programs.
- ***Rapidly advancing the development of our ARI product candidates, AT-001, AT-007 and AT-003***. We advanced AT-001 into a pivotal clinical trial in September 2019 for the treatment of DbCM. We plan to collect data on motor nerve conduction velocity, or MNCV, in this study in DbCM patients that also have DPN, which we expect will provide a basis for dose selection in Phase 3 clinical trials of DPN.
- ***Taking advantage of regulatory pathways designed for accelerated drug development in indications with high unmet need and seeking strategic partnerships in other indications***. We plan to leverage abbreviated development programs and biomarker-based approaches for rapid drug development and regulatory approval. For indications that require standard development programs, we plan to seek strategic partnerships.
- ***Expanding our pipeline to products targeting other validated molecules and pathways outside of AR***. We plan to further characterize our novel PI3K inhibitors and select lead compounds for preclinical development. Utilizing our biomarker-based approach, we intend

to target urgent hematological oncology indications and specific solid tumors. We will continue leveraging our relationships with academic institutions and universities to acquire or license additional technologies that are consistent with our strategy of applying new technologies to validated molecular pathways.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on January 20, 2016. Our principal executive offices are located at 545 Fifth Avenue, Suite 1400, New York, New York 10017, and our telephone number is (212) 220-9226. Our corporate website address is www.appliedtherapeutics.com. Information contained on, or accessible through, our website is not a part of this prospectus. We have included our website in this prospectus solely as an inactive textual reference.

Recent Developments

Restart of Pediatric Galactosemia Study

On February 1, 2021, we announced that the FDA had lifted the hold on the AT-007 ACTION-Galactosemia Kids pediatric study, and the trial resumed immediately. Through the period of the partial hold, we worked closely with the FDA to modify the trial, with the shared goal of ensuring that all patients have the opportunity to receive clinical benefit. Previously, the ACTION-Galactosemia Kids program was split into two separate clinical studies — a dose escalation and biomarker study followed by a separate long-term clinical outcomes study. The two studies have now been combined into a single two-part study to ensure that all patients who complete the dose escalation and biomarker portion of the study will seamlessly continue into the long-term outcomes study without treatment interruption. Additionally, the dose-escalation portion of the study has been operationally modified to ensure continuous drug treatment and participation throughout the study.

Cash Update

As of December 31, 2020, we had approximately $96.8 million of cash, cash equivalents and marketable securities. As of December 31, 2020, after giving effect to the issuance and sale of 3,000,000 shares of our common stock by us in this offering at the public offering price of $23.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, we would have had approximately $161.4 million of cash, cash equivalents and marketable securities. These amounts are unaudited and preliminary, and do not present all information necessary for an understanding of our financial condition as of December 31, 2020. The audit of our financial statements for the year ended December 31, 2020 is ongoing and could result in changes to these amounts. Our financial statements for the year ended December 31, 2020 will not be available until after this offering is completed, and consequently will not be available to you prior to investing in this offering.

Our expectations with respect to our unaudited results for the period discussed above are based upon management estimates and are the responsibility of management. Our independent registered public accounting firm has not audited, reviewed or performed any procedures with respect to these preliminary results and, accordingly, does not express an opinion or any other form of assurance about them.

	THE OFFERING
Common stock to be offered	3,000,000 shares.
Common stock to be outstanding immediately after this offering	25,493,661 shares (or 25,943,661 shares if the underwriters exercise in full their option to purchase additional shares).
Option to purchase additional shares	We have granted the underwriters an option to purchase up to 450,000 additional shares of our common stock at the public offering price, less the underwriting discount. This option is exercisable, in whole or in part, for a period of 30 days following the date of this prospectus supplement.
Use of proceeds	We intend to use the net proceeds from this offering, together with our existing cash, to advance clinical and preclinical development of our product candidates, prepare for commercialization and other general corporate purposes. See “Use of Proceeds.”
Risk factors	Investing in our securities involves significant risks. See “Risk Factors” on page S-11 and in the documents incorporated by reference herein (including under “Risk Factors” in our Form 10-Q for the quarter ended September 30, 2020) for a discussion of the risks you should carefully consider before deciding to invest in our securities.
Nasdaq Global Market symbol	“APLT”

The number of shares of our common stock to be outstanding immediately after this offering is based on 22,493,661 shares of our common stock outstanding as of December 31, 2020, and excludes:

- options to purchase 4,529,675 shares of common stock outstanding under the 2016 Plan and the 2019 Plan;
- restricted stock units to purchase 206,679 shares of common stock outstanding under the 2019 Plan;
- 1,400,451 shares reserved to grant under the 2016 and 2019 Plans and zero shares available for future grants under the 2019 Plan;
- 153,473 shares of our common stock issuable upon the exercise of warrants outstanding; and
- 365,315 shares of our common stock reserved for future issuance under our 2019 Employee Stock Purchase Plan, or ESPP, as well as any future increases in the number of shares of common stock reserved for issuance under our ESPP.

Except as otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase additional shares.

RISK FACTORS

Investing in our common stock is speculative and involves a high degree of risk. The following risk factors, as well as risks currently unknown to us, could materially adversely affect our future business, operations and financial condition and could cause them to differ materially from the estimates described in forward-looking information relating to us, or our business, property or financial results, each of which could cause purchasers of our common stock to lose part or all of their investment. In addition to the other information contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein, prospective investors should carefully consider the factors set out under "Risk Factors" in the accompanying prospectus and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, as applicable, and the factors set out below before deciding to invest in our common stock.

Risks Related to This Offering and Ownership of Our Common Stock

The market price of our common stock may be volatile and fluctuate substantially which could result in substantial losses for purchasers of our common stock.

The market price of our common stock is likely to be volatile. The stock market in general and the market for biopharmaceutical and pharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the price the public offering price. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this prospectus supplement and the accompanying prospectus, the market price for our common stock may be influenced by the following:

- the potential impact of the Covid-19 pandemic on the timing and progress of our ongoing clinical trials, our business, results of operations, liquidity, and operations and our ability to mitigate those potential impacts;
- the commencement, enrollment or results of our planned or future clinical trials of our product candidates or those of our competitors;
- the success of competitive drugs or therapies;
- regulatory or legal developments in the United States and other countries;
- the success of competitive products or technologies;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- our inability to obtain or delays in obtaining adequate drug supply for any approved drug or inability to do so at acceptable prices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- significant lawsuits, including patent or stockholder litigation;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems, including coverage and adequate reimbursement for any approved drug;

- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, political, and market conditions and overall fluctuations in the financial markets in the United States and abroad; and
- investors' general perception of us and our business.

These and other market and industry factors may cause the market price and demand for our common stock to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from selling their shares at or above the public offering price and may otherwise negatively affect the liquidity of our common stock. Furthermore, our stock has been, and may in the future be, adversely affected by third-parties trying to drive down the market price. Short sellers and others, some of whom post anonymously on social media, may be positioned to profit if our stock declines and their activities can negatively affect our stock price.

Some companies that have experienced volatility in the trading price of their shares have been the subject of securities class action litigation. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our business practices.

Defending against litigation is costly and time-consuming, and could divert our management's attention and our resources. Furthermore, during the course of litigation, there could be negative public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a negative effect on the market price of our common stock.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Based upon shares of our common stock outstanding as of December 31, 2020, our executive officers, directors and stockholders who owned more than 5% of our outstanding common stock, in the aggregate, beneficially own shares representing approximately 38% of our outstanding common stock. If our executive officers, directors and stockholders who owned more than 5% of our outstanding common stock acted together, they may be able to significantly influence all matters requiring stockholder approval, including the election and removal of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. The concentration of voting power and transfer restrictions could delay or prevent an acquisition of our company on terms that other stockholders may desire or result in the management of our company in ways with which other stockholders disagree.

If research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business or our market, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or financial analysts publish about us or our business. Equity research analysts may discontinue research coverage of our common stock, and such lack of research coverage may adversely affect the market price of our common stock. We do not have any control over the analysts or the content and opinions included in their reports. The price of our shares could decline if one or more equity research analysts downgrade our shares or issue other unfavorable commentary or research about us. If one or more equity research analysts cease coverage of us or fail to publish reports on us regularly, demand for our shares could decrease, which in turn could cause the trading price or trading volume of our common stock to decline.

If you purchase shares of common stock in this offering, you will suffer immediate dilution of your investment.

We cannot predict the effect, if any, that future sales of our common stock, including sales pursuant to the equity distribution agreement, or the availability of our common stock for future sale,

will have on the market price of our common stock. Future sales or issuances of our common stock may dilute the ownership interests of our existing stockholders, including purchasers of common stock in this offering. In addition, we also have outstanding options and warrants to purchase common stock with exercise prices lower than the price we expect investors in this offering to pay for shares of common stock. To the extent these outstanding options or warrants are exercised, there will be further dilution to investors. The perception that such sales or issuances may occur could also negatively impact the market price of our common stock.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

You should not rely on an investment in our common stock to provide dividend income. We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. Investors seeking cash dividends should not purchase our common stock.

We have broad discretion in the use of our cash and cash equivalents, including the net proceeds from this offering, and may use them ineffectively, in ways with which you do not agree or in ways that do not increase the value of your investment.

Our management has broad discretion in the application of our cash and cash equivalents, including the net proceeds from this offering, and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in additional operating losses that could have a negative impact on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest our cash and cash equivalents, including the net proceeds from this offering, in a manner that does not produce income or that loses value. See “Use of Proceeds” for additional information.

Future sales of common stock by holders of our common stock, or the perception that such sales may occur, could depress the market price of our common stock.

Sales of a substantial number of shares of our common stock in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. As of December 31, 2020, we had outstanding 22,493,661 shares of common stock. A substantial number of such shares are currently restricted as a result of securities laws but will be able to be sold in the future.

We further have registered all shares of common stock that we may issue in the future or have issued to date under our equity compensation plans. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates. Sales of a large number of the shares issued under these plans in the public market could have an adverse effect on the market price of our common stock.

We are an “emerging growth company,” and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an “emerging growth company,” or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not EGCs, including:

- 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; 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 cannot predict whether investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our share price may be more volatile. We currently take advantage of some or all of these reporting exemptions until we are no longer an EGC. We will remain an EGC until the earlier of (i) December 31, 2024, (ii) the last day of the fiscal year in which we have total annual gross revenue of at least $1.07 billion, (iii) the last day of the first fiscal year 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 (iv) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

In addition, under Section 107(b) of the JOBS Act, EGCs 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 requirements to adopt new or revised accounting standards as other public companies that are not EGCs.

We have incurred increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.

As a public company, and particularly after we are no longer an EGC, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and rules subsequently implemented by the SEC and The Nasdaq Stock Market LLC have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to comply with these requirements. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance.

Pursuant to Section 404 of the Sarbanes-Oxley Act, or Section 404, we will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions also could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a stockholder rights plan, or so-called “poison pill,” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 66⅔% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, or DGCL, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders’ ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that, with respect to any state actions or proceedings under Delaware statutory or common law, the Court of Chancery of the State of Delaware is 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 or any of our directors, officers, employees or agents arising under the DGCL, our amended and restated certificate of incorporation or our amended and restated bylaws;
- any action or proceeding to interpret, apply, enforce or determine the validity of our amended and restated certificate of incorporation or our amended and restated bylaws; and
- any action asserting a claim against us or any of our directors, officers, employees or agents that is governed by the internal-affairs doctrine.

These exclusive-forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage lawsuits against us and our directors, officers and other employees. If a court were to find an exclusive-forum provision in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could harm our business.

USE OF PROCEEDS

We estimate that the net proceeds to us from this offering will be approximately $64.6 million, or approximately $74.3 million if the underwriters exercise in full their option to purchase additional shares, in each case after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering, together with our existing cash, to advance clinical and preclinical development of our product candidates, prepare for commercialization and other general corporate purposes.

Pending such use of the net proceeds from this offering, we intend to hold some amounts as cash and to invest the remaining net proceeds in a variety of capital preservation investments, including short-term investment-grade, interest-bearing instruments denominated in currencies.

The expected use of the net proceeds from this offering represents our intentions based on our current plans and business conditions, which could change in the future as our plans and business conditions evolve. Further, due to the uncertainties inherent in the drug development process, it is difficult to estimate with certainty the exact amounts of the net proceeds from this offering that may be used for the above purposes.

DILUTION

Our net tangible book value as of September 30, 2020 was approximately $102.9 million, or $4.58 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 September 30, 2020. 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 3,000,000 shares of our common stock by us in this offering at the public offering price of $23.00 per share and before deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2020 would have been approximately $171.9 million, or $6.75 per share. This represents an immediate increase in net tangible book value of $2.17 per share to existing stockholders and immediate dilution in value of $16.25 per share to investors purchasing our common stock in this offering.

The following table illustrates this dilution on a per share basis:

Public offering price per share		$ 23.00
Net tangible book value per share as of September 30, 2020	$ 4.58	
Increase in net tangible book value per share attributable to new investors purchasing our common stock in this offering	$ 2.17	
As adjusted net tangible book value per share on September 30, 2020, after giving effect to this offering		$ 6.75
Dilution per share to new investors purchasing our common stock in this offering		$ 16.25

If the underwriters exercise in full their option to purchase additional shares of common stock in this offering at the public offering price, the as adjusted net tangible book value after this offering would be $7.04 per share, representing an increase in net tangible book value of $2.45 per share to existing stockholders and immediate dilution in value of $15.96 per share to investors purchasing our common stock in this offering at the public offering price.

The above discussion is based on 22,456,686 shares of our common stock outstanding as of September 30, 2020, and excludes:

- options to purchase 3,942,536 shares of common stock outstanding under the 2016 Plan and the 2019 Plan;
- restricted stock units to purchase 145,126 shares of common stock outstanding under the 2019 Plan;
- 2,086,118 shares reserved to grant under the 2016 and 2019 Plans and 801,745 shares available for future grants under the 2019 Plan;
- 153,473 shares of our common stock issuable upon the exercise of warrants outstanding; and
- 365,315 shares of our common stock reserved for future issuance under our 2019 Employee Stock Purchase Plan, or ESPP, as well as any future increases in the number of shares of common stock reserved for issuance under our ESPP.

To the extent that any outstanding options or warrants are exercised, new options or other equity awards are issued under our equity incentive plans, or we issue additional shares in the future, there will be further dilution to new investors participating in this offering. 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.

U.S. FEDERAL INCOME TAX CONSIDERATIONS FOR NON-U.S. HOLDERS

The following discussion is a summary of U.S. federal income tax considerations generally applicable to non-U.S. holders of shares of our common stock that hold such shares as capital assets (generally, for investment). This summary does not consider specific facts and circumstances that may be relevant to a particular holder's tax position and does not consider the non-income tax consequences or the state, local, or non-U.S. tax consequences of an investment in shares of our common stock. It also does not apply to non-U.S. holders subject to special tax treatment under the U.S. federal income tax laws (including a broker, dealer, or trader in securities or currencies; a financial institution; an insurance company; a tax-exempt organization; a person holding shares of our common stock as part of a hedging, integrated, or conversion transaction, a constructive sale, or a straddle; a person that received shares of our common stock as compensation; a controlled foreign corporation; a passive foreign investment company; or a former U.S. citizen). This summary is based upon the United States Internal Revenue Code of 1986, as amended (the "Code"), existing and proposed Treasury regulations, Internal Revenue Service ("IRS") rulings and pronouncements, and judicial decisions in effect, all of which are subject to change, possibly on a retroactive basis, or differing interpretations.

The discussion included herein is only a summary. Accordingly, we urge you to consult your tax advisor with respect to your U.S. federal, state, local, and non-U.S. income and other tax consequences in light of your particular situation with respect to holding and disposing of shares of our common stock.

For purposes of this discussion, a "U.S. holder" is a beneficial owner of shares of our common stock who is:

- an individual citizen or resident of the U.S.;
- a corporation or other entity taxable as a corporation created or organized in or under the laws of the U.S., any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust (i) if a court within the U.S. is able to exercise primary supervision over the administration of such trust and one or more U.S. persons have the authority to control all substantial decisions of such trust or (ii) that has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

A "non-U.S. holder" is any beneficial owner of shares of our common stock that is not an entity classified as a partnership for U.S. federal income tax purposes and is not a U.S. holder.

If a partnership or other pass-through entity holds shares of our common stock, the U.S. federal income tax treatment of a partner or a member will generally depend upon the status of the partner or member and the activities of the partnership or other entity. Accordingly, partnerships or other pass-through entities that hold shares of our common stock and partners or members in these partnerships or other entities should consult their tax advisors regarding the U.S. federal income and estate tax consequences of the purchase, ownership, and disposition of shares of our common stock.

Taxation of Ownership of Our Common Stock

Dividends

We have not paid and do not anticipate paying dividends. However, any dividends we pay to a non-U.S. Holder with respect to shares of our common stock will generally be subject to withholding tax at a 30% rate (or such lower rate specified by an applicable income tax treaty). To obtain the benefit of a reduced rate under an applicable income tax treaty, a non-U.S. holder must certify as to its non-U.S. status, that no withholding is required pursuant to FATCA (discussed below), and to such right under the applicable income tax treaty on a properly completed IRS Form W-8BEN or IRS Form W-8BEN-E. If, however, a non-U.S. holder provides an IRS Form W-8ECI, certifying that the dividend is effectively connected with the non-U.S. Holder's conduct of a trade or business within the U.S. (and, in the case

of certain income tax treaties, is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the U.S.), the dividend will not be subject to withholding. Instead, such dividends are subject to U.S. federal income tax at regular rates applicable to U.S. persons generally and, for corporate holders, may also be subject to a 30% "branch profits tax" unless the non-U.S. holder qualifies for a lower rate under an applicable U.S. income tax treaty.

Dispositions

A non-U.S. holder will generally not be subject to U.S. federal income or withholding tax in respect of any gain on a sale, exchange or other taxable disposition of shares of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of trade or business in the U.S. and, in the case of certain income tax treaties, is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the U.S.;
- the Non-U.S. holder is an individual who is present in the U.S. for 183 or more days in the tax year of the disposition and meets certain other conditions; or
- we are or have been a "U.S. real property holding corporation" ("USRPHC") under Section 897 of the Code during the applicable statutory period and the non-U.S. holder's shares in us represented more than 5% of the shares of our common stock outstanding at any time within the shorter of (a) the five-year period preceding the disposition and (b) the non-U.S. holder's holding period and are otherwise a "U.S. real property interest" under the Foreign Investment in Real Property Tax Act (and the non-U.S. holder is not eligible for any treaty exemption). We do not believe that we currently are a USRPHC, and we do not anticipate becoming a USRPHC in the future.

U.S. Federal Estate Taxes

Shares of our common stock owned or treated as owned by an individual at the time of death will be included in the individual's gross estate for U.S. federal estate tax purposes and may be subject to U.S. federal estate tax, unless an applicable estate tax treaty provides otherwise.

Information Reporting and Backup Withholding

Information reporting and, in certain circumstances, backup withholding will apply to the payment of dividends and proceeds of a sale or other disposition of shares of our common stock made within the U.S. or conducted through certain U.S.-related financial intermediaries, unless the beneficial owner certifies under penalty of perjury that it is a non-U.S. holder, such as by providing a properly completed IRS Form W-8BEN, W-8BEN-E, or W-8ECI (and the payor does not have actual knowledge or reason to know that the beneficial owner is a United States person as defined under the Code), or such owner otherwise establishes an exemption.

Foreign Account Tax Compliance Act

Under the Foreign Account Tax Compliance Act ("FATCA"), withholding at a rate of 30% will generally be required on dividends in respect of shares of our common stock held by or through certain foreign financial institutions (including investment funds), unless such institution (i) enters into an agreement with the U.S. Department of the Treasury to report, on an annual basis, information with respect to shares in, and accounts maintained by, the institution to the extent such shares or accounts are held by certain U.S. persons and by certain non-U.S. entities that are wholly or partially owned by U.S. persons and to withhold on certain payments, or (ii) complies with the terms of an intergovernmental agreement between the U.S. and an applicable foreign country. An intergovernmental agreement between the U.S. and an applicable foreign country, or future Treasury regulations or other guidance, may modify these requirements. Accordingly, the entity through which shares of our common stock is held will affect the determination of whether such withholding is required. Similarly, dividends in respect of shares of our common stock held by a holder that is a non-financial non-U.S. entity that does not qualify under certain exemptions will be subject to withholding at a rate of 30%, unless such entity either (i) certifies that such entity does not have any "substantial United States owners" or (ii) provides certain

information regarding the entity's "substantial United States owners," which we or the applicable withholding agent will in turn provide to the Secretary of the Treasury. We will not pay any additional amounts to holders in respect of any amounts withheld. Non-U.S. holders are encouraged to consult their tax advisors regarding the possible implications of this withholding tax on their investment in shares of our common stock.

UNDERWRITING

Goldman Sachs & Co. LLC, Cowen and Company, LLC and UBS Securities LLC are acting as representatives of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement dated the date of this prospectus, each underwriter named below has severally agreed to purchase, and we have agreed to sell to that underwriter, the number of shares set forth opposite the underwriter's name.

Underwriters	Number of Shares
Goldman Sachs & Co. LLC	1,350,000
Cowen and Company, LLC	870,000
UBS Securities LLC	480,000
Robert W. Baird & Co. Incorporated	300,000
Total	3,000,000

The underwriting agreement provides that the obligations of the underwriters to purchase the shares included in this offering are subject to approval of legal matters by counsel and to other conditions. The underwriters are obligated to purchase all the shares (other than those covered by the underwriters' option to purchase additional shares described below) if they purchase any of the shares.

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount from the public offering price not to exceed $0.828 per share. If all the shares are not sold at the public offering price, the underwriters may change the offering price and the other selling terms. The representatives have advised us that the underwriters do not intend to make sales to discretionary accounts. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

If the underwriters sell more shares than the total number set forth in the table above, we have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to 450,000 additional shares of our common stock at the public offering price less the underwriting discount.

We, our officers and directors, and certain holders of more than 5% of our outstanding shares of common stock, or securities convertible into or exchangeable for shares of our common stock, have agreed that, for a period of 90 days from the date of this prospectus, or the restricted period, we and they will not, without the prior written consent of the representatives, dispose of or hedge any shares or any securities convertible into or exchangeable for our common stock.

With respect to us, the restrictions described above are subject to specified exceptions including the:

- sale of shares to the underwriters;
- issuance and sale of shares of common stock or securities convertible into, or exercisable or exchangeable for, shares of common stock, pursuant to any employee stock option plan, stock ownership plan, dividend reinvestment plan or any other plan or arrangement described in this prospectus;
- issuance of shares of common stock upon the conversion of securities outstanding as of the date of this prospectus, or the exercise of warrants or options or the settlement of restricted stock units outstanding as of the date of this prospectus or issued thereafter pursuant to any employee stock option plan or similar plan described above; filing of one or more registration statements on Form S-8 relating to any employee stock option plan or similar plan described above; and
- issuance of, or the entry into an agreement to issue, shares of common stock, or securities convertible into, exercisable or exchangeable for shares of common stock, in connection with

any merger, joint venture, strategic alliance or partnership; *provided* that the aggregate number of shares of common stock, or securities convertible or exercisable or exchangeable for shares of common stock, so issued does not exceed 5.0% of the total shares of common stock outstanding immediately following the issuance of shares in this offering, and the recipients of any such securities provide the representatives with a lock-up agreement containing the restrictions described above.

With respect to our officers and directors, and holders of more than 5% of our outstanding shares of common stock, the restrictions described above are subject to specified exceptions, including for any transfer of shares of common stock or any security convertible into or exercisable or exchangeable for common stock, subject to certain requirements:

- as a bona fide gift;
- by will, testamentary document or intestate succession upon the death of the officer, director or stockholder to the legal representative, heir, beneficiary or a member of the immediate family of the officer, director or stockholder;
- to an immediate family member of the officer, director or stockholder or to any trust for the direct or indirect benefit of the officer, director or stockholder or their immediate family;
- if the stockholder is a trust, to a trustor, trustee or beneficiary of the trust or to the estate of a trustor, trustee or beneficiary of such trust;
- as a distribution by a partnership to its limited or general partners or by a limited liability company to its members or by a corporation to its stockholders or to any wholly owned subsidiary of such corporation or by any other entity to its equityholders;
- to any affiliate of the stockholder, or any investment fund or other entity under common control or management by entities that are affiliates of the stockholder;
- pursuant to a domestic order or negotiated divorce settlement;
- in connection with the withholding of shares by, or surrender of shares to, us to cover the payment of taxes due upon or consideration required in connection with the vesting, conversion or exercise of securities issued under our equity incentive or stock purchase plans described in this prospectus, or pursuant to a “net” or “cashless” exercise or settlement feature;
- transfers under an existing trading plan pursuant to Rule 10b5-1 under the Exchange Act;
- transfers related to shares of common stock acquired in this offering or in open market transactions after the completion of this offering;
- transfers in connection with the termination of the employment with us or pursuant to contractual arrangements under which we have the option to repurchase such shares;
- the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock; *provided* that such plan does not provide for any transfers of shares of common stock during the restricted period;
- the exercise, vesting or settlement of any option to purchase any shares of common stock or other equity awards pursuant to any stock incentive plan or stock purchase plan described in this prospectus; and
- transfers pursuant to a bona fide third-party tender offer, merger, consolidation or other similar transaction made to all holders of our common stock involving a change of control that has been approved by our board of directors.

The representatives in their sole discretion may release any of the securities subject to these lock-up agreements at any time, which, in the case of officers and directors, shall be with notice.

Our common stock is listed on The Nasdaq Global Market under the symbol “APLT.”

The following table shows the underwriting discounts and commissions that we are to pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	Without option to purchase additional shares exercised	With full option to purchase additional shares exercised
Per Share	$ 1.38	$ 1.38
Total	$4,140,000	$4,761,000

We estimate that our portion of the total expenses of this offering will be approximately $295,000. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority up to $30,000.

In connection with the offering, the underwriters may purchase and sell shares in the open market. Purchases and sales in the open market may include short sales, purchases to cover short positions, which may include purchases pursuant to the underwriters' option to purchase additional shares, and stabilizing purchases.

- Short sales involve secondary market sales by the underwriters of a greater number of shares than they are required to purchase in the offering.
    - "Covered" short sales are sales of shares in an amount up to the number of shares represented by the underwriters' option to purchase additional shares.
    - "Naked" short sales are sales of shares in an amount in excess of the number of shares represented by the underwriters' option to purchase additional shares.
- Covering transactions involve purchases of shares either pursuant to the underwriters' option to purchase additional shares or in the open market in order to cover short positions.
    - To close a naked short position, the underwriters must purchase shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares in the open market after pricing that could adversely affect investors who purchase in the offering.
    - To close a covered short position, the underwriters must purchase shares in the open market or must exercise the option to purchase additional shares. In determining the source of shares to close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares.
- Stabilizing transactions involve bids to purchase shares so long as the stabilizing bids do not exceed a specified maximum.

Purchases to cover short positions and stabilizing purchases, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the shares. They may also cause the price of the shares to be higher than the price that would otherwise exist in the open market in the absence of these transactions. The underwriters may conduct these transactions on The Nasdaq Global Market in the over-the-counter market or otherwise. If the underwriters commence any of these transactions, they may discontinue them at any time. The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Conflicts of Interest

The underwriters are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment

management, principal investment, hedging, financing and brokerage activities. The underwriters and their respective affiliates have in the past performed commercial banking, investment banking and advisory services for us from time to time for which they have received customary fees and reimbursement of expenses and may, from time to time, engage in transactions with and perform services for us in the ordinary course of their business for which they may receive customary fees and reimbursement of expenses. In the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (which may include bank loans and/or credit default swaps) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make because of any of those liabilities.

European Economic Area and the United Kingdom

In relation to each Member State of the European Economic Area and the United Kingdom (each a "Relevant State"), no shares of common stock have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the publication of a prospectus in relation to the shares which has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that it may make an offer to the public in that Relevant State of any shares at any time under the following exemptions under the Prospectus Regulation:

(a) to any legal entity which is a qualified investor as defined under the Prospectus Regulation;

(b) to fewer than 150 natural or legal persons (other than qualified investors as defined under the Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation;

provided that no such offer of shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

For the purposes of this provision, the expression an "offer to the public" in relation to the shares in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase or subscribe for any shares, and the expression "Prospectus Regulation" means Regulation (EU) 2017/1129.

The above selling restriction is in addition to any other selling restrictions set out below.

United Kingdom

This prospectus supplement and the accompanying prospectus are only being distributed to, and are only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the "Order") or (ii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (each such person being referred to as a "relevant person"). This prospectus supplement and its contents are confidential and should not be distributed, published or

reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation; *provided* that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Hong Kong

The shares may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32 of the Laws of Hong Kong) ("Companies (Winding Up and Miscellaneous Provisions) Ordinance") or which do not constitute an invitation to the public within the meaning of the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong) ("Securities and Futures Ordinance"), or (ii) to "professional investors" as defined in the Securities and Futures Ordinance and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance, and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" in Hong Kong as defined in the Securities and Futures Ordinance and any rules made thereunder.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor (as defined under Section 4A of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA")) under Section 274 of the SFA, (ii) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to conditions set forth in the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person that is a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole

business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor, the securities (as defined in Section 239(1) of the SFA) of that corporation shall not be transferable for six months after that corporation has acquired the shares under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer in that corporation's securities pursuant to Section 275(1A) of the SFA, (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore ("Regulation 32").

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is a trust (where the trustee is not an accredited investor (as defined in Section 4A of the SFA)) whose sole purpose is to hold investments and each beneficiary of the trust is an accredited investor, the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferable for six months after that trust has acquired the shares under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer that is made on terms that such rights or interest are acquired at a consideration of not less than $200,000 (or its equivalent in a foreign currency) for each transaction (whether such amount is to be paid for in cash or by exchange of securities or other assets), (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32.

Solely for the purposes of its obligations pursuant to Sections 309B(1)(a) and 309B(1)(c) of the SFA, we have determined, and hereby notify all relevant persons (as defined in Section 309A of the SFA) that the shares are "prescribed capital markets products" (as defined in the Securities and Futures (Capital Markets Products) Regulations 2018) and Excluded Investment Products (as defined in MAS Notice SFA 04- N12: Notice on the Sale of Investment Products and MAS Notice FAA-N16: Notice on Recommendations on Investment Products).

Japan

The shares have not been and will not be registered under the Financial Instruments and Exchange Act of Japan (Act No. 25 of 1948, as amended), or the FIEA. The shares may not be offered or sold, directly or indirectly, in Japan or to or for the benefit of any resident of Japan (including any person resident in Japan or any corporation or other entity organized under the laws of Japan) or to others for reoffering or resale, directly or indirectly, in Japan or to or for the benefit of any resident of Japan, except pursuant to an exemption from the registration requirements of the FIEA and otherwise in compliance with any relevant laws and regulations of Japan.

Israel

In the State of Israel this prospectus shall not be regarded as an offer to the public to purchase shares of common stock under the Israeli Securities Law, 5728 - 1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728 - 1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the "Addressed Investors"); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728 - 1968, subject to certain conditions (the "Qualified Investors"). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. The company has not and will not take any action that would require it to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728 - 1968. We have not and will not distribute this prospectus or make, distribute or direct an offer to subscribe for our common stock to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728 - 1968. In particular, we may request, as a

condition to be offered common stock, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728 - 1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728 - 1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728 - 1968 and the regulations promulgated thereunder in connection with the offer to be issued common stock; (iv) that the shares of common stock that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728 - 1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728 - 1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor’s name, address and passport number or Israeli identification number.

LEGAL MATTERS

Certain legal matters will be passed upon for us by Skadden, Arps, Slate, Meagher & Flom LLP, New York, New York. Certain legal matters in connection with this offering will be passed upon for the underwriters by Davis Polk & Wardwell LLP, New York, New York.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2019, as set forth in their report, which is incorporated by reference in this prospectus supplement and the accompanying prospectus. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

Prospectus

Applied Therapeutics, Inc.

Common Stock
Preferred Stock
Depositary Shares
Debt Securities
and
Warrants

We may offer, issue and sell, together or separately:

- shares of our common stock;
- shares of our preferred stock, which may be issued in one or more series;
- depositary receipts, representing fractional shares of our preferred stock, which are called depositary shares;
- debt securities, which may be issued in one or more series and which may be senior debt securities or subordinated debt securities; and
- warrants to purchase shares of our common stock, shares of our preferred stock or our debt securities.

We will provide the specific prices and terms of these securities in one or more supplements to this prospectus at the time of offering. You should read this prospectus and the accompanying prospectus supplement carefully before you make your investment decision.

This prospectus may not be used to sell securities unless accompanied by a prospectus supplement.

Investing in our securities involves a number of risks. See "Risk Factors" on page 6 before you make your investment decision.

We may offer securities through underwriting syndicates managed or co-managed by one or more underwriters or dealers, through agents or directly to purchasers. If required, the prospectus supplement for each offering of securities will describe the plan of distribution for that offering. For general information about the distribution of securities offered, please see "Plan of Distribution" in this prospectus.

Our common stock is listed on The Nasdaq Global Market under the trading symbol "APLT." On June 11, 2020, the last reported price of our common stock was $39.96 per share. Each prospectus supplement will indicate whether the securities offered thereby will be listed on any securities exchange.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus or any accompanying prospectus supplement is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is June 15, 2020

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission (the "SEC"), using a "shelf" registration process. Under this process, we may sell from time to time any combination of the securities described in this prospectus. This prospectus only provides you with a general description of the securities that we may offer. Each time we sell securities, we will provide a supplement to this prospectus that contains specific information about the terms of that offering, including the specific amounts, prices and terms of the securities offered. The prospectus supplement may also add, update or change information contained in this prospectus. You should carefully read both this prospectus, any accompanying prospectus supplement and any free writing prospectus prepared by or on behalf of us, together with the additional information described under the heading "Where You Can Find More Information."

We have not authorized anyone to provide you with any information other than that contained in or incorporated by reference into this prospectus, any accompanying prospectus supplement and any free writing prospectus prepared by or on behalf of us. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are not making offers to sell the securities in any jurisdiction in which an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation.

The information in this prospectus is accurate as of the date on the front cover. You should not assume that the information contained in this prospectus is accurate as of any other date.

When used in this prospectus, the terms "Applied," "Applied Therapeutics," the "company," "we," "our" and "us" refer to Applied Therapeutics, Inc., unless otherwise specified or the context otherwise requires.

"Applied Therapeutics," the Applied Therapeutics logo and other trademarks, trade names or service marks of Applied Therapeutics, Inc. appearing in this prospectus are the property of Applied Therapeutics, Inc. All other trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert their rights thereto.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC under the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Our SEC filings are available to the public at the SEC's website at www.sec.gov.

The SEC allows us to "incorporate by reference" information into this prospectus and any accompanying prospectus supplement, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus and any accompanying prospectus supplement, except for any information superseded by information contained directly in this prospectus, any accompanying prospectus supplement, any subsequently filed document deemed incorporated by reference or any free writing prospectus prepared by or on behalf of us. This prospectus and any accompanying prospectus supplement incorporate by reference the documents set forth below that we have previously filed with the SEC (other than information deemed furnished and not filed in accordance with SEC rules, including Items 2.02 and 7.01 of Form 8-K).

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, filed with the SEC on March 13, 2020;
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2019 from our definitive proxy statement on Schedule 14A, filed with the SEC on April 23, 2020;

- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2020, filed with the SEC on May 11, 2020;
- our Current Reports on Form 8-K, filed with the SEC on February 14, 2020, April 1, 2020, April 21, 2020 (only with respect to Item 8.01), May and June 5, 2020; and
- the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on May 6, 2019, and any amendment or report filed for the purpose of updating such description.

All documents filed by us 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 is a part and prior to effectiveness of the registration statement and (ii) after the date of this prospectus and before the termination of the offering also shall be deemed to be incorporated herein by reference. We are not, however, incorporating by reference any documents or portions thereof that are not deemed "filed" with the SEC, including any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K.

Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, including any amendments to those reports, and other information that we file with or furnish to the SEC pursuant to Section 13(a) or 15(d) of the Exchange Act, can also be accessed free of charge from our website at http://www.appliedtherapeutics.com. These filings will be available as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information contained on our website is not part of this prospectus.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and any accompanying prospectus supplement and any documents incorporated by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934 (the "Exchange Act") about us and our industry that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this prospectus and any accompanying prospectus supplement and any documents incorporated by reference, including statements regarding our strategy, future financial condition, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "goal," "intend," "may," "objective," "plan," "predict," "positioned," "potential," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of known and unknown risks, uncertainties and assumptions, including risks described in the section titled "Risk Factors" and elsewhere in this prospectus and any accompanying prospectus supplement and any documents incorporated by reference, regarding, among other things:

- the potential impact of the Covid-19 pandemic on the timing and progress of our ongoing clinical trials, our business, results of operations, liquidity, and operations and our ability to mitigate those potential impacts;
- our plans to develop and commercialize our product candidates;
- the initiation, timing, progress and results of our current and future preclinical studies and clinical trials and our research and development programs;
- our ability to take advantage of expedited regulatory pathways for any of our product candidates;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to successfully acquire or in-license additional product candidates on reasonable terms;
- our ability to maintain and establish collaborations or obtain additional funding;
- our ability to obtain regulatory approval of our current and future product candidates;
- our expectations regarding the potential market size and the rate and degree of market acceptance of such product candidates;
- our ability to fund our working capital requirements and expectations regarding the sufficiency of our capital resources;
- the implementation of our business model and strategic plans for our business and product candidates;
- our intellectual property position and the duration of our patent rights;
- developments or disputes concerning our intellectual property or other proprietary rights;
- our expectations regarding government and third-party payor coverage and reimbursement;
- our ability to compete in the markets we serve;
- the impact of government laws and regulations and liabilities thereunder;
- developments relating to our competitors and our industry; and
- other factors that may impact our financial results.

The foregoing list of factors is not exhaustive. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

In light of the significant uncertainties in these forward-looking statements, you should not rely upon forward-looking statements as predictions of future events. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus and any accompanying prospectus supplement and any documents incorporated by reference, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur at all. You should refer to the section titled “Risk Factors” in this prospectus, any accompanying prospectus supplement or documents incorporated by reference for discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. Except as required by law, we undertake no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

THE COMPANY

Overview

We are a clinical-stage biopharmaceutical company developing a pipeline of novel product candidates against validated molecular targets in indications of high unmet medical need. We focus on molecules and pathways whose role in the disease process is well known based on prior research, but have previously failed to yield successful products due to poor efficacy and tolerability. Our unique approach to drug development leverages recent technological advances to design improved drugs, employs early use of biomarkers to confirm biological activity and focuses on potential use of expedited regulatory pathways. Our first molecular target is aldose reductase, or AR, an enzyme that converts glucose to sorbitol under oxidative stress conditions, and is implicated in multiple diseases. Prior attempts to inhibit this enzyme were hindered by nonselective, nonspecific inhibition, which resulted in limited efficacy and significant off-target safety effects. The detrimental consequences of AR activation have been well established by decades of prior research. Our AR program currently includes three small molecules, which are all potent and selective inhibitors of AR, but are engineered to have unique tissue permeability profiles to target different disease states, including diabetic complications, heart disease and rare pediatric metabolic diseases. Using similar strategies to our AR inhibitors, or ARI, program, we have also developed a program targeting selective inhibition of phosphatidylinositol 3-kinase, or PI3K, subunits that produced an early-stage oncology pipeline. The result of this unique multifaceted approach to drug development is a portfolio of highly specific and selective product candidates that we believe are significantly de-risked and can move quickly through the development process. We plan to initiate our clinical program in these indications in 2021.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on January 20, 2016. Our principal executive offices are located at 545 Fifth Avenue, Suite 1400, New York, New York 10017, and our telephone number is (212) 220-9226. Our corporate website address is www.appliedtherapeutics.com. Information contained on, or accessible through, our website is not a part of this prospectus. We have included our website in this prospectus solely as an inactive textual reference.

RISK FACTORS

Investing in our securities involves risk. See the risk factors described in our most recent Annual Report on Form 10-K or Quarterly Report on Form 10-Q, as applicable, and those contained in our other filings with the SEC that are incorporated by reference in this prospectus and any accompanying prospectus supplement. Before making an investment decision, you should carefully consider these risks as well as other information we include or incorporate by reference in this prospectus and any accompanying prospectus supplement. These risks could materially affect our business, financial condition or results of operations and cause the value of our securities to decline. You could lose all or part of your investment.

USE OF PROCEEDS

Except as otherwise set forth in any accompanying prospectus supplement, we expect to use the net proceeds from the sale of securities for general corporate purposes. General corporate purposes may include research and development costs, including the conduct of clinical trials and process development and manufacturing of our product candidates, expansion of our research and development capabilities, working capital and capital expenditures.

DESCRIPTION OF SECURITIES

This prospectus contains summary descriptions of the common stock, preferred stock, depositary shares, debt securities and warrants that may be offered and sold from time to time. These summary descriptions are not meant to be complete descriptions of each security. However, at the time of an offering and sale, this prospectus together with the accompanying prospectus supplement will contain the material terms of the securities being offered.

DESCRIPTION OF CAPITAL STOCK

General

The following summary description of our capital stock is based on the provisions of the General Corporation Law of the State of Delaware (the “DGCL”), our amended and restated certificate of incorporation and our amended and restated bylaws. This description does not purport to be complete and is qualified in its entirety by reference to the full text of the DGCL, as it may be amended from time to time, and to the terms of our amended and restated certificate of incorporation and amended and restated bylaws, as each may be amended from time to time, which are incorporated by reference as exhibits to the registration statement of which this prospectus is a part. See “Where You Can Find More Information.” As used in this “Description of Capital Stock,” the terms “Applied,” “Applied Therapeutics,” the “company,” “we,” “our” and “us” refer to Applied Therapeutics, Inc., a Delaware corporation.

Our authorized capital stock consists of 100,000,000 shares of common stock, par value $0.0001 per share, and 10,000,000 shares of preferred stock, par value $0.0001 per share. The number of authorized shares of any class may be increased or decreased by an amendment to our amended and restated certificate of incorporation proposed by our board of directors and approved by an affirmative vote of the holders of shares of capital stock of the company representing a majority of the votes represented by all outstanding shares of capital stock of the company entitled to vote. As of June 1, 2020, 22,126,772 shares of common stock were issued and outstanding and no shares of preferred stock were issued and outstanding.

Common Stock

Voting Rights

Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders. Our common stockholders will not be entitled to cumulate their votes in the election of directors. Generally, all matters to be voted on by stockholders must be approved by a majority (or, in the case of election of directors, by a plurality) of the votes entitled to be cast by all holders of

our common stock present in person or represented by proxy, voting together as a single class. Except as otherwise provided by law, amendments to our amended and restated certificate of incorporation must be approved by the affirmative vote of holders of at least a majority (and, in some cases, sixty-six and two-thirds percent (66-2/3%)) of the voting power of all of the then-outstanding shares of capital stock entitled to vote generally in the election of directors, voting in a single class. Except as otherwise provided by law, amendments to our amended and restated bylaws must be approved by an affirmative vote of the holders of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all the then-outstanding shares of the capital stock of the company entitled to vote generally in the election of directors, voting together as a single class.

Dividends

Subject to preferences that may apply to any outstanding preferred stock, holders of our common stock are entitled to receive ratably any dividends that our board of directors may declare out of funds legally available for that purpose on a non-cumulative basis.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of our common stock are 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, subject to the satisfaction of any liquidation preference granted to the holders of any outstanding shares of preferred stock.

Rights and Preferences

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

Registration Rights

Certain holders of shares of our common stock, including those shares of our common stock that were issued upon the conversion of our preferred stock in connection with our initial public offering in May 2019 (“IPO”), are entitled to certain rights with respect to registration of such shares under the Securities Act. These shares are referred to herein as “registrable securities.” The holders of these registrable securities possess registration rights pursuant to the terms of the amended and restated investors’ rights agreement, by and among us and certain of our stockholders, dated as of November 5, 2018 (the “Investors’ Rights Agreement”). The registration of shares of our common stock pursuant to the exercise of such registration rights would enable the holders to trade these shares without restriction under the Securities Act when the applicable registration statement is declared effective. We will pay the registration expenses, other than underwriting discounts, selling commissions and stock transfer taxes, of the shares registered pursuant to the demand, piggyback and Form S-3 registrations described in the Investors’ Rights Agreement.

Generally, in an underwritten offering, the managing underwriter, if any, has the right, subject to specified conditions and limitations, to limit the number of shares the holders may include. The demand, piggyback and Form S-3 registration rights described in the Investors’ Rights Agreement will expire no later than three years after the completion of the IPO, or with respect to any particular holder, at such time that such holder can sell its shares under Rule 144 of the Securities Act during any three-month period.

Preferred Stock

This section describes the general terms and provisions of preferred stock that we are authorized to issue. An accompanying prospectus supplement will describe the specific terms of the shares of preferred stock offered through that prospectus supplement, as well as any general terms described in

this section that will not apply to those shares of preferred stock. If there are differences between the prospectus supplement relating to a particular series of preferred stock and this prospectus, the prospectus supplement will control. We will file a copy of the certificate of amendment to our amended and restated certificate of incorporation that contains the terms of each new series of preferred stock with the Secretary of the State of Delaware and with the SEC each time we issue a new series of preferred stock. Each such certificate of amendment will establish the number of shares included in a designated series and fix the designation, powers, privileges, preferences and rights of the shares of each series as well as any applicable qualifications, limitations or restrictions. As of the date of this prospectus, there are no restrictions on the repurchase or redemption of our preferred shares while there is any arrearage in the payment of dividends or sinking fund installments. You should refer to the applicable certificate of amendment as well as our amended and restated certificate of incorporation before deciding to buy shares of our preferred stock as described in any accompanying prospectus supplement.

Our board of directors has been authorized to provide for the issuance of up to 10,000,000 shares of our preferred stock in multiple series without the approval of shareholders. With respect to each series of our preferred stock, our board of directors has the authority to fix the following terms:

- the designation of the series, which may be by distinguishing number, letter or title;
- the number of shares within the series;
- whether dividends are cumulative and, if cumulative, the dates from which dividends are cumulative;
- the rate of any dividends, any conditions upon which dividends are payable, and the dates of payment of dividends;
- whether the shares are redeemable, the redemption price and the terms of redemption;
- the amount payable for each share if we dissolve or liquidate;
- whether the shares are convertible or exchangeable, the price or rate of conversion or exchange, and the applicable terms and conditions;
- any restrictions on issuance of shares in the same series or any other series;
- voting rights applicable to the series of preferred stock; and
- any other rights, priorities, preferences, restrictions or limitations of such series.

The right of a holder of preferred stock to receive payment in respect thereof upon any liquidation, dissolution or winding up of us will be subordinate to the rights of our general creditors.

Anti-Takeover Provisions of Delaware Law and Our Charter Documents

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the DGCL, 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 662/3% 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; and
- 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.

The statute could prohibit or delay mergers or other takeover or change in control attempts and, accordingly, may discourage attempts to acquire us even though such a transaction may offer our stockholders the opportunity to sell their stock at a price above the prevailing market price.

Amended and Restated Certificate of Incorporation, Amended and Restated Bylaws and Other Agreements

Among other things, our amended and restated certificate of incorporation and amended and restated bylaws:

- permit our board of directors to issue up to 10,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate, including the right to approve an acquisition or other change in control;
- provide that the authorized number of directors may be changed only by resolution of our board of directors;
- provide that our board of directors be classified into three classes of directors;
- provide that, subject to the rights of any series of preferred stock to elect directors, directors may only be removed for cause, which removal may be effected, subject to any limitation imposed by law, by the holders of at least sixty-six and two-thirds percent (66 2/3%) of the voting power of all of our then-outstanding shares of the capital stock entitled to vote generally at an election of directors;
- provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;
- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent or electronic transmission;
- 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 advance notice in writing, and also specify requirements as to the form and content of a stockholder's notice;

- provide that special meetings of our stockholders may be called only by the chairman of our board of directors, our chief executive officer or by our board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors; and
- not provide for cumulative voting rights, therefore allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose.

The amendment of any of these provisions would require, in the case of provisions of the amended and restated certificate of incorporation, approval by affirmative vote of holders of at least a majority of the voting power of all of the then-outstanding shares of capital stock, voting as a single class, and in the case of provisions of the amended and restated bylaws, approval by affirmative vote of the holders of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all the then-outstanding shares of the capital stock of the company entitled to vote generally in the election of directors, voting together as a single class.

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. Because our board of directors has the power to retain and discharge our officers, these provisions could 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, with respect to any state actions or proceedings under Delaware statutory or common law, 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 DGCL, 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 one or more actions or proceedings described above, a court could find the choice of forum provisions contained in our amended and restated certificate of incorporation to be inapplicable or unenforceable.

Listing

Our common stock is listed on The Nasdaq Global Market under the trading symbol "APLT."

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

DESCRIPTION OF DEPOSITARY SHARES

We may offer depositary receipts representing fractional shares of our preferred stock, rather than full shares of preferred stock. The shares of preferred stock represented by depositary shares will be deposited under a depositary agreement between us and a bank or trust company that meets certain requirements and is selected by us (the "Bank Depositary"). Each owner of a depositary share will be entitled to all the rights and preferences of the preferred stock represented by the depositary share.

The description in an accompanying prospectus supplement of any depositary shares we offer will not necessarily be complete and will be qualified in its entirety by reference to the applicable depositary agreement, which will be filed with the SEC if we offer depositary shares. For more information on how you can obtain copies of any depositary agreement if we offer depositary shares, see "Where You Can Find More Information." We urge you to read the applicable depositary agreement and any accompanying prospectus supplement in their entirety.

Dividends and Other Distributions

If we pay a cash distribution or dividend on a series of preferred stock represented by depositary shares, the Bank Depositary will distribute such dividends to the record holders of such depositary shares. If the distributions are in property other than cash, the Bank Depositary will distribute the property to the record holders of the depositary shares. However, if the Bank Depositary determines that it is not feasible to make the distribution of property, the Bank Depositary may, with our approval, sell such property and distribute the net proceeds from such sale to the record holders of the depositary shares.

Redemption of Depositary Shares

If we redeem a series of preferred stock represented by depositary shares, the Bank Depositary will redeem the depositary shares from the proceeds received by the Bank Depositary in connection with the redemption. The redemption price per depositary share will equal the applicable fraction of the redemption price per share of the preferred stock. If fewer than all the depositary shares are redeemed, the depositary shares to be redeemed will be selected by lot or pro rata as the Bank Depositary may determine.

Voting the Preferred Stock

Upon receipt of notice of any meeting at which the holders of the preferred stock represented by depositary shares are entitled to vote, the Bank Depositary will mail the notice to the record holders of the depositary shares relating to such preferred stock. Each record holder of these depositary shares on the record date, which will be the same date as the record date for the preferred stock, may instruct the Bank Depositary as to how to vote the preferred stock represented by such holder's depositary shares. The Bank Depositary will endeavor, insofar as practicable, to vote the amount of the preferred stock represented by such depositary shares in accordance with such instructions, and we will take all action that the Bank Depositary deems necessary in order to enable the Bank Depositary to do so. The Bank Depositary will abstain from voting shares of the preferred stock to the extent it does not receive specific instructions from the holders of depositary shares representing such preferred stock.

Amendment and Termination of the Depositary Agreement

The form of depositary receipt evidencing the depositary shares and any provision of the depositary agreement may be amended by agreement between the Bank Depositary and us. However, any amendment that materially and adversely alters the rights of the holders of depositary shares will not be effective unless such amendment has been approved by the holders of at least a majority of the depositary shares then outstanding. The depositary agreement may be terminated by the Bank Depositary or us only if (1) all outstanding depositary shares have been redeemed or (2) there has been a final distribution in respect of the preferred stock in connection with any liquidation, dissolution or winding up of our company and such distribution has been distributed to the holders of depositary receipts.

DESCRIPTION OF DEBT SECURITIES

We may offer debt securities in one or more series, which may be senior debt securities or subordinated debt securities and which may be convertible into another security.

The following description briefly sets forth certain general terms and provisions of the debt securities. The particular terms of the debt securities offered by any prospectus supplement and the extent, if any, to which the following general terms and provisions may apply to the debt securities, will be described in an accompanying prospectus supplement. Our debt securities will be issued in one or more series under an indenture to be entered into between us and a trustee to be named in a prospectus supplement, as amended or supplemented from time to time. A form of the indenture is attached as an exhibit to the registration statement of which this prospectus forms a part. The terms of the debt securities will include those set forth in the indenture and those made a part of the indenture by the Trust Indenture Act of 1939 ("TIA"). You should read the summary below, any accompanying prospectus supplement and the provisions of the indenture in their entirety before investing in our debt securities.

The aggregate principal amount of debt securities that may be issued under the indenture is unlimited. The prospectus supplement relating to any series of debt securities that we may offer will contain the specific terms of the debt securities. These terms may include, among others, the following:

- the title and aggregate principal amount of the debt securities and any limit on the aggregate principal amount of such series;
- any applicable subordination provisions for any subordinated debt securities;
- the maturity date(s) or method for determining same;
- the interest rate(s) or the method for determining same;
- the dates on which interest will accrue or the method for determining dates on which interest will accrue and dates on which interest will be payable and whether interest will be payable in cash, additional securities or some combination thereof;
- whether the debt securities are convertible or exchangeable into other securities and any related terms and conditions;
- redemption or early repayment provisions;
- authorized denominations;
- if other than the principal amount, the principal amount of debt securities payable upon acceleration;
- place(s) where payment of principal and interest may be made, where debt securities may be presented and where notices or demands upon the company may be made;
- the form or forms of the debt securities of the series including such legends as may be required by applicable law;
- whether the debt securities will be issued in whole or in part in the form of one or more global securities and the date as of which the securities are dated if other than the date of original issuance;
- whether the debt securities are secured and the terms of such security;
- the amount of discount or premium, if any, with which the debt securities will be issued;
- any covenants applicable to the particular debt securities being issued;
- any additions or changes in the defaults and events of default applicable to the particular debt securities being issued;
- the guarantors of each series, if any, and the extent of the guarantees (including provisions relating to seniority, subordination and release of the guarantees), if any;

- the currency, currencies or currency units in which the purchase price for, the principal of and any premium and any interest on, the debt securities will be payable;
- the time period within which, the manner in which and the terms and conditions upon which we or the holders of the debt securities can select the payment currency;
- our obligation or right to redeem, purchase or repay debt securities under a sinking fund, amortization or analogous provision;
- any restriction or conditions on the transferability of the debt securities;
- provisions granting special rights to holders of the debt securities upon occurrence of specified events;
- additions or changes relating to compensation or reimbursement of the trustee of the series of debt securities;
- provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture and the execution of supplemental indentures for such series; and
- any other terms of the debt securities (which terms shall not be inconsistent with the provisions of the TIA, but may modify, amend, supplement or delete any of the terms of the indenture with respect to such series of debt securities).

General

We may sell the debt securities, including original issue discount securities, at par or at a substantial discount below their stated principal amount. Unless we inform you otherwise in a prospectus supplement, we may issue additional debt securities of a particular series without the consent of the holders of the debt securities of such series or any other series outstanding at the time of issuance. Any such additional debt securities, together with all other outstanding debt securities of that series, will constitute a single series of securities under the indenture.

We will describe in an accompanying prospectus supplement any other special considerations for any debt securities we sell that are denominated in a currency or currency unit other than U.S. dollars. In addition, debt securities may be issued where the amount of principal and/or interest payable is determined by reference to one or more currency exchange rates, commodity prices, equity indices or other factors. Holders of such securities may receive a principal amount or a payment of interest that is greater than or less than the amount of principal or interest otherwise payable on such dates, depending upon the value of the applicable currencies, commodities, equity indices or other factors. Information as to the methods for determining the amount of principal or interest, if any, payable on any date, and the currencies, commodities, equity indices or other factors to which the amount payable on such date is linked will be described in an accompanying prospectus supplement.

United States federal income tax consequences and special considerations, if any, applicable to any such series will be described in an accompanying prospectus supplement.

We expect most debt securities to be issued in fully registered form without coupons and in denominations of $2,000 and any integral multiple of $1,000 in excess thereof. Subject to the limitations provided in the indenture and in an accompanying prospectus supplement, debt securities that are issued in registered form may be transferred or exchanged at the designated corporate trust office of the trustee, without the payment of any service charge, other than any tax or other governmental charge payable in connection therewith.

Global Securities

Unless we inform you otherwise in an accompanying prospectus supplement, the debt securities of a series may be issued in whole or in part in the form of one or more global securities that will be deposited with, or on behalf of, a depositary identified in an accompanying prospectus supplement. Unless and until a global security is exchanged in whole or in part for the individual debt securities, a

global security may not be transferred except as a whole by the depositary for such global security to a nominee of such depositary or by a nominee of such depositary to such depositary or another nominee of such depositary or by such depositary or any such nominee to a successor of such depositary or a nominee of such successor.

Governing Law

The indenture and the debt securities shall be construed in accordance with and governed by the laws of the State of New York.

DESCRIPTION OF WARRANTS

We may issue warrants for the purchase of shares of our common stock, shares of preferred stock or our debt securities. We may issue warrants independently or together with other securities, and they may be attached to or separate from the other securities. Each series of warrants will be issued under a separate warrant agreement that we will enter into with a bank or trust company, as warrant agent, as detailed in an accompanying prospectus supplement. The warrant agent will act solely as our agent in connection with the warrants and will not assume any obligation, or agency or trust relationship, with you.

The prospectus supplement relating to a particular issue of warrants will describe the terms of those warrants, including, when applicable:

- the offering price;
- the currency or currencies, including composite currencies, in which the purchase price and/or exercise price of the warrants may be payable;
- the number of warrants offered;
- the exercise price and the amount of securities you will receive upon exercise;
- the procedure for exercise of the warrants and the circumstances, if any, that will cause the warrants to be automatically exercised;
- the rights, if any, we have to redeem the warrants;
- the date on which the right to exercise the warrants will commence and the date on which the warrants will expire;
- the name of the warrant agent; and
- any other material terms of the warrants.

After warrants expire they will become void. The prospectus supplement may provide for the adjustment of the exercise price of the warrants.

Warrants may be exercised at the appropriate office of the warrant agent or any other office indicated in an accompanying prospectus supplement. Before the exercise of warrants, holders will not have any of the rights of holders of the securities purchasable upon exercise and will not be entitled to payments made to holders of those securities.

The description in an accompanying prospectus supplement of any warrants we offer will not necessarily be complete and will be qualified in its entirety by reference to the applicable warrant agreement, which will be filed with the SEC if we offer warrants. For more information on how you can obtain copies of any warrant agreement if we offer warrants, see “Where You Can Find More Information.” We urge you to read the applicable warrant agreement and any accompanying prospectus supplement in their entirety.

PLAN OF DISTRIBUTION

We may sell the securities offered by this prospectus from time to time in one or more transactions, including without limitation:

- through underwriters or dealers;
- directly to purchasers;
- in a rights offering;
- in “at the market” offerings, within the meaning of Rule 415(a)(4) of the Securities Act, to or through a market maker or into an existing trading market on an exchange or otherwise;
- through agents;
- through a combination of any of these methods; or
- through any other method permitted by applicable law and described in a prospectus supplement.

In addition, we may enter into derivative or hedging transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. In connection with such a transaction, the third parties may sell securities covered by and pursuant to this prospectus and any accompanying prospectus supplement. If so, the third party may use securities borrowed from us or others to settle such sales and may use securities received from us to close out any related short positions. We may also loan or pledge securities covered by this prospectus and any accompanying prospectus supplement to third parties, who may sell the loaned securities or, in an event of default in the case of a pledge, sell the pledged securities pursuant to this prospectus and any accompanying prospectus supplement.

The prospectus supplement with respect to any offering of securities will include the following information:

- the terms of the offering;
- the names of any underwriters, dealers or direct purchasers;
- the name or names of any managing underwriter or underwriters;
- the purchase price or initial public offering price of the securities;
- the net proceeds from the sale of the securities;
- any delayed delivery arrangements;
- any underwriting discounts, commissions and other items constituting underwriters’ compensation;
- any discounts or concessions allowed or reallowed or paid to dealers;
- any commissions paid to agents; and
- any securities exchange on which the securities may be listed.

Sale through Underwriters or Dealers

If underwriters are used in the sale, the underwriters will acquire the securities for their own account. The underwriters may resell the securities from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. Underwriters may offer securities to the public either through underwriting syndicates represented by one or more managing underwriters or directly by one or more firms acting as underwriters. Unless we inform you otherwise in the applicable prospectus supplement, the obligations of the underwriters to purchase the securities will be subject to certain conditions, and the underwriters will be obligated to purchase all of the offered securities if they purchase any of them. The underwriters may change from time to time any initial public offering price and any discounts or concessions allowed or reallowed or paid to dealers.

During and after an offering through underwriters, the underwriters may purchase and sell the securities in the open market. These transactions may include overallotment and stabilizing transactions and purchases to cover syndicate short positions created in connection with the offering. The underwriters may also impose a penalty bid, which means that selling concessions allowed to syndicate members or other broker-dealers for the offered securities sold for their account may be reclaimed by the syndicate if the offered securities are repurchased by the syndicate in stabilizing or covering transactions. These activities may stabilize, maintain or otherwise affect the market price of the offered securities, which may be higher than the price that might otherwise prevail in the open market. If commenced, the underwriters may discontinue these activities at any time.

Some or all of the securities that we offer through this prospectus may be new issues of securities with no established trading market. Any underwriters to whom we sell our securities for public offering and sale may make a market in those securities, but they will not be obligated to do so and they may discontinue any market making at any time without notice. Accordingly, we cannot assure you of the liquidity of, or continued trading markets for, any securities that we offer.

If dealers are used in the sale of securities, we will sell the securities to them as principals. They may then resell those securities to the public at fixed prices or at varying prices determined by the dealers at the time of resale. We will include in the applicable prospectus supplement the names of the dealers and the terms of the transaction.

If agents are used in an offering, the names of the agents and the terms of the agency will be specified in a prospectus supplement. Unless otherwise indicated in a prospectus supplement, the agents will act on a best-efforts basis for the period of their appointment.

Dealers and agents named in a prospectus supplement may be underwriters as defined in the Securities Act and any discounts or commissions they receive from us and any profit on their resale of the securities may be treated as underwriting discounts and commissions under the Securities Act. We will identify in the applicable prospectus supplement any underwriters, dealers or agents and will describe their compensation. We may have agreements with the underwriters, dealers and agents to indemnify them against specified civil liabilities, including liabilities under the Securities Act.

Underwriters, dealers or agents and their associates may engage in other transactions with and perform other services for us in the ordinary course of business.

If so indicated in a prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by institutional investors to purchase securities pursuant to contracts providing for payment and delivery on a future date. We may enter contracts with commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutional investors. The obligations of any institutional investor will be subject to the condition that its purchase of the offered securities will not be illegal at the time of delivery. The underwriters and other agents will not be responsible for the validity or performance of contracts.

Direct Sales and Sales through Agents

We may sell the securities directly. In this case, no underwriters or agents would be involved. We may also sell the securities through agents designated by us from time to time. In the applicable prospectus supplement, we will name any agent involved in the offer or sale of the offered securities, and we will describe any commissions payable to the agent. Unless we inform you otherwise in the applicable prospectus supplement, any agent will agree to use its reasonable best efforts to solicit purchases for the period of its appointment.

We may sell the securities directly to institutional investors or others who may be deemed to be underwriters within the meaning of the Securities Act with respect to any sale of those securities. We will describe the terms of any sales of these securities in the applicable prospectus supplement.

At the Market Offerings

We may also sell the securities offered by any applicable prospectus supplement in “at the market offerings” within the meaning of Rule 415(a)(4) of the Securities Act, to or through a market maker or into an existing trading market, on an exchange or otherwise.

Remarketing Arrangements

Securities may also be offered and sold, if so indicated in the applicable prospectus supplement, in connection with a remarketing upon their purchase, in accordance with a redemption or repayment pursuant to their terms, or otherwise, by one or more remarketing firms, acting as principals for their own accounts or as agents for us. Any remarketing firm will be identified and the terms of its agreements, if any, with us and its compensation will be described in the applicable prospectus supplement.

Delayed Delivery Contracts

If we so indicate in the applicable prospectus supplement, we may authorize agents, underwriters or dealers to solicit offers from certain types of institutions to purchase securities from us at the public offering price under delayed delivery contracts. These contracts would provide for payment and delivery on a specified date in the future.

The contracts would be subject only to those conditions described in the applicable prospectus supplement. The applicable prospectus supplement will describe the commission payable for solicitation of those contracts.

General Information

We may have agreements with the underwriters, dealers, agents and remarketing firms to indemnify them against certain civil liabilities, including liabilities under the Securities Act, or to contribute with respect to payments that the underwriters, dealers, agents or remarketing firms may be required to make. Underwriters, dealers, agents and remarketing firms may be customers of, engage in transactions with or perform services for us in the ordinary course of their businesses.

LEGAL MATTERS

Unless otherwise indicated in any accompanying prospectus supplement, Skadden, Arps, Slate, Meagher & Flom LLP will provide opinions regarding the authorization and validity of the securities. Skadden, Arps, Slate, Meagher & Flom LLP may also provide opinions regarding certain other matters. Any underwriters will be advised about legal matters by their own counsel, which will be named in an accompanying prospectus supplement.

EXPERTS

The financial statements of Applied Therapeutics, Inc. appearing in Applied Therapeutics, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2019, 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 incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

Applied Therapeutics, Inc.

3,000,000 Shares of
Common Stock

PROSPECTUS SUPPLEMENT

Goldman Sachs & Co. LLC
Cowen
UBS Investment Bank
Baird