UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 03, 2021

DAY ONE BIOPHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-40431**	**83-2415215**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

395 Oyster Point Blvd., Suite 217	
South San Francisco, California	**94080**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (650) 484-0899

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, par value $0.0001 per share	DAWN	NASDAQ Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On November 3, 2021, the Company issued a press release announcing an upcoming poster presentation (the "Poster Presentation") to be made by the Company at the 2021 Connective Tissue Oncology Society (CTOS) Virtual Annual Meeting, to be held from November 10 to 13, 2021. A copy of this press release is attached hereto as Exhibit 99.1 and is incorporated by reference herein. A copy of the Poster Presentation is attached hereto as Exhibit 99.2 and is incorporated by reference herein.

The information in this Item 7.01, including Exhibit 99.1 and Exhibit 99.2 to this report, shall not be deemed to be "filed" for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section or Sections 11 and 12(a)(2) of the Securities Act. The information contained in this Item 7.01 and in the accompanying Exhibit 99.1 and Exhibit 99.2 shall not be incorporated by reference into any other filing under the Exchange Act or under the Securities Act, except as shall be expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press release issued by Day One Biopharmaceuticals, Inc. regarding the presentation at the 2021 Connective Tissue Oncology Society (CTOS) virtual meeting.
99.2	Poster Presentation to be made by Day One Biopharmaceuticals, Inc. at the 2021 at the 2021 Connective Tissue Oncology Society (CTOS) virtual meeting.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

DAY ONE BIOPHARMACEUTICALS, INC.

Date: November 3, 2021

By: /s/ Charles N. York II, M.B.A.
Name: Charles N. York II, M.B.A.
Title: Chief Operating Officer and Chief Financial Officer

Day One Announces Presentation at 2021 Connective Tissue Oncology Society (CTOS) Virtual Annual Meeting

- Compassionate use case of DAY101 demonstrates a complete response in a pediatric patient with a recurrent spindle cell sarcoma harboring a BRAF gene fusion

SOUTH SAN FRANCISCO, CA, November 3, 2021 – Day One Biopharmaceuticals (Nasdaq: DAWN), a clinical-stage biopharmaceutical company dedicated to developing and commercializing targeted therapies for patients of all ages with genomically-defined cancers, today announced an upcoming poster presentation at the 2021 Connective Tissue Oncology Society (CTOS) Virtual Annual Meeting, being held from November 10-13, 2021.

The poster reviews a compassionate use case of a child with recurrent spindle cell sarcoma harboring a novel SNX8-BRAF gene fusion who had exhausted all treatment options, including a MEK inhibitor, and was treated with DAY101 monotherapy. Following treatment, the patient's symptoms had resolved and there was no evidence of measurable disease at the site of previously visualized tumor, indicating a complete response to treatment with DAY101.

"This compassionate use case provides an important experiential data point about the therapeutic activity of DAY101 in pediatric patients with soft tissue sarcomas harboring BRAF gene fusions," said Samuel Blackman, M.D., Ph.D., co-founder and chief medical officer of Day One. "We remain committed to making a difference in the lives of all people with cancer and plan to study DAY101 further in pediatric patients with extracranial RAF-altered tumors."

Details of the poster presentation are as follows:

Title: Activity of Pan-RAF Inhibitor DAY101 in a Pediatric Patient with a Recurrent Spindle Cell Sarcoma Harboring a Novel SNX8-BRAF Gene Fusion
Abstract ID: 1818945
Poster Session: Poster Session 2
Poster Category: Translocation-Associated Sarcomas
Poster Number: P 250
Date: Friday November 12, 2021
Time: 2:30 PM - 3:15 PM EST

A copy of the poster is available on the Company's website here.

About DAY101
DAY101 is an investigational, oral, brain-penetrant, highly-selective type II pan-RAF kinase inhibitor designed to target a key enzyme in the MAPK signaling pathway. Studies have shown DAY101 has high

brain distribution and exposure in comparison to other MAPK pathway inhibitors, thus potentially benefiting patients with primary brain tumors or brain metastases of solid tumors. DAY101 is an investigational type II RAF inhibitor designed to selectively inhibit both monomeric and dimeric RAF kinase, which may broaden its potential clinical application to treat an array of RAF-altered tumors.

DAY101 has been studied in over 250 patients, and as a monotherapy demonstrated good tolerability and encouraging anti-tumor activity in pediatric and adult populations with specific MAPK pathway-alterations. In November 2020, Day One announced preliminary results from PNOC014, an ongoing Phase 1 Pacific Pediatric Neuro-Oncology Consortium (PNOC) network study with DAY101 sponsored by the Dana-Farber Cancer Institute. Preliminary results demonstrated that of the eight relapsed pLGG patients in the study with RAF fusions, two patients achieved a complete response by Response Assessment for Neuro-Oncology (RANO), three had a partial response, two achieved prolonged stable disease, and one experienced progressive disease. DAY101 also demonstrated a tolerable safety profile with the most common side effects being skin rash and hair color changes.

DAY101 has been granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of patients with pLGG harboring an activating RAF alteration who require systemic therapy and who have either progressed following prior treatment or who have no satisfactory alternative treatment options. The FDA has also granted Rare Pediatric Disease Designation to DAY101 for the treatment of low-grade gliomas harboring an activating RAF alteration that disproportionately affects children. In addition, DAY101 has received Orphan Drug designation from the FDA for the treatment of malignant glioma and orphan designation from the European Commission for the treatment of glioma.

Day One is conducting a pivotal Phase 2 trial (FIREFLY-1) of DAY101 in pediatric, adolescent and young adult patients with pLGG. Day One also plans to study DAY101 alone or in combination with other agents that target key signaling nodes in the MAPK pathway, such as the Company’s MEK inhibitor pimasertib, in patient populations where various RAS and RAF alterations are believed to play an important role in driving disease.

About Day One Biopharmaceuticals
Day One Biopharmaceuticals is a clinical-stage biopharmaceutical company dedicated to developing and commercializing targeted therapies for patients of all ages with genomically-defined cancers. Day One was founded to address a critical unmet need: children with cancer are being left behind in a cancer drug development revolution. Our name was inspired by the “The Day One Talk”[1] that physicians have with patients and their families about an initial cancer diagnosis and treatment plan. We aim to re-envision cancer drug development and redefine what’s possible for all people living with cancer—regardless of age—starting from Day One.

Day One partners with leading clinical oncologists, families, and scientists to identify, acquire, and develop important emerging cancer treatments. The Company’s lead product candidate, DAY101, is an oral, highly-selective type II pan-RAF kinase inhibitor, and is being evaluated in a pivotal Phase 2 clinical trial (FIREFLY-1) in pediatric, adolescent and young adult patients with recurrent or progressive low-grade glioma (pLGG). The Company’s pipeline also includes the investigational agent pimasertib, a

clinical-stage, oral, small molecule designed to selectively inhibit mitogen-activated protein kinase kinases 1 and 2 (MEK). Through Day One and its collaborators, cancer drug development comes of age. Day One is based in South San Francisco. For more information, please visit www.dayonebio.com.

Cautionary Note Regarding Forward-Looking Statements
This press release contains “forward-looking” statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: Day One’s plans to develop cancer therapies, expectations from current clinical trials, the execution of the Phase 2 clinical trial for DAY101 as designed, any expectations about safety, efficacy, timing and ability to complete clinical trials and to obtain regulatory approvals for DAY101 and other candidates in development, and the ability of DAY101 to treat pLGG or related indications.

Statements including words such as “believe,” “plan,” “continue,” “expect,” “will,” “develop,” “signal,” “potential,” or “ongoing” and statements in the future tense are forward-looking statements. These forward-looking statements involve risks and uncertainties, as well as assumptions, which, if they do not fully materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements.

Forward-looking statements are subject to risks and uncertainties that may cause Day One’s actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties in this press release and other risks set forth in our filings with the Securities and Exchange Commission, including Day One’s ability to develop, obtain regulatory approval for or commercialize any product candidate, Day One’s ability to protect intellectual property, the potential impact of the COVID-19 pandemic and the sufficiency of Day One’s cash, cash equivalents and investments to fund its operations. These forward-looking statements speak only as of the date hereof and Day One specifically disclaims any obligation to update these forward-looking statements or reasons why actual results might differ, whether as a result of new information, future events or otherwise, except as required by law.

[1]Jennifer W. Mack and Holcombe E. Grier; Journal of Clinical Oncology 2004 22:3, 563-566

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Activity of pan-RAF inhibitor DAY101 in a pediatric patient with a recurrent spindle cell sarcoma harboring a novel *SNX8-BRAF* gene fusion

Katharine Offer,[1] Michael McGuire,[2] Eleni Venetsanakos,[3] Samuel C. Blackman,[3] Kunchang Song,[4] Michael Goldfischer,[4] Michael C. Cox[3]

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Poster #: P250

Background

- Genomic alterations resulting in dysregulation of the RAS-RAF-MEK-ERK (MAPK) pathway have been described in many different types of pediatric and adult malignancies and include:
  - Activating point mutations of *BRAF*[1]
  - *BRAF* gene fusions that drive constitutive activation of the pathway through RAS-independent BRAF dimers[2]
  - In-frame *BRAF* deletions[3]
- *BRAF* fusions and activating mutations have recently been reported in mesenchymal tumors with an infantile fibrosarcoma (IFS)-like morphology[4]
- DAY101 (TAK-580, MLN2480, or BIIB-024) is an oral, selective, central nervous system-penetrant, type II pan-RAF inhibitor that is in clinical development for patients with cancers harboring an activating *BRAF* alteration
- In biochemical assays, DAY101 demonstrated potency against BRAF V600E mutation, wild-type BRAF and wild-type CRAF. DAY101 can inhibit both monomeric and dimeric RAF
  - Preclinical *in vitro* studies have shown that DAY101 does not induce paradoxical activation of MAPK signaling in tumor models driven by the *KIAA1549-BRAF* gene fusion[5]
- In an ongoing pediatric phase 1 study, DAY101 was well tolerated and induced rapid and durable responses in 5 of 8 pediatric patients with low-grade glioma harboring a *BRAF* or *CRAF* fusion (3 partial responses and 2 complete responses, based on response assessment in neuro-oncology criteria)[6]
- DAY101 was granted **breakthrough therapy designation** by the U.S. Food and Drug Administration (FDA) for the treatment of pediatric patients with an advanced low-grade glioma harboring an activating *RAF* alteration, who require systemic therapy and who have either progressed following prior treatment or have no satisfactory alternative treatment options
- DAY101 has also received **orphan drug designation** from the FDA and the European Commission for the treatment of malignant gliomas
- We explored whether DAY101 might be an effective treatment option for a child with recurrent spindle cell sarcoma harboring a novel *SNX8-BRAF* gene fusion who had exhausted all treatment options including trametinib, a MEK inhibitor

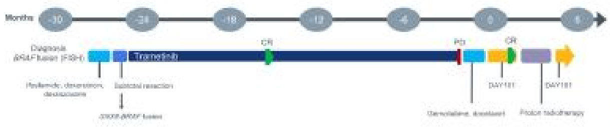
Methods

- *BRAF* fluorescence *in situ* hybridization (FISH) analysis was undertaken in a research setting using a break-apart assay incorporating bacterial artificial chromosome probes
- Whole exome sequencing was performed on DNA extracted from normal (buccal swab) and tumor (snap frozen) tissue samples (Laboratory of Personalized Genomic Medicine, Department of Pathology and Cell Biology, Columbia University Irving Medical Center)
- Transcriptome sequencing was performed on RNA isolated from the frozen tumor sample
- Targeted next-generation sequencing to screen for gene fusion events was performed on RNA extracted from the frozen tumor tissue using anchored multiplex PCR technology (Genomic Testing Cooperative, Irvine, CA)
- The pan-RAF inhibitor DAY101 was administered once weekly at a dose of 420 mg/m² in 28-day cycles on a compassionate use basis

Case description

- A male patient, aged 5 years, presented with a one-week history of fever, cough, and respiratory distress
- Following worsening shortness of breath and tachypnea, MRI revealed an 11.2 x 9.4 x 11.9 cm dominant right lower hemithorax mass that was partially encasing the aorta, and likely arising from the posterior mediastinum
- Biopsy of the mediastinal mass revealed a diagnosis of spindle cell sarcoma and FISH indicated that the tumor harbored a *BRAF* gene fusion
- PET/CT showed a hypermetabolic supraclavicular node of concern in relation to metastatic disease as well as hypermetabolic right-sided pleura and subcarinal lymph nodes
- The patient's treatment history is summarized in **Figure 1**
- He received 3 cycles of ifosfamide, doxorubicin, and dexrazoxane as initial systemic therapy
  - Subsequent chest CT scan showed an interval decrease in the size of the right hemithoracic mass and associated pleural effusion
  - The patient underwent a right thoracotomy with subtotal resection of the right chest mass, leaving a 2.1 x 2.7 cm residual soft tissue mass
- Whole exome/transcriptome sequencing of the tumor revealed a novel *SNX8-BRAF* gene fusion, with breakpoints 3' to exon 10 of *SNX8* and 5' to exon 9 of *BRAF* (**Figure 2**)

Figure 1. Treatment summary

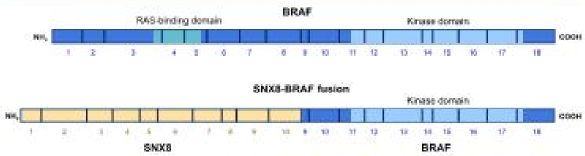


Data cut-off: Sep 30, 2021

CR, complete response; FISH, fluorescence *in situ* hybridization; PD, progressive disease.

- As the SNX8-BRAF fusion was deemed potentially to be a MAPK pathway activating alteration, trametinib treatment was started:
  - Following the first month of treatment, the size of residual tumor reduced and hypervascularity resolved
  - CT was repeated 2 months later, and showed no evidence of measurable tumor at the primary site
  - However, several months later, CT showed a new recurrence of a 4.0 x 3.7 x 4.5 cm left posterior mediastinal mass extending circumferentially around the aorta and impressing on the left atrium and pulmonary veins as well as abutting the T7-T8 disc space
- Pending the results of targeted RNA-based next-generation sequencing to rescreen the tumor for gene fusion events, the patient started gemcitabine and docetaxel as second-line therapy for recurrent disease (**Figure 1**):
  - Following 2 cycles of treatment, there was no objective response on imaging and symptoms persisted
- Molecular test results reconfirmed the presence of an *SNX8-BRAF* fusion:
  - The patient was not considered to be eligible for an ERK inhibitor clinical trial as the novel fusion was not detected in the trial-specified panel
- As the tumor had likely developed resistance to MEK inhibition, treatment with pan-RAF inhibitor DAY101 was initiated under a compassionate use protocol

Figure 2. Structure of the SNX8-BRAF fusion protein



The structure of the canonical BRAF protein sequence (UniProtKB - P15056 [BRAF_HUMAN]; https://www.uniprot.org/uniprot/P15056) and the predicted SNX8-BRAF fusion protein, including functional domains are shown. The *SNX8* and *BRAF* exons, from which the protein sequences are derived, are represented by the numbers below the bars. This rearrangement is predicted to replace the N-terminal regulatory domain of BRAF with almost the entire SNX8 sequence, while leaving the BRAF kinase domain intact.

Results

- Following 2 cycles of DAY101, symptoms had resolved, and an MRI scan showed no evidence of measurable disease at the site of previously visualized tumor (**Figure 3**)
- A week after a complete response was documented, DAY101 was stopped and the patient underwent a course of definitive proton radiotherapy, receiving a total dose of 6660 cGE in 37 fractions
- DAY101 treatment was subsequently resumed after radiotherapy and follow-up is ongoing
- After the first dose of DAY101, the patient experienced grade 2 rash, which resolved in a day following a dose of diphenhydramine
- Radiotherapy-related adverse events included hyperpigmentation overlying the spine on the upper back with no skin breaks, and mild dysphagia

Figure 3. Activity of DAY101

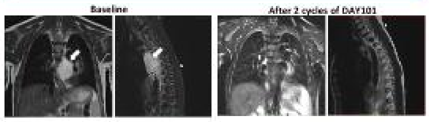


Figure 3: Magnetic resonance imaging (MRI) revealed a mediastinal mass extending circumferentially around the aorta and impressing on the left atrium and pulmonary veins as indicated by white arrows in AP and lateral views. Following 2 cycles of treatment with DAY101, MRI scans revealed only a trace of non-enhancing soft tissue surrounding the descending thoracic aorta.

Conclusions

- The rapid and durable response to DAY101 in this patient indicates that the novel *SNX8-BRAF* gene fusion is a targetable oncogenic driver
- DAY101 is a potentially effective treatment in pediatric patients with soft tissue sarcomas harboring *BRAF* gene fusions and warrants further investigation in other *BRAF* fusion-driven solid tumors
- Tumors with IFS-like morphology should undergo comprehensive genomic profiling to identify novel oncogenic fusions
- DAY101 is currently being investigated in a phase 2 trial for the treatment of *BRAF*-altered, relapsed or progressive low-grade glioma in patients 6 months to 25 years of age (FIREFLY-1, NCT04775485):
  - Plan to include patients with extracranial *RAF*-altered tumors in 2022
- A phase 1/2 trial to evaluate DAY101 in combination with the MEKi pimasertib to treat solid tumors with MAPK pathway aberrations is planned

References

1. Davies H, et al. *Nature*. 2002;417:949-54.
2. Ross JS, et al. *Int J Cancer*. 2016;138:881-90.
3. Chen S-H, et al. *Cancer Discov*. 2016;6:300-15.
4. Penning AJ, et al. *Mod Pathol*. 2021;34:1320-48.
5. Sun Y, et al. *Neuro Oncol*. 2017;19:774-85.
6. Wright K, et al. *Neuro Oncol*. 2020;22(Suppl 3):iii. and associated presentation.